LASER-ASSISTED CORONARY ANASTOMOTIC CONNECTOR

A Journey into the Development and Preclinical Evaluation

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LASER-GEASSISTEERDE CORONAIRE ANASTOMOSE CONNECTOR

Een Reis door de Ontwikkeling en Preklinische Evaluatie

(met een samenvatting in het Nederlands)

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Though the road's been rocky it sure feels good to me
Bob Marley

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INTRODUCTION AND OBJECTIVES

Anastomosis Construction

The intellectual father of the sutured vascular anastomosis is Alexis Carrel (1873-1944), born in France. While most people think he was the first developing a technique of connecting blood vessels, actually, the first scientific report (less than two pages), describing the construction of an anastomosis with sutures, was written by the Russian military surgeon Nicholas Eck (1849-1908) and dated 1877.[1] He constructed an end-to-side portacaval anastomosis (later known as Eck's fistula) in 8 dogs, trying to demonstrate that a liver deprived of its portal blood could sustain life, with the ultimate goal to treat ascites. Seven dogs died, but the last one survived. The dog, in good condition, was observed for 2.5 months, after which he escaped from the laboratory and was never to be found. Eck concluded that the procedure was safe, but he could not perform more experiments; he had to go back to join the army. Ivan Pavlov (1849-1936) repeated Eck's experiments in 20 dogs in 1893, also suturing a portacaval anastomosis.[2] He mentioned in his report that the anastomotic size was unpredictable and not consistent. Nevertheless, the liver was deprived from blood by ligating the portal vein and the dogs with a good anastomosis suffered from ataxia and convulsions, followed by death. According to the authors, the dogs suffered from a syndrome called "meat intoxication", because the symptoms could be augmented by a meat diet (modern diagnosis: hepatic encephalopathy). Years later (1906), Carrel ameliorated the anastomotic technique described by Eck and Pavlov and was the first to develop a successful and reproducible technique of suturing blood vessels together.[3,4] A few years later (1912), he was awarded a Nobel Prize for his contribution to vascular anastomosis and transplantation.

Interestingly, the first report of an anastomosis construction, described a technique of connecting blood vessels without sutures, but with a "connector". In 1774, a French medical student, LeConte, used a quill pen to treat an injured femoral artery.[5] Unfortunately, the successful treatment failed due to an infection. Moreover, before Carrel developed his suturing technique, Abbe described a sutureless technique to connect vessels with an intraluminal glass prosthesis in 1894,[6] Nitze used ivory cuffs in 1897,[7] and Payr used absorbable extraluminal magnesium rings in 1900,[8] and a flanged ring-pin system in 1904[9]: all sutureless anastomotic connectors.

So, in fact, an anastomotic connector is an old-fashioned idea. After Carrel's suturing success, physicians have always been trying to develop a simplified and automated alternative to the demanding, hand-sutured, surgeon-dependent anastomosis, requiring high dexterity. The additional incentive for the pioneering physicians in cardiac surgery was the high degree of difficulty to suture on a moving target, since cardiopulmonary bypass (CPB) and cardiac arrest was not available and the materials and instruments were far from ideal. Finally, six decades later, in the first clinical coronary artery bypass grafting (CABG) operation by Goetz,[10] a sutureless anastomotic connector was used: a modified version of the ring-pin system of Payr.

Coronary Artery Bypass Grafting

As early as 1945, Vineberg was the first to use an internal thoracic artery (ITA) to treat angina pectoris in humans caused by coronary artery disease.[11-13] Instead of anastomosing the mammary artery directly to a coronary artery, he implanted the graft into the myocardium, with variable results in the relief of symptoms. In 1953, Demikhov described the use of the left internal thoracic artery (LITA) to directly graft the left anterior descending artery (LAD) in dogs, with graft patency confirmed for up to two years.[14] Demikhov used a sutureless connector: his personal adaptation of Payr's technique.

In 1960, Goetz performed the very first clinical CABG at the Albert Einstein College of Medicine – Bronx Municipal Hospital Center (New York, USA).[10] He connected the right internal thoracic artery (RITA) directly to a coronary artery with a sutureless connector device: a modified Payr's cannula made of tantalum (ie, also known as the Rosenbach ring). The anastomotic construction time was only fifteen seconds and did not require CPB. The patient, a 38-year-old male, survived, the postoperative angiography demonstrated a patent bypass, and he was free of angina for 12 months. Unfortunately, the patient died and this intervention was the first and last bypass operation Goetz performed. His colleagues were violently against the procedure; the new and innovative technique did not fit in the world of cardiothoracic surgery. A decade later, the procedure was

more accepted, and then, others got the credit.

Sabiston, at Johns Hopkins Hospital (Baltimore, USA), performed the first CABG operation using a saphenous vein conduit in 1962 and two years later Kolesov did the first successful CABG using a LITA and anastomosed it to the left circumflex artery by standard hand-suturing.[15] Over the next five years he performed 33 sutured and mechanically stapled anastomoses in Leningrad (now St. Petersburg). At that time, Spencer was also pioneering, and he was the first American constructing a LITA-to-LAD coronary artery anastomosis in humans.[16]

Since then, CABG has evolved into the gold standard therapy for patients with multivessel coronary artery disease. Despite advances in percutaneous interventional techniques, CABG remains among the most frequently performed operations.[17]

Off-Pump and Minimally Invasive Coronary Artery Bypass Surgery

In the nineties, "off-pump" coronary artery bypass surgery (OPCAB) gained renewed interest[18-20] due to the desire to reduce the morbidity associated with "on-pump" CABG. Essential components of the operation such as the use of CPB, clamping of the aorta, and the necessity to arrest the heart could lead to thromboembolic complications, excessive fluid retention, blood transfusions, neurologic complications, global myocardial ischemia, renal failure, lung dysfunction, and a systemic inflammatory response.[21-23] Kolesov already observed these drawbacks.[24] In addition to be the first surgeon to use a coronary stapling device clinically, he was also the first "OPCAB-believer". In the sixties, he believed that the global inflammatory response following CPB introduced too great a risk to justify its application in CABG. So, Kolesov continued to perform CABG off-pump with the purpose to reduce the associated surgical trauma. Between 1964 and 1974, only 18% of the CABG procedures performed by him were on-pump.[25]

The renewed interest for OPCAB surgery was also driven by innovation, specifically by the development of cardiac stabilization devices. The Utrecht group of Borst et al. played a major role in this global boost toward off-pump and "less invasive" CABG.[26-28]They developed a cardiac stabilization device, the Octopus,[29-31] and performed a thorough experimental and clinical evaluation of this device, which eliminated the need for CPB, aortic clamping, and cardiac arrest.

Current studies comparing off-pump versus on-pump CABG do not show superiority of off-pump over on-pump surgery. In low risk patients, no significant reduction in mortality or major postoperative complications has been demonstrated.[32, 33] However, many reports of experienced off-pump surgeons have shown favorable results applying off-pump techniques in high-risk patients with left ventricular dysfunction, prior stroke, renal insufficiency, and significant atherosclerotic disease of the ascending aorta. Advances in these patients included reduced risk of early morbidity such as stroke, wound and respiratory infection. These patients had a lower demand for blood transfusion and a shorter hospital stay.[34-43] The evidence from meta-analysis is strong that clamping the aorta during CABG increases the risk of postoperative stroke. Hence, a no-touch aorta technique has the lowest risk for postoperative stroke for patients undergoing CABG.[44, 45] More insight in the benefit of OPCAB surgery might be demonstrated with a future large prospective randomized trial, performed by experienced off-pump surgeons, ideally with a reliable anastomotic connector. This facilitates the construction of the anastomosis onto the beating heart and thus simplifies the OPCAB procedure. Such a connector could eliminate the potential flaws of the surgeons' skill by hand-suturing the anastomosis and will result in a more standardized and reproducible construction with a more predictable result and less bias.

Minimally invasive CABG with thoracoscopic or robot-assisted operation techniques,[46-48] and less invasive CABG via a lateral thoracotomy,[49, 50] are sternal-sparing procedures that reduce the size of the incisions. These procedures may reduce morbidity like deep sternal wound infection and can markedly reduce transfusion rates, patient recovery time, hospital stay, and costs.[50-52] Despite the potential benefits for a subset of patients (eg, patients with diabetes, chronic obstructive pulmonary disease, or obese patients) in need of coronary revascularization and satisfactory results,[53] adoption of these techniques has not been widespread. One of the reasons is that an off-pump, minimally invasive approach for CABG is technically very challenging: the

dexterity requirements to construct the anastomosis increase significantly, potentially resulting in a less quality anastomosis, and hence, unfavorable long-term patency results. Moreover, complete revascularization is often not feasible, or extremely challenging, with prolonged operative time and prolonged operator learning curves.[53]

Some surgeons argue that in high-risk CABG patients, the potential best treatment is a "hit-and-run" hybrid procedure.[54-56] In this minimally invasive, sternal sparing procedure, a LITA-to-LAD bypass graft is combined with a PCI of the remaining obstructed coronary arteries. However, not all coronary arteries are suitable for additional PCI and the benefit of complete surgical revascularization may outweigh the operative risk.[57]

In case an anastomotic connector could alleviate the increased dexterity required for anastomosis construction in minimally invasive CABG, complete revascularization could be realized. This thought boosted the revival of old concepts and the development of new anastomotic connectors. However, in contradiction to the incentive of the pioneers in the beginning of the 20th century, now with the incentive to reduce the morbidity associated with the surgical trauma of CABG. Thus without CPB, aortic clamping, and cardiac arrest, and via small surgical incisions with almost a "PCI-like invasiveness", though with the long-term benefits of total arterial complete surgical revascularization.[57]

Coronary Anastomotic Connectors

The trend toward less invasive CABG resulted in the development of anastomotic connectors. Reducing the dexterity requirements for anastomosis construction by a connector could facilitate minimally invasive construction. Century old concepts[58] were recycled and revitalized and in a fast tempo clinically evaluated. Due to disappointing results or insufficient commercial support, many ideas had to be rejected.[59] Staplers, surgical glue and sealants, rings, frames, and clips, magnetic connectors, and laser-welding, to mention a few of the techniques which have been evaluated.[60-71] According to a report by Scheltes et al., 57 patents for distal coronary anastomotic connectors had been published between 1970 and 2001.[72]

A program to develop a coronary anastomotic connector is demanding, due to the major consequences and risks of its application during and after bypass surgery. Flaws in the anastomotic construction may cause immediate technical failure by vessel obstruction and myocardial infarction or late failures due to a disturbed anastomotic healing and intimal hyperplasia. The small size of the coronary arteries and the relatively low blood-flow in the coronary circulation, involving thrombogenic risks, pose high demands for precision.[73-75] There is hardly any room for mistakes when one is working in this delicate area.

One of the key principles in anastomosis construction is the intima-to-intima apposition.[4] Opposing the graft's intima to the intima of the receiving coronary artery is believed to be the "holy grail" in anastomosis construction. It is believed to result in superior long-term results regarding anastomotic patency. Accordingly, an anastomotic connector should respect this principle to minimize the thrombogenic risks and maximize anastomotic patency, however, it poses major limitations for design strategies.

Intima-to-intima apposition requires vessel wall eversion. Deforming the vessel wall for this purpose leads to a high stress concentration in the corners of the coronary arteriotomy. The vessel wall tends to rupture when folded over the anvil of a connector and excessive wall strain may promote early anastomosis occlusion.[72]

Experimental studies have been exploring the possibilities for alternative vessel wall apposition. Despite the afore mentioned key principles of anastomosis surgery, it was demonstrated that intima-to-adventitia vessel wall apposition could yield patent anastomoses with a limited intimal hyperplasia response in a porcine carotid artery bypass graft model.[76] The patency of an intima-to-adventitia anastomosis, with a small adventitial edge of 0.2 mm exposed to blood, was not inferior to conventional intima-to-intima constructed anastomoses in an internal thoracic-to-coronary artery anastomosis in a porcine model. Even under low-flow conditions (up to 15 mL/min), no difference in patency was observed.[77] These findings expanded the horizon for design strategies toward accepting unconventional alternative vessel wall apposition other than intima-to-intima.

Scheltes et al. described the concept of blood-exposed non-intimal surface (= BENIS) and compared the BENIS area in device-constructed anastomoses to the conventionally sutured anastomosis.[72] In their connector-facilitated anastomoses, the total BENIS area ranged from 4.3 - 80 mm^2, compared to 1 - 6 mm^2 in hand-sutured anastomoses. The BENIS can be further subdivided in tissue- and foreign-BENIS. The tissue-BENIS depends on the apposition, anastomotic orifice size, and wall thickness, whereas the foreign-BENIS depends on the connector component's location and size. In developing anastomotic connectors, the BENIS area should ideally be kept to a minimum.[59]

The patency rate does not depend solely on the amount of BENIS. A significant factor in anastomotic patency is the amount of tissue injury resulting from the anastomosis construction. Mechanical damage and stresses onto the vessel wall could result in late stenosis or occlusion by gradual intimal hyperplasia, or acute thrombosis by intimal damage.[78, 79] Additionally, flow profiles directly related to the geometry of the anastomosis,[80, 81] anastomotic compliance,[82, 83] wall shear stresses,[75] and flow through the anastomosis,[73, 74] affect intimal hyperplasia and anastomotic patency.

If foreign material is being used and positioned intraluminal, it is permanently exposed to the bloodstream, unless it is endothelialized. Not only the quantity or foreign BENIS area, but also compliance,[82, 83] and material characteristics[84] play an important role in the biological healing process. Anastomotic non-compliance results in more wall stress around the anastomosis, potentially increasing the development of intimal hyperplasia.[85, 86]The biological characteristics of the foreign material with regard to inflammation response, platelet binding, and thrombin formation, play an important role in selecting a suitable material for the connector. Some materials could promote intimal hyperplasia and lead to a gradual stenosis or even induce a direct thrombotic occlusion. The mechanical behavior in terms of strength, flexibility, and durability and the treatment of the surface of a foreign material can completely alter the biological behavior of the material.[87]

The Ideal Coronary Anastomotic Connector

Taking all the above in consideration, theoretically, an anastomotic connector should accord to the following conditions:

Handling and Practical Use

- Easy-to-use: simplified construction.
- Safe, reliable, and standardized construction with predictable and reproducible results in terms of:
  - vessel wall apposition
  - strong but atraumatic approximation resisting a supraphysiologic blood pressure (300 mm Hg)
  - hemostasis: avoiding extra handling like an extra hemostatic stitch
  - anastomotic geometry: no impediment to flow
- Feasible on the arrested, as well as on the beating heart: enabling a simplified and reliable construction on a moving target.
- Low-profile device: facilitating minimally invasive approaches, thus enabling expediency in a small, impaired workspace, in a direct approach (eg, MIDCAB) or endoscopic (TECAB).
- Fast construction time: timesaving, with this minimizing myocardial ischemia and operating time.
- Safe bail-out in case of device malfunctioning: possibility to re-do the anastomosis (connector-facilitated or hand-sutured).

Vessel Wall Damage and BENIS

- Minimize tissue trauma, minimize graft manipulation, and avoid intimal contact: minimizing thrombogenic risks and intimal hyperplasia formation.
- BENIS area close to zero. Ideally, an intima-to-intima configuration (tissue-BENIS zero) and minimal exposure of the implanted device to the blood stream (material-BENIS). When there is exposure, controlled neointimal growth covering the implanted device is required: minimizing thrombogenic risks.
- Biocompatibility: avoid a chronic excessive inflammation or rejection reaction as a result of the used

material.

Patency

- Durable and long-term effectiveness: non-inferior long-term patency compared to the conventional hand-sutured anastomosis.

Versatility

- Applicable to remote (ie, difficult to reach) regions of the heart, with distal and proximal coronary targets: accommodating a coronary diameter and vessel wall thickness encountered in clinical practice (± 1.0 – 3.5 mm inner diameter and 0.3 – 1.2 mm, respectively).[88, 89]
- Applicable to all conduit types: venous (eg, saphenous vein) and arterial (eg, ITA and radial artery), accommodating a graft diameter and vessel wall thickness encountered in clinical practice (± 1.5 – 6.0 mm and 0.1 – 0.7 mm, respectively).[90-92]
- Feasible with different approaches of grafting: side-to-side, end-to-side, single, sequential, Y- or T-graft anastomosis.
- Interchangeable proximal/distal sequencing of the anastomosis.

Atherosclerotic Coronary Arteries

- Feasible to both healthy and atherosclerotic coronary arteries: same targets a hand-sutured anastomosis is constructed on.

Clinical Distal Coronary Connector - Micromechanical Bonding

At this time, only one distal coronary anastomotic connector is clinically in use, the C-Port System (Cardica, Inc., Redwood City, CA, USA). This stapler-based device enables construction of an end-to-side distal coronary anastomosis, resulting in an intima-to-adventitia apposition, and is applicable to a vein or arterial graft. It is suitable up to 1.25 mm diameter vessels and the new generation (ie, Flex A) is developed for minimally invasive approaches.

In a prospective randomized controlled study, Verberkmoes et al. constructed distal coronary anastomoses with a vein graft by using the C-Port xA system and demonstrated comparable patency results to the conventional hand-sutured anastomosis at 12-month follow-up (86 versus 88%).[93] Additional stitches were necessary in 22 (76%) patients of the device group to obtain hemostasis and 7 (9%) patients with severely diseased coronary arteries were excluded. However, the authors comment that the highly selected patient group could have positively influenced the patency results.

Balkhy et al. described 120 patients undergoing totally endoscopic coronary artery bypass grafting using the da Vinci robot with the aid of the Flex A distal anastomotic device and U-clips.[94] Eighty-five Flex A constructed anastomoses with the internal mammary artery graft in 68 patients were evaluated and 80 were patent at a mean of 4 months (94.1%). The patency in 56 LITA-to-LAD grafts was 98.2%. The surgeon of this group anticipated bleeding of the anvil hole by placing an anvil stitch before anastomosis construction.

Despite the excellent clinical results, this micromechanical bonding technique is not widely and routinely used in everyday practice. This could be explained by the technical challenges starting with the technique; it takes a while before a certain level of confidence exists (ie, learning curve). More importantly, in about 20% of cases leakage from the toe can be expected,[94] and in addition, the need for an additional hemostatic suture to close the anvil hole is undesirable, especially in minimally invasive approaches. Finally, the application mechanism is quite bulky and the cost for this technology is high. Thus, this connector is not particularly easy-to-use, with an extended learning curve, not reliable in terms of hemostasis, it cannot facilitate side-to-side and sequential grafting, and the application system is not low-profile, potentially introducing difficulties in facilitating construction on remote areas of the heart.

Lasers in Anastomosis Construction

Various ways to connect vessels have been described, from magnetic couplers to several stapler devices,

but also lasers. After Yahr et al. described the use of a neodymium laser to construct an anastomosis for the first time in the sixties,[95] various kinds of lasers have been used in anastomosis construction and vessel repair by melting or welding vessel walls. In 1979, Jain et al. demonstrated a technique for repair of incisions in small blood vessels (diameter, 0.3 – 1.0 mm) in the rat using a Neodymium - Yttrium-Aluminium-Garnet (Nd:YAG) laser.[96] It was possible to seal the incision without the use of sutures and to preserve the lumen of the vessel. Frazier used in 1985 a low-powered carbon dioxide laser to perform end-to-end anastomoses of growing femoral arteries (diameter, 1.6 mm) in miniature swine.[97] After 13 weeks, all nine laser-assisted anastomoses were patent, functional, and free of stenosis and the laser induced minimal or no fibrosis. Quigley et al. assessed the extent of myointimal proliferation after both suture and carbon dioxide laser-assisted microvascular anastomosis in the rat femoral artery model.[98, 99] At 2 weeks the average intimal height of the laser-anastomosed vessels was significantly smaller than found in the sutured arteries, however, the results were equivalent by 6 weeks. Their next paper, however, showed the major drawback of laser-welding with a carbon dioxide laser: aneurysm formation.[100] In a series of 125 adult rats, end-to-end anastomoses of the femoral artery were constructed, using either a carbon dioxide laser or the conventional suture technique. The rate of late aneurysm formation (1 week or longer after operation) for the laser group was 30% (20/67). In addition, in 1989, Shapiro described end-to-side, laser-assisted vascular anastomosis construction by using a Nd:YAG laser on rat carotid arteries.[101] The anastomotic patency was 86%, however, aneurysm formation occurred in 23%. Laser welding thus introduces a significant amount of vessel wall damage, resulting in adverse remodeling over time.

Consequently, laser-assisted anastomosis construction lost interest, until in 1993 Tulleken et al. found a new way for laser-assisted anastomosis construction with an excimer laser: the excimer laser-assisted nonocclusive anastomosis (ELANA) technique.[102] This technique enables a nonocclusive connection of a bypass graft to a recipient artery. First, the 2 vessels are connected with sutures, and subsequently, a laser creates an opening by laser-punching the arterial wall (ie, no laser welding) without occlusion of the recipient artery. Hence, the construction is associated with zero ischemia during the whole construction.

ELANA Technique – A Paradigm Shift

Former chief of the Department of Neurosurgery of the University Medical Center Utrecht, the Netherlands, neurosurgeon prof. dr. Tulleken, is founder of the ELANA technique. He started in 1979 to develop techniques to operate on cerebral arteries with reduced ischemia time, enabling treatment of patients never considered treatable. Those patients suffer for example from life threatening giant cerebral artery aneurysms. If operated conventionally, with a hand-sutured bypass, the arterial occlusion time required for constructing the bypass would result in brain ischemia with subsequent brain damage. This stresses the significance of a nonocclusive (ie, zero ischemia) technique.

Interestingly, to reduce ischemia time, prof. Tulleken ignored the general assumption in anastomosis construction, ie, to appose the intima of the graft to the intima of the recipient, and hence, Tulleken's first step in anastomosis construction was to suture the graft onto the recipient, before the arteriotomy.[103] Just before placing the final sutures, the recipient artery was occluded and the arteriotomy created by excising a disk of arterial wall. A small rim of adventitia of the recipient artery remained blood-exposed inside the anastomosis. Strikingly, after 3 weeks, scanning electron microscopy showed complete endothelialization of the anastomotic line. This idea was further developed toward complete nonocclusive anastomosis construction. Via a side-port of the graft a Nd:YAG laser was introduced and positioned onto the recipient artery.[104] Following lasering through the arterial wall, the laser was retrieved, and the side port closed with sutures, all without occlusion of the recipient artery. After experimental testing in a rabbit model, the first patient was treated successfully. The laser-assisted technique was further ameliorated, because the adventitia of the recipient artery had first to be dissected before lasering, introducing potential surgical risks (ie, bleeding).

An excimer laser was then evaluated for the nonocclusive anastomosis construction. However, the solid tip of the laser created separate small holes in the recipient artery, instead of one sufficient orifice, which resulted

in disappointing patency results. Therefore, the laser catheter was modified to enable laser-punching a round disk of arterial wall. The new laser catheter consists of a double circular row of laser fibers with centrally located a vacuum lumen.[102, 105] The vacuum lumen enables retrieval of the laser-punched round fragment of the arterial wall by vacuum suction. However, experimental testing demonstrated that the laser-punched fragment was not completely circumferentially excised and remained inside the lumen of the anastomosis. The lateral sides were not adequately excised, which was caused by the natural curvature of the recipient artery. The excimer laser requires tissue contact to adequately laser through the vessel wall. Without a straight surface, the laser-tissue contact is inadequate. Tulleken and his team found the solution: a ring. A round open platinum ring was sutured onto the recipient artery, ensuring a straight surface of the recipient artery wall. With the ring, the lateral sides of the laser catheter do have perpendicular laser-tissue contact. Subsequent experimental studies with the Excimer Laser-Assisted Nonocclusive Anastomosis (ELANA) technique showed favorable patency results and the first patient was operated in 1993 in the UMC Utrecht.[105] Currently, this technique is still being clinically applied in neurosurgical practice and in 2011 the ELANA technique received its Food Drug Administration (FDA)-approval. In medical science this technique is quite unique and revolutionary; after years of conventional anastomosis construction (ie, first the arteriotomy and second suturing the intima-to-intima vessel wall approximation, all with interrupted recipient blood flow), a paradigm shift was introduced of first the vessel wall apposition (ie, adventitia-to-intima) and second the lasered-arteriotomy, resulting in zero-ischemia during construction, hence, enabling treatment of patients never considered treatable.

Aim and Outline of the Thesis

The aim of the described research in this thesis is to develop and evaluate a new coronary anastomotic connector, which is based on the unconventional principles and simplified basics of the ELANA technique. It should ultimately enable a simplified, sutureless, and reliable connection of the graft to the coronary artery and it should result in a comparable patency as the conventional hand-sutured anastomosis on the long-term. Moreover, the easy-to-use connector should enable construction of the anastomosis via a less invasive surgical approach (sternal-sparing), and ultimately, via a (robot-assisted) thoracoscopic approach.

As earlier described, many attempts have been made to develop a coronary anastomotic connector, but currently, only 1 distal coronary anastomotic connector is sparsely being used clinically (ie, Cardica C-Port). Undoubtedly, our aim to develop an anastomotic connector is extremely challenging. However, owing to the unique characteristics of the ELANA technique, it basically introduces a whole new concept of anastomosis construction that has potential to fill the missing link toward expansion of minimally invasive CABG. The essential of the ELANA technique is the two-step approach: first, the graft is connected to the recipient artery with a connector device, without occlusion of the recipient artery and before making the arteriotomy of the recipient artery, this in sharp contrast to the conventional anastomosis construction. The second step is making the arteriotomy, which is created in a standardized, simplified, and automated fashion by a laser, completely nonocclusive, ie, without interrupting the native coronary artery flow. This step enables the construction of an anastomosis in a bloodless surgical field and without occlusion of the coronary artery, so hence, resulting in zero myocardial ischemia. In comparison to the single distal coronary anastomotic connector clinically in use (ie, Cardica C-Port), this two-step approach is particularly unique: it discards the need for snaring or handling of the coronary artery with a separate incision or a standard hemostatic stitch, thus resulting in less manipulation, and the application system is low-profile. Thus hereby simplifying the off-pump procedure and being a particular interesting concept for minimally invasive CABG.

This research project did not start with a finalized, cardio-surgical market ready product, but instead, it began with the original and unique concept used in neurosurgery, in which the approximation of the graft to the recipient is executed by suturing a ring onto the vessels and, moreover, which is only applicable to large caliber vessels (> 3 mm outer diameter) with a much higher arterial flow compared to the smaller coronary targets in CABG surgery.[73, 74] Hence, the amelioration and further development of the basic concept of the ELANA technique toward a preclinical, sutureless, coronary anastomotic connector, applicable to small

caliber coronary arteries in a minimal invasive surgical approach, will be described in the course of this thesis: *A Journey into the Development and Preclinical Evaluation*.

Part A – The Slide Connector

Chapter 2: The feasibility of a first-generation ELANA-based prototype connector, the "Slide connector", is evaluated in an acute rabbit abdominal aortic-bypass model. In addition, two surgical sealants are tested to facilitate optimal anastomotic hemostasis in the current device prototype.

Part B – The Clip Connector

Chapter 3: The feasibility and anastomotic healing of an ameliorated second-generation ELANA-based prototype connector, the "Clip connector", is evaluated in an acute rabbit study and in a long-term porcine OPCAB study.

Chapter 4: This pilot study extensively evaluated the anastomotic healing of the Clip connector at 6 months in a porcine OPCAB model by multiple imaging modalities.

Part C – The Trinity Clip Connector

Chapter 5: This protocol-based paper is supported by an online video of a third-generation ELANA-based prototype connector, the "Trinity Clip connector", which is further ameliorated toward clinical application. Design modifications of the connector and the excimer laser catheter enable a completely sutureless construction on to clinically relevant, small caliber coronary arteries. The paper extensively outlined the procedural steps of the anastomotic construction in a porcine OPCAB model. Furthermore, multiple options are described for intraoperative, postoperative, and postmortem assessment of the anastomotic quality.

Chapter 6: In this study, the efficacy of the Trinity Clip is evaluated on human diseased ex vivo coronary arteries. Additionally, the acute laser effects onto small caliber target coronary arteries were initially assessed in an ex vivo (porcine heart) model, which was subsequently followed by the evaluation in an in vivo rabbit model (carotid and femoral arteries), and finally validated in the porcine OPCAB model.

Chapter 7: This pilot study evaluated the feasibility of total arterial minimally invasive direct coronary artery bypass (MIDCAB) surgery by using the Trinity Clip anastomotic connector in an acute porcine model.

Chapter 8: This preclinical safety study evaluated the Trinity Clip on small caliber coronary arteries in a long-term porcine OPCAB model. The patency, healing, and hemodynamic function of the connector-facilitated anastomoses were compared to the hand-sewn anastomoses.

Part D – Discussion and Future Development

Chapter 9: This chapter discusses the findings in this thesis in the light of the in Chapter 1 mentioned criteria for an ideal coronary anastomotic connector.

Chapter 10: This final chapter outlines the future development and challenges toward clinical application.

REFERENCES

1. Eck NV. K voprosu o perevyazkie vorotnois veni: Predvaritelnoye soobschjenye. *Voen Med J.* 1877;130:1-2.
2. Hahn M, Massen O, Nencki M, Pawlow J. Die Eck'sche Fistel zwischen der unteren Hohlvene und der Pfortader und ihre Folgen für den Organismus. *Arch Exp Pathol Pharmakol.* 1893;32:161-210.
3. Carrel A, Guthrie CC. Methode simple pour etablir une fistule d'Eck. *Compt Rend Soc Biol.* 1906;60:1104-6.
4. Carrel A. La technique operatoire des anastomoses vasculaires et la transplantation des visceres. *Lyon Med.* 1902;98:859-63.
5. Callow AD. Historical overview of experimental and clinical development of vascular grafts. In: Stanley J, Burkel W, Lindenauer S, Barlett R, Turcotte J, eds. *Biologic and synthetic vascular prostheses*: Grune & Stratton (NY); 1982.11–6.
6. Abbe R. The surgery of the hand. *NY Med J.* 1894;59:33.
7. Nitze M. Kongress in Moskau. *Centralbl Chir.* 1897;24:1042.
8. Payr E. Beiträge zur Technik der Blutgefäss-und Nervennaht nebst Mitteilungen über die Verwendung eines resorbierbaren Metalles in der Chirurgie. *Arch Klein Chir.* 1900;62:67–93.
9. Payr E. Zur Frage der zirkularen Vereinigung von Blutgefässe mit resorbierbaren Prothesen. *Arch Klein Chir.* 1904;72:32–54.
10. Goetz RH, Rohman M, Haller JD. Internal mammary-coronary artery anastomosis. A nonsuture method employing tantalum rings. *J Thorac Cardiovasc Surg.* 1961;41:378-86.
11. Vineberg A, Munro DD, Cohen H, Buller W. Four years' clinical experience with internal mammary artery implantation in the treatment of human coronary artery insufficiency including additional experimental studies. *J Thorac Surg.* 1955;29:1-32.
12. Vineberg A, Buller W. Technical factors which favor mammary-coronary anastomosis; with report of forty-five cases of human coronary artery disease thus treated. *J Thorac Surg.* 1955;30:411-31.
13. Vineberg A. Restoration of coronary circulation by anastomosis. *Can Med Assoc J.* 1946;55:117-9.
14. Demikhov VP. Experimental transplantation of vital organs. *Basil Haigh, transl New York: Consultant's Bureau Enterprises, Inc.* 1962.
15. Kolessov VI. Mammary artery-coronary artery anastomosis as method of treatment for angina pectoris. *J Thorac Cardiovasc Surg.* 1967;54:535-44.
16. Spencer FC, Yong NK, Prachuabmoh K. Internal Mammary-Coronary Artery Anastomoses Performed during Cardiopulmonary Bypass. *J Cardiovasc Surg (Torino).* 1964;5:292-7.
17. http://www.cdc.gov/.
18. Benetti FJ, Naselli G, Wood M, Geffner L. Direct myocardial revascularization without extracorporeal circulation. Experience in 700 patients. *Chest.* 1991;100:312-6.
19. Buffolo E, de Andrade CS, Branco JN, Teles CA, Aguiar LF, Gomes WJ. Coronary artery bypass grafting without cardiopulmonary bypass. *Ann Thorac Surg.* 1996;61:63-6.
20. Moshkovitz Y, Lusky A, Mohr R. Coronary artery bypass without cardiopulmonary bypass: analysis of short-term and mid-term outcome in 220 patients. *J Thorac Cardiovasc Surg.* 1995;110:979-87.
21. Edmunds LH, Jr. Inflammatory response to cardiopulmonary bypass. *Ann Thorac Surg.* 1998;66:S12-6; discussion S25-8.
22. Weiland AP, Walker WE. Physiologic principles and clinical sequelae of cardiopulmonary bypass. *Heart Lung.* 1986;15:34-9.
23. Hammon JW. Extracorporeal circulation. In: LH C, ed. *Cardiac surgery in the adult.* 3rd ed: Columbus (OH): McGraw-Hill; 2008.370–414.
24. Kolesov VI, Levin AO, Vinogradov AG, Danilova LD. [On changes of morphological and functional properties of the blood and hemodynamics during the use of the Niiekhaii (AIK-59) and Baliuzek's (ISL-2) artificial circulation apparatus]. *Grudn Khir.* 1963;5:34-40.

25. Kolesov VI. [Late results of a mammary-coronary anastomosis]. *Vestn Khir Im I I Grek.* 1982;128:49-53.
26. Borst C, Jansen EW, Grundeman PF. Less invasive coronary artery bypass grafting: without cardiopulmonary bypass and via reduced surgical access. *Heart.* 1997;77:302-3.
27. Borst C, Santamore WP, Smedira NG, Bredee JJ. Minimally invasive coronary artery bypass grafting: on the beating heart and via limited access. *Ann Thorac Surg.* 1997;63:S1-5.
28. Borst C, Grundeman PF. Minimally invasive coronary artery bypass grafting: an experimental perspective. *Circulation.* 1999;99:1400-3.
29. Borst C, Jansen EW, Tulleken CA, Grundeman PF, Mansvelt Beck HJ, van Dongen JW, et al. Coronary artery bypass grafting without cardiopulmonary bypass and without interruption of native coronary flow using a novel anastomosis site restraining device ("Octopus"). *J Am Coll Cardiol.* 1996;27:1356-64.
30. Jansen EW, Borst C, Lahpor JR, Grundeman PF, Eefting FD, Nierich A, et al. Coronary artery bypass grafting without cardiopulmonary bypass using the octopus method: results in the first one hundred patients. *J Thorac Cardiovasc Surg.* 1998;116:60-7.
31. Jansen EW, Grundeman PF, Borst C, Eefting F, Diephuis J, Nierich A, et al. Less invasive off-pump CABG using a suction device for immobilization: the 'Octopus' method. *Eur J Cardiothorac Surg.* 1997;12:406-12.
32. Moller CH, Penninga L, Wetterslev J, Steinbruchel DA, Gluud C. Clinical outcomes in randomized trials of off- vs. on-pump coronary artery bypass surgery: systematic review with meta-analyses and trial sequential analyses. *Eur Heart J.* 2008;29:2601-16.
33. Nathoe HM, van Dijk D, Jansen EW, Suyker WJ, Diephuis JC, van Boven WJ, et al. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. *N Engl J Med.* 2003;348:394-402.
34. Halkos ME, Puskas JD, Lattouf OM, Kilgo P, Guyton RA, Thourani VH. Impact of preoperative neurologic events on outcomes after coronary artery bypass grafting. *Ann Thorac Surg.* 2008;86:504-10; discussion 10.
35. Panesar SS, Athanasiou T, Nair S, Rao C, Jones C, Nicolaou M, et al. Early outcomes in the elderly: a meta-analysis of 4921 patients undergoing coronary artery bypass grafting--comparison between off-pump and on-pump techniques. *Heart.* 2006;92:1808-16.
36. Youn YN, Chang BC, Hong YS, Kwak YL, Yoo KJ. Early and mid-term impacts of cardiopulmonary bypass on coronary artery bypass grafting in patients with poor left ventricular dysfunction: a propensity score analysis. *Circ J.* 2007;71:1387-94.
37. Dewey TM, Herbert MA, Prince SL, Robbins CL, Worley CM, Magee MJ, et al. Does coronary artery bypass graft surgery improve survival among patients with end-stage renal disease? *Ann Thorac Surg.* 2006;81:591-8; discussion 8.
38. Sajja LR, Mannam G, Chakravarthi RM, Sompalli S, Naidu SK, Somaraju B, et al. Coronary artery bypass grafting with or without cardiopulmonary bypass in patients with preoperative non-dialysis dependent renal insufficiency: a randomized study. *J Thorac Cardiovasc Surg.* 2007;133:378-88.
39. Chawla LS, Zhao Y, Lough FC, Schroeder E, Seneff MG, Brennan JM. Off-pump versus on-pump coronary artery bypass grafting outcomes stratified by preoperative renal function. *J Am Soc Nephrol.* 2012;23:1389-97.
40. Puskas JD, Thourani VH, Kilgo P, Cooper W, Vassiliades T, Vega JD, et al. Off-pump coronary artery bypass disproportionately benefits high-risk patients. *Ann Thorac Surg.* 2009;88:1142-7.
41. Puskas JD, Williams WH, O'Donnell R, Patterson RE, Sigman SR, Smith AS, et al. Off-pump and on-pump coronary artery bypass grafting are associated with similar graft patency, myocardial ischemia, and freedom from reintervention: long-term follow-up of a randomized trial. *Ann Thorac Surg.* 2011;91:1836-42; discussion 42-3.
42. Keeling WB, Kilgo PD, Puskas JD, Halkos ME, Lattouf OM, Guyton RA, et al. Off-pump coronary artery bypass grafting attenuates morbidity and mortality for patients with low and high body mass index. *J Thorac Cardiovasc Surg.* 2013;146:1442-8.

43. Sedrakyan A, Wu AW, Parashar A, Bass EB, Treasure T. Off-pump surgery is associated with reduced occurrence of stroke and other morbidity as compared with traditional coronary artery bypass grafting: a meta-analysis of systematically reviewed trials. *Stroke.* 2006;37:2759-69.
44. Moss E, Puskas JD, Thourani VH, Kilgo P, Chen EP, Leshnower BG, et al. Avoiding aortic clamping during coronary artery bypass grafting reduces postoperative stroke. *J Thorac Cardiovasc Surg.* 2015;149:175-80.
45. Misfeld M, Brereton RJ, Sweetman EA, Doig GS. Neurologic complications after off-pump coronary artery bypass grafting with and without aortic manipulation: meta-analysis of 11,398 cases from 8 studies. *J Thorac Cardiovasc Surg.* 2011;142:e11-7.
46. Landreneau RJ, Mack MJ, Magovern JA, Acuff TA, Benckart DH, Sakert TA, et al. "Keyhole" coronary artery bypass surgery. *Ann Surg.* 1996;224:453-9; discussion 9-62.
47. Acuff TE, Landreneau RJ, Griffith BP, Mack MJ. Minimally invasive coronary artery bypass grafting. *Ann Thorac Surg.* 1996;61:135-7.
48. Bonatti J, Schachner T, Bonaros N, Oehlinger A, Wiedemann D, Ruetzler E, et al. Effectiveness and safety of total endoscopic left internal mammary artery bypass graft to the left anterior descending artery. *Am J Cardiol.* 2009;104:1684-8.
49. Lemma M, Atanasiou T, Contino M. Minimally invasive cardiac surgery-coronary artery bypass graft. *Multimed Man Cardiothorac Surg.* 2013;2013:mmt007.
50. Lapierre H, Chan V, Sohmer B, Mesana TG, Ruel M. Minimally invasive coronary artery bypass grafting via a small thoracotomy versus off-pump: a case-matched study. *Eur J Cardiothorac Surg.* 2011;40:804-10.
51. Diegeler A, Walther T, Metz S, Falk V, Krakor R, Autschbach R, et al. Comparison of MIDCAP versus conventional CABG surgery regarding pain and quality of life. *Heart Surg Forum.* 1999;2:290-5; discussion 5-6.
52. Groh MA, Sutherland SE, Burton HG, 3rd, Johnson AM, Ely SW. Port-access coronary artery bypass grafting: technique and comparative results. *Ann Thorac Surg.* 1999;68:1506-8.
53. Bonatti J, Lee JD, Bonaros N, Schachner T, Lehr EJ. Robotic totally endoscopic multivessel coronary artery bypass grafting: procedure development, challenges, results. *Innovations (Phila).* 2012;7:3-8.
54. Harskamp RE, Walker PF, Alexander JH, Xian Y, Liberman HA, de Winter RJ, et al. Clinical outcomes of hybrid coronary revascularization versus coronary artery bypass surgery in patients with diabetes mellitus. *Am Heart J.* 2014;168:471-8.
55. Puskas JD, Pawale A, Sharma SK. Hybrid coronary revascularization: a new treatment paradigm for selected patients with multivessel coronary artery disease. *JACC Cardiovasc Interv.* 2014;7:1284-6.
56. Bonaros N, Schachner T, Kofler M, Lehr E, Lee J, Vesely M, et al. Advanced hybrid closed chest revascularization: an innovative strategy for the treatment of multivessel coronary artery disease. *Eur J Cardiothorac Surg.* 2014;46:e94-102.
57. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet.* 2013;381:629-38.
58. Tozzi P, Corno AF, von Segesser LK. Sutureless coronary anastomoses: revival of old concepts. *Eur J Cardiothorac Surg.* 2002;22:565-70.
59. Suyker WJ, Borst C. Coronary connector devices: analysis of 1,469 anastomoses in 1,216 patients. *Ann Thorac Surg.* 2008;85:1828-36.
60. Androsov PI. New method of surgical treatment of blood vessel lesions. *AMA Arch Surg.* 1956;73:902-10.
61. Suyker WJ, Buijsrogge MP, Suyker PT, Verlaan CW, Borst C, Grundeman PF. Stapled coronary anastomosis with minimal intraluminal artifact: The S2 Anastomotic System in the off-pump porcine model. *J Thorac Cardiovasc Surg.* 2004;127:498-503.
62. Buijsrogge MP, Verlaan CW, van Rijen MH, Grundeman PF, Borst C. Coronary end-to-side sleeve anastomosis using adhesive in off-pump bypass grafting in the pig. *Ann Thorac Surg.* 2002;73:1451-6.

63. Buijsrogge MP, Scheltes JS, Heikens M, Grundeman PF, Pistecky PV, Borst C. Sutureless coronary anastomosis with an anastomotic device and tissue adhesive in off-pump porcine coronary bypass grafting. *J Thorac Cardiovasc Surg.* 2002;123:788-94.
64. Carrel T, Englberger L, Keller D, Windecker S, Meier B, Eckstein F. Clinical and angiographic results after mechanical connection for distal anastomosis in coronary surgery. *J Thorac Cardiovasc Surg.* 2004;127:1632-40.
65. Klima U, Kofidis T, Boening A, Haverich A. Long term angiographic monitoring reveals safety and efficacy of the Converge end-to-side anastomotic coupler. *Interact Cardiovasc Thorac Surg.* 2005;4:505-8.
66. Klima U, Falk V, Maringka M, Bargenda S, Badack S, Moritz A, et al. Magnetic vascular coupling for distal anastomosis in coronary artery bypass grafting: a multicenter trial. *J Thorac Cardiovasc Surg.* 2003;126:1568-74.
67. Filsoufi F, Farivar RS, Aklog L, Anderson CA, Chen RH, Lichtenstein S, et al. Automated distal coronary bypass with a novel magnetic coupler (MVP system). *J Thorac Cardiovasc Surg.* 2004;127:185-92.
68. Obora Y, Tamaki N, Matsumoto S. Nonsuture microvascular anastomosis using magnet rings: preliminary report. *Surg Neurol.* 1978;9:117-20.
69. Phillips AB, Ginsburg BY, Shin SJ, Soslow R, Ko W, Poppas DP. Laser welding for vascular anastomosis using albumin solder: an approach for MID-CAB. *Lasers Surg Med.* 1999;24:264-8.
70. Werker PM, Kon M. Review of facilitated approaches to vascular anastomosis surgery. *Ann Thorac Surg.* 1997;63:S122-7.
71. Scheltes JS, Heikens M, Pistecky PV, van Andel CJ, Borst C. Assessment of patented coronary end-to-side anastomotic devices using micromechanical bonding. *Ann Thorac Surg.* 2000;70:218-21.
72. Scheltes JS, van Andel CJ, Pistecky PV, Borst C. Coronary anastomotic devices: blood-exposed non-intimal surface and coronary wall stress. *J Thorac Cardiovasc Surg.* 2003;126:191-9.
73. Berguer R, Higgins RF, Reddy DJ. Intimal hyperplasia. An experimental study. *Arch Surg.* 1980;115:332-5.
74. Hehrlein C, Chuang CH, Tuntelder JR, Tatsis GP, Littmann L, Svenson RH. Effects of vascular runoff on myointimal hyperplasia after mechanical balloon or thermal laser arterial injury in dogs. *Circulation.* 1991;84:884-90.
75. Meyerson SL, Skelly CL, Curi MA, Shakur UM, Vosicky JE, Glagov S, et al. The effects of extremely low shear stress on cellular proliferation and neointimal thickening in the failing bypass graft. *J Vasc Surg.* 2001;34:90-7.
76. Heijmen RH, Grundeman PF, Borst C. Intima-adventitia apposition in end-to-side arterial anastomosis: an experimental study in the pig. *Ann Thorac Surg.* 1998;65:705-11.
77. Buijsrogge MP, Grundeman PF, Verlaan CW, Borst C. Unconventional vessel wall apposition in off-pump porcine coronary artery bypass grafting: low versus high graft flow. *J Thorac Cardiovasc Surg.* 2002;123:341-7.
78. Ip JH, Fuster V, Badimon L, Badimon J, Taubman MB, Chesebro JH. Syndromes of accelerated atherosclerosis: role of vascular injury and smooth muscle cell proliferation. *J Am Coll Cardiol.* 1990;15:1667-87.
79. Virchow R. Der atheromatous Prozess der Arteries. *Wien Med Wochenschr.* 1856;6:825-9.
80. Leva C, Engstrom KG. Flow resistance over technical anastomoses in relation to the angle of distal end-to-side connections. *Scand Cardiovasc J.* 2003;37:165-71.
81. Walsh MT, Kavanagh EG, O'Brien T, Grace PA, McGloughlin T. On the existence of an optimum end-to-side junctional geometry in peripheral bypass surgery--a computer generated study. *Eur J Vasc Endovasc Surg.* 2003;26:649-56.
82. Klein SR, Goldberg L, Miranda RM, Bosco P, Nelson RJ, White RA. Effect of suture technique on arterial anastomotic compliance. *Arch Surg.* 1982;117:45-7.
83. Tozzi P, Hayoz D, Ruchat P, Corno A, Oedman C, Botta U, et al. Animal model to compare the effects of suture technique on cross-sectional compliance on end-to-side anastomoses. *Eur J Cardiothorac Surg.*

2001;19:477-81.
84. Gotman I. Characteristics of metals used in implants. *J Endourol.* 1997;11:383-9.
85. Ballyk PD, Walsh C, Butany J, Ojha M. Compliance mismatch may promote graft-artery intimal hyperplasia by altering suture-line stresses. *J Biomech.* 1998;31:229-37.
86. Hasson JE, Megerman J, Abbott WM. Increased compliance near vascular anastomoses. *J Vasc Surg.* 1985;2:419-23.
87. Wever DJ, Veldhuizen AG, de Vries J, Busscher HJ, Uges DR, van Horn JR. Electrochemical and surface characterization of a nickel-titanium alloy. *Biomaterials.* 1998;19:761-9.
88. Dodge JT, Jr., Brown BG, Bolson EL, Dodge HT. Lumen diameter of normal human coronary arteries. Influence of age, sex, anatomic variation, and left ventricular hypertrophy or dilation. *Circulation.* 1992;86:232-46.
89. Perry R, Joseph MX, Chew DP, Aylward PE, De Pasquale CG. Coronary artery wall thickness of the left anterior descending artery using high resolution transthoracic echocardiography--normal range of values. *Echocardiography.* 2013;30:759-64.
90. Jacot JG, Abdullah I, Belkin M, Gerhard-Herman M, Gaccione P, Polak JF, et al. Early adaptation of human lower extremity vein grafts: wall stiffness changes accompany geometric remodeling. *J Vasc Surg.* 2004;39:547-55.
91. Girerd X, London G, Boutouyrie P, Mourad JJ, Safar M, Laurent S. Remodeling of the radial artery in response to a chronic increase in shear stress. *Hypertension.* 1996;27:799-803.
92. Otsuka F, Yahagi K, Sakakura K, Virmani R. Why is the mammary artery so special and what protects it from atherosclerosis? *Ann Cardiothorac Surg.* 2013;2:519-26.
93. Verberkmoes NJ, Wolters SL, Post JC, Soliman-Hamad MA, ter Woorst JF, Berreklouw E. Distal anastomotic patency of the Cardica C-PORT(R) xA system versus the hand-sewn technique: a prospective randomized controlled study in patients undergoing coronary artery bypass grafting. *Eur J Cardiothorac Surg.* 2013;44:512-8; discussion 8-9.
94. Balkhy HH, Wann LS, Krienbring D, Arnsdorf SE. Integrating coronary anastomotic connectors and robotics toward a totally endoscopic beating heart approach: review of 120 cases. *Ann Thorac Surg.* 2011;92:821-7.
95. Yahr WZ, Strully KJ, Hurwitt ES. Non-occlusive small arterial anastomosis with a neodymium laser. *Surg Forum.* 1964;15:224-6.
96. Jain KK, Gorisch W. Repair of small blood vessels with the neodymium-YAG laser: a preliminary report. *Surgery.* 1979;85:684-8.
97. Frazier OH, Painvin GA, Morris JR, Thomsen S, Neblett CR. Laser-assisted microvascular anastomoses: angiographic and anatomopathologic studies on growing microvascular anastomoses: preliminary report. *Surgery.* 1985;97:585-90.
98. Quigley MR, Bailes JE, Kwaan HC, Cerullo LJ. Laser-assisted vascular anastomosis. *Lancet.* 1985;1:334.
99. Quigley MR, Bailes JE, Kwaan HC, Cerullo LJ, Block S. Comparison of myointimal hyperplasia in laser-assisted and suture anastomosed arteries. A preliminary report. *J Vasc Surg.* 1986;4:217-9.
100. Quigley MR, Bailes JE, Kwaan HC, Cerullo LJ, Brown JT. Aneurysm formation after low power carbon dioxide laser-assisted vascular anastomosis. *Neurosurgery.* 1986;18:292-9.
101. Shapiro S, Sartorius C, Sanders S, Clark S. Microvascular end-to-side arterial anastomosis using the Nd: YAG laser. *Neurosurgery.* 1989;25:584-8; discussion 8-9.
102. Tulleken CA, Verdaasdonk RM, Berendsen W, Mali WP. Use of the excimer laser in high-flow bypass surgery of the brain. *J Neurosurg.* 1993;78:477-80.
103. Tulleken CA, Hoogland P, Slooff J. A new technique for end-to-side anastomosis between small arteries. *Acta Neurochir Suppl (Wien).* 1979;28:236-40.
104. Tulleken CA, van Dieren A, Verdaasdonk RM, Berendsen W. End-to-side anastomosis of small vessels using an Nd:YAG laser with a hemispherical contact probe. Technical note. *J Neurosurg.* 1992;76:546-9.

105. Tulleken CA, Verdaasdonk RM. First clinical experience with Excimer assisted high flow bypass surgery of the brain. *Acta Neurochir (Wien).* 1995;134:66-70.

PREFACE PART A
THE SLIDE CONNECTOR

Device Development:

A Journey from Ring to Slide

The ELANA Ring

As described in the Introduction of this thesis, Tulleken and his team ameliorated the laser-assisted anastomosis technique by developing a round open platinum ring, which was sutured onto the recipient artery, ensuring a straight surface of the recipient artery wall. The first experimental studies with the ELANA technique showed favorable patency results and subsequently, the first patient was operated in 1993 in the UMC Utrecht.

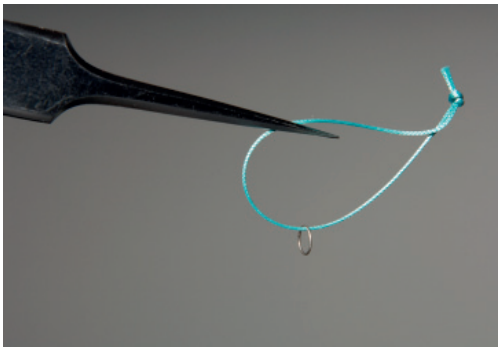

Figure 1. The round platinum ELANA ring (ELANA b.v., Utrecht, The Netherlands), with an inner diameter of 2.8 mm

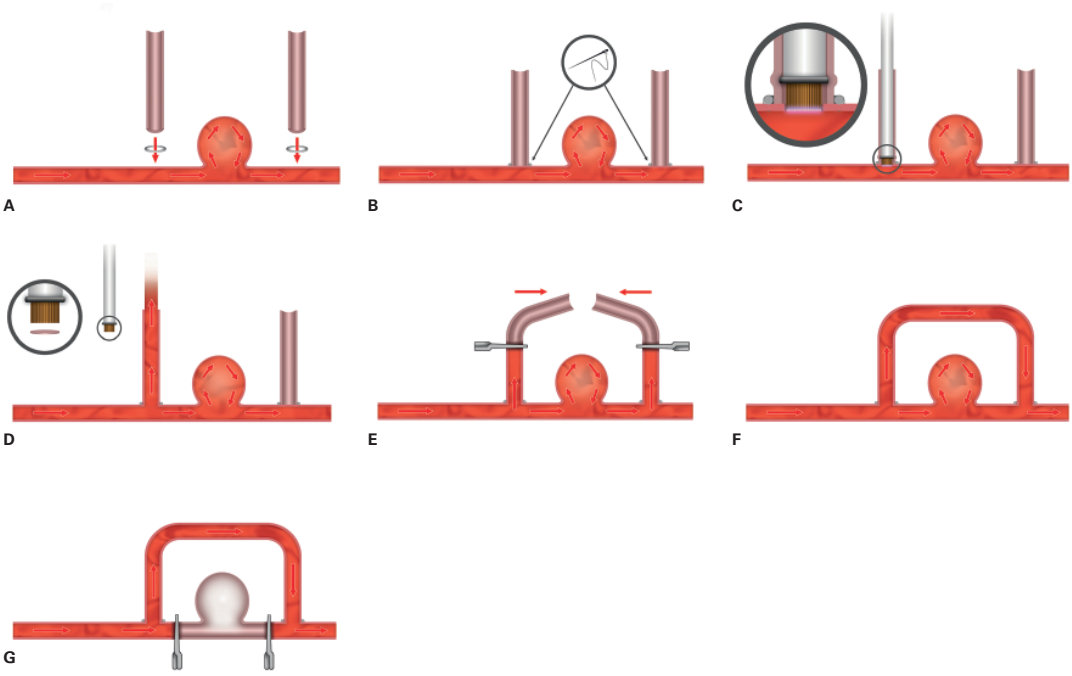

Figure 2. ELANA technique

A and **B:** Two grafts are mounted onto the platinum ring and subsequently sutured end-to-side to the recipient artery, proximal and distal of the aneurysm.

C: The ELANA catheter is introduced via the graft, exactly into the ring and onto the recipient artery (see magnified subsection). Vacuum suction is initiated and an opening into the recipient artery is laser-punched under full native flow, without occlusion of the recipient artery.

D: The laser catheter is retrieved, including the laser-punched disk of arterial wall, the flap. This is repeated for the distal bypass.

E: Both grafts are temporarily occluded with a clip and the free ends of the two bypass grafts are sutured together in an end-to-end fashion.

F: The clips are removed from the donor vessels, completing the bypass.

G: The aneurysm is totally excluded from the circulation and the bypass replaces the flow.

The round extravascular platinum ring (Figure 1), with an inner diameter of 2.8 mm, is used for apposition of the graft and recipient vessel wall by conventional suturing. First, one end of the bypass graft is everted from inside the ring and anchored with 8 sutures (Figure 2). Subsequently, the mounted ring is sutured, with again 8 sutures, onto the unopened recipient artery under full native arterial flow. Once the ring is sutured onto the recipient artery, the ring ensures a straight surface of the recipient artery wall.

Next, the laser catheter (Chapter 2, Figure 1B), which fits exactly into the ring, is introduced intravascularly into the graft, and is perpendicularly positioned onto the recipient artery. Tactile feedback is used to verify correct positioning. Gentle upward traction onto the graft with pick-ups is performed, to prevent dislocation of the laser catheter. Vacuum suction by a vacuum pump (Figure 3) through the lumen of the laser catheter, onto the recipient arterial wall, is initiated. The Excimer Laser (Figure 4) activates the laser fibers, and the laser catheter laser-punches the recipient arterial wall, hereby creating a round opening. The laser catheter is retrieved, including the laser-punched fragment of the recipient arterial wall (the so-called "flap"), which is attached to the laser catheter by vacuum suction. Directly following removal of the laser catheter from the graft, a temporary clip is placed onto the graft to prevent blood loss. Consequently, with this technique, the anastomosis is constructed without occluding the recipient artery and, hence, without ischemia.

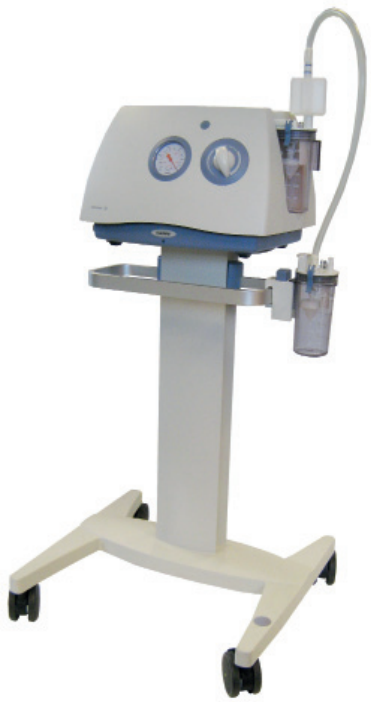

Figure 3. Vacuum pump (Medela Dominant 50 Pump, Baar, Switzerland)

Figure 4. Excimer laser (CVX-300, Spectranetics Corp., Colorado Springs, CO, USA)

To bypass a lesion (eg, a cerebral aneurysm), a second ELANA anastomosis is created on the other side of the lesion (Figure 1). Finally, both free ends of the two grafts are connected by hand suturing, end-to-end, to complete the bypass. Subsequently, the temporary clips are removed and if indicated, the aneurysm is excluded from the circulation.

The ELANA technique thus requires hand suturing for the connection of the graft to the ring, and the ring to the recipient artery. Suturing the ring onto the graft can be done easily on a side table, outside the patient. However, suturing the ring onto the recipient cerebral artery, deep inside the brain of the patient, is performed

in a reduced working space, often with a suboptimal view, and can be very challenging, even for well-trained and skilled surgeons. Therefore, the need for a simplified connection of graft to recipient artery existed. And so, Tulleken and his team started development of a sutureless connection.

The Slide Connector

The next generation ELANA anastomotic connector is called the sutureless ELANA (SELANA), or the ELANA Slide connector, and consists of a ring with attached 2 pins with a circumferential part (ie, a 'fork'; stainless steel; developed by prof. Tulleken, ELANA b.v.; Chapter 2, Figure 1A). To construct an end-to-side anastomosis, mounting of the graft onto the Slide connector still requires several sutures. However, the most difficult connection, ie, connection of the mounted Slide connector onto the recipient artery, is sutureless, hereby significantly reducing surgical dexterity requirements and, thus, simplifying the anastomosis construction. However, the Slide does not actively compress the vessel walls of both the bypass graft and recipient artery, and therefore, sealing of the anastomosis with a surgical sealant (ie, glue) is required to obtain complete hemostasis. Moreover, in contrast to the conventional ELANA ring, which remains completely extravascular after construction (ie, no foreign material exposure into the bloodstream), the circumferential part of the pins of the Slide connector is positioned intraluminal, and hence, is exposed to blood.

Similar to the anastomosis construction with the conventional ELANA ring, first, one end of the graft is everted over the ring of the Slide connector and anchored by several sutures. Next, by using a standard needle holder, the mounted Slide is connected to the recipient artery by introduction of the 2 pins. The pins puncture the recipient wall and the device is pushed forward. The pins are penetrated outward again, and the connector is pushed further until the recipient arterial wall 'clicks' over the circumferential part of the pins of the device. Subsequently, the anastomosis is circumferentially sealed with a surgical sealant to achieve complete hemostasis following lasering. Then, the laser catheter is introduced, laser-punches an opening, and the anastomosis is completed similarly to the conventional ELANA technique.

Van Doormaal et al. extensively assessed the Slide in experimental animal[1, 2] and cadaver[3] studies. They showed in a porcine carotid-bypass model that the SELANA technique is not inferior to the conventional ELANA technique, regarding (long-term) patency and bypass flow. Endothelialization of the intraluminal exposed foreign material was seen within 3 weeks with scanning electron microscopy (SEM) and histology. Furthermore, the construction time was significantly reduced from 14.8 ± 2.6 min to 2.5 ± 1.8 minutes[2] and it was easier to reach difficult area's within the surgical field, with less manipulation of the surrounding structures.[3]

In the search to facilitate CABG, in the first study of this thesis (Chapter 2), the Slide was evaluated in an acute rabbit model in a side-to-side configuration, in contrast to the end-to-side configuration used in neurosurgery, due to a favorable bypass angle for coronary bypass application. Feasibility was demonstrated and this was the first evidence showing that the ELANA technique has potential to facilitate CABG.

REFERENCES

1. van Doormaal TP, van der Zwan A, Redegeld S, Verweij BH, Tulleken CA, Regli L. Patency, flow, and endothelialization of the sutureless Excimer Laser Assisted Non-occlusive Anastomosis (ELANA) technique in a pig model. *J Neurosurg.* 2011;115:1221-30.
2. van Doormaal TP, van der Zwan A, Verweij BH, Biesbroek M, Regli L, Tulleken CA. Experimental simplification of the excimer laser-assisted nonocclusive anastomosis (ELANA) technique. *Neurosurgery.* 2010;67:ons283-90.
3. van Doormaal TP, van der Zwan A, Aboud E, Berkelbach van der Sprenkel JW, Tulleken CA, Krisht AF, et al. The sutureless excimer laser assisted non-occlusive anastomosis (SELANA); a feasibility study in a pressurized cadaver model. *Acta Neurochir (Wien).* 2010;152:1603-8.

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A NEW NONOCCLUSIVE LASER-ASSISTED CORONARY ANASTOMOTIC CONNECTOR IN A RABBIT MODEL

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ABSTRACT

Objective: The Excimer Laser Assisted Non-occlusive Anastomosis (ELANA) technique is a non-occlusive, facilitated bypass technique that is currently CE- and FDA-approved for clinical application in neurosurgery. In the current study we assessed the safety and feasibility of a newly developed ELANA-based prototype coronary anastomotic connector in an acute rabbit abdominal aortic-bypass model prior to the application in experimental coronary bypass surgery. In addition, two sealants were tested to facilitate anastomotic hemostasis in the current device prototype.

Methods: 40 anastomoses were constructed on the abdominal aorta (outer diameter 3.5 mm) of 10 rabbits. The anastomotic circumference was sealed by a surgical sealant to obtain complete hemostasis (BioGlue versus TachoSil). The anastomoses were evaluated by flow measurements, construction time, hemostasis, histological analysis and burst pressure testing.

Results: The connector enabled a non-occlusive and fast (6.0 ± 1.7 minutes, mean ± SD [including sealing]) anastomosis construction and complete hemostasis in 95% (35/37). Sealing with BioGlue was faster compared to TachoSil (19% versus 53% of construction time). Despite technical imperfections (7/40 failures to completely retrieve the flap by the laser), all 40 anastomoses were patent, showed a reproducible construction with intima-adventitia apposition, streamlining thrombus coverage of the intraluminal laser rim and no vessel wall damage. All anastomoses resisted ex-vivo supra-physiological pressures (>300 mm Hg).

Conclusions: This study demonstrated that the ELANA connector is safe, reliable and can be efficiently applied in an acute rabbit abdominal aortic-bypass model. Provided limitations can be addressed, this easy-to-use and non-occlusive technique has potential for minimally invasive coronary bypass surgery.

INTRODUCTION

To facilitate minimal access coronary artery bypass surgery (CABG), a reliable and simplified alternative for hand-sutured coronary anastomosis has to be developed. The Excimer Laser Assisted Non-occlusive Anastomosis (ELANA) technique[1] is a non-occlusive, facilitated bypass technique that is currently CE- and FDA-approved for clinical application in neurosurgery. In the current study, we evaluated the safety and feasibility of a newly developed ELANA-based prototype coronary anastomotic connector in an acute rabbit abdominal aortic-bypass model prior to application in experimental coronary bypass surgery. In addition, two types of sealant were tested (BioGlue versus TachoSil) to facilitate optimal anastomotic hemostasis in the current device prototype.

METHODS

ELANA Prototype Anastomotic Connector and Procedure

The ELANA anastomotic connector consists of a 2.6 mm (inner diameter [ID]) stainless steel ring (thickness 0.25 mm) with 2 pins (6.2 mm length, Figure 1A). The current prototype is suitable for target vessels of 3-5 mm outer diameter (OD) in either an end-to-side or a side-to-side configuration. The bypass graft (OD 5-6 mm) is currently mounted onto the connector (arteriotomy of 2.5-mm length) using 6 Prolene 8-0 stitches (Ethicon Inc, Somerville, NJ) in such a way the intima of the graft completely covers the inner surface of the ring (Figure 2A). The mounted ELANA connector is inserted into the recipient artery by introduction of the 2 pins using a standard needle holder (Spring-style needle holder, Scanlan International Inc., Saint Paul, MN), prior to the - lasered - arteriotomy. The pins puncture the recipient arterial wall and the device is pushed forward (Figure 2B). Subsequently, the pins penetrate outwards again and the connector is pushed further until the recipient arterial wall 'clicks' over the circumferential part of the pins of the device (Figure 2C). If proper positioning is established, the anastomotic circumference, in the current prototype, is sealed by a surgical sealant in order to achieve complete hemostasis. After polymerization of the sealant, the anastomotic site and donor are rinsed intraluminal with heparinized saline to prevent hindering of the laser-to-tissue contact by blood. Subsequently, a laser catheter (OD 2.5 mm, laser fibers OD 2.0 mm, Figure 1B) is introduced through the laser introduction-conduit, ie, the free distal - not blood exposed - end of the graft, and perpendicularly positioned into the ring of the mounted device onto the recipient artery vessel wall (Figure 2D). Vacuum suction through the lumen of the catheter is initiated onto the recipient artery wall and the anastomosis is lasered open, without occluding the recipient artery, resulting in an anastomotic orifice with a diameter of 2 mm. Subsequently, the laser catheter is retrieved, including the lasered fragment of the arterial wall ('flap') attached to the grid of the vacuum lumen (Figure 2E). A small protruding adventitial rim of the abdominal aorta, the laser edge, is exposed intraluminal after lasering the anastomosis (Figure 2E, magnified section). To complete the anastomosis, the distal end (laser introduction conduit or 'cul de sac') of the graft is ligated using a hemoclip (Weck Hemoclip, Teleflex Medical, NC) and after construction of the second anastomosis flow over the bypass is initiated (Figure 2F).

Animals

Ten New Zealand White rabbits (3 kg) were used. The animals were fed a normal diet and received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (Institute of Laboratory Animal Resources, National Research Council [revised 1996]). The animal experimentation committee of the Utrecht University approved the protocol. The animals did not receive any anticoagulant or antiplatelet medication preoperatively.

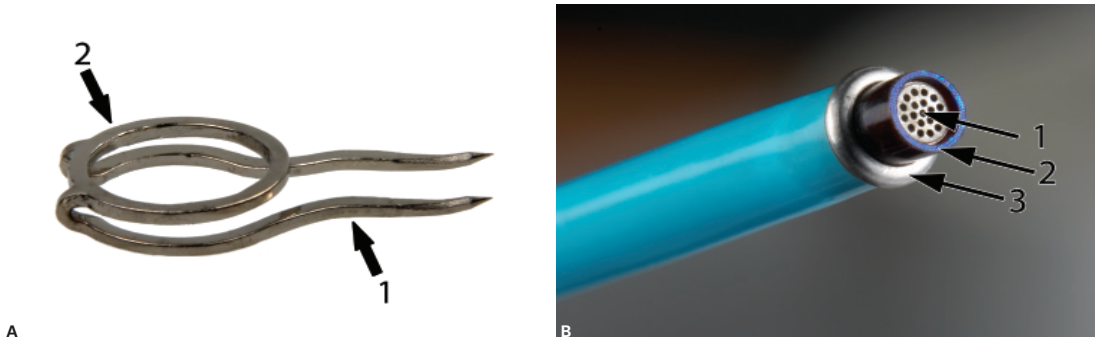


Figure 1. ELANA prototype anastomotic connector (A) and laser catheter (B)

A: The prototype anastomotic connector: 2 sharp pins [1] (6.2 mm length) attached to a ring [2] (2.6 mm ID).

B: Laser catheter (2.5 mm OD): the grid of the vacuum channel [1] is located centrally and surrounded by laser fibers [2] (OD 2.0 mm). The outer band [3] (OD 3.0 mm) provides safety and stabilization into the ring of the anastomotic connector.

Inner diameter = ID; outer diameter = OD.

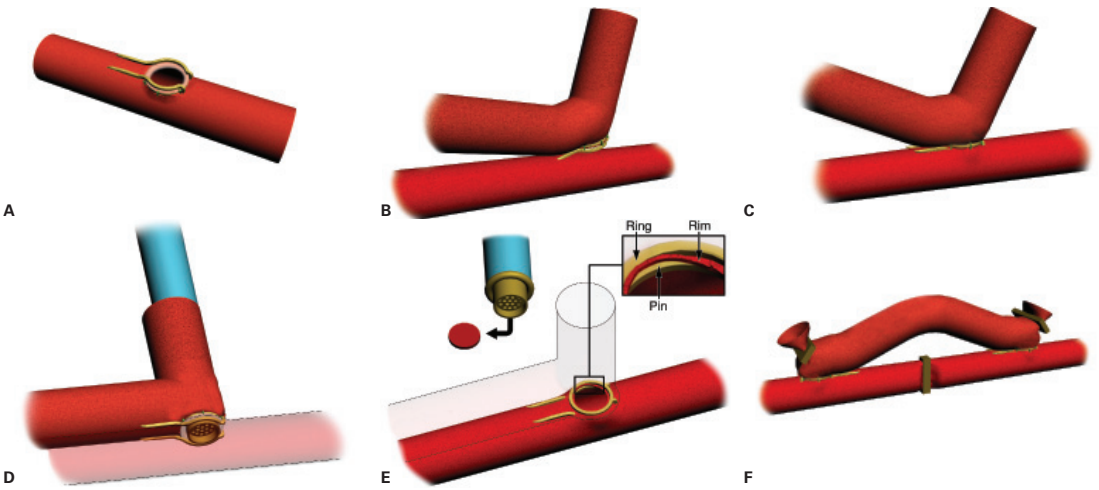


Figure 2. ELANA anastomotic procedure in the rabbit abdominal aortic-bypass model

A: The graft is mounted onto the connector by 6 stitches. The intima of the graft (enlightened) completely covers the inner surface of the ring of the connector.

B: A standard needle holder (not shown) is used to insert the connector. The pins of the connector puncture the abdominal aortic wall.

C: The pins penetrate outwards again. The anastomotic circumference is sealed by a surgical sealant (not shown).

D: Perpendicular positioning of the laser catheter (intima of the graft is enlightened).

E: The catheter with a lasered fragment ('flap') of the abdominal aortic wall (graft is illustrated transparently). A small protruding adventitial rim of the abdominal aorta, the laser edge, is exposed intraluminal (see magnified section [not shown: complete coverage of the ring of the connector by the graft]).

F: Final abdominal aortic-bypass with 2 anastomoses. Ligating hemoclips are placed at both ends of the graft and a clip occludes the abdominal aorta in between the 2 anastomoses.

Anesthesia and Euthanasia

Anesthesia was induced with acepromazine (0.5 mg/kg), methadone (1 mg/kg) intramuscularly and etomidate (0.3 mg/kg) intravenously. After intubation and ventilation, anesthesia was maintained by continuous intravenous infusion of midazolam (50 µg/h/kg) and sufentanil (50 µg/h/kg). The rabbit was put in a supine position and mean arterial blood pressure was kept at 60 mm Hg during the whole procedure. The rabbits were terminated with 200 mg/kg sodium pentobarbital intravenously.

Surgery and Experimental Model

The abdominal aorta (OD 3.5 mm) was dissected from its bifurcation up to the left renal artery using a microscope (Leica MS1, Leica Microsystems GmbH Wetzlar, Germany) and loose periadventitial tissue was removed. Before anastomosis construction, heparin was administered intravenously to obtain an activated clotting time (ACT) (Hemotec, Inc, Englewood, CO) of at least 4 times the normal value. Two bypass constructions, each consisting of 2 side-to-side anastomoses (Figure 2F), were constructed on the abdominal aorta with the use of an ex vivo rabbit thoracic aorta bypass graft (5-6 mm OD) (total 10 animals, 40 anastomoses). In this study, 2 different sealants were evaluated to seal the anastomosis: (1) BioGlue (Cryolife Inc., Kennesaw, GA) and (2) TachoSil (Nycomed Inc., Zurich, Switzerland). After construction of 2 anastomoses, the native abdominal aorta was occluded in between the anastomoses by an aneurysm clip (Yasargil aneurysm-clip system, Peter Lazic, GmbH, Germany) after flow over the bypass was initiated.

The safety and feasibility of the anastomosis technique were assessed (in a non-blinded fashion by either 1 or 2 independent investigators) by anastomosis construction time (assessed by 1 investigator), patency (ie, flow measurements and histology), vessel wall apposition, thrombus formation and vessel wall damage. Furthermore, the reliability of 2 surgical sealants was assessed by application time (assessed by 1 investigator), hemostasis, sealant localization (histology), any potential acute inflammatory cell reactions and burst pressure testing. The anastomoses (n=40) were evaluated intraoperative and at 1 hour at sacrifice.

Flow Measurements

Baseline abdominal aortic flow (mL/min) was measured with a calibrated transit time flow probe (3S model T208; Transonic Systems, Inc, Ithaca, NY) before anastomosis construction at a mean blood pressure of 60 mm Hg. After anastomosis construction, aortic flow was continuously measured and recorded for at least 1 hour at 60 mm Hg until termination.

Hemostasis

After anastomotic construction, leakage was assessed. Hemostasis was quantified as either completely hemostatic or oozing or brisk leakage. Any leakage that was self-limiting or could be controlled by short tamponation (maximally 3 minutes) was defined as oozing. If it was necessary to add more sealant, place a stitch or occlude the artery temporarily to obtain hemostasis, the leakage was defined as brisk.

Histologic Examination

After sacrifice, the anastomoses were removed and flushed under low pressure with heparinized saline. Of each bypass, 1 anastomosis was fixated overnight in 4% formalin for histological analysis (n=20). The anastomoses were embedded in plastic (methyl methacrylate) and subsequently sectioned in transversal (n=10) or longitudinal (n=10) planes (at 300-µm intervals), starting at 5 mm downstream up to 5 mm upstream of the anastomosis. The sections were stained with hematoxylin and eosin. Vessel wall apposition (eg, intima-adventitia, intima-intima), protrusion of the intraluminal rim (mm), thrombus formation at the intraluminal rim (height of thrombus [µm]) and blood exposed non-intimal surface (BENIS[2]; medial and adventitial surface [intraluminal exposed rim] and intraluminal connector surface area) were recorded. Tissue damage (eg, medial necrosis of recipient vessel: ie, opposite and lateral vessel walls and intraluminal vessel wall rim [pyknosis of smooth muscle cell nuclei]), acute inflammatory cell reaction (polymorphonuclear cells and macrophages) of the recipient vessel wall and sealant localization (eg, in-/outside the anastomosis) were assessed. Measurements were performed with use of software package AnalySiS (Soft-Imaging Software GmbH, Münster, Germany).

Burst Pressure

Of each bypass, 1 anastomosis was used for burst pressure testing (n=20). The anastomoses that were intraoperative classified as oozing or complete hemostatic, were included in the burst pressure analysis. To test the burst pressure, the anastomoses were attached to a calibrated pulsatile pressure system with water.

The pressure was increased by 100 mm Hg/min until a maximum of 300 mm Hg was reached. If detachment occurred and/or leakage appeared at the anastomotic line, the anastomosis was scored as bursted and pressure recorded.

Statistical Analysis

Data are presented as means ± SD or as otherwise noted. To assess differences in sealing time between the 2 subgroups, P-values were calculated using a Mann-Whitney test (SPSS 17.0). Wilcoxon Signed Ranks test was used to assess differences in aortic flow before and after anastomosis construction (SPSS version 17.0, SPSS Inc, Chicago, Ill).

RESULTS

Surgery

All anastomoses were performed by 1 investigator (D.S.). Mean anastomosis construction time was 6.0 ± 1.7 minutes (Table 1) of which an average of 2.3 ± 1.6 minutes (38% of construction time) was required for sealing the anastomosis. Sealing with BioGlue was faster compared to TachoSil (19% versus 53% of construction time, p<0.01 [Table 1]). Mounting of the graft onto the prototype connector took 20.3 ± 3.2 minutes. Other operative data are given in Table 2. After lasering the anastomosis, a flap was successfully retrieved in 33 of 40 anastomoses (83%, Table 2).

Flow Measurements

All individual anastomoses (n=40) showed consistent graft flow until termination. Mean aortic flow following construction of all the anastomoses (n=4 per aorta) was lower compared to baseline aortic flow (45 ± 18 mL/min versus 72 ± 28 mL/min, p<0.01).

Table 1. Anastomotic Construction and Sealing Time

	Construction time (min)	Sealing time (min)
Total	6.0 ± 1.7	2.3 ± 1.6 (38%*)
BioGlue	4.5 ± 0.5	0.9 ± 0.4 (19%*) P < 0.01
TachoSil	7.3 ± 0.8	3.9 ± 0.8 (53%*)

Data presented as mean minutes ± SD.

Construction time: insertion, sealing, positioning laser catheter, vacuum suction, lasering and closure of distal end of the graft (mounting time not included). Sealing time: time needed for circumferential anastomosis sealing.

* Sealing time as a percentage of construction time.

Table 2. Operative Data

	Anastomoses (n)	Flap retrieval rate (%)	Complete hemostasis (%)*	Bursted (%)#
Total	40	83	95	0
BioGlue	20	85	100	0
TachoSil	20	80	89	0

* 3 of 40 anastomoses were excluded for hemostasis assessment due to vessel wall lesions after incorrect lasering.

3 of 20 anastomoses were excluded for burst pressure testing due to leakage through a side-branch of the donor vessel.

Hemostasis

95% of all anastomoses were completely hemostatic after construction (35/37, Table 2) and in 5% brisk leakage occurred (2/37). In the latter 2 cases (TachoSil subgroup), the leakage was caused by insufficient application or detachment of the sealant. In both cases, reapplication of sealant resulted in complete hemostasis. Complete direct hemostasis was achieved in all anastomoses of the BioGlue subgroup.

Histology

Vessel wall apposition. In all anastomoses, the intima of the graft was opposed to the adventitia of the recipient aorta along the full circumference of the anastomosis and a small protruding rim of the recipient artery (mean length 0.11 ± 0.12 mm) was exposed intraluminal (Figure 3). A sharp laser-cut edge with a streamlined cover of platelets and fibrin (mean height 37 ± 21 µm) was observed. No platelets or fibrin were seen at the intraluminal exposed part of the connector. In cases in which the flap was not retrieved directly by the catheter, an incompletely lasered flap resided in the anastomotic orifice partly attached via a small, non-lasered bridge of aortic vessel wall. No evidence of distal embolization of parts of the flap was found.

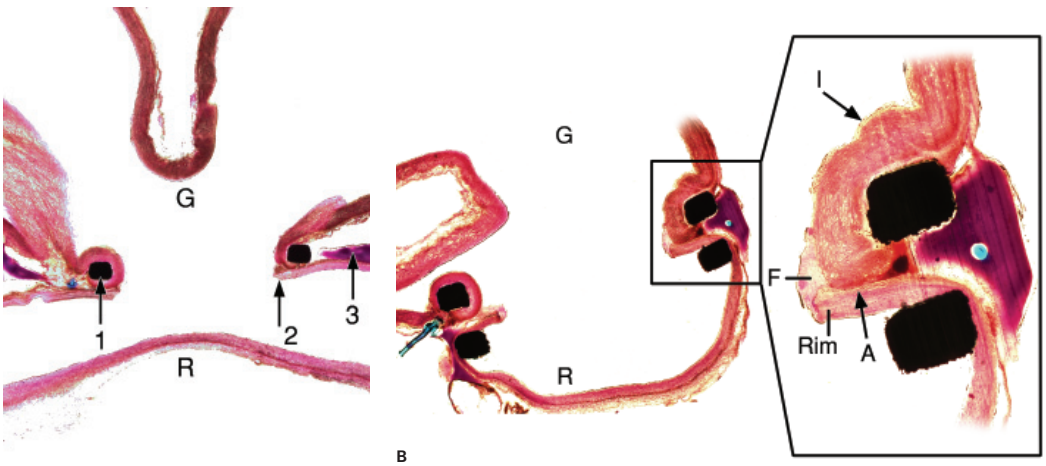
BENIS. The anastomoses showed a BENIS area of approximately 4.4 mm^2 (intraluminal connector surface area: ~2.5 mm^2 and intraluminal exposed rim: ~1.9 mm^2).

Medial necrosis. No medial necrosis was observed near the connector or sealant. In addition, at the intraluminal rim, we did not observe medial cell damage caused by the laser, but a sharp cut-edged viable rim of recipient vessel wall. No medial necrosis was observed at the recipient arterial wall. However, compression of the recipient vessel wall was seen between the ring and the pins of the device.

Sealant localization. Intraluminal exposure of sealant was seen in 1 anastomosis in the BioGlue subgroup and in 1 of the TachoSil subgroup. No acute inflammatory cell reaction was found.

Burst Pressure

All anastomoses resisted a pressure of 300 mm Hg (Table 2).



A B

Figure 3. Histological sections of the ELANA anastomosis in the rabbit abdominal aortic-bypass model

A: Longitudinal section at the middle of the anastomosis (12.5x magnification). The ring of the anastomotic connector is visible [1]. A small protruding rim [2] of the abdominal aorta [R] is exposed to blood. No sealant [3] is in contact with blood. Lumen of the graft [G].

B: Transverse section (12.5x magnification). The magnified (40x) subsection demonstrates the intima [I] - to - adventitia [A] vessel wall apposition and a sharp laser-cut edge [Rim] with a streamlined cover of platelets and fibrin [F].

Graft = G; recipient artery = R.

DISCUSSION

The principal results of the study are the following: (1) Despite technical imperfections (ie, failure to retrieve the flap by the laser catheter), all 40 anastomoses were patent and showed a predictable and consistent construction with intima-adventitia apposition in a rabbit abdominal aortic-bypass model. (2) The technique enabled easy-to-use, non-occlusive and fast (mean 6.0 ± 1.7 minutes) anastomosis construction and the anastomosis resisted ex-vivo supra-physiological pressures. (3) Anastomoses sealed with BioGlue demonstrated more favorable results with regard to construction time and hemostasis.

Common objections to the ELANA technique are related to a relatively large BENIS. The non-occlusive character of the ELANA anastomotic technique and inherent lasering of the recipient artery wall (ie, unconventional intima-adventitia apposition) causes a relatively large BENIS (inherent to distal anastomotic connectors[2-6]) of 4.4 mm^2 compared to 1.3 mm^2 in conventional hand-sewn anastomosis.[2] However, Buijsrogge et al. demonstrated that this unconventional intima-adventitia vessel wall apposition did not adversely affect early patency rates in a pig coronary bypass model, even under prothrombotic low base flow conditions.[7] Furthermore, healing of the unconventional apposition in the ELANA anastomosis has been extensively investigated by histological and scanning electron microscopy analyses in a pig carotic-bypass model, which demonstrated complete re-endothelialization of intravascular pins and adventitial rim after 21 days without detriment on patency.[8] However, the long-term effects of the specific characteristics (ie, large BENIS) of the new ELANA anastomotic technique have to be investigated in an off-pump porcine coronary artery bypass survival study.

Potential Key Features of the ELANA Anastomotic Connector to Facilitate Distal Coronary Anastomosis

Despite imperfections of the studied prototype, the ELANA connector comprises several interesting features - compared with other coronary anastomotic connectors[2-6] - to facilitate the distal coronary anastomosis construction. (1) It is completely non-occlusive. Thus, the technique's first action is the apposition of the graft onto the recipient artery, prior to the - lasered - arteriotomy, without cardiac ischemia during construction. Consequently, it is possible to check for proper positioning of the connector in a bloodless field, without time-constraint. In case of malposition, it is feasible to bail-out and reposition the connector. (2) The laser catheter creates a rounded anastomotic orifice of 2 mm in a standardized and reproducible fashion. (3) The anastomotic construction is simple, fast and safe without the use of bulky applicators. Hence, it might be applicable to limited access CABG.

Limitations of the Procedure

However, the current ELANA prototype connector has limitations. Essential improvements have to be implemented to make the technique successful in minimally invasive coronary bypass surgery.

First, with the current prototype it is necessary to seal the anastomosis with a sealant to obtain complete hemostasis. This procedural step increases the amount of surgical maneuvers, ie, increases surgical dexterity requirements. Moreover, the potential risk of intraluminal introduction of the sealant is a major drawback in its application. Second, while most coronary bypasses are constructed in a coronary diameter range of 1.5 - 2.5 mm OD, downsizing of the anastomotic connector is of paramount importance. Third, the achieved flap retrieval rate in the current study (83%) may be lower compared to our experience in earlier studies using the same prototype connector.[8] In contrast to previous studies,[8] the connector was used for side-to-side anastomotic configurations. In the current study, the side-to-side anastomotic configuration combined with the bulkiness of the polymerized sealant hampered perpendicular laser catheter positioning, introducing errors. Fourth, in the current design, mounting of the graft requires stitching which is time-consuming and increases dexterity requirements.

Future Perspectives

In order to address the mentioned limitations, a new - downsizable - prototype is designed. This new modified ELANA-based connector actively compresses the intravascular fork (ie, pins) and extravascular ring of the connector by a spring at the back of the device, resulting in an immediate leak-free anastomosis. With this design change sealant is redundant, which will simplify and accelerate anastomotic construction. In addition, in case of incomplete flap retrieval, it offers the potential for bail-out, ie, retrieve the flap manually.

Conclusion

This study demonstrated that the ELANA-based prototype anastomotic connector is safe, feasible and can be efficiently applied in an acute rabbit abdominal aortic-bypass model. Provided the limitations can be addressed, this easy-to-use and non-occlusive technique has the potential for minimally invasive coronary bypass surgery.

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DISCLOSURES

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REFERENCES

1. van Doormaal TP, van der Zwan A, Verweij BH, Regli L, Tulleken CA. Giant aneurysm clipping under protection of an excimer laser-assisted non-occlusive anastomosis bypass. *Neurosurgery.* 2010;66:439-47.
2. Scheltes JS, van Andel CJ, Pistecky PV, Borst C. Coronary anastomotic devices: blood-exposed non-intimal surface and coronary wall stress. *J Thorac Cardiovasc Surg.* 2003;126:191-9.
3. Suyker WJ, Buijsrogge MP, Suyker PT, Verlaan CW, Borst C, Grundeman PF. Stapled coronary anastomosis with minimal intraluminal artifact: The S2 Anastomotic System in the off-pump porcine model. *J Thorac Cardiovasc Surg.* 2004;127:498-503.
4. Matschke KE, Gummert JF, Demertzis S, Kappert U, Anssar MB, Siclari F, et al. The Cardica C-Port System: clinical and angiographic evaluation of a new device for automated, compliant distal anastomoses in coronary artery bypass grafting surgery--a multicenter prospective clinical trial. *J Thorac Cardiovasc Surg.* 2005;130:1645-52.
5. Carrel T, Englberger L, Keller D, Windecker S, Meier B, Eckstein F. Clinical and angiographic results after mechanical connection for distal anastomosis in coronary surgery. *J Thorac Cardiovasc Surg.* 2004;127:1632-40.
6. Filsoufi F, Farivar RS, Aklog L, Anderson CA, Chen RH, Lichtenstein S, et al. Automated distal coronary bypass with a novel magnetic coupler (MVP system). *J Thorac Cardiovasc Surg.* 2004;127:185-92.
7. Buijsrogge MP, Grundeman PF, Verlaan CW, Borst C. Unconventional vessel wall apposition in off-pump porcine coronary artery bypass grafting: low versus high graft flow. *J Thorac Cardiovasc Surg.* 2002;123:341-7.
8. van Doormaal TP, van der Zwan A, Redegeld S, Verweij BH, Tulleken CA, Regli L. Patency, flow, and endothelialization of the sutureless Excimer Laser Assisted Non-occlusive Anastomosis (ELANA) technique in a pig model. *J Neurosurg.* 2011;115:1221-30.

PREFACE PART B
THE CLIP CONNECTOR

Device Development:

A Journey from Slide to Clip

The Clip Connector

In the search to facilitate CABG surgery, a new generation ELANA anastomotic connector, the ELANA Clip connector, was designed to address several limitations of the Slide connector. The design of the ELANA Clip is based on the Lazic Miniclip (aneurysm clip, Peter Lazic, GmbH, Tuttlingen, Germany) and the ELANA Slide. The current prototype is suitable for target vessels with a 3- to 5-mm outer diameter, similar to the Slide.

The Clip connector (Chapter 3, Figure 1) now actively compresses the intravascular fork (ie, pins) and extravascular ring of the connector by a spring at the back of the device, resulting in an immediate leak-free anastomosis and, hence, sealant is redundant. An extra advantage of the clip design is opening and closing of the connector, at any time, by an applicator, offering a potential "bail out" in the case of incomplete flap retrieval (ie, manual retrieval of the laser-punched flap). In contrast, the ELANA Slide had a fixed distance between the upper ring and lower fork segment, in this way not accounting for the variable thickness of vessel walls. The ELANA Clip connector is opened during insertion, hereby considerably decreasing resistance during application and, moreover, enhancing visibility.

A potential downside of the new design is the following. Due to the small size of the target vessels, the relative large extravascular spring needs to be miniaturized. In terms of clinical acceptance, the mass of the connector outside (and inside) the vessel should be minimized.

Pilot Study

After the initial idea of connecting the pins and ring of the Slide to a hinge, multiple prototypes were designed, fine-tuning the concept of the ELANA Clip connector, and these were all evaluated in vitro. Subsequently, a pilot study in a rabbit model (n=6 rabbits, 30 anastomoses) was initiated, comparing two final designs (Figure 1). In the first design, the ring is positioned straight on top of the fork. The second design was named the "push-button" design: the fork is positioned within the upper ring, as a push-button. The fork protrudes upwards inside the ring, so that the fork and ring aligns horizontally at the level of the anastomotic orifice. Following the anastomosis construction, the fork and ring should adequately compress the two vessel walls circumferentially in both designs, hereby preventing anastomotic leakage.

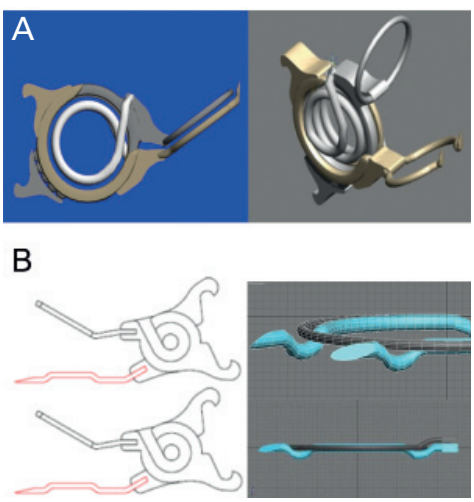

Figure 1. Prototypes of the Clip connector

All parts are made out of titanium.

A: Ring straight on top of the fork. The fork and ring have both an inner diameter of 2.4 mm and an outer diameter of 2.9 mm (material thickness of 0.25 mm).

B: The push-button design: the fork is positioned within the upper ring. The fork protrudes upwards inside the ring, so that the fork and ring aligns horizontally at the level of the anastomotic orifice. The fork has an inner diameter of 2.4 mm and an outer diameter of 2.9 mm and the ring an inner diameter of 2.9 mm and an outer diameter of 3.4 mm (material thickness of 0.25 mm).

The results of the pilot study showed that hemostasis after application was in favor of the push-button design (83% [15/18] versus 50% [6/12], directly hemostatic), burst pressure tests (up to 400 mm Hg) were comparable (91% [10/11] versus 88% [14/16], not bursted), and slip force tests were in favor of the push-button design (ie, more force was needed to dislocate the connector after application).

After the first 4 animals, it appeared that the fork and ring of the push-button design did not align precisely. Therefore, the prototypes were revised, in such a way the ring and fork aligned perfectly, and the following experiments did not show any anastomotic leakage, and, moreover, the anastomoses did not burst during the burst-pressure tests.

Another important finding during the study was that the ELANA laser catheter did not optimally fit into the push-button prototype connector, which caused failures to retrieve the flap in the first two rabbits (50% [3/6]). In order to facilitate laser positioning and stabilization into the push-button design, a cone-shaped tip was engineered at the tip of the laser catheter (Chapter 3, Figure 1B; conventional laser catheter in Chapter 2, Figure 1B). After implementing the cone-shaped catheter, a 100% (12/12) flap retrieval rate in the push-button design was demonstrated. Importantly, by using the new cone-shaped laser catheter in the Clip connector, visual feedback of correct laser positioning was introduced, whereas before, the surgeon had only tactile feedback and his or her experience. Once introduced via the graft into the connector, by moving the laser from left to right, one can see the connector move synchronically, suggesting correct positioning. In addition, to prevent dislocation of the laser catheter a temporary fixation clip (Figure 2) is placed onto the graft and laser catheter.

Figure 2. Fixation clip

Based on this pilot study, the push-button principle did show superior results. Moreover, most essential for the future downsizing process, is that the graft is mounted onto the ring by everting the graft, from inside the ring. In contrast to the "fork on top of the ring" design, the everted graft will not reduce the anastomotic surface or orifice in the push-button design, since the ring is larger than the fork.

However, mounting of the graft still requires suturing, which requires a significant amount of dexterity in minimal access settings. In addition, the connector is suitable for coronary arteries with a minimal inner diameter of 2.4 mm and, ultimately, the connector should be suitable for coronaries of 1.5 – 3.0 mm inner diameter.

Feasibility on the Beating Heart and Long Term Evaluation in a Porcine Model

The previous prototype (ie, Slide connector) was evaluated in an acute abdominal aortic bypass model in the rabbit, leaving questions regarding the healing and patency at the long-term unanswered. Tulleken et al. described the healing of the unconventional adventitia-to-intima apposition in the ELANA Ring facilitated anastomosis extensively in earlier reports.[1-3] In addition, Buijsrogge et al., described the healing of unconventional vessel wall apposition in hand-sutured anastomoses in a porcine off-pump bypass model.[4] However, the specific characteristics of the Clip connector, with a compression device, introduction of a nonintimal surface inside the anastomosis, laser-punching through the coronary artery, and the spring outside the anastomosis resting onto the coronary artery, are all factors not earlier studied or described elsewhere.

In the next chapters, the Clip connector was first studied in a pilot feasibility study in an acute rabbit

model, and subsequently studied in a long-term porcine off-pump bypass model, described in Chapter 3 and 4. Different techniques were used to evaluate the anastomosis technique on the short- and long-term (eg, graft flow measurements, coronary angiography, fractional flow reserve, coronary flow reserve, intravascular ultrasound, optical coherence tomography, histology, and electron microscopy). These studies showed for the first time the proof-of-concept of the anastomotic technique on the beating heart and the long-term effects of the specific characteristics of the Clip connector facilitated anastomosis on the process of anastomotic healing and remodeling.

REFERENCES

1. Streefkerk HJ, Kleinveld S, Koedam EL, Bulder MM, Meelduk HD, Verdaasdonk RM, et al. Long-term reendothelialization of excimer laser-assisted nonocclusive anastomoses compared with conventionally sutured anastomoses in pigs. *J Neurosurg.* 2005;103:328-36.
2. Tulleken CA, Verdaasdonk RM, Beck RJ, Mali WP. The modified excimer laser-assisted high-flow bypass operation. *Surg Neurol.* 1996;46:424-9.
3. Wolfs JF, van den Ham LF, ter Laak MP, van der Zwan A, Tulleken CA. Scanning electron microscopic evaluation of nonocclusive excimer laser-assisted anastomosis in rabbits. *Acta Neurochir (Wien).* 2000;142:1399-407.
4. Buijsrogge MP, Grundeman PF, Verlaan CW, Borst C. Unconventional vessel wall apposition in off-pump porcine coronary artery bypass grafting: low versus high graft flow. *J Thorac Cardiovasc Surg.* 2002;123:341-7.

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THE NONOCCLUSIVE LASER-ASSISTED CORONARY ANASTOMOTIC CONNECTOR IN AN OFF-PUMP PORCINE BYPASS MODEL

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ABSTRACT

Objective: To facilitate minimally invasive coronary artery bypass grafting, a simplified alternative for hand-sutured anastomoses has to be developed. We assessed the feasibility and anastomotic healing of the ameliorated Excimer laser-assisted nonocclusive anastomosis (ELANA) coronary prototype connector in an acute rabbit study (Study 1) and in a long-term porcine off-pump coronary bypass (OPCAB) study (Study 2).

Methods: Eighteen anastomoses were constructed on the abdominal aorta of the rabbit. In the porcine model, 15 left internal thoracic artery to left anterior descending coronary artery bypasses were evaluated intraoperatively and at 4 hours, 4 days, 10 days, 2 weeks, 3 weeks, 5 weeks, and 6 months (each n=2 anastomoses). The anastomoses were examined by angiography, flow measurements, fractional flow reserve (FFR), coronary flow reserve, histology, and scanning electron microscopy (SEM).

Results: Study 1: All anastomoses (n=18) were patent and resisted supraphysiologic pressures (n=12, 300 mm Hg). Study 2: The connector enabled nonocclusive and fast (mean 7.7 ± 2.2 minutes) anastomosis construction. All but 1 of 15 anastomoses (due to a technical error) were fully patent (FitzGibbon grade A) at follow-up. Histology and SEM demonstrated complete endothelialization of the anastomoses at 10 days. At 6 months, no flow-limiting but streamline-covering intimal hyperplasia was shown (FFR 0.93 ± 0.07).

Conclusions: The new nonocclusive coronary connector is easy-to-use and long-term results suggest favorable healing and remodeling in the porcine model. Following downsizing, this anastomotic device, with its emphasis on zero ischemia and simplified prebounding of vessel walls, has intrinsic potential for minimally invasive OPCAB surgery.

INTRODUCTION

To facilitate the distal coronary anastomosis construction for minimal invasive CABG, we recently developed an Excimer laser-assisted nonocclusive anastomosis (ELANA) prototype coronary connector and assessed its feasibility in an acute rabbit abdominal aortic bypass model.[1] As a result, we implemented several design modifications (ie, improving anastomotic hemostasis without mandatory sealing[1]).

In the present study, the initial safety and feasibility of the ameliorated ELANA coronary prototype connector were assessed in the same acute rabbit model (Study 1). Subsequently, the connector was evaluated (ie, anastomotic healing and hemodynamic function) in an off-pump porcine LITA-to-LAD survival study up to 6 months (Study 2).

METHODS

ELANA Coronary Connector and Procedure

In contrast to the previous prototype,[1] the novel ELANA connector (Figure 1A) consists of a ring and a fork with 2 sharp pins. A spring (Peter Lazic, GmbH, Tuttlingen, Germany) at the back of the device enables the fork and ring of the connector to open and close, with the use of an applicator (Aneurysm clip applier; Peter Lazic, GmbH, Tuttlingen, Germany). The connector (titanium, thickness 0.25 mm) is currently applicable to target vessels with an inner diameter (ID) of ± 2.4 mm (≈ 3.0 mm outer diameter [OD], lumen 4.5 mm^2).

1) Mounting the graft. The graft (minimal OD of 2.0 mm) is mounted onto the extravascular ring of the opened connector (arteriotomy, ± 3.0 mm long), using 4-8 Prolene 8-0 stitches (Ethicon, Somerville, NJ), such that the intima of the graft completely covered the inner surface of the ring (Figure 1C).
2) Nonocclusive prebounding of graft to coronary. The mounted connector is opened by the applicator and the fork is inserted into the recipient artery with the pins directed downstream (Figure 1D). Subsequently, the connector is closed by releasing the applicator (the connector stays in situ and is not removed). Hence, it is possible - due to the nonocclusive prebounding of the graft onto the artery, prior to the arteriotomy - to check for proper positioning of the connector without a time constraint, nor blood actively obscuring the field. In the case of malposition, it is feasible to reopen the connector and reposition the device.
3) Laser-punched arteriotomy. Subsequently, a cone-shaped laser catheter (2.5 mm OD, laser fibers 2.0 mm OD; Figure 1B) is introduced intravascularly, via the distal - not blood exposed - end of the graft, into the connector. Vacuum suction (2 minutes) through the lumen of thelaser catheter onto the recipient (eg, coronary) wall is initiated, the laser is activated, and the anastomosis is lasered open, resulting in an anastomotic orifice of ± 1.8-2.0 mm diameter (≈ 2.5-3.1 mm^2, cave LAD 4.5 mm^2). Subsequently, the laser catheter is retrieved, including the laser-punched fragment of the recipient wall (ie, "flap") by vacuum suction (the laser catheter does not weld or seal the anastomosis, but laser-punches an opening). Hence, an adventitial rim of the recipient wall, the laser edge, is exposed intraluminally (Figure 1E)[1] In case the flap is not retrieved by the catheter (ie, an incompletely lasered flap is still partly attached to the recipient wall), the flap is retrieved manually (by micro-forceps) after opening the connector.
4) Bypass completion. Following flap retrieval, the distal end of the graft is ligated using a hemoclip (Weck Hemoclip; Teleflex Medical, Research Triangle Park, NC; Figure 1F).

Initial Feasibility Study (Study 1) of the ELANA Coronary Connector in a Rabbit Model

Eighteen anastomoses were constructed on the abdominal aorta (3.0 mm OD) of 3 New Zealand white rabbits (female, 3 kg; see Supplemental Methods) and evaluated intraoperatively and after death (follow-up: 2.5 hours).[1] All anastomotic procedures (see Supplemental Figure 1) were performed by 1 investigator (D.S.). The flap was directly retrieved in 16 (89%) of 18 anastomoses (2 of 18 flaps were retrieved manually after opening the connector) and consistent graft flow was seen until termination (26 ± 8 mL/min versus 27 ± 8 mL/min). Hemostasis was established in 89% (16/18) and all anastomoses were patent. Histological analysis

Figure 1. ELANA coronary connector, laser catheter, and procedure

A: The slightly opened prototype connector with a fork (1; 2.9 mm outer diameter [OD]) with 2 sharp pins (4.5 mm length) and a ring (2; 3.4 mm OD). A spring (3) at the back of the device enables the ring and fork of the connector to open and close, with the use of an applicator (4).

B: Laser catheter (2.5 mm OD): the grid of the vacuum channel (1) is located centrally and surrounded by laser fibers (2; 2.0 mm OD). The cone-shaped tip (3) (widest part, 3.0 mm OD) facilitates positioning and stabilization into the anastomotic connector.

C: The graft is mounted onto the connector using stitches. The intima of the graft (highlighted) completely covers the inner surface of the ring of the connector.

D: An applicator (not shown) is used to insert the connector. The pins of the connector puncture the recipient wall.

E: After laser-punching an opening into the anastomosis, the catheter - with a lasered fragment ("flap") of the recipient wall (graft illustrated transparently) - is retrieved. A small protruding adventitial rim of the recipient artery, the laser edge, is exposed intraluminally (see magnified subsection [complete intimal coverage of the ring of the connector by the graft not shown]).

F: Final anastomosis. A ligating hemoclip placed at the distal end of the graft.

(n=6) showed reproducible and consistent constructions without detriment of the opposite and lateral walls of the recipient artery (see Supplemental Figure 2). Twelve ex vivo anastomoses were attached to a pressure system with water and the pressure was increased by 100 mm Hg/min. All anastomoses (n=12) resisted supraphysiologic pressures (300 mm Hg).

This initial evaluation demonstrated the safety and feasibility of the new ELANA connector in a rabbit model. The improved features of the connector are as follows. First, the connector provides active compression of the graft onto the recipient artery by the spring at the back of the device, hereby eliminating the use of a

sealant,[1] thus simplifying and accelerating anastomotic construction, and still resisting supraphysiological pressures. Second, cone-shaping of the catheter ameliorates positioning and stabilization of the catheter into the connector and so enhances flap retrieval (89% versus 83% in our previous study[1]). Third, by reopening the connector, a "bail out" (ie, manual flap retrieval) is offered in case the flap is not retrieved directly by the laser catheter.

Evaluation of the ELANA Coronary Connector in the Off-pump Porcine LITA-to-LAD Survival Study (Study 2)

Animals

Fifteen Dutch Landrace pigs (female; 70-90 kg) were studied. The animals were fed a normal diet and received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council (revised 1996). The animal experimentation committee of the Utrecht University approved the protocol. All pigs received 80 mg of acetylsalicylic acid and 75 mg clopidogrel orally daily, starting 3 days before surgery. This anticoagulation protocol was continued until termination (anesthesia and euthanasia protocol: see Supplemental Methods).

Surgery and Experimental Model

After a partial sternotomy, LITA harvesting, and partial heparinization (activated clotting time [ACT] > 200; not counteracted at the end of the procedure), the ring of the connector was mounted onto the LITA (OD 2.0-4.0 mm; Figure 1C), as previously described. Subsequently, after the LAD was immobilized by the Octopus 3 Tissue Stabilizer (Medtronic, Inc, Minneapolis, Minn) at the intended site (OD 3.0 mm, measured with a caliper), the connector was inserted into the LAD. After bypass construction, the LAD was ligated ± 1.0 cm upstream with 3 medium hemoclips. Finally, the LITA was tagged onto the epicardium, using Prolene 6-0, and the pericardium closed. Before chest closure, graft flow (mL/min) was monitored continuously for 90 minutes with a calibrated transit time flow probe (size 3S; flowmeter model T208; Transonic Systems, Inc, Ithaca, NY), at a mean blood pressure of 90 mm Hg.

The safety of the technique was assessed by anastomotic hemostasis, graft flow measurements, hemodynamic function (angiography, fractional flow reserve [FFR], and coronary flow reserve [CFR]), and anastomotic healing (ie, effects of implant and vessel wall compression by the connector; histologic examination and scanning electron microscopy [SEM]). The anastomoses were evaluated intraoperatively (n=15), at 4 hours, 4 days, 10 days, 2 weeks, 3 weeks, 5 weeks, and 6 months (each subgroup 2 anastomoses). The follow-up was completed for 14 animals (1 pig died postoperatively at ± 12 hours).

Hemostasis

Hemostasis was quantified as either completely hemostatic, or oozing, or brisk leakage. Any leakage that was self-limiting or could be controlled by short tamponation (maximally 3 minutes) was defined as oozing. If a stitch was necessary, or the anastomosis had to be tamponated for more than 3 minutes, or the artery needed to be occluded temporarily to obtain hemostasis, the leakage was defined as brisk.

Angiography, Fractional Flow Reserve (FFR), and Coronary Flow Reserve (CFR)

All anastomoses (n=15), including 1 dead animal, were visualized at follow-up by coronary angiography and graded by 2 observers according to the FitzGibbon criteria.

The FFR was calculated from (3 consecutive) measurements directly distal (coronary) and proximal (LITA) to the anastomoses (n=14; at follow-up), and in the circumflex coronary artery (Cx; control coronary artery). Measurements were performed at baseline and during maximal hyperemia, induced by a bolus of intracoronary adenosine (60 µg). The CFR was calculated as the ratio of maximal hyperemic flow velocity by the flow velocity at baseline (ComboWire XT, pressure/flow guide wire, Volcano Corporation, Rancho Cordova, CA).

Histological Analysis

One anastomoses per subgroup (n=8; including 1 dead animal) was embedded in methyl methacrylate and sectioned in transverse planes (at 300-µm intervals), starting at 5 mm downstream, and continuing up to 5 mm upstream of the anastomosis, and stained with hematoxylin and eosin.[1] The vessel wall apposition, protrusion of the intraluminal rim, anastomotic area, thrombus formation, intimal hyperplasia, blood-exposed nonintimal surface[2] (BENIS; intraluminal exposure of medial, adventitial [intraluminal exposed rim], and connector surface), acute and chronic inflammatory cell reaction (polymorphonuclear cells, macrophages, and foreign body giant cells), and tissue damage were recorded and assessed as previously.[1] Measurements were performed using the software package AnalySiS (Soft-Imaging Software GmbH, Münster, Germany).

Scanning Electron Microscopy (SEM)

The intravascular anastomotic surface of 1 anastomosis per subgroup (n=7) was evaluated (ie, assessment of endothelial and/or thrombocyte coverage) using a scanning electron microscope (Philips XL30LAB; FEI Europe, Eindhoven, The Netherlands; see Supplemental Methods).

Statistical Analysis

The data are presented as the mean ± standard deviation or as noted otherwise.

RESULTS

Surgery

All anastomotic procedures were performed by 1 investigator (D.S.; operative data Table 1). Following grafting, all anastomoses (n=15) demonstrated consistent graft flow (38 ± 14 mL/min at t=0; 36 ± 10 mL/min at t=90 min). Of all 15 anastomoses, 1 oozed, and in 1 brisk leakage occurred. However, after repositioning of the latter (ie, connector inserted slightly more distal into the LAD) complete hemostasis was obtained. None of the animals showed ventricular arrhythmias or died during the operative procedure. The ACT at 0 minutes, during the anastomotic procedure, and at 140 minutes after heparinization was 100 ± 9, 258 ± 89, and 145 ± 41 seconds, respectively.

Table 1. Operative Data

Anastomoses (n)	15
LITA (mm, OD)	3.6 ± 0.3
LAD (mm, OD)	3.3 ± 0.1
Arteriotomy (mm; LITA)	3.2 ± 0.2
Construction time (min)	7.7 ± 2.2
Mounting time (min)	27 ± 5
Flap retrieval rate % (n)	93 (14/15)*
Complete hemostasis % (n)	87 (13/15)
Extra stitch	0
Graft baseline flow (mL/min)	38 ± 13
Peak hyperemic flow response (peak/baseline flow)#	4.2 ± 0.8

Data presented as mean minutes ± SD or as noted otherwise. Construction time: insertion, positioning laser catheter, vacuum suction, lasering, and closure of distal end of the graft. *In 1 of 15 anastomoses the flap was not retrieved directly by the catheter, but the flap was removed manually. #Following LITA clamping for 30 seconds, the coronary peak hyperemic flow response was determined as the mean peak graft flow divided by the mean baseline flow at 90 mm Hg. OD=outer diameter

Follow-up

The scheduled follow-up was completed for 14 animals. All anastomoses were patent at follow-up, except 1 that was occluded (assessed by post-mortem angiography and histology; the animal was found dead at ± 12 hours postoperatively). A technical error of the laser during anastomotic construction resulted in an asymmetric fresh anastomotic-occluding thrombus attached to the rim.

Angiography, FFR, and CFR measurements

All but 1 of 15 anastomoses were fully patent at follow-up (FitzGibbon grade A; Figure 2A). The mean FFR of the anastomoses at 4 hours follow-up was 0.82 ± 0.17 and increased over time to 0.93 ± 0.07 at 6 months. The mean CFR increased over time to 4.6 ± 0.7 at 6 months. The mean FFR and CFR in the control Cx at 4 hours were 0.96 ± 0.01 and 4.7 ± 0.6, respectively, and at 6 months 0.99 ± 0.01 and 3.5 ± 0.1 (Table 2).

Table 2. Postoperative and Postmortem Measurements

	LAD	Anastomotic orifice	LITA-LAD		Cx	
Interval	(mm^2)	(mm^2)	FFR	CFR	FFR	CFR
4 h	4.5 ± 1.4	2.6 ± 0.3	0.82 ± 0.17	3.0 ± 0.2	0.96 ± 0.01	4.7 ± 0.6
35 d	6.4 ± 1.0	2.9 ± 0.2	0.95 ± 0.02	2.8 ± 0.1	0.98 ± 0.01	2.4 ± 1.0
180 d	8.7 ± 0.3	3.7 ± 0.5	0.93 ± 0.07	4.6 ± 0.7	0.99 ± 0.01	3.5 ± 0.1

Data presented as mean ± SD. LAD: lumen area, based on angiography (n=2) of reference LAD (1.0 cm downstream to the anastomosis). Anastomotic orifice: based on histology (n=1) and SEM (n=1). Note the anastomotic orifice increasing over time and increasing LAD due to animal growth. FFR=fractional flow reserve, CFR=coronary flow reserve, Cx=circumflex coronary artery (=control).

Histology

Anastomotic healing and remodeling.

In all anastomoses, the intima of the LITA was opposed to the adventitia of the LAD. A protruding rim of the latter (the laser rim; mean length 0.63 ± 0.09 mm and 0.42 ± 0.04, at 4 hours and at 4 days, respectively), with a sharp laser-cut edge and limited platelets and fibrin coverage, was observed at 4 hours (Figure 2B) and 4 days. The pins of the fork, distal to the anastomotic orifice, were compressed onto the upper wall of the LAD, without a detriment.

At 10 (Figure 2C) and 14 days, neointima formation covered both the retracted adventitial rim of the LAD and the intraluminally exposed fork of the connector. At 3 and 5 weeks, intimal hyperplasia completely covered the anastomotic line, without narrowing the lumen.

At 6 months, the spring of the connector was fully integrated between the LITA and LAD without erosion damage and the coronary adventitial laser rim was remodeled and replaced by neointima tissue (Figure 2D). In addition, the pins of the connector at the toe of the anastomosis were completely integrated into the upper wall of the LAD (see Supplemental Figure 3). At the mid of the anastomosis, the fork of the connector was covered by a thin layer of endothelial cells. The anastomotic recesses at both sides of the connector (ie, in- and outflow) were filled with streamlining intimal hyperplasia, which was, however, less abundant than seen at 5 weeks, suggesting at least stabilization of neointima formation. The anastomotic orifice area expanded over time from 2.6 ± 0.3 mm^2 at 4 hours (LAD 4.5 ± 1.4 mm^2) to 3.7 ± 0.5 mm^2 at 6 months (LAD 8.7 ± 0.3 mm^2; Table 2).

Blood-exposed nonintimal surface (BENIS).

The anastomosis showed a total BENIS-area of 7.9 mm^2 (intraluminal connector surface area, ~3.8 mm^2 and intraluminal exposed rim, ~4.1 mm^2) at 4 hours. The BENIS gradually reduced to zero over time (note: at 10 days, the nonintimal surface was fully covered with neointima).

Medial necrosis, tissue damage, and inflammation.

Compression of both vessel walls, between the ring and fork, was observed with some pyknosis (ie,

degeneration) of smooth muscle cell nuclei at 4 hours and 4 days. However, no medial necrosis was seen at the compression surface and no adverse remodeling (eg, erosion, luxation, or pseudoaneurysm formation) was demonstrated over time. The arterial walls of the LAD and LITA were unaffected, without thermal damage due to the laser, nor acute, nor long-term inflammation over time.

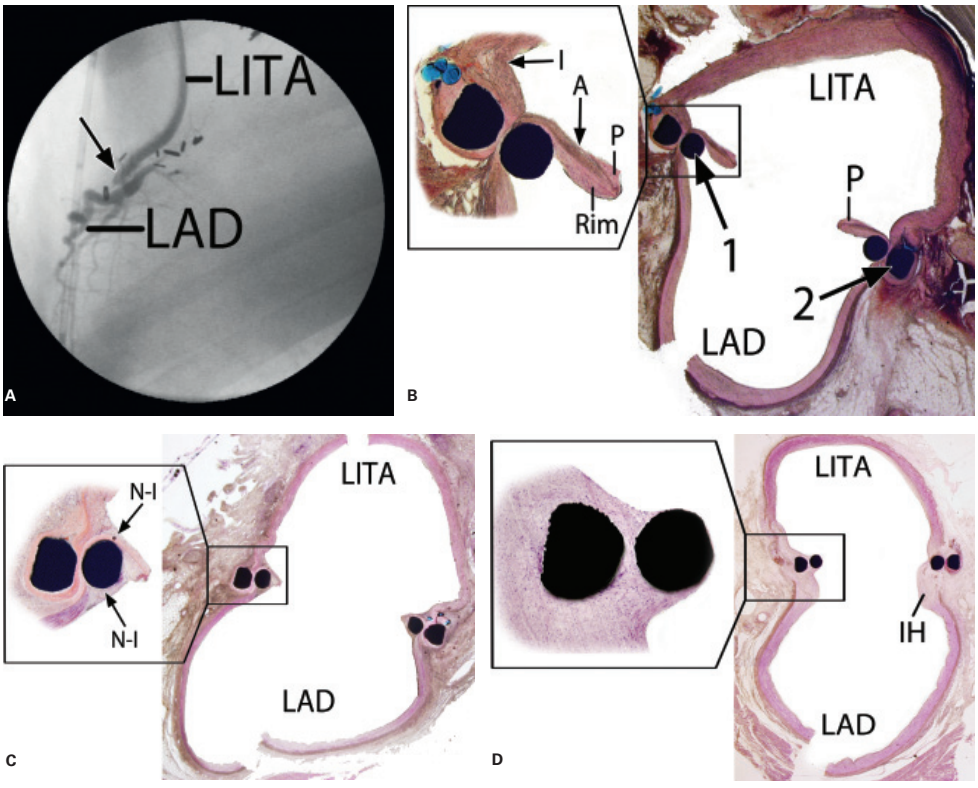

Figure 2. 6-month angiogram and histologic transverse sections of the ELANA LITA-to-LAD anastomosis at different time-points postoperatively

A: Angiogram of a LITA-to-LAD bypass at 6 months postoperatively. The arrow points at the anastomosis. Note the relatively undersized anastomosis due to the increased LAD (animal growth).

B: At 4 hours, mid-anastomosis (12.5x magnification). A 0.2-mm compression surface of LITA to LAD, between the fork (1) and the extravascular ring (2), is visible. The magnified (40x) subsection demonstrates the laser rim with a sharp laser-cut edge (Rim), with limited platelets and fibrin coverage (P), and the intima (I)–adventitia (A) vessel wall apposition.

C: At 10 days, mid-anastomosis (12.5x). The laser rim is retracting and neointima formation (N-I) covers the adventitial rim and the intraluminally exposed fork (subsection, 40x).

D: At 6 months, mid-anastomosis (12.5x). Streamlining intimal hyperplasia (IH) is seen. Note the remodeled laser rim and viable intima in between the fork and ring (ie, the compression surface), without medial necrosis. No chronic inflammatory cell reaction is seen (subsection, 100x). A small layer of endothelial cells covers the intraluminal fork of the connector.

Note: interruption of the inferior coronary wall being caused by longitudinally opening of the coronary artery prior to inspection.

Scanning Electron Microscopy

After 4 hours, a clear demarcation between the endothelial surface of the coronary artery and the connector (Figure 3A), and between the endothelium of the LITA and the adventitial laser rim (Figure 3B), was observed. No endothelial damage of either the coronary artery nor the graft (eg, due to laser damage), but limited platelets and fibrin coverage of the connector and the rim was seen. Additionally, a sharp laser cut through the coronary artery was demonstrated.

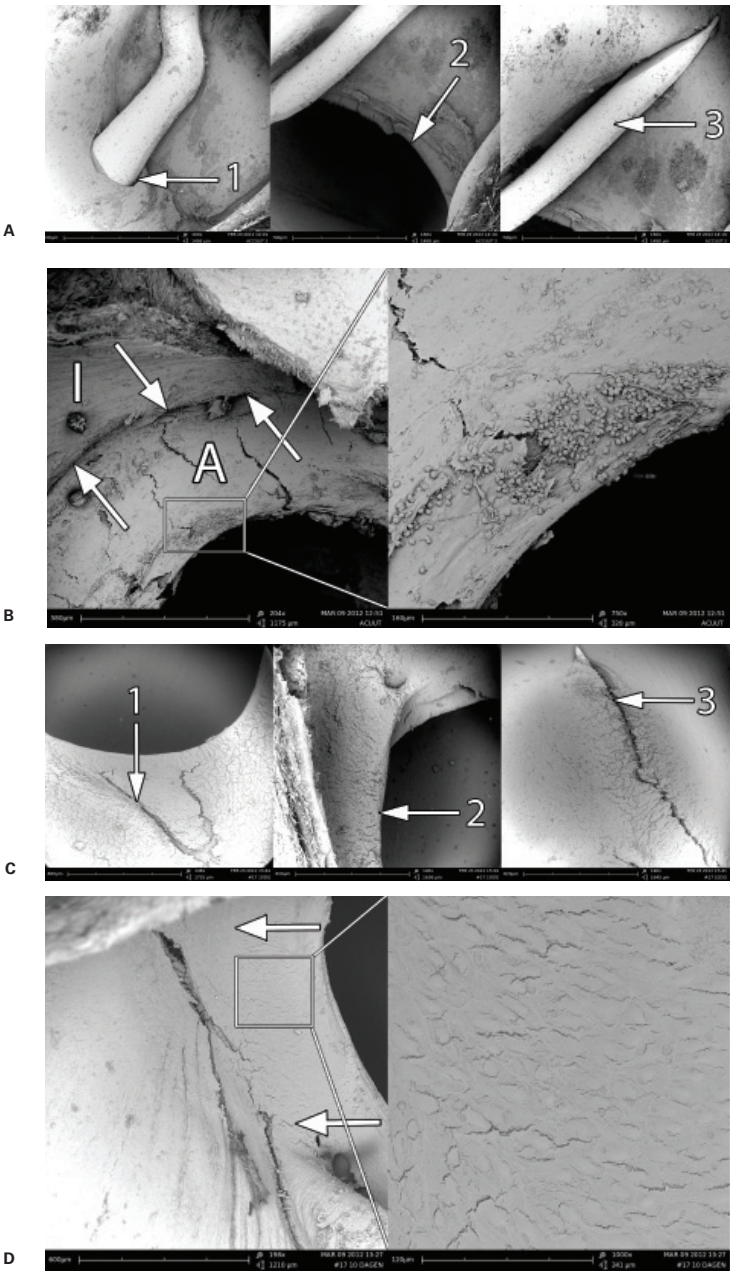

Figure 3. Scanning electron microscopy of the ELANA LITA-to-LAD anastomosis at different time-points postoperatively

A and **C:** View from inside the LAD. From left to right: heel, middle, and toe of the anastomosis.

B and **D:** View from inside the LITA.

A: At 4 hours (160x magnification). The puncture site of the fork through the coronary wall (1), laser rim (2), and pin of the fork (3). No endothelial damage and limited platelets and fibrin coverage of the fork is seen.

B: At 4 hours (204x). The intima (I)–adventitia (A) vessel wall apposition (arrows). The magnified (750x) subsection demonstrates the adventitial laser rim with limited fibrin and platelets coverage. Note the sharp laser cut through the coronary artery.

C and **D:** At 10 days (from left to right: 138x, 146x, and 146x). Complete endothelialization is demonstrated. Note the continuity of endothelial surface from the lumen of the coronary artery over the connector (**C:** 1, heel; 2, middle; 3, toe) and adventitial rim, to the LITA (**D:** 198x). Arrows are pointed at the former intima (I)–adventitia (A) vessel wall apposition border and the magnified (1000x) subsection shows a continuum of endothelium covering the rim.

At 4 days, partial coverage of the connector and rim with platelets, fibrin, and endothelial cells was seen, demonstrating initiation of endothelialization of the non-intimal surface, which was completed after 10 days (Figure 3C and D). Note a continuous endothelial surface from the coronary artery over the connector and the rim (Figure 3D: 1000x magnified subsection), into the LITA at 10 days.

At 14, 21, 35 days, and 6 months, no differences in anastomotic surface were found compared to the anastomosis at 10 days. All anastomoses showed patent anastomotic orifices, completely covered with endothelial cells, which expanded over time (Table 2).

DISCUSSION

After initial testing in the acute rabbit bypass model, the main purpose of the porcine OPCAB survival study was to investigate the healing of the novel ELANA coronary connector (ie, BENIS, the residual implant, and the active compression of vessel walls). Favorable healing and remodeling were demonstrated despite inherent undersizement of the anastomosis, with sufficient hemodynamic function over time.

Healing and Remodeling of the Alternative Vessel Wall Connection

Despite the unconventional construction (ie, apposition of the intima of the graft to the adventitia of the coronary artery) and the undersized anastomotic geometry, favorable anastomotic healing and remodeling were demonstrated. At 10 days, the non-intimal surface was completely covered with neointima (Figures 2 and 3). In addition, the anastomotic orifice tended to expand over time by retraction of the laser rim and no flow-limiting (FFR 0.93 ± 0.07) intimal hyperplasia was seen at 6 months in the porcine model (latter follow-up being comparable to 1.5 to 3-year follow-up in the stented human coronary artery[3]). Supported by earlier experiments with laser-assisted anastomosis constructions in rabbits[1,4] and pigs,[5] correspondingly, no endothelial damage or thermal effects of the laser were found in our experimental CABG study. Moreover, one of the concerns with the use of a laser and a compression device is the risk for pseudoaneurysm formation.[6] However, at 6 months no adverse remodeling or anastomotic aneurysm formation, and in addition, no erosion effects of the implant were observed.

Facilitating Minimally Invasive Distal Coronary Anastomosis Construction

The connector includes several interesting features, compared with other coronary anastomotic connectors,[2,7-10] to facilitate - minimally invasive or endoscopic - distal coronary anastomosis construction. First, the most discriminating feature is the relatively simple first step of nonocclusive prebounding of vessel walls, which enables anastomotic construction in a bloodless field, without a time constraint. Hence, coronary conditioning (ie, shunting or snaring[7-10]) is redundant. Similarly, neither placing additional stitches to obtain hemostasis,[8] nor a separate incision into the target coronary is necessary,[7-10] thus reducing manipulation and conditioning of the coronary artery and so, most importantly, simplifying the off-pump bypass procedure, especially in an endoscopic or minimally invasive setting. Moreover, due to the two-step approach it is feasible, in the case of malposition, prior to the point of no return (ie, the arteriotomy), to reopen and reposition the connector.

Second, in addition, the ELANA connector is a low-profile device, without a bulky device-deployment system,[7-10] so not hampering the bypass construction on difficult to reach or remote areas on the heart.

Limitations of the ELANA Coronary Connector

The connector requires optimization steps before clinical introduction. The round and fixed configuration of the anastomosis combined with the use of a cone-shaped laser catheter resulted, at least initially, in (1) a relative undersizing of the anastomosis (Table 2; FFR of 0.82 ± 0.17) by extension of the blood-exposed adventitial laser rim (Figure 2B; rim length 0.63 ± 0.09 mm versus 0.11 ± 0.12 mm in a previous study[1] without a cone-shaped catheter), and so (2) applied for more than half of the total BENIS. BENIS, however, is inherent to distal anastomotic connectors.[2,7-10] Buijsrogge and coworkers stated that BENIS intima-adventitia apposition

per se is not detrimental in a porcine low-flow LITA-to-LAD bypass model, but the tolerance to additional technical errors becomes smaller.[11] In the current study, the additional technical error of an asymmetrically lasered rim, hence resulted in a fatal thrombotic occlusion in 1 pig. So, modifications to both the laser catheter as well as the anastomotic configuration (ie, oval shaped) will result in a relatively larger anastomotic orifice (proper matching of anastomotic area to target coronary artery area), a reduction of the nonintimal surface within the anastomosis, and optimal flap retrieval.

Future Perspectives

A new downsized, oval-shaped ELANA connector (anastomotic orifice ≈ 1.3 mm^2) is being designed, which can be mounted completely sutureless and is applicable to target coronary arteries with an OD of 1.5 mm (ie, ± 1.2 mm ID ≈ 1.1 mm^2). Prior to clinical application in CABG, the safety and quality of this downsized connector will be evaluated both in a long-term experimental porcine OPCAB study, as well as in a human atherosclerotic model.

Conclusion

The new nonocclusive coronary connector is easy-to-use and the long-term results suggest favorable healing and remodeling in the porcine OPCAB model. Following downsizing, this coronary anastomotic device, with its emphasis on zero ischemia and simplified prebounding of vessel walls, has intrinsic potential for minimally invasive or endoscopic OPCAB surgery.

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DISCLOSURES

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REFERENCES

1. Stecher D, de Boer B, Tulleken CA, Pasterkamp G, van Herwerden LA, Buijsrogge MP. A new nonocclusive laser-assisted coronary anastomotic connector in a rabbit model. *J Thorac Cardiovasc Surg.* 2013;145(4):1124-9.
2. Scheltes JS, van Andel CJ, Pistecky PV, Borst C. Coronary anastomotic devices: blood-exposed non-intimal surface and coronary wall stress. *J Thorac Cardiovasc Surg.* 2003;126:191-9.
3. Fishell TA, Virmani R. Intracoronary brachytherapy in the porcine model. A different animal. *Circulation.* 2001;104:2388-90.
4. Tulleken CA, Verdaasdonk RM, Berendsen W, Mali WP. Use of the excimer laser in high-flow bypass surgery of the brain. *J Neurosurg.* 1993;78:477–480.
5. Streefkerk HJ, Bremmer JP, Tulleken CA. The ELANA technique: high flow revascularization of the brain. *Acta Neurochir Suppl.* 2005;94:143-8.
6. Grubbs PE, Wang S, Marini C, Rose DM, Cunningham JN. Enhancement of CO2 laser microvascular anastomoses by fibrin glue. *J Surg Res.* 1988;45:112–119.
7. Suyker WJ, Buijsrogge MP, Suyker PT, Verlaan CW, Borst C, Grundeman PF. Stapled coronary anastomosis with minimal intraluminal artifact: The S2 Anastomotic System in the off-pump porcine model. *J Thorac Cardiovasc Surg.* 2004;127:498-503.
8. Matschke KE, Gummert JF, Demertzis S, Kappert U, Anssar MB, Siclari F, et al. The Cardica C-Port System: clinical and angiographic evaluation of a new device for automated, compliant distal anastomoses in coronary artery bypass grafting surgery--a multicenter prospective clinical trial. *J Thorac Cardiovasc Surg.* 2005;130:1645-52.
9. Carrel T, Englberger L, Keller D, Windecker S, Meier B, Eckstein F. Clinical and angiographic results after mechanical connection for distal anastomosis in coronary surgery. *J Thorac Cardiovasc Surg.* 2004;127:1632-40.
10. Filsoufi F, Farivar RS, Aklog L, Anderson CA, Chen RH, Lichtenstein S, et al. Automated distal coronary bypass with a novel magnetic coupler (MVP system). *J Thorac Cardiovasc Surg.* 2004;127:185-92.
11. Buijsrogge MP, Grundeman PF, Verlaan CW, Borst C. Unconventional vessel wall apposition in off-pump porcine coronary artery bypass grafting: low versus high graft flow. *J Thorac Cardiovasc Surg.* 2002;123(2):341-7.

SUPPLEMENTAL METHODS

Animals

Rabbits

Three female New Zealand white rabbits (3 kg) were used. The rabbits were fed a normal diet and received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (Institute of Laboratory Animal Resources, National Research Council [revised 1996]). The animal experimentation committee of the Utrecht University approved the protocol. The rabbits did not receive any anticoagulant or antiplatelet medication preoperatively.

Anesthesia was induced with acepromazine (0.5 mg/kg), methadone (1 mg/kg) intramuscularly and etomidate (0.3 mg/kg) intravenously. After intubation and ventilation, anesthesia was maintained by continuous intravenous infusion of midazolam (50 µg/kg/h) and sufentanil (50 µg/kg/h). The rabbit was put in a supine position and mean arterial blood pressure was kept at 60 mm Hg during the whole procedure. The rabbits were terminated with 200 mg/kg sodium pentobarbital intravenously

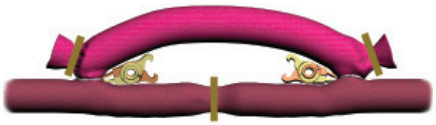
Pigs

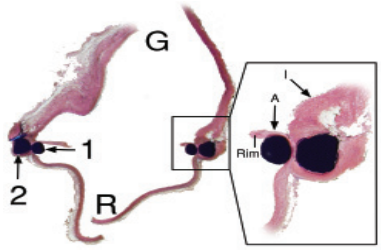
Anesthesia was induced with ketamine (10 mg/kg), midazolam (0.5 mg/kg), and atropine (0.04 mg/kg) intramuscularly. Each animal received antibiotic prophylaxis (augmentin 1000/100 mg), thiopental sodium (4 mg/kg), midazolam (0.5 mg/kg), and sufentanil citrate (6 µg/kg) through an intravenous line. The animals were intubated and ventilated with a mixture of oxygen and air (1:1 volume/volume). Anesthesia was maintained by a continuous intravenous infusion of midazolam (0.7 mg/kg/h), analgesia was obtained with an infusion of sufentanil citrate (6 µg/kg/h), and muscle relaxation with pancuronium bromide (0.1 mg/kg/h). During the operation, each animal received a continuous infusion of saline solution (300 mL/h). Metoprolol was administered intravenously (range, 5-20 mg) to reduce the mechanical irritability of the heart until a heart rate of approximately 70 beats/min was obtained. Postoperatively, amoxicillin-clavulanic acid (7.5 mg/kg) was administered and analgesia was obtained with durogesic 25 µg transdermally for 3 days. Animals were put to death with sodium pentobarbital (200 mg/kg) intravenously, after having been heparinized to obtain an activated clotting time (ACT; Hemotec, Inc, Englewood, Colo) of at least 4 times the control value.

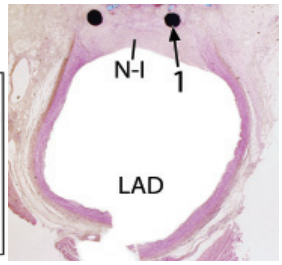
Scanning Electron Microscopy (SEM)

In the porcine model, 1 anastomosis per subgroup (n=7) was fixated in 2% glutaraldehyde solution buffered in 0.1 M purified phosphate buffer. Fixation was completed after the anastomosis was left in 1% buffered osmium tetroxide for 1 hour. After fixation, the anastomosis was dehydrated in a graded series (50, 70, 90, and 100%) of ethanol and dried in liquid CO2 by using the critical point method. Subsequently, the backwall of the LAD and the upper wall of the LITA at the anastomotic site were opened longitudinally, fixed on scan tubs, and covered with a thin layer of platinum by sputter processing to enhance the image quality.

The intravascular anastomotic surface was evaluated (ie, assessment of endothelial and/or thrombocyte coverage) using a scanning electron microscope (Philips XL30LAB; FEI Europe, Eindhoven, The Netherlands).







Supplemental figure E1 **Supplemental figure E2** **Supplemental figure E3**

Supplemental figure 1. The rabbit abdominal aortic ELANA bypass model

Final abdominal aortic bypass with 2 anastomoses. Ligating hemoclips are placed at both ends of the graft, and a hemoclip occludes the abdominal aorta in between the 2 anastomoses.

Supplemental figure 2. Histologic section of the ELANA anastomosis in the rabbit abdominal aortic bypass model

Transverse section (12.5x magnification). The fork (1) and the ring (2) of the anastomotic connector are visible. The magnified (40x) subsection demonstrates intima (I)–adventitia (A) vessel wall apposition and the sharp laser-cut edge (Rim). Compression of the recipient vessel wall between the ring and fork is seen. G, lumen of the graft; R, recipient artery.

Supplemental figure 3. Histologic section of the LITA-to-LAD ELANA anastomosis at 6-months in the porcine model

Transverse section (12.5x magnification). The pins of the connector (1) at the toe of the anastomosis (ie, distal to the anastomosis) are integrated into the upper wall of the LAD. N-I, neo-intima formation.

4

6-MONTH HEALING OF THE NONOCCLUSIVE CORONARY ANASTOMOTIC CONNECTOR IN AN OFF-PUMP PORCINE BYPASS MODEL

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ABSTRACT

Objective: This pilot study evaluates the anastomotic healing of the Excimer Laser Assisted Nonocclusive Anastomosis (ELANA) coronary connector at 6 months in a porcine off-pump coronary artery bypass (OPCAB) model.

Methods: In 2 animals, left internal thoracic artery (LITA) to left anterior descending (LAD) coronary artery and in 1 animal, LITA-to-LAD and right internal thoracic artery (RITA) to right coronary artery (RCA) bypasses were evaluated intraoperatively and at 6 months. The anastomoses (n=4) were examined by angiography, intravascular ultrasound (IVUS), optical coherence tomography (OCT), scanning electron microscopy (SEM), and histology.

Results: At follow-up, all anastomoses (n=4) were fully patent (FitzGibbon grade A). SEM demonstrated complete endothelial coverage of the anastomotic surface and histology showed minimal streamlining intimal hyperplasia. The in vivo IVUS and OCT acquisitions confirmed histologic findings. OCT demonstrated 0.06 mm intimal coverage of the intraluminal part of the connector along the full circumference of the anastomosis.

Conclusions: In this pilot study, the ELANA coronary connector showed an excellent healing response on the long-term in the porcine OPCAB model. Hence, this new concept might be a potential alternative to hand-sutured anastomosis in (minimally invasive) OPCAB surgery.

INTRODUCTION

A new coronary anastomotic connector has been developed to facilitate minimally invasive off-pump coronary artery bypass (OPCAB) surgery.[1] Initial short-term results showed that the zero ischemia Excimer Laser Assisted Nonocclusive Anastomosis (ELANA) coronary connector is easy-to-use and enables a reliable and standardized anastomotic construction in an off-pump porcine left internal thoracic artery (LITA) to left anterior descending (LAD) coronary artery bypass model,[2] presented at the ISMICS Annual Meeting 2012. However, the long-term results, particularly regarding the healing and remodeling of the unconventional construction (ie, laser-punched arteriotomy and apposition of the intima of the graft to the adventitia of the coronary artery) are unknown. This pilot study evaluated the coronary connector in the porcine OPCAB model at 6 months follow-up (comparable to 1.5 – 3 years of human clinical follow-up[3]) with angiography, intravascular ultrasound, optical coherence tomography, scanning electron microscopy, and histology.

METHODS

Animals

Three Dutch Landrace pigs (female; weighing 70-90 kg) were used. The animals were fed a normal diet and received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council (revised 1996). The animal experimentation committee of the Utrecht University approved the protocol. Starting 3 days before surgical intervention, all animals received 80 mg of acetylsalicylic acid and 75 mg clopidogrel orally daily. This anticoagulation protocol was continued until termination.

ELANA Coronary Connector and Procedure

The prototype connector (titanium; Figure 1A) is suitable for coronaries with an inner diameter (ID) of 2.4 mm. The graft (2.0-4.0 mm outer diameter [OD]) is mounted onto the ring of the opened connector, following an arteriotomy (3.0 mm long), using 4 to 8 Prolene 8-0 stitches (Ethicon, Somerville, NJ), such that the ring is completely covered with intima (Figure 2A). An applier (Aneurysm clip applier; Peter Lazic, GmbH, Tuttlingen, Germany) is used to open and insert the connector into the lumen of the unopened, non-occluded coronary artery (Figure 2B). The connector is closed by releasing the applicator, and hereby, it compresses both vessel walls by the spring of the connector. Subsequently, a laser catheter (2.5 mm OD, laser fibers 2.0 mm OD; Figure 1B) is introduced via the distal end of the graft and vacuum through the lumen of the laser onto the coronary is initiated. The laser punches an opening of ± 1.8-2.0 mm diameter (≈ 2.5-3.1 mm^2, cave lumen coronary ≈ 4.5 mm^2) into the coronary (the laser does not weld or seal the anastomosis), the lasered fragment

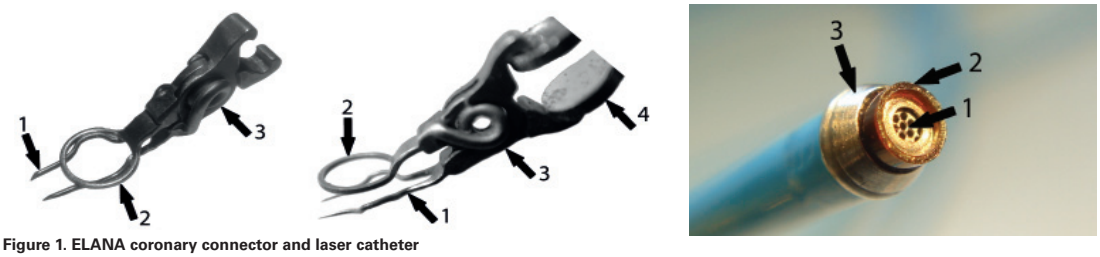

Figure 1. ELANA coronary connector and laser catheter

A: Prototype connector with a fork (1) (2.9 mm outer diameter, 2.4 mm inner diameter) with 2 sharp pins (4.5 mm length) and a ring (2) (3.4 mm outer diameter, 2.9 mm inner diameter). A spring (3) at the back of the device enables the ring (2) and fork (1) of the connector to open (right) and close (left), with the use of an applicator (4).

B: Laser catheter (2.5 mm outer diameter): the grid of the vacuum channel (1) is located centrally and surrounded by laser fibers (2) (2.0 mm outer diameter). The cone-shaped tip (3) (widest part, 3.0 mm outer diameter) facilitates positioning and stabilization into the anastomotic connector.

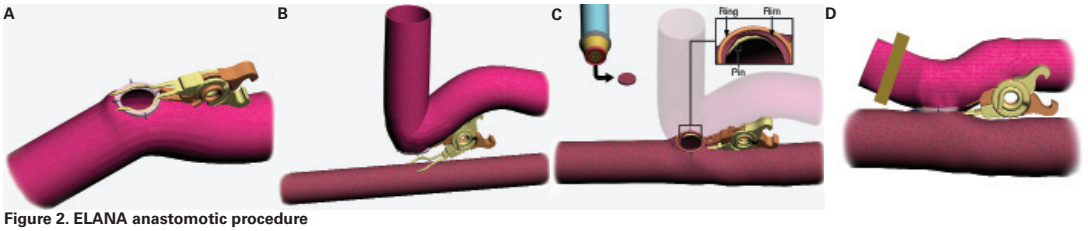

Figure 2. ELANA anastomotic procedure

A: The graft is mounted onto the connector using 4 to 8 stitches. The intima of the graft (highlighted) is everted over the ring from the inside, and, subsequently, completely covers the inner surface of the ring of the connector.

B: An applier (not shown) is used to open and insert the connector into the lumen of the coronary artery. The pins of the connector puncture the unopened, non-occluded coronary artery wall, downstream, towards the distal tract of the coronary.

C: After laser-punching an opening into the anastomosis, the catheter with a lasered fragment of the coronary artery wall ("flap", see curved arrow) is retrieved (graft illustrated transparently). A small protruding adventitial rim of the coronary artery, the laser edge, is exposed intraluminally (see magnified section [complete intimal coverage of the ring of the connector by the graft not shown]).

D: Final bypass. A ligating hemoclip is placed at the distal end of the graft. Note that the implanted connector stays in situ and is not removed afterwards.

of the coronary wall (ie, "flap") is vacuum-attached to the grid of the laser (Figure 1B), and subsequently the laser - including the flap - is retrieved. Hence, an adventitial rim of the coronary, the laser edge, is exposed intraluminally (Figure 2C).[1] The bypass is completed by ligation of the distal end of the graft using a hemoclip (Weck Hemoclip; Teleflex Medical, Research Triangle Park, NC; Figure 2D).

Anesthesia and Euthanasia

Anesthesia was induced with ketamine (10 mg/kg), midazolam (0.5 mg/kg), and atropine (0.04 mg/kg) intramuscularly. Each animal received antibiotic prophylaxis (amoxicillin-clavulanic acid 1000/100 mg), thiopental sodium (4 mg/kg/), midazolam (0.5 mg/kg), and sufentanil citrate (6 µg/kg) through an intravenous line. The animals were intubated and ventilated with a mixture of oxygen and air (1:1 volume/volume). Anesthesia was maintained by a continuous intravenous infusion of midazolam (0.7 mg/kg/h), analgesia was obtained with an infusion of sufentanil citrate (6 µg/kg/h), and muscle relaxation with pancuronium bromide (0.1 mg/kg/h). During the operation, each animal received a continuous infusion of saline solution (300 mL/ h). Metoprolol was administered intravenously (range, 5-20 mg) to reduce the mechanical irritability of the heart until a heart rate of approximately 70 beats/min was obtained. Postoperatively, amoxicillin-clavulanic acid (7.5 mg/kg) was administered and analgesia was obtained with fentanyl 25 µg transdermally for 3 days. Animals were put to death with pentobarbitalsodium (200 mg/kg) intravenously, after having been heparinized to obtain an activated clotting time (ACT; Hemotec, Inc, Englewood, Colo) of at least 4 times the control value.

Surgery and Experimental Model

After a partial sternotomy, harvesting the ITA, partial heparinization (activated clotting time [ACT] > 200; not counteracted), and immobilization of the coronary (OD 3.0 mm) by the Octopus 3 Tissue Stabilizer (Medtronic, Inc, Minneapolis, MN), the bypass was constructed. Following construction, the coronary was ligated ± 1.0 cm upstream with 3 medium hemoclips, the ITA was tagged onto the epicardium, and the pericardium closed.

Before chest closure, graft flow (mL/min) was monitored for 2 hours with a transit time flow probe (diameter 3.0 mm; flowmeter model T208; Transonic Systems, Inc, Ithaca, NY), at a mean blood pressure of 90 mm Hg. Following ITA clamping for 30 seconds, the coronary peak hyperemic flow response was determined (45 minutes after construction, in duplicate at an interval of at least 10 minutes) as the peak graft flow divided by the baseline flow.

In 2 animals, LITA-to-LAD and in 1 animal, LITA-to-LAD and RITA-to-RCA bypasses were constructed. The anastomoses (n=4) were evaluated intraoperatively by flow measurements, and at 6 months by angiography intravascular ultrasound (IVUS; n=1, RITA-RCA), optical coherence tomography (OCT; n=1, RITA-RCA),

scanning electron microscopy (SEM; n=1, LITA-LAD), and histology (n=2, LITA-LAD).

Catheterization Techniques

All catheterization was performed before death, at 6 months. All anastomoses (n=4) were visualized by angiography and graded by 2 independent observers according to the FitzGibbon criteria.

IVUS acquisition of the RITA-to-RCA bypass was performed using an ultrasound catheter (Revolution 45MHz Catheter, Volcano Corporation, Rancho Cordova, CA) with an automated pullback-speed of 0.5 mm/s. The frequency domain OCT system (C7 Dragonfly, LightLab Imaging, Inc., Westford, MA) was used for imaging the RITA-to-RCA bypass with an automated pullback-speed of 20 mm/s and a continuous flush of contrast by manual injection. Intimal hyperplasia and the dimension of the bypass (ie, the reference lumen area of the RCA and RITA 1.0 cm down- and upstream to the anastomosis, respectively, and the anastomotic orifice) were recorded and assessed by 2 independent investigators.

Scanning Electron Microscopy (SEM) and Histologic Analysis

The anastomotic surface of 1 anastomosis was evaluated using a scanning electron microscope (Philips XL30LAB; FEI Europe, Eindhoven, The Netherlands).

Two anastomoses were embedded in methyl methacrylate, sectioned in transverse planes (at 300-µm intervals), and stained with hematoxylin and eosin. The dimensions (ie, coronary lumen area [reference part, 1.0 cm distal to the anastomosis] and the anastomotic orifice), neointimal hyperplasia, adverse remodeling, and chronic inflammatory cell reaction were assessed (AnalySiS, Soft-Imaging Software GmbH, Münster, Germany).

Statistical Analysis

The data are presented as the mean ± standard deviation or as noted otherwise.

RESULTS

Surgery

All anastomotic procedures were performed by 1 investigator (D.S.). The mean anastomotic construction time was 6.8 ± 1.0 minutes, mounting of the graft required 28 ± 3 minutes, and all anastomoses were constructed without interrupting coronary flow. The intraoperative mean peak hyperemic flow response was 4.3 ± 1.3 (base flow 50 ± 17 mL/min) and all anastomoses showed consistent graft flow up to 2 hours after construction (43 ± 15 mL/min at t=2 hours).

Catheterization

At follow-up, all anastomoses (n=4) were fully patent (FitzGibbon grade A; Figure 3A). In 1 animal, an imperfect occlusion of the hemoclip at the LAD proximal to the anastomosis was found, resulting in a partial occlusion (approximately 40% residual lumen); however, it had not affected anastomotic patency.

IVUS acquisition of the RITA-to-RCA bypass demonstrated a lumen area of the RCA of 10.1 mm^2 and 11.8 mm^2 of the RITA. The anastomotic width, measured with both IVUS and OCT, was 2.2 mm. Limited neointimal formation and a 0.06 mm intimal coverage of the intraluminal part of the connector along the full circumference of the anastomosis was found with OCT (n=1; Figure 3B-D).

Scanning Electron Microscopy (SEM) and Histology

SEM demonstrated complete endothelial coverage of the anastomotic surface, and a smooth and patent orifice was seen. The endothelial surface is completely continuous from the coronary artery, covering the connector and the laser rim, to the LITA (Figure 4B).

Histology showed minimal intimal hyperplasia, without lumen-narrowing neointimal formation (Figure

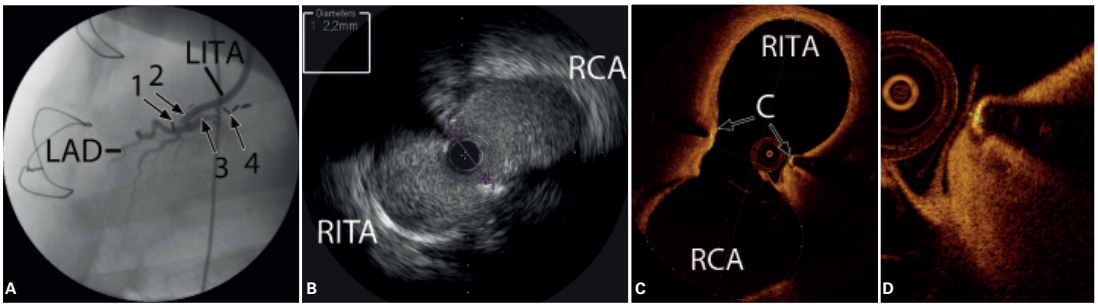

Figure 3. Angiogram, IVUS, and OCT images of a representative ELANA bypass at 6 months postoperatively

A: Angiogram at 6 months. Ligating hemoclips on the distal end of the mammary (1), and at the proximal part of the coronary (4), are visible. Note the relatively undersized anastomosis (2) due to an increased LAD (animal growth). The spring of the connector (3) is only slightly visible and over-projected by the mammary artery filled with contrast.

B: Intracoronary IVUS, transverse section. A minimal anastomotic width of 2.2 mm is demonstrated. Note: the IVUS wire is visible in the lumen.

C: Intracoronary OCT, transverse section. Note: the OCT wire is visible in the lumen. The arrows point at the fork of the connector (C). The ring of the connector cannot be seen owing to the scattering of the fork. C= fork of the connector.

D: Magnification of Figure 3C. The connector (radiopaque; on its right side its shadow) is covered by a layer of neointima of 0.06 mm.

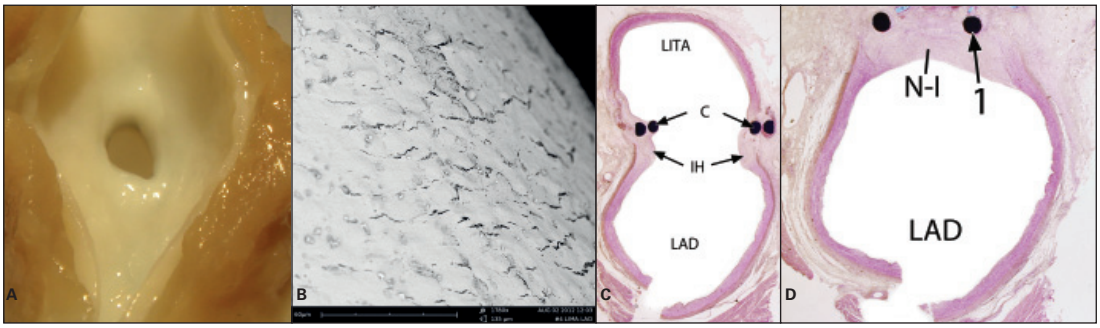

Figure 4. Macroscopic, SEM, and histologic images of the ELANA anastomosis at 6 months postoperatively

A: Macroscopic view onto an ex vivo anastomosis, with a longitudinally opened LAD. The connector is completely covered by neointima and hence not visible.

B: SEM image of the anastomotic edge (1780x magnification). Complete coverage - of initial nonintimal tissue - with endothelium is demonstrated.

C: Histologic transverse section, midanastomosis (12.5x magnification), stained with hematoxylin and eosin. Note that the black dots, on each lateral side of the fork of the connector (C), represent the ring of the connector. C = fork of the connector, IH = intimal hyperplasia.

D: Histologic transverse section (12.5x magnification), stained with hematoxylin and eosin. The pins of the connector (1) at the toe of the anastomosis (ie, distal to the anastomosis) are integrated into the upper wall of the LAD. N-I = neointimal formation.

4C). The initial intraluminal exposed coronary adventitial rim (Figure 2C) was completely remodeled and replaced by streamlining neointimal tissue, which caused the anastomotic orifice to expand over time from ± 2.5-3.1 mm^2 (LAD ± 4.5 mm^2) at the time of construction to 3.8 ± 0.6 mm^2 at 6 months (LAD 8.6 ± 0.7 mm^2). The extravascular spring of the connector (Figure 1A-*3*) was fully integrated in a maze of connective tissue, between the LITA and LAD, and did not induce adverse erosion effects to neither one of the adjacent arteries. In addition, the initial intraluminal exposed fork was incorporated into the upper wall of the outflow tract of the LAD and covered by a layer of neointima (Figure 4D). No adverse remodeling (eg, erosion, luxation, or pseudoaneurysm formation) was demonstrated over time and no excessive chronic inflammatory cell reaction was found.

DISCUSSION

This pilot study evaluated the long-term results of the zero ischemia ELANA coronary connector in a porcine OPCAB model at 6 months. The ELANA bypass was assessed by multiple imaging modalities at 6 months, which demonstrated fully patent anastomoses and consistent healing and remodeling with minimal intimal hyperplasia.

The ELANA Connector: Healing of an Unconventionally Constructed Anastomosis

In contrast to other coronary anastomotic connectors,[4,5] the unconventional 'reciprocal' construction requires connection of the vessel walls as a first step, before making the arteriotomy; hence, allowing a completely nonocclusive, simple, and bloodless construction. In addition, in contrast to the conventional hand-sewn, intima apposed to intima, anastomosis, the facilitated ELANA anastomosis has some unconventional features, which were comprehensively examined in this pilot study at 6 months follow-up. The unconventional anastomosis construction, with 1) a laser-punched arteriotomy, 2) active compression of the vessel walls between the fork and ring of the connector, 3) apposition of the intima of the graft to the adventitia of the coronary artery, and 4) the residual implant (ie, the extravascular spring at the back of the connector and the intraluminal, blood-exposed fork), had no detriment on the long-term patency or remodeling of the anastomosis. Moreover, neither erosion effects, nor lumen-narrowing intimal hyperplasia, but rather consistent and streamlining neointimal coverage along the full circumference of the connector was seen at 6 months follow-up. Despite the preexistent undersizing (ie, mismatch of the anastomotic area [± 2.5-3.1 mm^2] to the target coronary [± 4.5 mm^2]), which increased over time due to the physiological growth of the porcine coronaries (lumen LAD 8.6 ± 0.7 mm^2), the anastomotic area expanded (3.8 ± 0.6 mm^2).

OCT acquired high resolution, in vivo "near-histological" images. This imaging technique offers a ten-fold higher resolution than IVUS, which results in acquisition of easy-to-interpret images without loose of detail.[6,7] This technique is the gold standard for the assessment of coronary device (eg, stents) coverage; however, its resolution is just above the dimension of endothelial cells and therefore it cannot characterize tissues. Thus, its implication in the current application (ie, assessment of intimal coverage of the intraluminal fork) is not validated. However, OCT has potential in the (experimental) ad interim assessment of the anastomosis coverage (ie, acquiring "near-histological" data), without the need to sacrifice the animal. In addition, it might have clinical implications as a follow-up assessment technique (ie, assessment of connector and vessel wall apposition, anastomotic healing, and remodeling).

Limitations and Future Perspectives

There are some limitations. This is a pilot study, and inherently, a limited number of anastomoses were evaluated. However, the obtained long-term data in this study provide a "proof of concept" and hence it stimulates the ongoing quest and research towards a clinically useful, unconventional anastomotic connector. With regard to the undersizing of the anastomosis, the connector will be downsized to an oval shaped-configuration, with proper matching of anastomotic flow area to coronary lumen area, in order to target clinically relevant small caliber coronary arteries (1.2 mm ID). Moreover, to further simplify and accelerate the anastomosis construction, the newly designed connector will be completely sutureless, applicable for (robotic assisted) minimally invasive or totally endoscopic off-pump coronary artery bypass procedures.[8-12]

Conclusion

In this pilot study, the ELANA coronary connector showed an excellent healing response with only minimal streamlining intimal hyperplasia formation on the long-term in the porcine OPCAB model. Hence, this new concept, following ameliorations, might be a potential alternative to hand-sutured anastomosis in (minimally invasive) OPCAB surgery.

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DISCLOSURES

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REFERENCES

1. Stecher D, de Boer B, Tulleken CA, et al. A new nonocclusive laser-assisted coronary anastomotic connector in a rabbit model. *J Thorac Cardiovasc Surg.* 2013;145:1124-1129.
2. Stecher D, Pasterkamp G, van Herwerden LA, et al. A New Sutureless Coronary Anastomotic Device - Excimer Laser Assisted Non-occlusive Anastomosis (ELANA) - in an Off-Pump Porcine Bypass Model. *Innovations*. 2012;7:111.
3. Fishell TA, Virmani R. Intracoronary brachytherapy in the porcine model. A different animal. *Circulation*. 2001;104:2388-2390.
4. Suyker WJ, Buijsrogge MP, Suyker PT, et al. Stapled coronary anastomosis with minimal intraluminal artifact: the S2 Anastomotic System in the off-pump porcine model. *J Thorac Cardiovasc Surg.* 2004;127:498-503.
5. Matschke KE, Gummert JF, Demertzis S, et al. The Cardica C-Port System: clinical and angiographic evaluation of a new device for automated, compliant distal anastomoses in coronary artery bypass grafting surgery—a multicenter prospective clinical trial. *J Thorac Cardiovasc Surg.* 2005;130:1645-52.
6. Agostoni P, Stella PR. Optical coherence tomography: new (near-infrared) light on stent implantation? *Heart*. 2009;95:1895-1896.
7. Burris N, Schwartz K, Brown J, et al. Incidence of Residual Clot Strands in Saphenous Vein Grafts After Endoscopic Harvest. *Innovations*. 2006;1:323-327.
8. Balkhy HH, Wann LS, Krienbring D, et al. Integrating coronary anastomotic connectors and robotics toward a totally endoscopic beating heart approach: review of 120 cases. *Ann Thoracic Surg.* 2011;92:821-827.
9. Bonatti J, Lee JD, Bonaros N, et al. Robotic Totally Endoscopic Multivessel Coronary Artery Bypass Grafting: Procedure Development, Challenges, Results. *Innovations*. 2012;7:3-8.
10. Srivastava S, Gadasalli S, Agusala M, et al. Robotically Assisted Beating Heart Totally Endoscopic Coronary Artery Bypass (TECAB). Is There a Future? *Innovations*. 2008;3:52-58.
11. Diegeler A, Matin M, Kayser S, et al. Angiographic results after minimally invasive coronary bypass grafting using the minimally invasive direct coronary bypass grafting (MIDCAB) approach. *Eur J Cardiothorac Surg.* 1999;15:680-684.
12. Falk V, Diegeler A, Walther T, et al. Total endoscopic computer enhanced coronary artery bypass grafting. *Eur J Cardiothorac Surg.* 2000;17:38–45.

PREFACE PART C
THE TRINITY CLIP CONNECTOR

Device Development:

A Journey from Clip to Trinity Clip

From Clip to Trinity Clip

After the proof-of-concept of the Clip connector was demonstrated in the porcine off-pump bypass model and favorable long-term patency results and anastomotic healing was confirmed (Part B of this thesis), the experimental anastomosis concept was further ameliorated towards clinical application. Therefore, two major obstacles had to be addressed: 1) its size (ie, suitable for relatively large caliber coronary arteries) and 2) the need for mounting sutures, to connect the graft to the connector. How these two obstacles have been tackled is described in the following paragraphs.

Downsizing of the Connector

Oval shaping of the initial round connector and laser catheter (Figure 1 and Chapter 5, Figure 2) enabled the technique to target smaller caliber coronary arteries. The final sizing of the connector is based on the following principle: the surface of the anastomotic orifice (ie, anastomotic flow area) has to be at least equal to the cross-sectional area of the target coronary artery (ie, coronary luminal flow area). To obtain sufficient anastomotic orifice, logically, only a maximum in anastomotic width is allowed for: if the device is too wide, the connector will deform the coronary artery (ie, flattening or sea-gulling effect). The maximal anastomotic width for a particular target coronary artery was determined in an ex vivo study (not published). In porcine cadaver hearts, connector-prototypes with different sizes (from 1.0 – 3.0 mm width, with a 0.2 mm interval between each prototype) were introduced into coronary arteries (from 1.0 – 3.0 mm outer diameter). In the first part of the study, deforming of the coronary artery after connector introduction was assessed by the formation of luminal casts of the coronary artery (by alginate dental impression material), and in the second part of the study by coronary angiography. The results indicated that the maximum width of the connector is allowed for to be 85% of the outer diameter of the target coronary artery.

To cover target coronary arteries in the range of 1.6 – 3.0 mm outer diameter (ie, clinically relevant target sizes; covering the majority of coronary targets), multiple connector sizes have to be developed to be sufficient in anastomotic flow surface in the indicated range. One size connector will not fit all: it will be too large for the smallest coronary artery in the range and too small and undersized for the largest. To evaluate the potential of the technique, first a connector developed for the smallest range (ie, highest risk) will be evaluated in a long-term animal series (Chapter 8). If the technique is proven to be safe in this model on the long-term, subsequently, the connector will be up-sized. The smallest coronary target range was set at 1.6 – 1.8 mm outer diameter. Developing a connector based on the ELANA technique for coronary targets smaller than 1.6 mm outer diameter is technically extremely challenging and due to the specific characteristics of the connector (ie, intraluminal connector positioning), will probably not yield a viable device; the anastomotic orifice will be too small and consequently, prone for (acute) thrombotic occlusions.

The connector should not be wider than 1.4 mm (85% of the width of the smallest in the range), according to the results of the above-described study. Subsequently, the anastomotic orifice width is dependent of the following two variables: 1) the laser rim (ie, the length of the edge of the coronary wall that resides afterlasering) and 2) the connector material thickness (ie, the thickness of the pins of the fork). Regarding the length of the laser rim inside the anastomosis, the length was empirically set at 0.10 mm; this is enough vessel wall length in case of minor vessel wall slippage.

The second factor that limits the size of the anastomotic flow area is the material thickness of the pins of the fork. Ideally, the material thickness is kept as low as possible to introduce a minimum amount of foreign body into the bloodstream. However, the connector should be strong enough to resist pressures and forces, for example while introducing it into a stiff coronary wall. Therefore, various sizes of forks of the connector (titanium), up to 0.10 mm thickness in combination with different heights, were assessed in an ex vivo study (not published). We demonstrated that the ideal material thickness of a pin of a fork is 0.2 by 0.2 mm, with regard to strength and stabilization of the device in relation to the foreign material surface inside the anastomosis (ie, BENIS).

Now, with all known variables, the anastomotic orifice width can be calculated:
Anastomotic orifice width = 1.4 – (2*0.20 [material thickness]) – (2*0.1 [laser rim]) = 0.8 mm.

The anastomotic orifice length could be determined with the before mentioned rationale 'anastomotic flow area = coronary luminal flow area'. The anastomotic flow area should be at least equal to the luminal flow area of the biggest coronary artery in the range of 1.6 – 1.8 mm outer diameter. Hence, assuming that the coronary wall thickness is 0.2 mm, the luminal flow area = $Pi*r^2 = Pi*((1.8-(0.2*2))/2)^2 = 1.5\ mm^2$. Consequently, the anastomotic flow area should be at least 1.5 mm^2 and so, with the previously determined width of 0.8 mm, the length is calculated and should be at least 2.0 mm.

As much as we would like to oversize the anastomotic flow area, the length of the anastomotic orifice could not be infinite. The laser catheter mainly limits the length of the anastomotic orifice. The laser catheter laser-punches the exact size of the anastomotic orifice and therefore, the tip of the laser catheter thus will be as big as the size of the anastomotic orifice. If the tip of the laser catheter is too long, the laser catheter does not fit into the graft. In addition, the longer the connector is, the more difficult it is to introduce it correctly into the lumen of a small tortuous coronary artery. With the above determined anastomotic orifice width and length of 0.8 by 2.0 mm for the target coronary artery range of 1.6 – 1.8 mm, the calculated minimal inner diameter of the graft is 2.2 mm. However, assuming a 15% extension/distension possibility of the graft,[1] the inner diameter of the target graft could be smaller (1.9 mm).

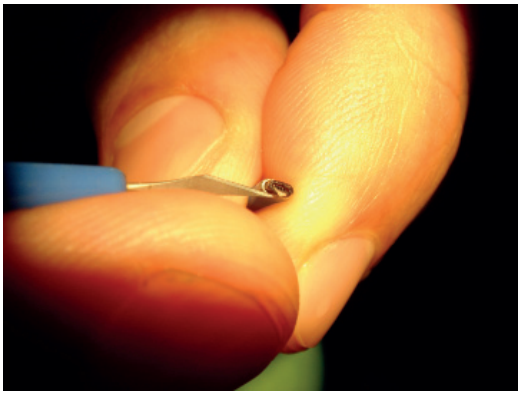

Figure 1. The tip of the laser catheter with a laser-punched fragment of an arterial wall

Sutureless Connection of Graft to Coronary Artery

Tag-points

The need for mounting sutures, to connect the graft to the connector, was a major obstacle towards future less invasive application of the technique. The first attempt to realize a sutureless connection was the attachment of tag-points onto the upper ring of the ovalized Clip connector (Figure 2). Initially the position of the tag-points was lateral onto the ring of the device. In case the graft was relatively small, the connection resulted in a stenosis of the graft at the side of the anastomosis, hereby blocking the way for the laser catheter. Several prototypes were evaluated and tested ex vivo with different forms (to make them sharper) and different positions of the tag-points (on the lower side of the ring to reduce the stenosis). However, it was cumbersome and not practical and hence seemed to have limited potential in facilitating minimally invasive coronary artery bypass surgery.

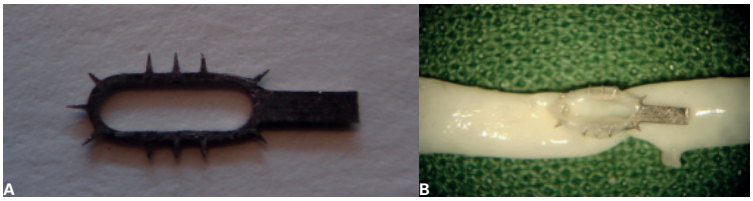

Figure 2. Oval ring with tag-points attached for connection of the graft to the connector

A: The ring only.

B: The oval ring with a graft mounted. Everting the graft results in a stenosis of the graft.

Double Forks and Premounting of the Laser Catheter

A different idea was the use of two forks (Figure 3). A second fork replaced the ring of the Clip connector and the now called 'upper fork' will be simply inserted into the graft. Hence, the graft could be connected totally sutureless onto the connector and subsequently onto the coronary artery. This whole new concept brought along some new challenges and subsequent solutions.

Figure 3. Double fork prototypes

A: Fork-fork on top.

B and **C:** Fork-fork push-button.

One potential problem, especially by targeting small caliber coronary arteries, is the introduction of a second fork into the bloodstream. This increases the amount of material BENIS (3.8 in the Clip connector to 6.3 mm^2). However, the intima-adventitia apposition, found in the Clip connector facilitated anastomosis, is now changed into an adventitia-adventitia apposition (ie, only an edge of media and adventitia exposure) by using the double fork design, thus reducing the tissue BENIS (4.1 to 1.9 mm^2). Long-term studies should elucidate the exact effects of these shifts in BENIS on patency and healing.

One of the essentials in the anastomosis construction changed significantly: the laser now also laser-punches the graft. This new construction method introduced some opportunities in simplifying the construction but also raised some questions regarding the effects of laser-punching the grafts vessel wall. We found out that the laser cannot effectively and safely laser-punch the wall of the graft and coronary artery and retrieve both tissue flaps at the same time. Moreover, if the graft is laser-punched, the laser is removed, and the lower fork is subsequently inserted into the coronary artery, we observed that after re-introduction of the laser and opening of the coronary artery, the two anastomotic orifices (ie, the opening of the graft and the opening of the coronary) are not exactly positioned on top of each other, and overlap (resulting in adventitia exposure and a smaller anastomotic orifice). Therefore, to avoid repetitive introduction of the laser catheter (ie, time-costly and potential damaging), and hereby the risk of slippage of the grafts vessel wall (and thus overlapping orifices predisposing to occlusion of the anastomosis), the new idea of 'premounting the laser catheter' was developed.

After introduction of the upper fork of the connector into the graft, the laser is introduced via the distal end of the graft into the connector, were it is temporary fixated by a fixation clip (Chapter 5, Figure 3). The laser is activated, laser-punches the graft, and the flap is removed *a vue.* Importantly, now, the laser catheter

is not removed and stays in situ (ie, premounted for insertion into the coronary artery). The next step is introducing the lower fork of the connector into the coronary artery, while the laser catheter is still positioned and fixated exactly in the connector. Hence, after application onto the coronary artery, the laser catheter is directly correctly positioned and the surgeon can laser-punch without wondering if the laser catheter is correctly positioned. This in contrast to the procedure with the Clip connector, in which the laser catheter is manually positioned after the Clip connector is inserted into the coronary artery. Finally, the coronary artery is opened, the fixation clip is removed, and the laser catheter retracted.

The fixation clip (Chapter 5, Figure 3) is key in the premounting concept. The fixation clip should form a robust and stabile complex with the laser catheter, graft, and connector. It ensures the correct position and prevents dislocation of the laser catheter, especially during the insertion of the lower fork of the connector into the coronary artery, where most forces will challenge the complex, and thus dislocation. We designed the fixation clip in such a way that it has two fulcra: the premounted laser catheter (ie, the graft and laser catheter; the graft is pulled up) and a fixed standardized point at the connector itself (ie, the neck, between the fork and the spring).

The initial experience with premounting was most promising, with 100% flap retrieval rates. However, the design of upper fork on top of the lower fork resulted in unstable anastomoses with brisk anastomotic leakage at the toe. Different prototype designs were tried, amongst other designs also a 'fork-fork push-button', in which the lower fork falls into the slightly bigger upper fork. However, none resulted in satisfactory anastomoses.

Trinity Clip

The unstable design of the clip with the two forks was greatly enhanced by the introduction of a band or ring placed around the two forks. This novel idea leaded to the development of the Trinity Clip.

The spring of the clip is modified in such a way two shafts at the back of the spring enables the 2 forks to open and close, individually one by one by placing an applicator into one of the two shafts of the spring. An extravascular immovable band (2 times the thickness of the fork) is positioned adjacent to the forks over their full length, hereby obtaining extra lateral compression, and it provides stabilization of the mechanics of the connector (Chapter 5, Figure 1). While opening the lower fork during insertion into the coronary artery, the upper fork maintains compression (of the graft) onto the band, hereby preventing shifting of the grafts vessel wall. The upper fork is longer than the lower fork and its tip is positioned in an indentation at the front of the extravascular band, so compression of its full length onto the lower fork is obtained. The shorter lower fork is completely positioned inside the outer band.

The introduction of a new spring with two shafts led to the development of a new applier. The standard applier of the Clip connector opened the lower fork of the Trinity Clip connector in such a way both the lower fork and upper fork (plus band) moved, divergently. This is unfavorable, because this will introduce extra forces onto the premounted complex during insertion of the lower fork into the coronary artery and will therefore increase the risk of dislocation of the laser catheter. In addition, it can also promote slippage of the grafts vessel wall and subsequent overlapping orifices. Hence, our team developed a new applicator (Chapter 5, Figure 4B), suitable for open chest bypass surgery and MIDCAB approaches, which opens the lower fork of the connector and only results in movement of the lower fork, away from the upper fork (plus band). The upper fork will be compressed against the band and will not move.

Preclinical Evaluation

The above described design modifications of the connector and the laser catheter enables a simplified and accelerated construction on to clinically relevant, small caliber coronary arteries. The next part of this Thesis will describe the preclinical evaluation of the Trinity Clip, with in Chapter 5 an extensive protocol of how to use and evaluate the Trinity Clip in an experimental porcine model (supported by an online video). Chapter 6 describes the feasibility and efficacy of the anastomotic technique in a human atherosclerotic model and additionally, the acute laser effects onto small caliber target coronary arteries. A pilot study is described in Chapter 7, in

which the feasibility of total arterial minimally invasive direct coronary artery bypass (MIDCAB) surgery by using the Trinity Clip anastomotic connector was evaluated in an acute porcine model. Finally, Chapter 8 describes the preclinical safety study on small caliber coronary arteries in a long-term porcine OPCAB model in which the patency, healing, and hemodynamic function of the connector-facilitated anastomoses were compared to the hand-sewn anastomoses.

REFERENCES

1. van Andel CJ, Pistecky PV, Borst C. Mechanical properties of porcine and human arteries: implications for coronary anastomotic connectors. *Ann Thorac Surg.* 2003;76:58-64.

5

EVALUATION OF A NOVEL LASER-ASSISTED CORONARY ANASTOMOTIC CONNECTOR – THE TRINITY CLIP – IN A PORCINE OFF-PUMP BYPASS MODEL

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ABSTRACT

To simplify and facilitate beating heart (ie, off-pump), minimally invasive coronary artery bypass surgery, a new coronary anastomotic connector, the Trinity Clip, is developed based on the excimer laser-assisted nonocclusive anastomosis technique. The Trinity Clip connector enables simplified, sutureless, and nonocclusive connection of the graft to the coronary artery, and an excimer laser catheter laser-punches the opening of the anastomosis. Consequently, owing to the complete nonocclusive anastomosis construction, coronary conditioning (ie, occluding or shunting) is not necessary, in contrast to the conventional anastomotic technique, hence simplifying the off-pump bypass procedure. Prior to clinical application in coronary artery bypass grafting, the safety and quality of this novel connector will be evaluated in a long-term experimental porcine off-pump coronary artery bypass (OPCAB) study. In this paper, we describe how to evaluate the coronary anastomosis in the porcine OPCAB model using various techniques to assess its quality. Representative results are summarized and visually demonstrated.

INTRODUCTION

Off-pump coronary artery bypass (OPCAB) surgery can potentially reduce the morbidity associated with the use of cardiopulmonary bypass in coronary artery bypass surgery (eg, thromboembolic complications, excessive retain of fluid, blood transfusions, and activation of the immune system) and can be of benefit for patients at high risk for complications associated with cardiopulmonary bypass and aortic manipulation.[1] Minimally invasive coronary artery bypass surgery (eg, thoracoscopic or robotic-assisted surgery), reduces the size of the incisions, and hence, reduces patient recovery time, hospital stay, and morbidity rates.[2] Despite the potential benefits for (a subset of) patients in need for coronary revascularization, adoption of these techniques has not been widespread. One of the reasons is that an off-pump minimally invasive approach for coronary bypass surgery is technically very challenging.

To simplify and facilitate beating heart (ie, off-pump), minimally invasive coronary artery bypass surgery, a new coronary anastomotic connector is developed, the Trinity Clip,[3,4] based on the excimer laser-assisted nonocclusive anastomosis (ELANA) technique.[5-9] The connector enables simplified, sutureless, and nonocclusive connection of the graft to the coronary artery, and an excimer laser catheter laser-punches the opening of the anastomosis. Consequently, owing to the complete nonocclusive anastomosis construction, coronary conditioning (ie, occluding or snaring and shunting) is not necessary, in contrast to the conventional anastomotic technique, hence simplifying the bypass procedure.

Preceding studies regarding a predecessor prototype ELANA coronary connector, demonstrated its feasibility on relatively large arteries (inner diameter [ID] 2.4 millimeter [mm]) in an acute rabbit model.[5] Moreover, in a porcine open sternotomy OPCAB model, proper healing with minimal intimal hyperplasia was found at the long-term.[6,7]

Recently, the coronary anastomotic technique was further ameliorated towards clinical application. Design modifications of the connector and the excimer laser catheter enable a simplified and accelerated construction (ie, sutureless mounting of the graft) on to clinically relevant, small caliber coronary arteries (ID 1.4-1.6 mm). Prior to clinical application in coronary artery bypass grafting, the safety and quality of this novel connector will be evaluated in a porcine open sternotomy OPCAB model at the long-term (6 month follow-up), according to the protocol described in this paper.

This protocol describes our experimental porcine OPCAB model and provides a detailed description of the coronary anastomotic procedure. Furthermore, options are described for intraoperative, postoperative, and post-mortem assessment of the anastomosis, which are of paramount importance in evaluating the anastomotic quality. In this paper, the Representative Results section summarizes the findings of a pilot study in the porcine OPCAB model (n=3 pigs, with a follow-up of 5 hours), which was performed prior to the preclinical study.

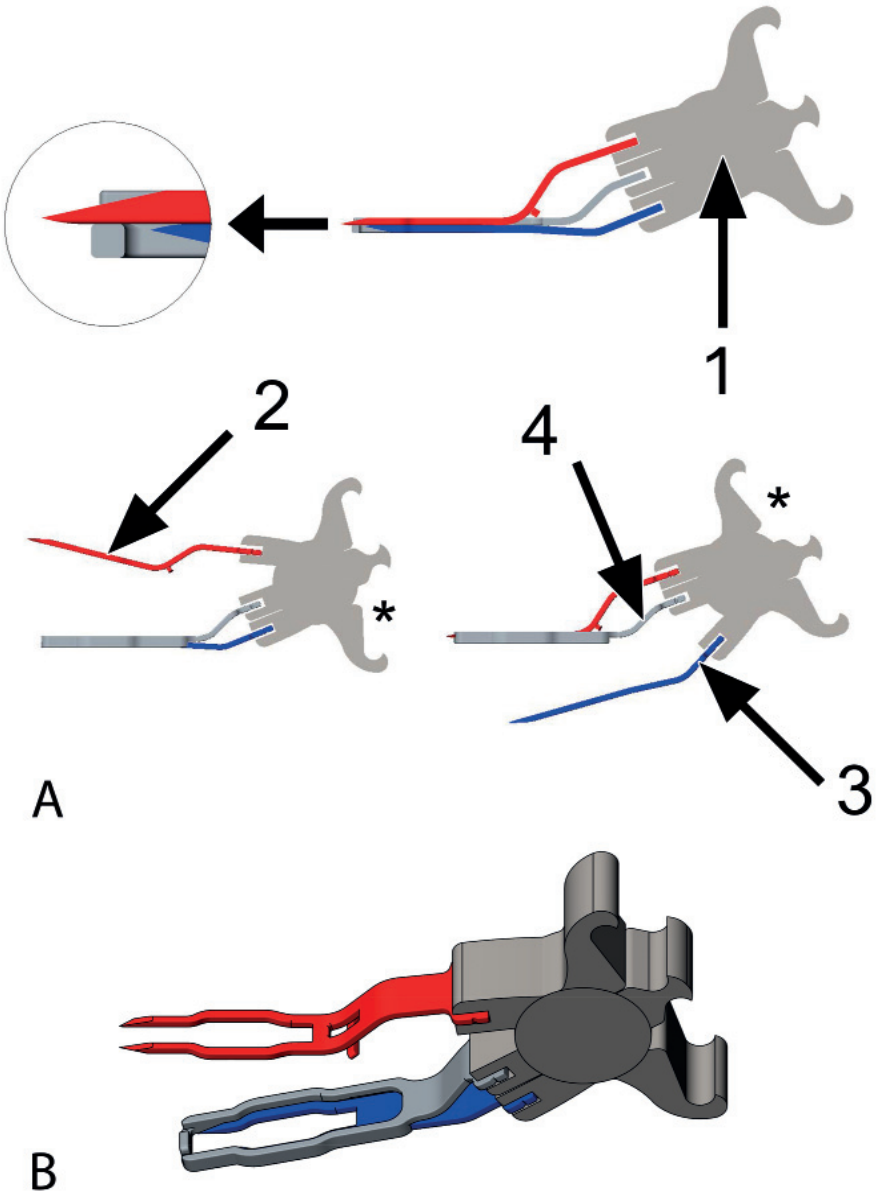


Figure 1. The Trinity Clip

A: Animated images of the coronary anastomotic connector, a side view. The connector is constructed of titanium and is suitable for target coronary arteries with an inner diameter (ID) between 1.4 and 1.6 mm.

The connector consists of:

1: A spring, which enables the 2 forks to open and close, individually one by one (lower left and right panel), by placing an applicator into 1 of the shafts of the spring (see asterisks, applicator not shown). Additionally, it provides active compression of the 2 forks.

2 and 3: Two forks with each 2 sharp pins, attached to the spring (1); the upper fork (2, red) will be inserted into the graft, the lower fork (3, blue) will be inserted into the coronary artery.

4: An extravascular band (2 times the thickness of the pins; illustrated transparently in the upper panel), adjacent to the forks over their full length, hereby obtaining extra lateral compression. It is attached to the spring, in between the anchor-points of the forks. While opening the lower fork (3, blue; lower right), the upper fork (2, red) maintains compression (of the graft) onto the band (4). The magnified subsection (top left) demonstrates the position of the tip of the longer upper fork (2, red) in an indentation at the front of the extravascular band (4).

B: Animated image of the connector, a diagonal top view. The upper fork is opened (applicator not shown).

PROTOCOL TEXT

The animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council (revised 1996). The animal experimentation committee of the Utrecht University approved the protocol.

1. The Coronary Anastomosis Procedure

CAUTION: Always use laser protection glasses when the laser is active.

1.1 Mounting of the Trinity Clip

1.1.1 Open the upper fork of the connector[3] (Figure 1) with the Aneurysm clip applier (Figure 4A) and insert into the lumen of the perfused graft, directed distally (Figure 5A). Make sure the full length of the fork is positioned intraluminally. Subsequently, release the applicator.

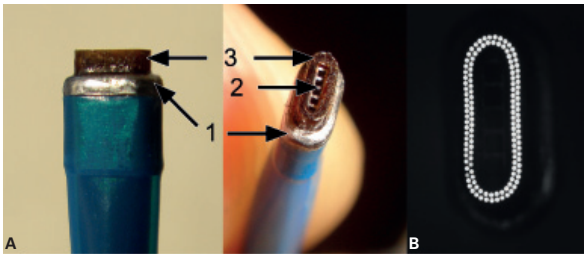


Figure 2. The oval laser catheter

The oval laser catheter is used for the laser-punched arteriotomy into the graft and the coronary artery. Please note that the laser catheter does not weld or seal the anastomosis.

A: The outer band (1; widest part) facilitates positioning and stabilization into the anastomotic connector and provides safety (ie, it prevents the laser catheter of slipping through the connector and damaging the inferior wall of the coronary artery). The vacuum channel (2) is located centrally and is surrounded by laser fibers (3).

B: A top view at the tip of the laser catheter. A row of 2 laser fibers is visualized.

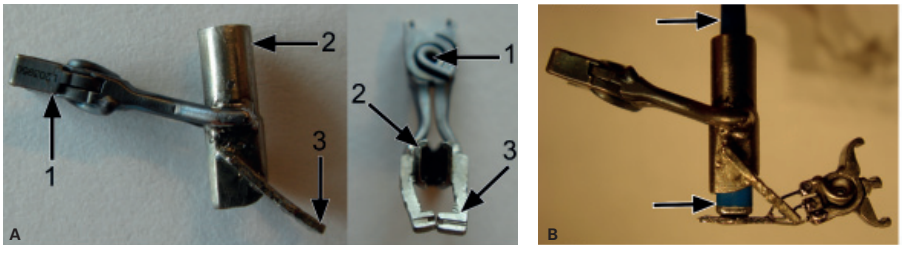
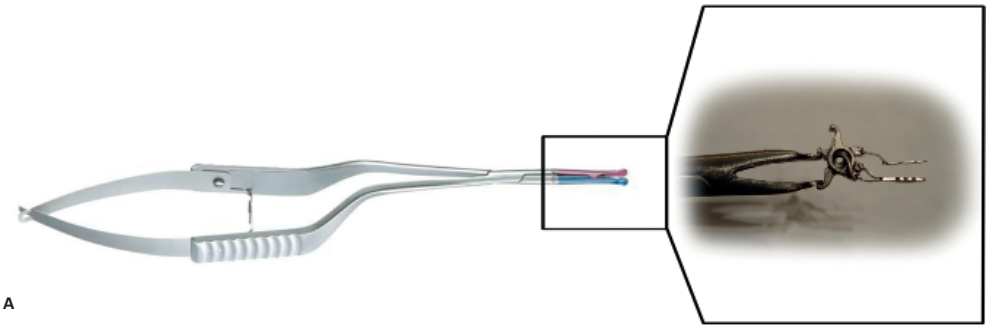


Figure 3. The fixation clip

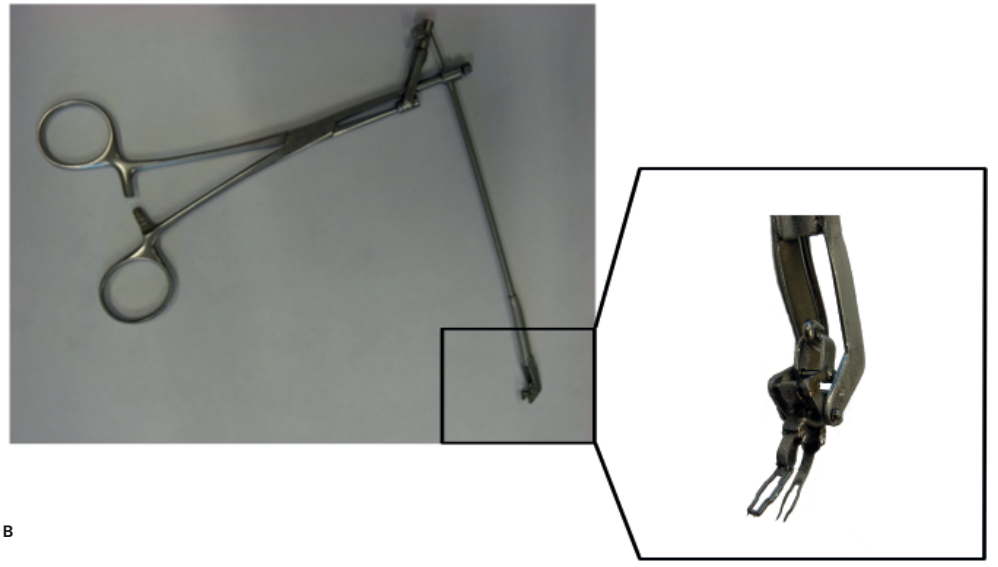
An external, temporary fixation clip is used to fixate and stabilize the laser catheter into the mounted anastomotic connector, ensuring proper perpendicular positioning of the catheter during the anastomosis construction.

A: A side view (left) and an inferior view (right). The spring (1) provides force onto both the shell (2), which holds the catheter, and the bars (3), which catch the connector.

B: The arrows point at the catheter, which is perpendicularly fixated by the fixation clip and forms a stabilized complex with the connector and the graft (not shown).



A



B

Figure 4. The applicators

A: A standard Aneurysm clip applier controls the upper fork via the lower application shaft of the spring (see the subsection) and, in addition, the fixation clip.

B: A prototype VasCo applicator controls the lower fork via the upper application shaft of the spring (see the subsection).

1.1.2 Occlude the mammary artery proximally with an atraumatic bulldog clip and carefully rinse the graft's lumen with a heparin-saline solution. Subsequently, introduce the laser catheter[4] (Figure 2) intravascularly, through the distal free end of the graft, into the connector, and fixate it by the external fixation clip (Figure 3).

1.1.3 Initiate vacuum suction through the catheter onto the graft (to apply vacuum through the catheter, connect a vacuum tube to the catheter and to a vacuum pump), activate the laser and laser-punch the graft a vue, resulting in an anastomotic orifice of 0.8 by 2.0 mm. Release the vacuum suction directly after lasering. Visually check if the arterial wall is fully excised.

1.1.4 Remove the laser-punched fragment of the graft (ie, "flap"), which is attached to the vacuum channel of the catheter, and leave the catheter fixated in the graft and the connector (Figure 5B).

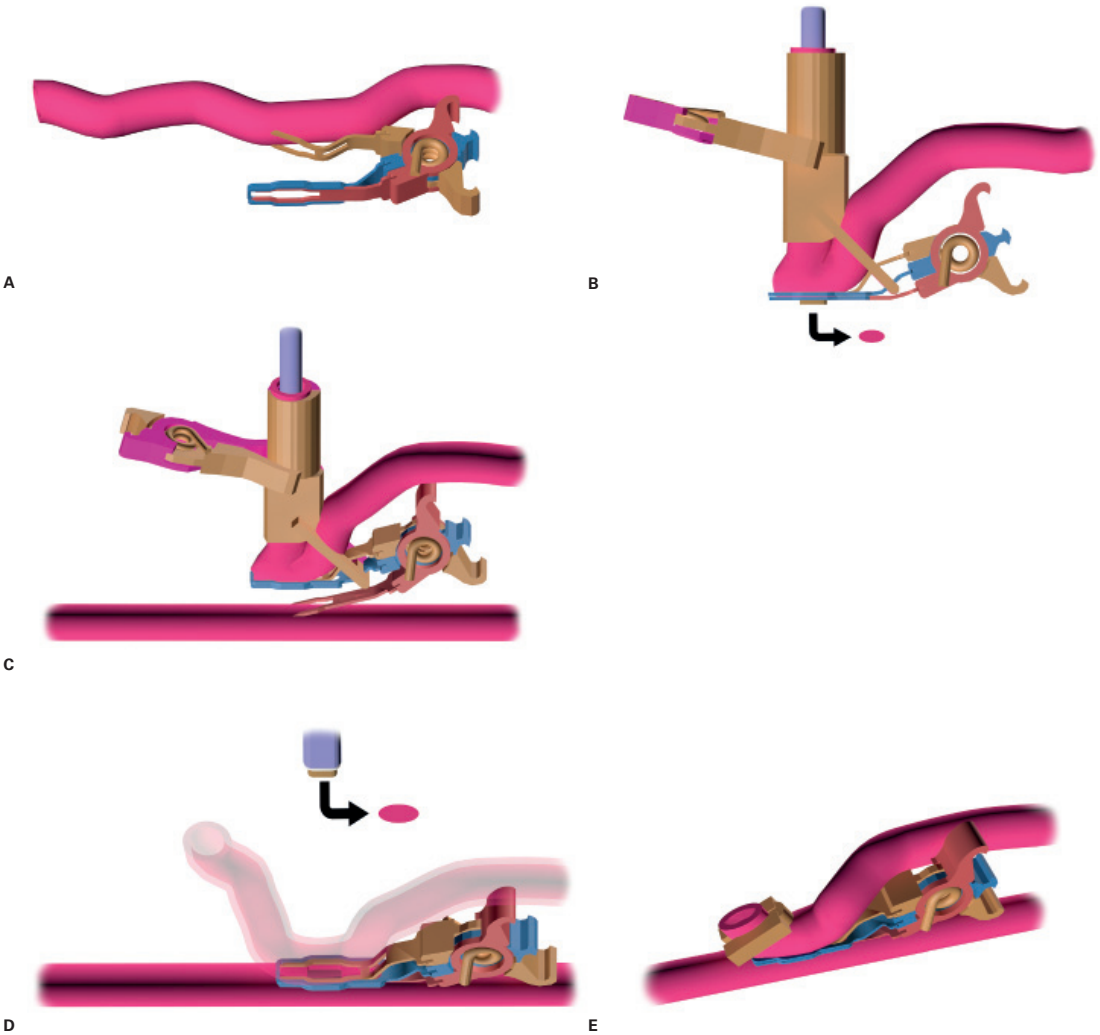


Figure 5. The coronary anastomosis procedure with the Trinity Clip System

A: Mounting of the coronary anastomotic connector: an applier (not shown) is used to insert the upper fork of the connector into the lumen of the perfused graft, directed distally.

Note: by releasing the applicator, the connector closes and actively compresses the graft between the 2 forks and the extravascular band.

B: The mounted and laser-punched graft: the connector actively compresses the graft between the 2 forks and the extravascular band. The laser catheter is introduced intravascularly, through the distal free end of the graft, into the connector, and is perpendicularly fixated by the external fixation clip. The graft is laser-punched. The arrow points at the laser-punched fragment of the graft (ie, "flap").

C: Nonocclusive connection of the graft to the coronary: an applier (not shown) is used to insert the lower fork. The fork punctures the coronary wall and is fully inserted into the lumen of the perfused coronary, directed distally. During the insertion, the upper fork maintains compression of the graft onto the extravascular band, ensuring proper fixation of the graft during this maneuver, while the fixation clip ensures proper perpendicular positioning of the laser catheter.

D: Laser-punched arteriotomy of the coronary artery: the connector is closed and compresses both vessel walls (ie, graft and coronary artery) between the 2 intraluminal forks and the extravascular band. The coronary wall is laser-punched by the fixated catheter, perpendicularly positioned onto the coronary artery wall. Subsequently, the fixation clip is removed and the catheter retracted, including the retrieved flap (see arrow).

E: Final anastomosis. A ligating hemoclip is placed at the distal end of the graft.

Note: The complete connector stays in situ and is not removed after anastomosis construction.

1.2 Nonocclusive Connection of Graft to Recipient

1.2.1 Open the lower fork of the connector with the VasCo applicator (Figure 4B) and insert into the lumen of the perfused coronary artery, directed distally (Figure 5C). Make sure the full length of the fork is positioned intraluminally. Subsequently, release the applicator.

1.3 Laser-punched Arteriotomy

1.3.1 Initiate vacuum suction onto the coronary wall and subsequently laser-punch the coronary wall under full native coronary flow, resulting in an orifice of 0.8 by 2.0 mm. Do not apply force onto the catheter during the construction.

1.3.2 Remove the fixation clip with the Aneurysm clip applier and subsequently retract the catheter. Check if the laser-punched flap is attached to the vacuum channel of the catheter and cease the vacuum suction (Figure 5D).

1.3.3 Following the flap retrieval, occlude the distal end of the graft by a temporary clip (eg, bulldog clip). If a functional bypass is confirmed (ie, successful flap retrieval and adequate bypass flow), permanently ligate the distal end of the graft using a hemoclip (Figure 5E).

1.3.4 In case of a flap retrieval failure (ie, an incompletely lasered flap is still partly attached to the coronary wall), retract the connector, close the partially lasered coronary artery with sutures (8-0 prolene), and create a new anastomosis, starting at step 1.1.2.

2. Animals, Anaesthesia, and Euthanasia

2.1 Animals and Anaesthesia

2.1.1 Use female (eg, Dutch Landrace) pigs (70-90 kilogram [kg]) and feed a normal diet.

2.1.2 Administer 320 milligram (mg) of acetylsalicylic acid and 75 mg clopidogrel orally daily, starting 3 days before surgery. Continue this anticoagulation protocol until termination.

2.1.3 Administer fentanyl 25 microgram (mcg) transdermally for 3 days: 25 mcg 24 hours preoperatively and 25 mcg at day 1 postoperatively for post-surgical analgesia.

2.1.4 For anaesthesia induction administer ketamine (10 mg/kg), midazolam (0.5 mg/kg), and atropine (0.04 mg/kg) intramuscularly.

2.1.5 Subsequently, administer thiopental sodium (4 mg/kg), midazolam (0.5 mg/kg), sufentanil citrate (6 mcg/kg), and 1000/100 mg amoxicillin-clavulanic acid (antibiotic prophylaxis) through an intravenous line.

2.1.6 Intubate and ventilate with a mixture of oxygen and air (1:1 volume/volume).

2.1.7 Use an eye salve and subsequently close the eyes to prevent dehydration of the eyes.

2.1.8 Then administer as a continuous intravenous infusion midazolam (0.7 mg/kg/h), sufentanil citrate (6 mcg/kg/h), pancuronium bromide (0.1 mg/kg/h), and saline solution (300 mL/h). Start with 300 mg amiodaron in 500 mL hydroxyethyl starch solution through the intravenous line.

2.1.9 Insert an arterial line in the femoral artery for intra-arterial blood pressure monitoring and arterial blood samples.

Note: No surgery will be started before this pressure line is functional. One can detect pain, in case the animal is not sufficiently anaesthetized, by an increase of heart rate and blood pressure. If an increase of heart rate and blood pressure is detected, increase the administration of midazolam and sufentanil citrate.

2.1.10 Administer metoprolol intravenously (range, 5-20 mg) to reduce the mechanical irritability of the heart until a heart rate of approximately 50-70 beats/min is obtained.

2.1.11 Catheterize the bladder via the urethra during the procedure.

2.2 Recovery

2.2.1 Stop the anesthesia if the drains are removed.

2.2.2 If the animal is alert and regained sufficient consciousness to breath adequately after extubation, return the animal to the stable (ie, dormitory). Do not leave the animal unattended before this point.

2.2.3 Place a 0.5 liter (L) oxygen mask in front of the snout.

2.2.4 Do not return an animal that has undergone a surgical treatment to the company of other animals until fully recovered.

2.2.5 Postoperatively, administer synolux (amoxicillin-clavulanic acid; 250 mg/20 kg) orally twice a day at day 1 as an antibiotic prophylaxis, and meloxicam (0.4 mg/kg) intramuscularly daily at day 1 and 2 for post-surgical analgesia.

2.3 Euthanasia

2.3.1 Fully heparinize by 25,000 I.U. of heparin (obtain an activated clotting time [ACT] of at least 4 times the control value) to prevent post-mortem coagulation.

2.3.2 Euthanize the animals with pentobarbital sodium (200 mg/kg) intravenously.

3. Surgery

Note: A standard operating room is required for the procedure, containing all standard material and equipment (at least a blood pressure monitor, an electrocardiography device, and a pulse oximeter). A standard thoracotomy set, an internal thoracic artery (ITA) retractor, a microsurgical set and the experiment-specific instruments must be prepared and sterilized. The use of a surgical loop and a surgical headlight is recommended.

3.1 Open the thorax through a sternotomy. Bluntly dissect (with your finger) the pericardium of the sternum. Then saw or split (with a hammer and graver) the sternum from the xyphoid process up to the manubrium. Use bonewax to prevent leakage from the sternal marrow.

3.2 Harvest the left (or right) ITA from the second rib up to the diaphragm, partially heparinize (ACT at least 2.5 times the control value), and clip and dissect the ITA at the distal site.

3.3 Immobilize and present the target coronary artery by a tissue stabilizer at the intended site (outer diameter [OD] 1.6-1.9 mm, measured with a caliper; or, ID 1.4-1.6 mm, measured with epicardial ultrasound [ECUS]). Dissect the target coronary, remove the loose peri-adventitial tissue, and cover the target coronary with a papaverine-soaked gauze.

3.4 Prepare the permanent ligation of the native coronary artery ± 2.0-3.0 cm proximally to the anastomosis (see section 3.7) by extensive lateral dissection of the coronary artery, in such a way a hemoclip can completely ligate the coronary artery.

3.5 Dissect the target area of the ITA, ± 2.0-3.0 cm proximally to the distal free end, remove the peri-adventitial tissue, and measure the caliber (OD 2.0-4.0 mm).

3.6 Construct the anastomosis with the Trinity Clip as previously described, or alternatively, construct a hand-sutured anastomosis and use a shunt to minimize myocardial ischemia.

3.7 Ligate the coronary artery proximally with 3 medium hemoclips. Make sure no side branches are occluded and the ligation is 100% occlusive, preventing competitive flow.

Note: Adjust and set the graft flow by placing temporary atraumatic ligation clips at the coronary artery, while maintaining a representative mean arterial blood pressure and physiological position of the heart; to create a low-flow bypass, ligate the coronary sufficiently distally, and to allow more graft flow, ligate the coronary relatively more proximal.[10]

3.8 Cover the anastomosis with a pericardial patch to prevent uncontrolled traction onto the anastomosis, after closing the thorax.

3.9 Place a mediastinal and/or a pleural drain and connect to a suction system.

3.10 Close the chest.

3.11 Once the drains stop producing, remove the drains.

4. Intraoperative Examination

4.1 General Intraoperative Data

4.1.1 Record the target dimensions of the ITA and coronary artery with a caliper (OD) or ECUS (ID; see section 3.3), the anastomotic construction time (minutes or seconds), any anastomotic leakage (categorize: eg, direct hemostasis, oozing, or brisk leakage[5,6]), and note if extra stitches are needed to obtain hemostasis.

4.2 Transit Time Flow Measurement (TTFM)

4.2.1 Record the mean flow, flow curves, diastolic filling percentage, and the pulsatility index (PI), combined with the mean arterial pressure.

Note: Modern TTFM consoles calculate these variables automatically.

4.2.2 Place the transit time flow probe on a skeletonized segment of the distal graft with aqueous gel to improve probe contact. Use different probe sizes to avoid distortion or compression of the graft.

4.2.3 Measure by an adequate systemic blood pressure, before and after releasing the tissue stabilizer, with the heart in its physiological position, and again before chest closure.

4.2.4 Calculate the PI by (max flow-min flow) / mean flow. The PI is an indicator of the quality of the anastomosis.[11,12]

4.3 Optional: Peak Hyperemic Flow Response

4.3.1 At a mean arterial pressure of 90 mm Hg, clamp the graft for 30 seconds and subsequently measure the peak hyperemic flow response, ± 30 minutes after release of the tissue stabilizer.[6]

4.3.2 Calculate the coronary peak hyperemic flow response (ie, anastomotic flow reserve) by the mean peak graft flow divided by the mean baseline flow at 90 mm Hg.

4.3.3 Duplicate the measurement after 10 minutes.

4.4 Optional: Epicardial Ultrasound

4.4.1 Place the ECUS probe onto the anastomosis with aqueous gel to improve probe contact. Acquire a transverse and longitudinal image of the ITA-LAD anastomosis with the heart stabilized by the tissue stabilizer.

4.4.2 Record the width, length, and height of the anastomosis with the ECUS system and assess the quality of the geometry of the anastomosis and the coronary outflow tract.[13] If narrowed (eg, by back- or sidewall capture), revise the anastomosis.

Note: Metal (eg, a hemoclip or an anastomotic connector) influences the imaging quality.

4.5 Optional: Intraoperative Coronary Angiography

4.5.1 Visualize the bypass by a standard coronary angiography. Introduce a catheter through the iliac artery. Grade the patency according to the FitzGibbon criteria.

5. Follow-up Examination

5.1 Coronary Angiography

5.1.1 Visualize the bypass by a standard coronary angiography and grade the patency according to the FitzGibbon criteria.

5.2 Optional: Transit Time Flow Measurement

5.2.1 Make a subaxillary incision in the dorsal-ventrally line, following the rib curvature. If needed, partially remove the second or third rib, and dissect the proximal ITA.

5.2.2 Measure and record the graft flow by transit time flow measurement (see section 4.2).

5.3 Optional: Fractional Flow Reserve and Coronary Flow Reserve

5.3.1 Administer intracoronary nitroglycerin (200 mcg) to prevent spasms. Measure simultaneously the intracoronary pressure and flow velocity. Record the pressure and flow, combined with aortic pressure and ECG signals.

5.3.2 Calculate the fractional flow reserve (FFR) from (3 consecutive) measurements directly distal (coronary) and proximal (LITA) to the anastomosis, and in the circumflex coronary artery (Cx; control coronary artery). Perform the measurements at baseline and during maximal hyperemia, induced by a bolus of intracoronary adenosine (60 mcg).

5.3.3 Calculate the coronary flow reserve (CFR) as the ratio of maximal hyperemic flow velocity by the flow velocity at baseline.[14]

5.4 Optional: Optical Coherence Tomography

5.4.1 Use a frequency domain optical coherence tomography (OCT) system for imaging the bypass with an automated pullback-speed of 20 mm/s and a continuous flush of contrast by manual injection.

5.4.2 Record intimal hyperplasia and the dimension of the bypass (ie, the reference lumen area of the coronary and ITA 1.0 cm down- and upstream to the anastomosis, respectively, and the anastomotic orifice).[7,15]

6. Postmortem Examinations

6.1 Explantation, Fixation, and Macroscopic Inspection

6.1.1 To minimize the risk of damaging the bypass, explant the heart en bloc, including the sternum and ribs, and mark the very proximal part of the ITA for formalin infusion.

Note: A few days after an open thorax procedure, the heart is completely attached to the sternum by connective tissue adhesions. Performing a sternotomy may damage the bypass, and, therefore, is not recommended.

6.1.2 Perform a perfused-fixation to fix the bypass in its physiological shape, allowing for subsequent proper histological interpretation. Infuse the ITA with formalin (4%) in a flow cabinet at ± 90 mm Hg:

6.1.3 Place a bottle with formalin (1 L) ± 1 meter higher than the heart.

6.1.4 Connect a tube (eg, a silicon tube of a standard infusion system or similar) between the bottle and the proximal ITA.

6.1.5 Infuse the formalin into the heart, via the ITA and the anastomosis, for about 60 minutes or until all formalin is completely infused.

6.1.6 Then, carefully excise the bypass with a blade, scissors, and forceps. Leave some fibrin/scar tissue, myocardium, proximal ITA and coronary, and distal coronary, attached to the anastomosis.

6.1.7 Fixate the anastomosis, a reference part of the ITA (± 1 cm upstream of the anastomosis), and a reference part of the LAD (± 1 cm downstream of the anastomosis), overnight in 4% formalin.

6.1.8 Open the coronary artery longitudinally at the inferior wall and inspect the anastomosis using 10 or 20 times magnification. Record the width and length of the anastomotic orifice by perpendicularly photographing the orifice with a ruler next to it. Subsequently, measure the width and length of the anastomosis digitally.

6.2 Histological Analysis

6.2.1 Embed the anastomosis and the reference parts in plastic (methyl methacrylate).

6.2.2 Section in transverse (or longitudinal) planes with a diamond saw, starting at 5 mm downstream, continuing up to 5 mm upstream of the anastomosis, and stain with hematoxylin and eosin.

6.2.3 Record and assess the vessel wall apposition, anastomotic area, thrombus formation, intimal hyperplasia, blood-exposed nonintimal surface[16] (BENIS; intraluminal exposure of the connector surface and the laser edge [ie, medial and adventitial surface of both the graft and the coronary artery]), acute and chronic inflammatory cell reaction (polymorphonuclear cells, macrophages, and foreign body giant cells), and tissue damage.[6]

6.2.4 Perform measurements using a software package.

6.3 Optional: Scanning Electron Microscopy

6.3.1 Fixate the anastomosis, after the perfused-fixation described above (see section 6.1.2), in 2% glutaraldehyde solution buffered in 0.1 M purified phosphate buffer.

6.3.2 Put the anastomosis 1 hour in 1% buffered osmium tetroxide to complete the fixation.

6.3.3 After fixation, dehydrate the anastomosis in a graded series (50, 70, 90, and 100%) of ethanol and in liquid CO_2 by using the critical point method.

6.3.4 Subsequently, open the backwall of the coronary and the upper wall of the ITA at the anastomotic site with a sharp surgical blade.

6.3.5 Fixate the specimen on scan tubs and cover with a thin layer of platinum by sputter processing to enhance the image quality.

6.3.6 Then evaluate the intravascular anastomotic surface (ie, assessment of endothelial and/or thrombocyte coverage) using a scanning electron microscope.[6]

REPRESENTATIVE RESULTS

We performed a pilot study prior to the evaluation of the new Trinity Clip in a large long-term preclinical safety study to assess the feasibility. In this pilot study, 3 LITA-to-LAD anastomoses (n=1 per animal) were constructed with the connector in the porcine OPCAB model by 1 investigator (D.S.). A 5-hour follow-up was scheduled.

The coronary anastomotic connector enabled completely nonocclusive, sutureless, and fast anastomotic construction (mean 3.4 ± 0.4 minutes). In all anastomoses complete hemostasis was demonstrated with a 100% flap retrieval rate. The operative data, listed in Table 1, show the feasibility of the coronary anastomotic connector in the porcine OPCAB model. Normal appealing flow curves with minimal systolic peaks, a PI below 5, and a predominant diastolic graft filling (diastolic filling [DF] 80%) were consistently measured during the follow-up, as seen in Figure 6, which is suggestive for a patent coronary graft. The mean peak hyperemic flow response, following 30-second graft occlusion, was 5.6 ± 0.5, indicating an adequate coronary flow reserve. At 5-hour follow-up, macroscopic inspection demonstrated patent anastomoses without intraluminal thrombus formation as can be seen in Figure 8A. Figure 7 demonstrates an example of an angiogram at 5 weeks follow-up, and an example of the post-mortem macroscopic and histologic inspection is showed in Figures 8B and C, both clearly demonstrating a remodeled and fully patent anastomosis at 5 weeks follow-up (initial results of the preclinical study). Moreover, examples of OCT and SEM images of a previous study with a predecessor ELANA coronary anastomotic connector[6,7] demonstrate a patent anastomosis without narrowing intima hyperplasia formation, and complete coverage with endothelium, respectively, at 6 months follow-up (Figure 9).

Table 1. Operative Data of the Pilot Study

Anastomoses (n)	3
LITA (mm, OD)	3.2 ± 0.2
LAD (mm, OD)	1.8 ± 0.0
Construction time (min)	3.4 ± 0.4 *
Flap retrieval rate (%)	100 (3/3)
Complete hemostasis (%)	100 (3/3)
Extra stitch	0
Graft baseline flow (mL/min)	20 ± 3
Graft flow at t=5 hrs (mL/min)	18 ± 5
Peak hyperemic flow response (peak/baseline flow)	5.6 ± 0.5

Data presented as mean ± standard deviation or % (n).

*Included: mounting of the connector, connection of graft to coronary, the laser-punched arteriotomy, and ligation of the distal graft.

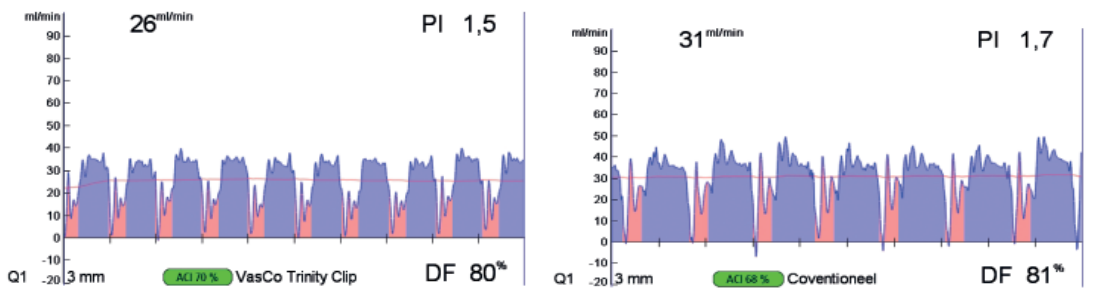
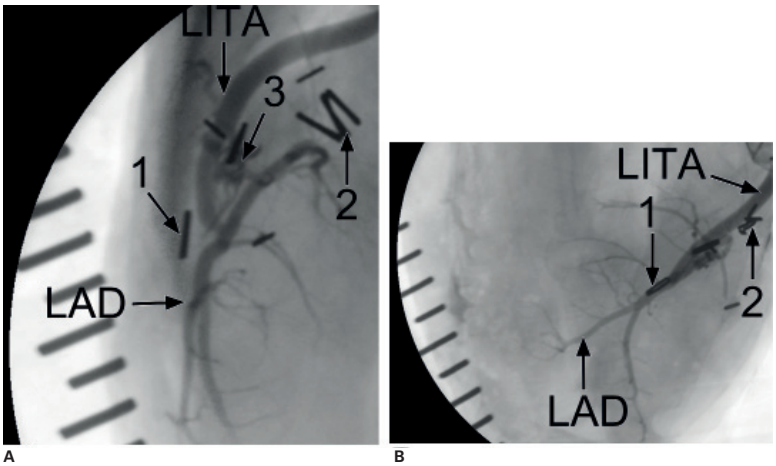


Figure 6. Intraoperative transit time flow measurements of the Trinity Clip facilitated left internal thoracic artery (LITA)-to-left anterior descending artery (LAD) anastomosis and a conventional hand-sutured LITA-to LAD anastomosis

Both the facilitated (**A**) and the hand-sutured (**B**) LITA-to-LAD bypass show a normal appealing flow curve, a PI below 5, and a predominant diastolic graft filling (diastolic filling [DF] 80%) with minimal systolic peaks, suggestive for a patent coronary graft.

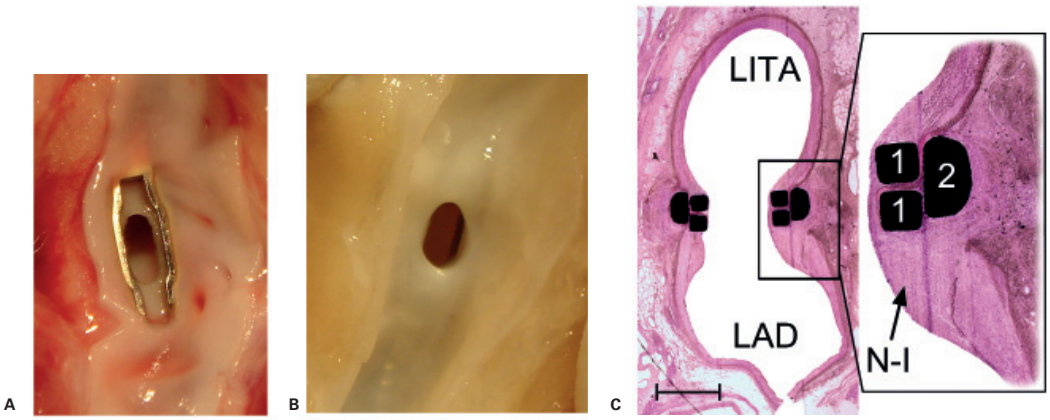


A B

Figure 7. Five-week coronary angiogram of the Trinity Clip facilitated left internal thoracic artery (LITA)-to-left anterior descending artery (LAD) anastomosis (an example of the preclinical study)

A: A lateral-side view. Ligating hemoclips are placed at the distal end of the LITA (1) and proximal native LAD (2). The connector (3) can be only seen at the side view. Note, coverage of the forks and extravascular band of the connector by non-radiopaque matter is seen. The distal end of the LITA is not filled with contrast, suggesting remodeling by streamlining neointima.

B: A top view.



A B C

Figure 8. Healing and remodeling of the Trinity Clip facilitated left internal thoracic artery (LITA)-to-left anterior descending artery (LAD) anastomosis: macroscopic and histological view

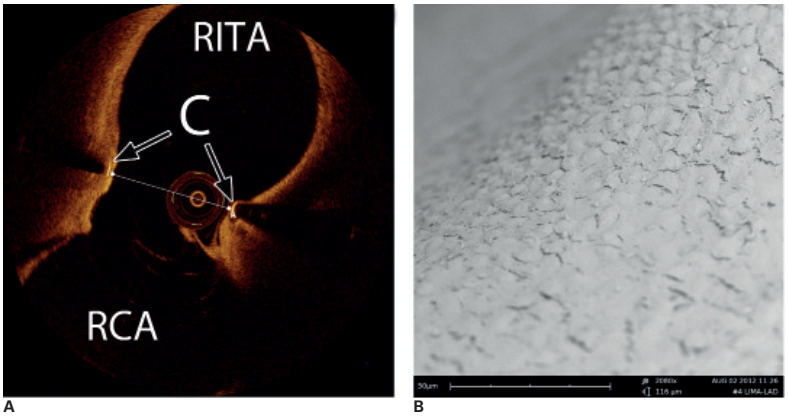
A: Macroscopic view from inside the LAD at 5 hours follow-up. A patent anastomosis without any intraluminal thrombus formation is demonstrated. Both forks of the connector are positioned intraluminally, without capturing or damaging the lateral or inferior coronary wall. A small and sharp laser-cut edge (0.1 mm), of both the LITA and the LAD, is visible in between the forks, and both vessel walls are positioned exactly on top of each other, without overlapping adventitial tissue.

B: Macroscopic view from inside the LAD at 5 weeks follow-up (an example of the preclinical study). A patent anastomosis is demonstrated and the intraluminal forks and the laser edge are completely covered by a tissue layer, without narrowing the anastomotic orifice.

C: Histologic transversal section, mid-anastomosis, at 5 weeks follow-up (12.5x magnified; an example of the preclinical study). Streamlining coverage of the (initially intraluminally exposed) forks (1) of the connector by neo-intima (N-I) is visible. The magnified subsection (40x magnification) demonstrates the retracted and remodeled laser edge. Between the forks and the extravascular band, compression of the arterial wall was seen without adverse remodeling (eg, erosion, luxation, or pseudoaneurysm formation). Moreover, the inferior wall was unaffected, without any intimal hyperplasia reactions (which could be suggestive for [laser-] damage), and no excessive inflammatory cell reactions were found (which could potentially be triggered by the foreign body implant). The distal end of the LITA, the 'cul de sac', was filled with organized thrombus, covered by neointimal tissue, streamlining the anastomosis. Finally, the spring of the connector was fully integrated, extravascularly, between the LITA and LAD, without erosion effects or damage to the adjacent arterial walls.

Note: interruption of the inferior coronary wall is caused by longitudinally opening of the coronary artery before inspection.

A scale bar (1 mm) is provided in the left lower corner.



A B

Figure 9. Examples of an intracoronary Optical Coherence Tomography (OCT) image of a right internal thoracic artery (RITA)-to-right coronary artery (RCA) anastomosis and a Scanning Electron Microscope (SEM) image of a left internal thoracic artery (LITA)-to-LAD anastomosis. Both were constructed with a predecessor ELANA coronary connector.[6,7]

A: An OCT image at 6 months follow-up, transverse section, mid-anastomosis.[7] Note: the OCT wire is visible in the lumen. The transversal line represents the minimal anastomotic width (=2.2 mm). C=connector; RITA=right internal thoracic artery; RCA=right coronary artery.

B: A detailed image at the level of the fork of the connector demonstrating complete coverage with endothelium (2080x magnification), at 6 month follow-up.[6,7]

DISCUSSION

This paper describes a novel coronary anastomotic connector, the Trinity Clip, and how to evaluate such a new device in a porcine off-pump bypass model. Different techniques are proposed to assess the quality of an anastomosis, facilitated by the new connector or conventionally constructed: intraoperative, postoperative, and post-mortem techniques. Assessment of the quality and safety of the facilitated anastomosis – as well as the healing and remodeling process – at the short- and long-term is of utmost importance prior to future clinical application of the coronary anastomotic connector.

Currently, only 1 coronary anastomotic connector is being used clinically,[17,18] multiple other devices demonstrated unfavorable experimental or clinical results, or developers failed to market the product.[19-21] Compared to other methods to facilitate the coronary anastomosis, the Trinity Clip includes several interesting features. First, owing to the nonocclusive connection of the vessel walls, coronary conditioning (ie, snaring or shunting) is redundant, enabling anastomotic construction in a bloodless field without a time constraint, and hence, reducing manipulation of the coronary artery. Second, the construction is relatively simple and straightforward, neither a separate incision into the coronary artery nor placing additional stitches to obtain hemostasis are necessary. Third, the connector is a low-profile device, without a bulky device-deployment system; thus, it will not hamper the bypass construction on difficult to reach or remote areas of the heart, and, so, it will potentially extend the possibilities for revascularization via minimally invasive approaches.

Important questions regarding the biological behavior of the facilitated anastomosis are yet unanswered. What are the effects of laser-punching the arteriotomy into both the ITA and the LAD? Could the blood-exposed non-intimal surface (ie, the material of the forks and the medial and adventitial laser rim), in relation to the small dimension target coronary, be a potential limitation by excessive intimal hyperplasia formation on the long-term? To answer these questions, a preclinical study, using the porcine model as described in this paper, will assess the long-term patency and, additionally, the healing and remodeling effects regarding intimal hyperplasia formation with subsequent potential narrowing of the anastomosis. Moreover, in this preclinical study, the patency, healing, and remodeling of the facilitated anastomosis will be compared to the control, conventionally hand-sutured, anastomosis. The porcine model is suitable for these research questions because of its to human resembling physiology and anatomy of the heart and coronary arteries,

and its expedite healing response (eg, intimal hyperplasia formation), in which a 6 months follow-up duration in the porcine model is comparable to 1.5-3 years of follow-up of the stented human coronary artery.[22] However, the arteries of the young and healthy pig are not diseased and compliant, and thus different to the human diseased vessels encountered in cardio-thoracic surgical practice. Therefore, prior to clinical introduction, the feasibility and safety of the connector will be also evaluated in a human atherosclerotic cadaveric model. Furthermore, a tendency to hypercoagulability is found in pigs.[23] Therefore, to assess facilitated anastomoses on small caliber coronaries, the porcine model is quite challenging. To this point, the in this protocol described antiplatelet therapy (75 mg clopidogrel and 320 mg acetylsalicylic acid) is justified. In addition, the antiplatelet and its expedite healing response (eg, intimal hyperplasia formation), in which a 6 months follow-up duration in the porcine model is comparable to 1.5-3 years of follow-up of the stented human coronary artery.[22] However, the arteries of the young and healthy pig are not diseased and compliant, and thus different to the human diseased vessels encountered in cardio-thoracic surgical practice. Therefore, prior to clinical introduction, the feasibility and safety of the connector will be also evaluated in a human atherosclerotic cadaveric model. Furthermore, a tendency to hypercoagulability is found in pigs[23]. Therefore, to assess facilitated anastomoses on small caliber coronaries, the porcine model is quite challenging. To this point, the in this protocol described antiplatelet therapy (75 mg clopidogrel and 320 mg acetylsalicylic acid) is justified. In addition, the antiplatelet regimen is in anticipation of the blood-exposed nonintimal surface of the anastomosis (BENIS). In our previous study, we showed that the anastomotic nonintimal surface of a predecessor coronary connector completely endothelialized after 10 days.[6,7] The role for antiplatelet therapy in clinics, using this connector, should be based on the rate of endothelialization. Once the nonintimal surface is endothelialized, the antiplatelet regimen might be lowered.

The excimer laser is a contact laser and will only successfully laser-punch the vessel wall in the case there is full direct circumferential laser-tissue contact. The most critical step in the anastomosis construction, therefore, is the correct position of the laser catheter onto the vessel wall of the graft and the coronary artery. This step has to be trained on ex vivo cadaver models (eg, pig heart) to minimize the learning curve. Possible scenarios that will result in a flap retrieval failure of the laser, and which should be taken into mind, are described here: 1) The coronary anastomotic connector is designed to connect the graft to the coronary artery, and secondly, to serve as a laser platform. The connector presents the vessel walls (ie, a straight tissue surface, without bumps) and allows a perpendicular position of the catheter onto the vessel wall. If the connector is mal-positioned (eg, incomplete insertion, back- or sidewall capture, intramural or –adventitial positioning), the vessel wall presentation is suboptimal (ie, no straight surface). Hence, in the case of a mal-position, one should always reposition the connector before to the point of no return (ie, the arteriotomy). 2) The fixation clip is designed to keep the laser catheter perpendicular into the connector during the construction. However, the fixation clip is not designed to resist lots of contra-force, so the surgeon has to support the laser catheter during the construction. If not sufficiently supported, the catheter can dislocate. 3) To ensure optimal laser-tissue contact, the coronary wall has to be dissected free of loose peri-adventitial tissue, towards the lateral wall. Be sure that the laser surface only consists of the coronary wall, from its intima up to its adventitia, and no peri-adventitial tissue is captured into the connector.

If unfortunately the anastomotic construction fails, one should retract the clip (by opening of the lower fork only) and then close the coronary lesion (± 2 mm length) with repair sutures (8-0 prolene). Pigs are usually quite sensitive to ischemic stress. Therefore, ischemic preconditioning is recommended before occluding the coronary for repairing the defect. Subsequently, a new anastomosis can be constructed distal to the first target. The graft is still mounted by the upper fork of the connector. So after catheter re-positioning and fixation, the connector can be directly inserted into the coronary artery.

The most important anastomosis evaluation techniques are the coronary angiogram (clinical gold standard) and histology (experimental gold standard, combined with the coronary angiogram). However, intraoperative quality assessment of the anastomosis by transit time flow measurements (TTFM) is extremely informative. TTFM is fast, non-invasive, real-time, and easy, and moreover, correct interpretation can reduce the number

of technical, not visible, errors.[11,12,24-26] The modern TTFM consoles automatically calculate and demonstrate real-time the mean flow, the flow curve, and the pulsatility index (PI), and lots of other parameters. The PI is calculated by (max flow-min flow) / mean flow and is an indicator of the quality of the anastomosis, whereas the mean flow on its own is not a reliable indicator. A low mean flow (<15 ml/min) with a good PI (<5) and a good diastolic flow curve can be found by a perfect anastomosis at a small target coronary with a moderate run-off, whereas a good mean flow (>15 ml/min) with an abnormal diastolic filling pattern and a high PI (>5) is suggestive of an anastomotic imperfection or a graft failure (ie, torsion, compression, or kinking of the graft). In this case, one should consider revising the anastomosis. Thus, a good assessment of the quality of the anastomosis should include the interpretation of the flow curve, the pulsatility index, and the mean flow, combined with the clinical status. However, the reported specificity and sensitivity of TTFM are not uniform, and, therefore, the diagnostic accuracy is under debate. In addition, the cut-off value of the PI is empirically determined on the basis of clinical experience rather than clinical studies. The TTFM console we currently use in the preclinical animal study disposes of epicardial ultrasound imaging. If there is still uncertainty regarding the quality of the anastomosis after the flow measurements, a real-time epicardial ultrasound image can be of great help in further evaluation of the anastomosis, hereby increasing the diagnostic accuracy.[27-31]

An experimental alternative to the TTF measurements is the peak hyperemic flow response,[32] ie, coronary flow reserve, which is the ratio of the peak hyperemic flow, following 30-second graft occlusion, and the base flow. The peak hyperemic flow response should be >4 for a distal anastomosis. If the anastomosis is targeted proximal on the coronary artery, the peak hyperemic flow response can be slightly lower and should be >3.[6] An absent hyperemic flow response is suggestive for a technical anastomotic error or a graft failure. In that case, consult the TTF measurements and clinical status, and consider revising the anastomosis. Please note that the absolute flow reserve varies with the arterial pressure (thus, always measure at the same mean arterial pressure, in duplicate) and that ischemic preconditioning can negatively influence the peak hyperemic flow response. Furthermore, the peak hyperemic flow response is not a validated method and an absolute cut-off value has not been defined. We have empirically selected the cut-off on the basis of our experimental experience.

Finally, the anastomosis technique described in this protocol is an experimental anastomotic technique with the aim and potential to be applied in the clinical minimally invasive setting. Currently, the materials for the application of the technique shown in this paper are not finalized or market-ready products, but rather prototype instruments. There is still a window of amelioration (eg, versatile applier and flexible laser catheter), which will be filled in soon. This new technology has interesting potential and will be evaluated thoroughly in a preclinical study by using this protocol.

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DISCLOSURES

The authors declare that they have no competing financial interests. C.A.F. Tulleken holds shares in AMJ b.v., Utrecht, The Netherlands. D. Stecher, G. Bronkers, J.O.T. Noest, C.A.F. Tulleken, and M.P. Buijsrogge are registered as co-inventors of patents regarding the ELANA technique, without financial benefits.

REFERENCES

1. Halkos, M.E. & Puskas, J.D. Off-pump coronary surgery: where do we stand in 2010? *Curr Opin Cardiol.* 25, 583-588, doi:10.1097/HCO.0b013e32833f04b0 (2010).
2. Lapierre, H., Chan, V., Sohmer, B., Mesana, T.G. & Ruel, M. Minimally invasive coronary artery bypass grafting via a small thoracotomy versus off-pump: a case-matched study. *Eur J Cardiothorac Surg*. 40, 804-810 (2011).
3. Tulleken, C.A.F. et al. Blood vessel connectors and methods for blood vessel connection. Patent application number WO2012NL50747 20121026.
4. Van Thoor, A.C.E., Stecher, D. & Keizer, D.M. Catheter apparatus and method. Patent application number WO2013NL50142 20130305.
5. Stecher, D., de Boer, B, Tulleken, C.A., Pasterkamp, G, van Herwerden, L.A. & Buijsrogge, M.P. A new nonocclusive laser-assisted coronary anastomotic connector in a rabbit model. *J Thorac Cardiovasc Surg.* 145, 1124-1129, doi:10.1016/j.jtcvs.2012.05.061 (2013).
6. Stecher, D. et al. The nonocclusive laser-assisted coronary anastomotic connector in an off-pump porcine bypass model. *J Thorac Cardiovasc Surg.* 147, 1390-1397, doi:10.1016/j.jtcvs.2013.07.018 (2014).
7. Stecher, D., Agostoni, P, Pasterkamp, G, Hoefer, IE, van Herwerden, L.A. & Buijsrogge, M.P. Six-Month Healing of the Nonocclusive Coronary Anastomotic Connector in an Off-Pump Porcine Bypass Model. *Innovations (Phila)*. 9, 130-136, doi:10.1097/imi.0000000000000055 (2014).
8. Tulleken, C.A., Verdaasdonk, R.M., Berendsen, W. & Mali, W.P. Use of the excimer laser in high-flow bypass surgery of the brain. *J Neurosurg*. 78, 477-480, doi:10.3171/jns.1993.78.3.0477 (1993).
9. van Doormaal, T.P., van der Zwan, A., Redegeld, S., Verweij, B.H., Tulleken, C.A. & Regli, L. Patency, flow, and endothelialization of the sutureless Excimer Laser Assisted Non-occlusive Anastomosis (ELANA) technique in a pig model. *J Neurosurg.* 115, 1221-1230, doi:10.3171/2011.6.jns101491 (2011).
10. Buijsrogge, M.P., Grundeman, P.F., Verlaan, C.W. & Borst, C. Unconventional vessel wall apposition in off-pump porcine coronary artery bypass grafting: low versus high graft flow. *J Thorac Cardiovasc Surg.* 123, 341-347 (2002).
11. Walpoth, B.H. et al. Transit-time flow measurement for detection of early graft failure during myocardial revascularization. *Ann Thorac Surg.* 66, 1097-1100 (1998).
12. D'Ancona, G., Karamanoukian, H.L., Salerno, T.A., Schmid, S. & Bergsland, J. Flow measurement in coronary surgery. *Heart Surg Forum.* 2, 121-124 (1999).
13. Lovstakken, L. et al. Blood flow imaging: a new two-dimensional ultrasound modality for enhanced intraoperative visualization of blood flow patterns in coronary anastomoses. *J Am Soc Echocardiogr.* 21, 969-975, doi:10.1016/j.echo.2008.01.019 (2008).
14. Koudstaal, S. et al. Assessment of coronary microvascular resistance in the chronic infarcted pig heart. *J Cell Mol Med.* 17, 1128-1135, doi:10.1111/jcmm.12089 (2013).
15. Agostoni, P. & Stella, P.R. Optical coherence tomography: new (near-infrared) light on stent implantation? *Heart.* 95, 1895-1896, doi:10.1136/hrt.2009.177337 (2009).
16. Scheltes, J.S., van Andel, C.J., Pistecky, P.V. & Borst, C. Coronary anastomotic devices: blood-exposed non-intimal surface and coronary wall stress. *J Thorac Cardiovasc Surg.* 126, 191-199 (2003).
17. Balkhy, H.H., Wann, L.S. & Arnsdorf, S. Early patency evaluation of new distal anastomotic device in internal mammary artery grafts using computed tomography angiography. *Innovations.* 5, 109-113, doi:10.1097/IMI.0b013e3181d714ba (2010).
18. Matschke, K.E. et al. The Cardica C-Port System: clinical and angiographic evaluation of a new device for automated, compliant distal anastomoses in coronary artery bypass grafting surgery--a multicenter prospective clinical trial. *J Thorac Cardiovasc Surg.* 130, 1645-1652, doi:10.1016/j.jtcvs.2005.08.033 (2005).
19. Suyker, W.J., Buijsrogge, M.P., Suyker, P.T., Verlaan, C.W., Borst, C. & Grundeman, P.F. Stapled coronary anastomosis with minimal intraluminal artifact: The S2 Anastomotic System in the off-pump porcine

model. *J Thorac Cardiovasc Surg.* 127, 498-503, doi:10.1016/j.jtcvs.2003.04.006 (2004).
20. Carrel, T., Englberger, L., Keller, D., Windecker, S., Meier, B. & Eckstein, F. Clinical and angiographic results after mechanical connection for distal anastomosis in coronary surgery. *J Thorac Cardiovasc Surg.* 127, 1632-1640, doi:10.1016/j.jtcvs.2003.11.039 (2004).
21. Filsoufi, F. *et al*. Automated distal coronary bypass with a novel magnetic coupler (MVP system). *J Thorac Cardiovasc Surg.* 127, 185-192, doi:10.1016/j.jtcvs.2003.04.005 (2004).
22. Fischell, T.A. & Virmani, R. Intracoronary brachytherapy in the porcine model: a different animal. *Circulation.* 104, 2388-2390 (2001).
23. Kostering, H., Mast, W.P., Kaethner, T., Nebendahl, K. & Holtz, W.H. Blood coagulation studies in domestic pigs (Hanover breed) and minipigs (Goettingen breed). *Lab Anim.* 17, 346-349 (1983).
24. D'Ancona, G., Karamanoukian, H.L., Ricci, M., Schmid, S., Bergsland, J. & Salerno, T.A. Graft revision after transit time flow measurement in off-pump coronary artery bypass grafting. *Eur J Cardiothorac Surg.* 17, 287-293 (2000).
25. Di Giammarco, G., Pano, M., Cirmeni, S., Pelini, P., Vitolla, G. & Di Mauro, M. Predictive value of intraoperative transit-time flow measurement for short-term graft patency in coronary surgery. *J Thorac Cardiovasc Surg.* 132, 468-474, doi:10.1016/j.jtcvs.2006.02.014 (2006).
26. Kieser, T.M., Rose, S., Kowalewski, R. & Belenkie, I. Transit-time flow predicts outcomes in coronary artery bypass graft patients: a series of 1000 consecutive arterial grafts. *Eur J Cardiothorac Surg.* 38, 155-162, doi:10.1016/j.ejcts.2010.01.026 (2010).
27. Haaverstad, R., Vitale, N., Tjomsland, O., Tromsdal, A., Torp, H. & Samstad, S.O. Intraoperative color Doppler ultrasound assessment of LIMA-to-LAD anastomoses in off-pump coronary artery bypass grafting. *Ann Thorac Surg.* 74, S1390-1394 (2002).
28. Klein, P., Meijer, R., Eikelaar, J.H., Grundeman, P.F. & Borst, C. Epicardial ultrasound in off-pump coronary artery bypass grafting: potential aid in intraoperative coronary diagnostics. *Ann Thorac Surg.* 73, 809-812 (2002).
29. Dessing, T.C., Budde, R.P., Meijer, R., Bakker, P.F., Borst, C. & Grundeman, P.F. Geometry assessment of coronary artery anastomoses with construction errors by epicardial ultrasound. *Eur J Cardiothorac Surg.* 26, 257-261, doi:10.1016/j.ejcts.2004.05.011 (2004).
30. Budde, R.P., Meijer, R., Dessing, T.C., Borst, C. & Grundeman, P.F. Detection of construction errors in ex vivo coronary artery anastomoses by 13-MHz epicardial ultrasonography. *J Thorac Cardiovasc Surg.* 129, 1078-1083, doi:10.1016/j.jtcvs.2004.09.002 (2005).
31. Di Giammarco, G. et al. Intraoperative graft verification in coronary surgery: increased diagnostic accuracy adding high-resolution epicardial ultrasonography to transit-time flow measurement. *Eur J Cardiothorac Surg.* doi:10.1093/ejcts/ezt580 (2013).
32. Pijls, N.H.J. Coronaire fysiologie en myocardischemie. In: *Cardiologie*. Volume 2, van der Wall, E.E., van de Werf, F., & Zijlstra, F., Bohn Stafleu van Loghum, 169-170 (2008).

6

A LASER-ASSISTED ANASTOMOTIC TECHNIQUE – FEASIBILITY ON HUMAN DISEASED CORONARY ARTERIES

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ABSTRACT

Objective: Atherosclerotic disease might hamper efficacy of the Excimer laser-assisted Trinity Clip anastomotic connector in coronary arteries. Therefore, its efficacy was evaluated on human diseased coronary arteries (study 1). Additionally, the acute laser effects onto the coronary wall were assessed (study 2).

Methods: Thirty-eight anastomoses were constructed on ex vivo human hearts. Atherosclerosis was histopathologically determined and subsequently related to the success of the technique (ie, connector positioning and laser-punching; study 1). Additionally, 20 anastomoses were constructed in an ex vivo (porcine, n=8) and in vivo (rabbit [n=9] and porcine [n=3]) model. Subsequently, the coronary was histologically studied on the presence of laser-induced damage (study 2).

Results: In 13 of 38 anastomoses (study 1), the connector was mal-positioned; 3 due to a severely diseased coronary wall and 10 due to an inner diameter below the intended target range. The laser-punch success rate on coronary arteries with an early and advanced lesion was 100% (16/16) and 89% (8/9; lesions were located in the inferolateral wall), respectively. In 1 case, an advanced lesion (ie, fibrocalcified plaque) was located in the superolateral wall and caused a laser-punch failure. No histological signs of laser-induced damage were observed, in case of correct use (study 2).

Conclusions: This study demonstrates the feasibility of an anastomotic connector on human diseased coronary arteries and shows that lasering does not induce coronary wall damage. However, careful selection of the coronary, regarding the target inner diameter and disease status, will prevent construction failures. This connector could facilitate less invasive CABG.

INTRODUCTION

A new Excimer laser-assisted nonocclusive anastomosis (ELANA)-based coronary connector is developed, which facilitates sutureless bypass grafting. A predecessor ELANA coronary connector was evaluated in our previous studies[1-4] and demonstrated good long-term healing and remodeling in a porcine off-pump coronary artery bypass (OPCAB) model.[3,4] To target clinically relevant coronary arteries, recent modifications resulted in a downsized, oval-shaped laser and connector - the Trinity Clip - suitable for coronary targets of 1.4–1.6 mm inner diameter (ID).[5]

Application of the connector and opening of the anastomosis by the laser are both potentially affected by an atherosclerotic coronary artery. Therefore, prior to clinical introduction, we assessed the feasibility of the laser-assisted anastomotic technique on human diseased ex vivo coronary arteries in the first part of this study (study 1). Histo-pathological evaluation determined the degree of coronary artery disease at the site of the anastomosis, which was subsequently related to the success rate of the technique (ie, connector positioning and laser-punch success).

Laser-punching the arteriotomy could potentially harm the surrounding or inferolateral wall of the coronary artery, specifically considering the small target vessel size.[6] The effect of exposing a small target vessel to the same levels of laser energy (10 mJ) as used in previous studies on larger caliber coronary arteries,[1-4] is unknown. Hence, in the second part of this study (study 2), we histologically assessed the potential presence of acute laser-induced arterial wall damage on small caliber targets. Initial testing was done in an ex vivo (porcine heart) model, which was subsequently followed by the evaluation in an in vivo rabbit model (carotid and femoral arteries), and finally validated in the porcine OPCAB model.

METHODS

Animals

In study 2, 3 rabbits (female, ±5.5 kg) and 3 pigs (female, ±75 kg) were studied. The animals were fed a normal diet and received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council (revised 1996). The animal experimentation committee of the Utrecht University approved the protocol. All pigs received 320 mg of acetylsalicylic acid and 75 mg clopidogrel orally daily, starting 3 days before surgery. All animals were operated under full anesthesia and terminated conforming previous described protocols.[1,3-5]

The Trinity Clip - Anastomotic Procedure (Figure 2)

The nonocclusive anastomosis construction is accomplished by:

1. Mounting of the connector and laser (Corvasco Medical b.v., Utrecht, The Netherlands; Figure 1) by inserting the upper fork of the connector into the distal end of the graft. Subsequently, the laser is introduced into the connector and laser-punches an opening into the graft (transmural, from intima to adventitia).
2. Prebounding of graft to coronary by inserting the lower fork into the lumen of the unopened and not occluded coronary artery.
3. Nonocclusive opening of the coronary by laser-punching under full native coronary flow (transmural, from adventitia to intima) and subsequent ligation of the distal end of the graft.

Study 1 – Feasibility on Human Diseased Ex Vivo Coronary Arteries

Six human ex vivo hearts were used and approximately 6 anastomoses per heart were constructed with the Trinity Clip onto heterogeneous diseased coronary arteries (total n=38; 1.5–2.5 mm OD). The human cadaver was not treated with formalin or other fixatives, but was stored after death at -20 degrees Celsius. The ostia of the coronary arteries were cannulated, tap water was infused with a continuous pressure (90 mm Hg),

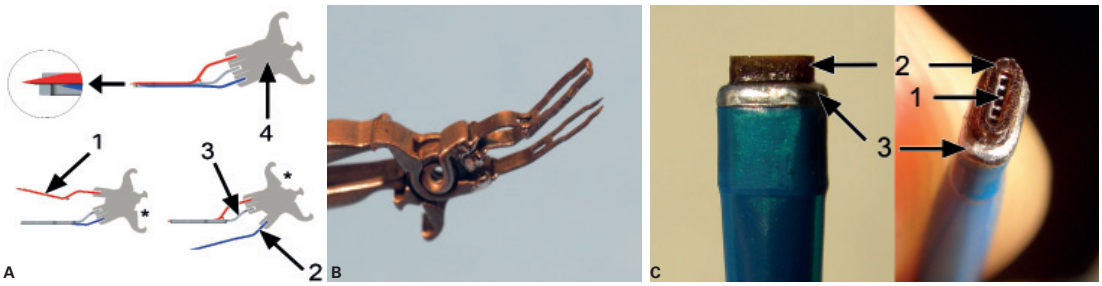

Figure 1. The Trinity Clip (A and B) and laser catheter (C)

A: The Trinity Clip (length, 9.6 mm) consists of 2 intravascular forks (upper fork, (1), and lower fork, (2); length, 4 mm and 3.5 mm, respectively; 1.4 mm width) and an extravascular band (3). The forks and band are connected to a spring (4) (height, 4.5 mm; 1.9 mm width), which enables the 2 forks to open and close, individually, one by one, with the use of an applicator.

B: The lower fork is opened by the applicator.

C: The laser catheter consists of a vacuum lumen (1), which is surrounded by laser fibers (2). An outer band (3) provides safety and stabilization into the anastomotic connector.

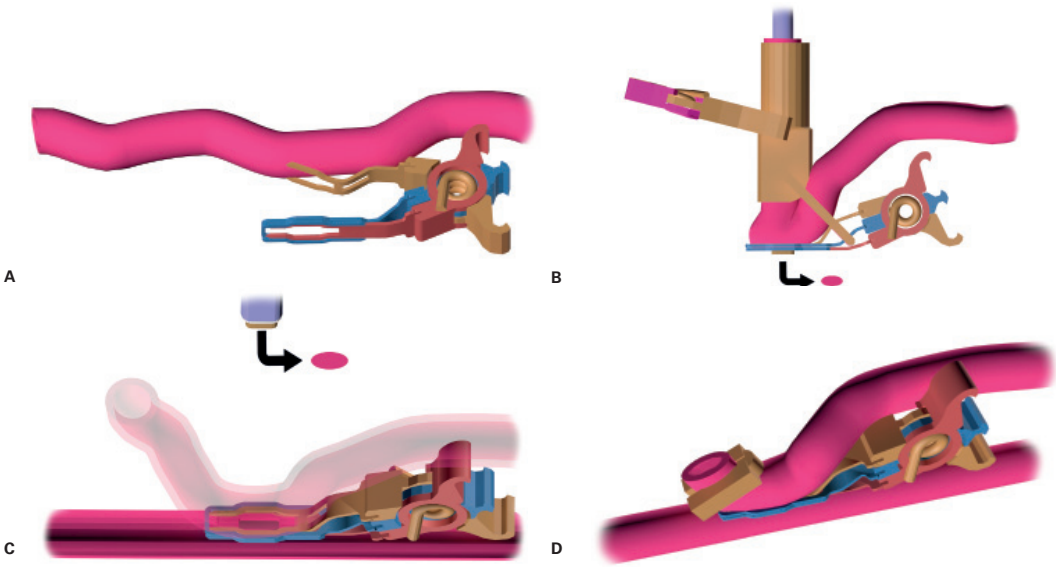

Figure 2. The coronary anastomotic procedure with the Trinity Clip connector

A: The upper fork of the connector is inserted into the lumen of the graft by using an applicator (not shown), approximately 2 cm before the distal end.

B: The laser is introduced and temporary secured by an external fixation clip, which fixates and stabilizes the laser into the connector, ensuring perpendicular positioning of the laser during the anastomosis construction. The graft is laser-punched and the laser-punched fragment is removed from the laser (arrow). Note that the laser is not removed.

C: The lower fork is inserted into the lumen of the coronary artery. The graft (illustrated transparently) and coronary artery are fixated between the 2 intraluminal forks and the extravascular band. The anastomosis is laser-punched under full native coronary flow and, subsequently, the fixation clip is removed and the laser is retrieved, including the laser-punched fragment of the coronary wall (arrow) by vacuum suction through the laser.

D: Directly following the nonocclusive opening of the anastomosis, the distal end of the graft is ligated.

and the target coronary artery was dissected free. As a graft, an ex vivo rabbit abdominal aorta (±3 mm OD; slaughterhouse) was used. A caliper was used to measure the OD (before anastomosis construction) and vessel wall thickness (after construction) of the coronary artery. Before the construction, the target was categorized as mildly or severely diseased by visual inspection and palpation, as an indication of the degree of atherosclerosis.

Feasibility of the anastomotic technique on human coronary arteries was assessed by connector

positioning (ie, proper intraluminal positioning of the lower fork of the connector into the coronary and anastomotic leakage) and laser-punch success. Post-construction, the success rate of the technique was related to the degree of coronary artery disease at the target site by histological analyses. Note: The laser-punch success rate decreases if the connector is mal-positioned (ie, the lower fork is positioned intramural or extraluminal), because there is not a straight surface of the coronary wall for laser-tissue contact and that will most certainly result in a laser-punch error. Therefore, the malpositioned anastomoses were excluded for subsequent laser-punch success rate analyses to specifically study the effect of coronary artery disease status on the laser-punch success rate.

Study 2 – Assessment of Laser-Induced Vessel Wall Damage

Ex vivo porcine model. Eight fresh porcine hearts (within 3 hours after termination) were used and 8 coronary anastomoses were constructed (1.5–2.0 mm OD) with the Trinity Clip. An ex vivo rabbit abdominal aorta was used as a graft. To mimic the in vivo setting (ie, perfusion with blood), we infused the coronary arteries with an oxybuprocaine (OBP; 3 g/L) solution, which has a similar absorption coefficient as blood (≈30 mm^{-1}).[7,8] As a negative control, at a distal (1.5 mm OD) and proximal (2.0 mm OD) coronary segment, we constructed an anastomosis, except for lasering the arteriotomy.

In vivo rabbit model. Three rabbits were used and 9 anastomoses were constructed with the Trinity Clip on the carotid and femoral arteries (1.7–2.0 mm OD). An ex vivo rabbit abdominal aorta was used as a graft. After a follow-up of 1 hour, the recipient arteries were collected and histologically assessed. In addition, a distal carotid and femoral segment was used as a negative control.

In vivo porcine model. In the porcine OPCAB LITA-to-LAD model,[2-5] 3 in vivo constructed anastomoses with the Trinity Clip (LAD 1.8 mm OD; n=1 anastomosis per pig) were explanted after a follow-up of 5 hours. The target LAD and a distal coronary segment (negative control) were collected and histologically assessed.

Histology

Study 1. After successful anastomotic construction, the Trinity Clip was retracted and the laser-punched coronary tissue and the corresponding target coronary wall (n=25) were fixed in 4% formalin. Subsequently, the tissue was embedded in paraffin, sectioned and stained with hematoxylin-and-eosin (H&E) and Elastin van Gieson (EvG) stain. The collected coronary tissue was histologically categorized according to the modified AHA classification[9] (ie, early lesions [intimal thickening, intimal xanthoma (fatty streak)] and advanced lesions [pathological intimal thickening, (thin) fibrous cap atheroma, and fibrocalcified plaque]) by 2 independent observers.

Study 2. The target segments of the recipient arterial wall of all anastomoses were collected in 4% formalin. Subsequently, the tissue was embedded in paraffin, sectioned in transverse planes, and stained with H&E, EvG, and Von Willebrand factor (vWF). The integrity of the internal elastic lamina, the media, and adventitia were assessed, and thrombocyte adherence (vWF; in vivo models) as an indication of arterial wall (ie, endothelial) damage, was recorded.

Statistical Analyses

Data are presented as the mean ± standard deviation, or as noted otherwise.

RESULTS

Study 1 – Feasibility on Human Diseased Ex Vivo Coronary Arteries

In 13 of 38 constructed anastomoses the connector was mal-positioned into the coronary artery and therefore excluded for further laser-punch success rate analyses (Table 1). Of these 13 anastomoses, 3 were mal-positioned due to a severely diseased coronary wall (ID>1.4 mm), 8 due to a mildly diseased and thickened coronary wall (0.5 ± 0.11 mm; ID<1.4 mm), and in 2 cases due to a small target coronary that was mildly

Table 1. Malposition versus correct position of the connector: Disease status, coronary wall thickness, and diameter of the target coronary artery

			Coronary wall thickness		Diameter target artery	
			n =	(mm)	OD (mm)	ID (mm)
Malposition	**Severe**	*Thickened*	1	0.4 ± 0.0	2.3 ± 0.0	1.5 ± 0.0
(n = 13)	(n = 3)	*Normal*	2	0.3 ± 0.02	2.3 ± 0.3	1.6 ± 0.2
	Mild	*Thickened*	8	0.5 ± 0.11	2.0 ± 0.4	0.9 ± 0.2
	(n = 10)	*Normal*	2	0.3 ± 0.0	1.7 ± 0.1	1.1 ± 0.1
Correct position	**Advanced**	*Thickened*	8	0.5 ± 0.06	2.4 ± 0.1	1.4 ± 0.2
(n = 25)	(n = 9)	*Normal*	1	0.3 ± 0.0	2.3 ± 0.0	1.6 ± 0.0
	Early	*Thickened*	5	0.5 ± 0.07	2.3 ± 0.2	1.6 ± 0.3
	(n = 16)	*Normal*	11	0.3 ± 0.05	2.0 ± 0.3	1.6 ± 0.4

Data presented as mean millimeters ± SD. Connector positioning errors were mainly found in target coronaries with an ID below the intended target range (n=10; ID<1.4 mm). The anastomoses are distributed by Malposition (ie, the lower fork of the connector is positioned intramural or extraluminal) and Correct position (ie, the lower fork is positioned intraluminal). The anastomoses are further distributed by the degree of atherosclerosis; Severe or Mild in the Malposition subgroup (categorized by manual and visual inspection before anastomosis construction; no histological data available) and Advanced and Early in the Correct position subgroup (histologically categorized). Furthermore, the Coronary wall thickness (measured by using a caliper) is categorized as Thickened (≥0.4 mm) or Normal (<0.4 mm) and the mean diameter of the target coronary artery is specified (OD and ID).

OD: Outer diameter. ID: Calculated inner diameter (ie, determined as the outer diameter minus 2 times the coronary wall thickness).

diseased with a normal thickened wall (0.3 ± 0.0 mm; ID<1.4 mm). In case of successful application (n=25), no anastomotic leakage was observed after construction.

A 100% laser-punch success rate was found on coronary arteries with an early lesion (16/16; Table 2). Of these histologically characterized early lesions, 15 showed intimal thickening and in 1 case an intimal xanthoma was observed. Nine anastomoses were constructed on target coronary arteries with an advanced lesion; all lesions were histologically characterized as a fibrocalcified plaque. In 1 case, the fibrocalcified plaque was located in the superolateral wall (ie, anastomotic site) and caused a failure to laser-punch a full thickness – transmural – disk of coronary wall (Figure 3A). All other cases were successfully laser-punched (8/9, 89%) and the eccentric atherosclerotic plaque was located in the inferolateral wall, whereas the laser-punch site revealed intimal thickening (Figure 3B).

Table 2. Laser-punch success rate in human diseased ex vivo coronary arteries

Degree of atherosclerosis	Failure to laser-punch (n/total)	Laser-punch success rate (%)
Early lesions	0/16	100%
Advanced lesions	1/9	89%

The degree of atherosclerosis at the target anastomotic site was histologically categorized into 2 groups: *Early lesions,* consisting of intimal thickening and intimal xanthoma (fatty streak), and *Advanced lesions*, consisting of pathological intimal thickening, (thin) fibrous cap atheroma, and fibrocalcified plaque. In 1 case, a fibrocalcified plaque in the superolateral wall caused a failure to laser-punch.

Study 2 – Assessment of Laser-Induced Vessel Wall Damage

In the ex vivo pig model, no histological signs of laser-induced damage were observed (n=8 anastomoses; Figure 3C). In the rabbit model, at 1-hour follow-up, no disruption of the internal elastic lamina or the elastin fibers of the medial layer was demonstrated (n=9 anastomoses). In some cases, minor adhesion of thrombocytes to the medial and adventitial layer of the inner site of the laser rim was seen. At the compression site, where the connector actively compressed the graft onto the recipient artery wall, compression effects

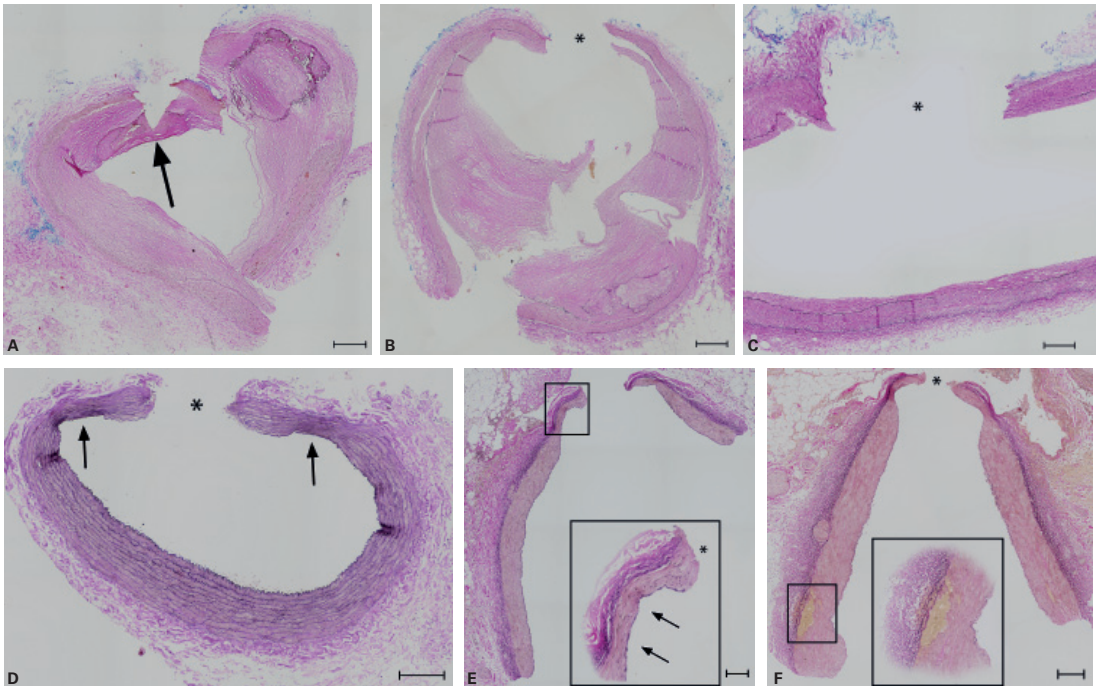

Figure 3. Histology of recipient arteries following anastomotic construction with the Trinity Clip

A: A fibrocalcified plaque in a human ex vivo coronary artery is located in the superolateral wall and caused a failure to laser-punch a full thickness disk of coronary wall. The incompletely lasered disk is still partly attached to one side *(arrow)*. EvG stain. Bar = 0.4 mm.

B: An example of a human diseased ex vivo coronary artery with a fibrocalcified plaque at the inferior wall of the target site. The *asterisk* indicates where the laser successfully punched through the coronary wall. EvG stain. Bar = 0.4 mm.

C: No laser-induced damage is observed in a longitudinal section of a left anterior descending artery, mid-anastomosis, constructed in an ex vivo porcine model. The *asterisk* indicates the anastomotic orifice. EvG stain. Bar = 0.4 mm.

D: No laser-induced damage is demonstrated in a transversal section of a rabbit carotid artery, mid-anastomosis, at 1-hour follow-up. However, compression effects *(arrows)* are seen. EvG stain. Bar = 0.2 mm.

E and **F:** A transversal section of a left anterior descending artery, mid-anastomosis, constructed in a porcine OPCAB model, at 5-hour follow-up. **E:** No laser-induced damage is observed. The inlay (higher magnification of the indicated area) demonstrates a sharp laser-cut edge *(asterisk)* and at the compression-site (arrows) compression of smooth muscle cells. EvG stain. Bar = 0.2 mm. **F:** Focal laser-induced damage of the coronary inferior wall is demonstrated. The damage is seen directly opposed to the anastomotic orifice *(asterisk)* and in between the adventitial and medial layer an abnormality (ie, hemorrhage, seen with vWF stain) is present (see magnified subsection). EvG stain. Bar = 0.4 mm.

Note, interruption of the inferolateral or inferior coronary wall is caused by longitudinally opening of the coronary artery before inspection.

were seen with starting pyknosis (ie, degeneration) of smooth muscle cell nuclei (Figure 3D).

In the porcine OPCAB model (n=3 anastomoses), acute vessel wall damage (ie, internal elastic lamina disruption or medial damage) was not observed histologically after laser-punching (Figure 3E), except for 1 case. In the latter, the surgeon (first author) did not support the laser during laser-punching, which resulted in uncontrolled pressure of the laser onto the coronary artery, and presumably, contact of the laser to the inferior wall. This caused disruption of the internal elastic lamina of the coronary inferior wall, opposed to the anastomotic orifice, and focally, a deposition of platelets was demonstrated at 5-hour follow-up. In addition, damage to the smooth muscle cells of the medial layer with pyknotic nuclei and adventitial hemorrhage in between the adventitial and medial layer was seen (Figure 3F).

In all anastomoses, a sharp laser-cut was seen without diffuse laser-induced vessel wall damage and with adherence of thrombocytes at the edges. Compression effects were seen at the compression site with pyknosis of smooth muscle cell nuclei (Figure 3E, magnified subsection). Furthermore, the negative controls in study 2 did not show any vessel wall damage.

DISCUSSION

The main findings of this study are 1) the coronary anastomotic connector is feasible on human diseased ex vivo coronary arteries, however, *a*) target coronary arteries with an ID below the intended target range can cause connector positioning failures, and *b*) advanced lesions in the superior coronary wall can cause connector positioning and laser-punch failures, and 2) the laser-assisted technique does not induce vessel wall damage in small caliber arteries, in case of correct use.

Clinical Application

According to the findings illustrated in Table 1, connector positioning errors were mainly found in targets that were severely diseased (n=3) or targets with an ID below the intended target range (ID<1.4 mm; n=10). Construction of an anastomosis on a target with an ID below the intended range and a thickened coronary wall resulted in an insertion failure (n=8). However, a thickened wall (≥0.4 mm) per se does not immediately result in an error: mal-positioning was recorded in 9 of 22 targets with a thickened wall and eight of those 9 had an ID lower than 1.4 mm; all 13 correctly positioned connectors, in targets with a thickened wall, had an ID in the intended target range. Hence, a coronary target with an ID below the intended target range, or a target that is severely diseased, should be avoided to prevent mal-positioning of the connector. Please note that in this study the targets were selected by measuring the OD. Since the vessel wall thickness (measured after construction) naturally varies with disease status, some anastomoses were constructed onto targets that were, in retrospect, not suitable (ID<1.4 mm; n=10; Table 1).

It is feasible to construct an anastomosis with the laser-assisted connector onto human atherosclerotic coronaries with a 100% success rate, even on severely diseased coronary arteries with thickened coronary arterial walls in which advanced lesions are located in the inferior or lateral wall. However, there is an increased risk of mal-positioning or a laser-punch failure in the case an advanced lesion is located in the superior wall. Therefore, similar to clinical practice, it is not recommended to graft a severely diseased coronary artery.

To prevent construction errors and enhance the anastomotic success rate, the coronary target should be carefully selected by measuring the ID (preoperative coronary angiogram or intraoperative epicardial ultrasound [ECUS][5]) and by assessment of disease status (tactile and visual inspection or ECUS). In addition, in situations in which target selection by palpation is not possible (ie, minimally invasive approaches), ECUS could guide and select a suitable target for this laser-assisted technique.[10,11] A human feasibility study in which the ID and wall thickness will be assessed in vivo by using ECUS is warranted to determine the applicability of the device in clinical scenarios.

Laser-Induced Vessel Wall Damage

One possible way for the excimer laser to damage the vessel wall is by direct laser-tissue contact, which is intentionally used to create the laser-punched arteriotomy by excising a disk of tissue. As demonstrated in this study, this procedure results in a sharp laser cut with minimal thrombocyte adherence. Please note that the laser can only hit the inferior wall if the complex of laser and connector is pushed on during activation of the laser. This could result in a collapse of the coronary artery, and thus, result in direct laser-tissue contact, causing damage to the inferior wall (Figure 3F). This kind of damage is simply prevented by adequately supporting the laser during laser-punching; an outer band at the tip of the laser (Figure 1B-*3*) prevents the laser from slipping through the connector. In addition, the penetration depth of the 308-nm laser light in blood is lower than 100 micrometer, and therefore the light cannot reach the opposite inferior wall.[7,8]

Another way to damage the vessel wall is by thermal energy, induced during lasering, potentially leading to diffuse damage, at the laser rim or the surrounding adjacent arterial wall. However, in this study, this was not observed. In addition, the connector could also harm the arterial wall by incorrect insertion (eg, intramural positioning) and by compression of the vessel wall. The latter was seen in the acute in vivo experiments in the rabbit and porcine model by pyknosis of the medial cells.

Limitations

The severely diseased coronary segments are targets that – similar to the facilitated technique – are avoided in the hand-sutured anastomosis construction. These are not coronary arteries that are regularly clinically targeted, and even in some cases in which the lesion is located in the lateral or superior wall, it is impossible to properly suture the calcified walls. A limitation of this study is that we did not perform a comparative analysis of the feasibility of the hand-sutured to the Trinity Clip construction in this atherosclerotic model.

In this study, vessel wall damage was studied in non-diseased targets and in the acute phase. More data on vessel wall damage after construction onto diseased coronary targets have to follow. The long-term effects of the specific characteristics of this technique (ie, insertion of the forks into the lumen of the artery, foreign intravascular exposed material, compression of the vessel walls, and the laser-punched arteriotomy) will be further evaluated in a long-term (follow-up 6 months) safety study in the porcine OPCAB model and compared to the hand-sewn anastomosis. Previous studies have shown a favorable healing response with thin intimal coverage of the intraluminal connector in a porcine model.[3,4,12] Therefore, we hypothesize that these results suggest a favorable healing reaction of the connector-facilitated anastomosis compared to hand-sewn anastomoses, due to a less traumatic anastomosis construction. In the connector-facilitated nonocclusive anastomosis construction, tissue trauma is minimized compared to the hand-sutured construction, which includes coronary snaring, a by hand incised arteriotomy, intracoronary shunting, and stitching. The introduction of the forks of the connector into the graft and coronary artery is likely to be less traumatic compared to approximately 12 separately placed stitches. Future functional endothelial studies could further support this hypothesis. In addition, emphasizing that the laser catheter is introduced through the distal free end of the graft, which is finally ligated and is not the actual functional conduit, stresses the fact that the necessity to manipulate the graft by laser introduction does not result in actual relevant intimal damage.

Key Features

The unique concept of nonocclusive anastomosis construction provides a simple, fast (approximately 3.5 minutes[5]), and bloodless connection. It is reversible in case of malposition, before to the point of laser-punching. Laser-punching the anastomosis is standardized and reproducible, with a sharply laser-cut oval-shaped orifice and no adverse coronary wall damage. In contrast to other connectors, the native coronary flow does not have to be interrupted and the anastomosis is constructed without the potentially harming effects and the dexterity of temporary occlusion of the coronary or intracoronary shunting,[13] and hence, there is no time-constraint related to myocardial ischemia.[14-19] Finally, no bulky applicators and no standard extra hemostatic stitches are required.[17-19] All these features simplify the off-pump, minimally invasive bypass procedure.

Conclusion

This study demonstrates the feasibility of a new laser-assisted coronary anastomotic connector on human diseased coronary arteries and shows that the lasered-arteriotomy does not induce vessel wall damage to the recipient vessel wall, in case of correct use. Careful selection of the coronary artery regarding the target - inner - diameter range and disease status will prevent anastomotic construction failures. After the long-term safety of this technique is shown in the porcine OPCAB model, clinical introduction will follow. Finally, the developed connector could be the key towards less invasive coronary artery bypass grafting.

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REFERENCES

1. Stecher D, de Boer B, Tulleken CA, et al. A new nonocclusive laser-assisted coronary anastomotic connector in a rabbit model. *J Thorac Cardiovasc Surg.* 2013;145:1124-9.
2. Stecher D, Pasterkamp G, van Herwerden LA, et al. A new sutureless coronary anastomotic device - Excimer Laser Assisted Non-occlusive Anastomosis (ELANA) - in an off-pump porcine bypass model. *Innovations*. 2012;7:111.
3. Stecher D, van Slochteren FJ, Hoefer IE, et al. The nonocclusive laser-assisted coronary anastomotic connector in an off-pump porcine bypass model. *J Thorac Cardiovasc Surg.* 2014;147:1390-7 e2.
4. Stecher D, Agostoni P, Pasterkamp G, et al. Six-month healing of the nonocclusive coronary anastomotic connector in an off-pump porcine bypass model. *Innovations.* 2014;9:130-6.
5. Stecher D, Bronkers G, Noest JOT, et al. Evaluation of a novel laser-assisted coronary anastomotic connector - the Trinity Clip - in a porcine off-pump bypass model. *J. Vis. Exp.* 2014;93:e52127, doi:10.3791/52127.
6. Biesbroek M, van Doormaal TP, van der Zwan A, et al. The acute effect of increased laser energy during the excimer laser-assisted non-occlusive anastomosis procedure on the vessel wall of the recipient artery: a histopathological study. *Lasers Surg Med.* 2011;43:522-7.
7. van Leeuwen TG, Jansen ED, Welch AJ, et al. Excimer laser induced bubble: dimensions, theory, and implications for laser angioplasty. *Lasers Surg Med.* 1996;18:381-90.
8. van Doormaal TP, van der Zwan A, van der Tweel I, et al. Optimization of the excimer laser assisted non-occlusive anastomosis (ELANA) flap retrieval rate. *Lasers Surg Med.* 2010;42:418-24.
9. Virmani R, Kolodgie FD, Burke AP, et al. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol.* 2000;20:1262-75.
10. Eikelaar JH, Meijer R, van Boven WJ, et al. Epicardial 10-MHz ultrasound in off-pump coronary bypass surgery: a clinical feasibility study using a minitransducer. *J Thorac Cardiovasc Surg.* 2002;124:785-9.
11. Budde RP, Meijer R, Dessing TC, et al. Detection of construction errors in ex vivo coronary artery anastomoses by 13-MHz epicardial ultrasonography. *J Thorac Cardiovasc Surg.* 2005;129:1078-83.
12. van Doormaal TP, van der Zwan A, Redegeld S, et al. Patency, flow, and endothelialization of the sutureless Excimer Laser Assisted Non-occlusive Anastomosis (ELANA) technique in a pig model. *J Neurosurg.* 2011;115:1221-30.
13. Gerosa G, Bottio T, Valente M, et al. Intracoronary artery shunt: an assessment of possible coronary artery wall damage. *J Thorac Cardiovasc Surg.* 2003;125:1160-2.
14. Carrel T, Englberger L, Keller D, et al. Clinical and angiographic results after mechanical connection for distal anastomosis in coronary surgery. *J Thorac Cardiovasc Surg.* 2004;127:1632-40.
15. Filsoufi F, Farivar RS, Aklog L, et al. Automated distal coronary bypass with a novel magnetic coupler (MVP system). *J Thorac Cardiovasc Surg.* 2004;127:185-92.
16. Suyker WJ, Buijsrogge MP, Suyker PT, et al. Stapled coronary anastomosis with minimal intraluminal artifact: The S2 Anastomotic System in the off-pump porcine model. *J Thorac Cardiovasc Surg.* 2004;127:498-503.
17. Matschke KE, Gummert JF, Demertzis S, et al. The Cardica C-Port System: clinical and angiographic evaluation of a new device for automated, compliant distal anastomoses in coronary artery bypass grafting surgery--a multicenter prospective clinical trial. *J Thorac Cardiovasc Surg.* 2005;130:1645-52.
18. Balkhy HH, Wann LS, Arnsdorf S. Early patency evaluation of new distal anastomotic device in internal mammary artery grafts using computed tomography angiography. *Innovations.* 2010;5:109-13.
19. Verberkmoes NJ, Wolters SL, Post JC, et al. Distal anastomotic patency of the Cardica C-PORT(R) xA system versus the hand-sewn technique: a prospective randomized controlled study in patients undergoing coronary artery bypass grafting. *Eur J Cardiothorac Surg.* 2013;44:512-8.

7

TOTAL ARTERIAL MIDCAB FACILITATED BY THE TRINITY CLIP CONNECTOR

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ABSTRACT

Objective: This pilot study evaluated the feasibility of total arterial minimally invasive direct coronary artery bypass (MIDCAB) surgery by using the Trinity Clip anastomotic connector in an acute porcine model.

Methods: In 3 pigs, the left and right internal thoracic artery (LITA and RITA) was harvested conventionally and the chest closed subsequently. After a left lateral thoracotomy, the coronary target was positioned and stabilized by an endo-starfish and octopus. A free RITA-to-LITA y-graft, with a LITA-to-left anterior descending coronary artery (LAD) and a free RITA-to-obtuse marginal (OM) or posterolateral (PLcx) or posterior descending artery (PDA), was constructed by using the Trinity Clip. Patency was assessed with angiography (n=3 anastomoses).

Results: The anastomotic procedure was feasible via a small lateral thoracotomy, with a fast construction of the y-graft, and successful application of the mounted complex (ie, graft, connector, and laser, temporarily fixated by a fixation clip) onto the LAD. Access to the OM, PLcx, and PDA was possible, with successful construction, resulting in patent anastomoses.

Conclusions: This experimental pilot study demonstrates the feasibility of the anastomotic technique in a total arterial MIDCAB approach. Revascularization of the anterior, lateral, and inferoposterior regions of the heart is possible. However, visibility during the introduction of the connector was limited and video-scopic assistance is essential to allow for successful construction. The anastomotic technique has potential to facilitate minimally invasive coronary bypass surgery.

INTRODUCTION

To facilitate minimal access CABG, our research group developed a simplified alternative for hand-sutured anastomosis, the Trinity Clip,[1-3] based on the Excimer Laser Assisted Nonocclusive Anastomosis (ELANA) technique.[4-7] This pilot study evaluated the feasibility of total arterial minimally invasive direct coronary artery bypass (MIDCAB) surgery by using the Trinity Clip in an acute porcine model.

METHODS

Animals

Three Dutch Landrace pigs (female; weighing 60-80 kg) were used. The animals were fed a normal diet and received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council. The animal experimentation committee of the Utrecht University approved the protocol. Starting 3 days before surgical intervention, all animals received 320 mg of acetylsalicylic acid and 75 mg clopidogrel orally daily. See the Supplemental Methods section regarding the anesthesia and euthanasia protocol.

Anesthesia and Euthanasia

Anesthesia was induced with ketamine (10 mg/kg), midazolam (0.5 mg/kg), and atropine (0.04 mg/kg) intramuscularly. Each animal received thiopental sodium (4 mg/kg), midazolam (0.5 mg/kg), and sufentanil citrate (6 µg/kg) through an intravenous line. The animals were intubated and ventilated with a mixture of oxygen and air (1:1 volume/volume). Anesthesia was maintained by a continuous intravenous infusion of midazolam (0.7 mg/kg/h), analgesia was obtained with an infusion of sufentanil citrate (6 µg/kg/h), and muscle relaxation with pancuronium bromide (0.1 mg/kg/h). During the operation, each animal received a continuous infusion of saline solution (300 mL/h). Metoprolol was administered intravenously (range, 5-20 mg) to reduce the mechanical irritability of the heart until a heart rate of approximately 70 beats/min was obtained.

Animals were put to death with pentobarbitalsodium (200 mg/kg) intravenously, after having been heparinized to obtain an activated clotting time (ACT; Hemotec, Inc, Englewood, Colo) of at least 4 times the control value.

The Trinity Clip - Anastomotic Procedure (Figure 1)

The nonocclusive anastomosis construction is accomplished by:

1. Mounting of the graft and laser by inserting the upper fork of the connector (Figure 2A) into the distal end of the graft. Subsequently, the laser (Corvasco Medical b.v., Utrecht, The Netherlands) is introduced into the connector and laser-punches an opening into the graft (transmural, from intima to adventitia).
2. Prebounding of graft to coronary by inserting the lower fork into the lumen of the unopened and not occluded coronary artery.
3. Nonocclusive opening of the coronary by laser-punching under full native coronary flow (transmural, from adventitia to intima) and subsequent ligation of the distal end of the graft.

Surgery and Experimental Model

After a partial sternotomy, conventional open harvesting of the left and right internal thoracic artery (LITA in situ and free RITA), partial heparinization, and subsequent closure, a lateral thoracotomy (10 cm) was created in the 5th intercostal space (ICS). A rib retractor was used to create a window of 6 cm width. After a T-shaped pericardiotomy (a medial incision from cranial to caudal and caudally up to the right chest wall and down to the left chest wall) and inspection of the target coronaries, the proximal free RITA was anastomosed to the LITA as a y-graft, by using the connector (length, 9.6 mm; maximum width, 1.9 mm, height, 4.5 mm) as earlier

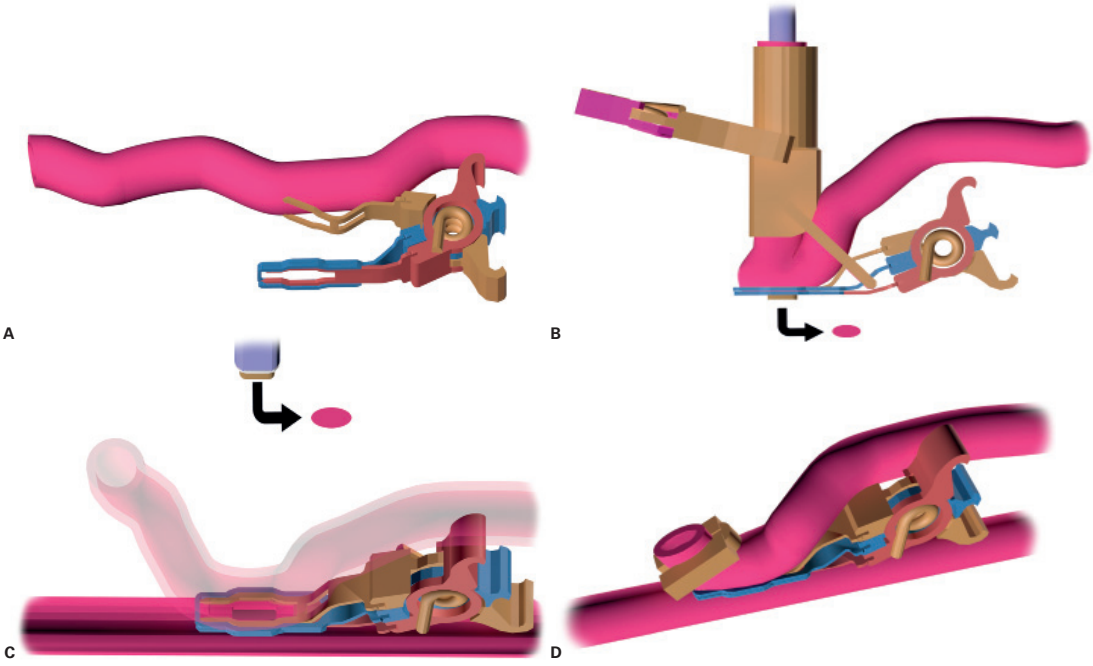

Figure 1. The anastomotic procedure

A: The upper fork of the connector is inserted into the graft.

B: The laser is introduced and secured by a fixation clip. The graft is laser-punched and the punched fragment is removed from the laser (arrow).

C: The lower fork is inserted into the coronary and the coronary is laser-punched. Subsequently, the laser is retrieved, including the laser-punched fragment of the coronary wall (arrow).

D: The distal end of the graft is ligated.

Figure 2. The Trinity Clip connector

A: The Trinity Clip connector: the lower fork is opened by an applicator.

B: The connector-facilitated LITA-to-LAD (top) and the RITA-LITA Y-graft (bottom) are visible through a left lateral thoracotomy.

described. Subsequently, an endo-starfish (prototype build in the nineties, University Medical Center Utrecht, The Netherlands) and endo-octopus (Octopus Nuvo, Medtronic, Inc, Minneapolis, Minn) were introduced subxiphoidal and via the 8th ICS in the mid-axillary line, respectively. After positioning and immobilization of the coronary artery (left anterior descending coronary artery [LAD] followed by either an obtuse marginal artery [OM], posterolateral artery [PLcx], or a posterior descending artery [PDA]; 1.6–1.9 mm OD) the bypass was constructed with the connector. Following construction, the native coronary artery was ligated ±1.0 cm upstream.

In 3 pigs, a total of 3 connector-facilitated y-grafts (free RITA-to-LITA anastomosis) and 6 distal anastomoses (LITA-to-LAD [n=3], either with a free RITA-to-OM [n=1], or a free RITA-to-PLcx [n=1], or a free RITA-to-PDA [n=1]) were constructed. The feasibility of the technique was evaluated intraoperative (n=9; assessed by anastomotic hemostasis, anastomotic success rate [insertion success and flap retrieval], and graft flow measurement) and before and after termination (by angiography [n=3] and macroscopic evaluation [n=9], respectively).

Coronary Angiography

Catheterization was performed before and after death in 1 animal (n=3 anastomoses) and 2 independent observers graded the angiogram according to the FitzGibbon criteria.

RESULTS

All anastomotic procedures were performed by 1 investigator (D.S.) and were feasible via a small lateral thoracotomy (Figure 2B), after conventional ITA harvesting. All anastomoses were constructed without interrupting coronary flow. Successful application of the mounted complex (ie, graft, connector, and laser, temporarily fixated by a fixation clip) onto the LAD was achieved after center positioning of the target anastomotic site in relation to the thoracotomy. However, only 1 side (ie, pin) of the lower fork was visible during insertion into the LAD due to the distal direction, away from the surgeon. Furthermore, access to the OM, PLcx, and PDA was possible, with successful construction.

All anastomoses (n=9) were fully patent (Figure 3) and post-mortem macroscopic evaluation revealed patent anastomoses without insertion and laser flaws or failures.

DISCUSSION

This experimental pilot study demonstrates the feasibility of the anastomotic technique in a total arterial MIDCAB approach. The technique enables successful anastomotic construction on all territories of the heart (including the LAD, OM, PLcx, and PDA), except for the proximal right coronary artery region.

To facilitate total arterial bypass grafting, the connector enables fast (less than 2 minutes) and standardized y-grafting, simply performed with straightforward maneuvers in a reduced workspace. Considering a clinical case, the radial artery instead of the free RITA used in the presented porcine model, could be anastomosed with the connector to the LITA, potentially with additional sequential anastomosis construction.[8]

In a previous experiment, the feasibility of robot-assistedTECAB by using the connector was demonstrated,[2] but the secured upright laser fulcrum (Figure 1B) limited expediency. In the MIDCAB setting, the secured laser was not a drawback, provided that the target was center-positioned in relation to the access site (ie, preventing collision of the fulcrum to the chest wall). However, in this setting, the reduced workspace hampered visualization during insertion. In addition, in absence of dedicated instruments, the construction took longer (± 20 minutes) compared to the construction time (3.5 minutes) found in an OPCAB porcine model.[1] Hence, to succeed in minimally invasive anastomosis construction, dedicated application tools (ie, flexible laser and versatile applicator) and optimization of visualization by video-scopic assistance, are essential.

The unique concept of nonocclusive anastomosis construction provides a fast and bloodless connection.

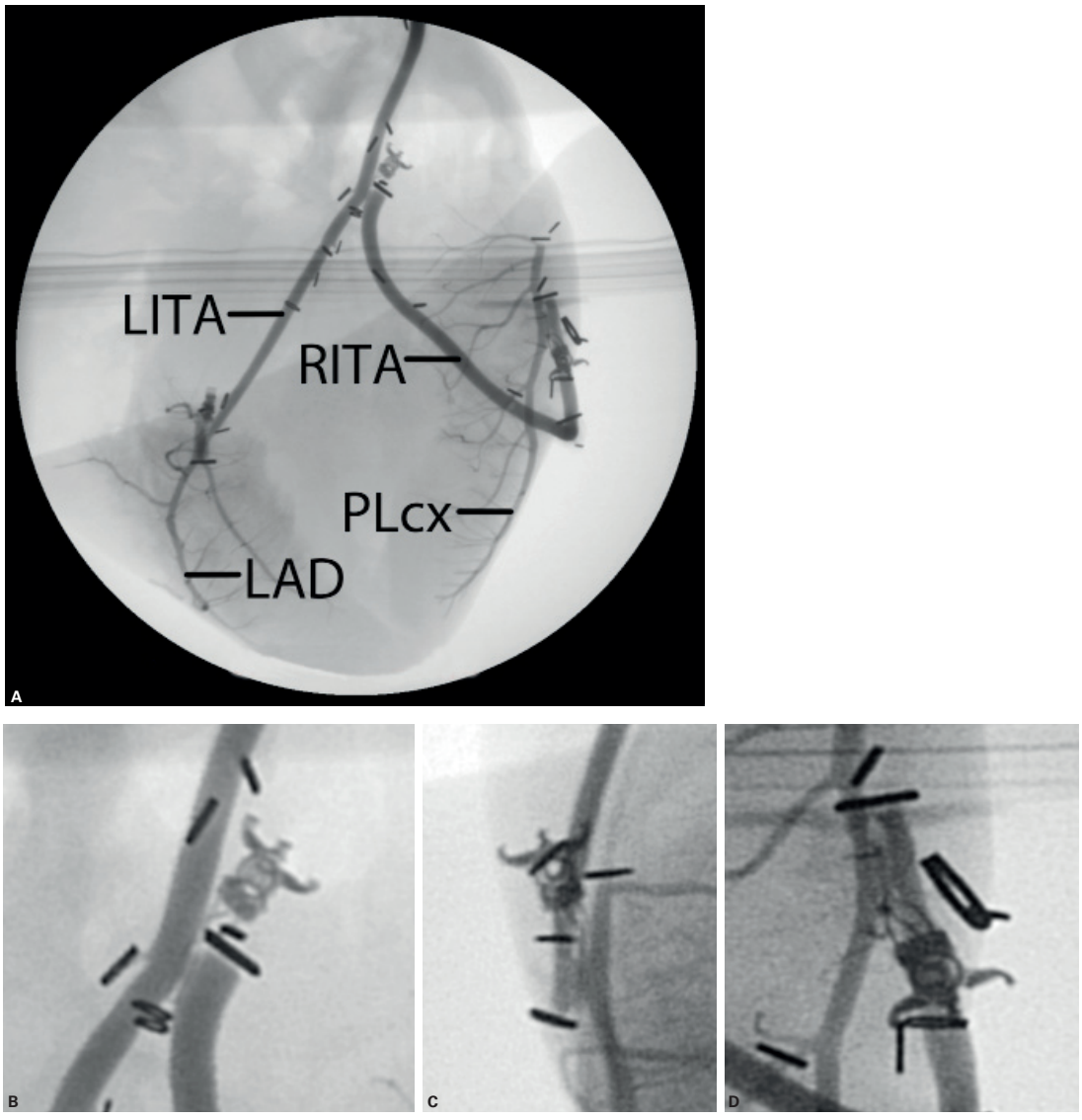

Figure 3. Angiogram of a y-graft anastomosed to the anterior and posterior wall

Overview of the angiogram (**A**) with a detailed side-view of the free RITA-to-LITA y-graft (**B**), the LITA-to-LAD (**C**), and the free RITA-to-PLcx (connector directed proximally; **D**).

In contrast to other connectors, the native coronary flow does not have to be interrupted, hence there is no need to snare or shunt the coronary artery and so the anastomotic construction is further simplified.[9-14] In addition, a standardized construction is offered, while both the graft and coronary artery are laser-punched and neither a separate incision[9-14] nor standard sutures are needed.[12-14] With respect to previous devices, all these features simplify the off-pump, minimally invasive bypass procedure.

Conclusion

The presented anastomotic technique is feasible in a porcine total arterial MIDCAB model and the connector has potential to facilitate minimally invasive coronary bypass surgery.

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DISCLOSURES

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REFERENCES

1. Stecher D, Bronkers G, Noest JOT, et al. Evaluation of a novel laser-assisted coronary anastomotic connector - the trinity clip - in a porcine off-pump bypass model. *J. Vis. Exp.* 2014;93:e52127. doi:10.3791/52127.
2. Stecher D, van Herwerden LA, Pasterkamp G, et al. Robot-Assisted Endoscopic Construction of a LITA-to-LAD Anastomosis Facilitated by the Trinity Clip (ELANA Anastomotic Connector): An Experimental Case Report. Abstract. *Innovations*. 2014;9:178. doi:10.1097/IMI.0000000000000067.
3. Stecher D, Pasterkamp G, Buijsrogge MP. A New Coronary Anastomotic Connector in a Preclinical Safety Study. Abstract. *Circulation*. 2014;130:A15504.
4. Stecher D, Agostoni P, Pasterkamp G, et al. Six-month healing of the nonocclusive coronary anastomotic connector in an off-pump porcine bypass model. *Innovations*. 2014;9:130-136.
5. Stecher D, Pasterkamp G, van Herwerden LA, et al. A new sutureless coronary anastomotic device - Excimer Laser Assisted Non-occlusive Anastomosis (ELANA) - in an off-pump porcine bypass model. Abstract. *Innovations*. 2012;7:111.
6. Stecher D, de Boer B, Tulleken CA, et al. A new nonocclusive laser-assisted coronary anastomotic connector in a rabbit model. *J Thorac Cardiovasc Surg.* 2013;145:1124-1129.
7. Stecher D, van Slochteren FJ, Hoefer IE, et al. The nonocclusive laser-assisted coronary anastomotic connector in an off-pump porcine bypass model. *J Thorac Cardiovasc Surg.* 2014;147:1390-1397 e1392.
8. Lemma M, Atanasiou T, Contino M. Minimally invasive cardiac surgery-coronary artery bypass graft. *Multimed Man Cardiothorac Surg*. 2013;2013:mmt007. doi:10.1093/mmcts/mmt007.
9. Carrel T, Englberger L, Keller D, et al. Clinical and angiographic results after mechanical connection for distal anastomosis in coronary surgery. *J Thorac Cardiovasc Surg.* 2004;127:1632-40.
10. Filsoufi F, Farivar RS, Aklog L, et al. Automated distal coronary bypass with a novel magnetic coupler (MVP system). *J Thorac Cardiovasc Surg.* 2004;127:185-92.
11. Suyker WJ, Buijsrogge MP, Suyker PT, et al. Stapled coronary anastomosis with minimal intraluminal artifact: The S2 Anastomotic System in the off-pump porcine model. *J Thorac Cardiovasc Surg.* 2004;127:498-503.
12. Matschke KE, Gummert JF, Demertzis S, et al. The Cardica C-Port System: clinical and angiographic evaluation of a new device for automated, compliant distal anastomoses in coronary artery bypass grafting surgery--a multicenter prospective clinical trial. *J Thorac Cardiovasc Surg.* 2005;130:1645-52.
13. Balkhy HH, Wann LS, Arnsdorf S. Early patency evaluation of new distal anastomotic device in internal mammary artery grafts using computed tomography angiography. *Innovations.* 2010;5:109-13.
14. Verberkmoes NJ, Wolters SL, Post JC, et al. Distal anastomotic patency of the Cardica C-PORT(R) xA system versus the hand-sewn technique: a prospective randomized controlled study in patients undergoing coronary artery bypass grafting. *Eur J Cardiothorac Surg.* 2013;44:512-8.

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THE LASER-ASSISTED CORONARY ANASTOMOTIC CONNECTOR –THE TRINITY CLIP– IN A PRECLINICAL SAFETY STUDY

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ABSTRACT

Objective: A facilitated construction of a coronary anastomosis is key toward expansion of less invasive bypass surgery. This preclinical safety study evaluated a laser-assisted, nonocclusive connector – the Trinity Clip – on small caliber coronary arteries in a porcine off-pump bypass model.

Methods: In 58 pigs, 33 left internal thoracic to left anterior descending coronary (1.6–1.9 mm outer diameter) artery anastomoses were facilitated by the connector, and 25 were hand-sutured. To assess anastomotic healing and patency, the anastomoses were evaluated at the short- (intraoperative and 4, 10, 14, 35 days) and long-term (90 and 180 days) follow-up, and were examined by flow measurements, angiography, histology, and scanning electron microscopy.

Results: A faster construction time was found (P<0.01) and hemostasis tended to be better (94% versus 80%, respectively; P=0.11) in the connector compared to the hand-sutured group. Long-term follow-up showed 100% (14/14) patency in the hand-sutured compared to 82% (18/22) in the connector group (P=0.12; long-term patency was 92% [12/13] before a connector design change halfway the study). The patent facilitated-anastomoses showed less intimal hyperplasia formation compared to the hand-sutured (0.08 ± 0.06 versus 0.26 ± 0.07 mm, respectively; P<0.01).

Conclusions: This study demonstrated the feasibility of the connector to facilitate off-pump CABG on small caliber arteries. Patency rates were inferior, however, were related to a design change halfway the study. Provided the technical limitations can be addressed, the presented concept of nonocclusive simplified anastomosis construction could fill the missing link toward expansion of minimally invasive CABG.

INTRODUCTION

A facilitated construction of a distal coronary anastomosis is key toward less invasive coronary bypass surgery. This preclinical safety study evaluates a new laser-assisted nonocclusive coronary anastomotic connector – the Trinity Clip – in comparison to the conventional hand-sutured anastomotic technique in a long-term follow-up porcine off-pump bypass model.[1] Following initial, successful testing on large caliber arteries (3.0 mm outer diameter [OD]),[2-4] the connector was downsized to target smaller range coronary arteries (1.6–1.9 mm OD) and the construction simplified by complete sutureless anastomotic construction.[5] In this study, we assessed the hypothesis that the coronary connector is not inferior to the hand-sutured technique in terms of patency, healing, and hemodynamic function.

METHODS

The Trinity Clip - Anastomotic Procedure

The Trinity Clip (Figure 1A; Corvasco Medical b.v., Utrecht, The Netherlands) is suitable for target coronary arteries with an inner diameter (ID) of 1.4–1.6 mm (comparable to an outer diameter [OD] of 1.6–1.9 mm in the porcine model). An online video of the procedure is available.[5]

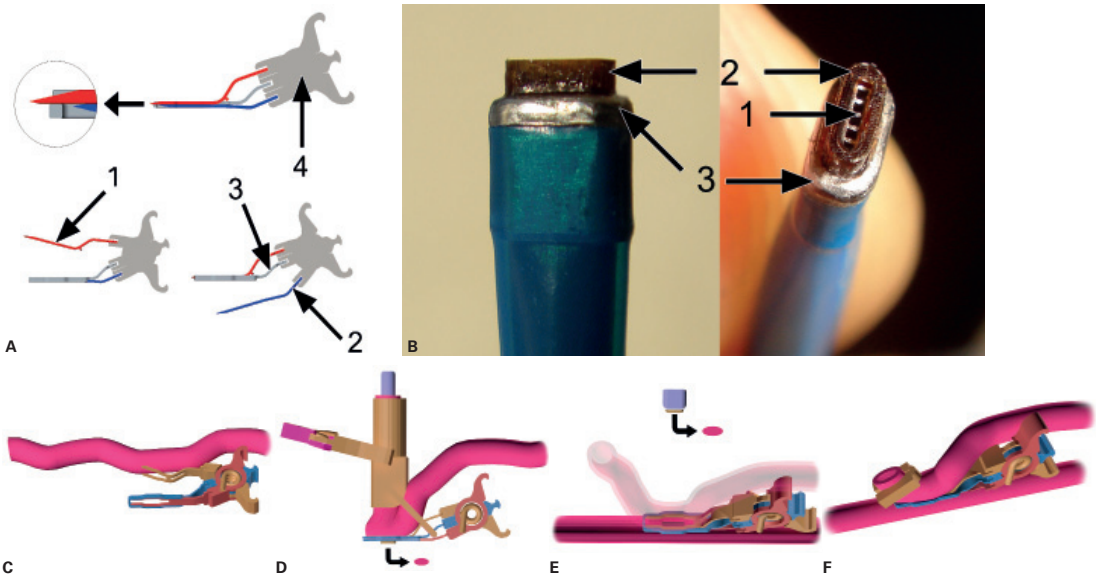

Figure 1. The coronary anastomotic procedure with the Trinity Clip connector and laser catheter

A: The Trinity Clip (titanium) consists of 2 intravascular forks (upper, *(1)*, and lower fork, *(2)*) and an extravascular band *(3)*. The forks and band are connected to a spring *(4)*, which enables the forks to open and close, individually, one by one, with the use of an applicator (not shown).

B: The laser consists of a vacuum lumen *(1)*, which is surrounded by laser fibers *(2)*. An outer band *(3)* provides safety and stabilization into the connector.

C: The upper fork is inserted into the lumen of the graft by using an applicator (not shown).

D: The laser is introduced and temporary secured by a fixation clip, which fixates and stabilizes the laser into the connector, ensuring perpendicular positioning of the laser during construction. The graft is laser-punched and the laser-punched fragment is removed from the laser (arrow). Note that the laser is not removed.

E: The lower fork is inserted into the lumen of the coronary. The graft (illustrated transparently) and coronary are fixated between the 2 intraluminal forks and the extravascular band. The coronary is laser-punched under full native coronary flow and, subsequently, the fixation clip is removed and the laser is retrieved, including the laser-punched fragment of the coronary wall (arrow) by vacuum suction through the laser.

F: Directly following the nonocclusive opening of the anastomosis, the distal end of the graft is ligated.

The nonocclusive anastomosis construction is accomplished by:

1. Mounting of the graft and laser by inserting the upper fork of the connector into the distal end of the graft (Figure 1C). Subsequently, the laser (Corvasco Medical b.v., Utrecht, The Netherlands; Figure 1B) is introduced into the connector and laser-punches an opening into the graft (transmural, from intima to adventitia; Figure 1D).
2. Prebounding of graft to coronary by inserting the lower fork into the lumen of the unopened and not occluded coronary artery.
3. Nonocclusive opening of the coronary by laser-punching under full native coronary flow (transmural, from adventitia to intima; Figure 1E) and subsequent ligation of the distal end of the graft (Figure 1F).

Animals

Fifty-eight Dutch Landrace pigs (female, ±70 kg) were studied. The animals were fed a normal diet and received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council. The animal experimentation committee of the Utrecht University approved the protocol. All pigs received 320 mg of acetylsalicylic acid and 75 mg clopidogrel orally daily, starting 3 days before surgery. This anticoagulation protocol was continued until termination.

Anesthesia and Euthanasia

Anesthesia was induced with ketamine (10 mg/kg), midazolam (0.5 mg/kg), and atropine (0.04 mg/kg) intramuscularly. Each animal received antibiotic prophylaxis (amoxicillin-clavulanic acid 1000/100 mg), thiopental sodium (4 mg/kg), midazolam (0.5 mg/kg), and sufentanil citrate (6 μg/kg) through an intravenous line. The animals were intubated and ventilated with a mixture of oxygen and air (1:1 volume/ volume). Anesthesia was maintained by a continuous intravenous infusion of midazolam (0.7 mg/kg/h), analgesia was obtained with an infusion of sufentanil citrate (6 μg/kg/h), and muscle relaxation with pancuronium bromide (0.1 mg/kg/h). During the operation, each animal received a continuous infusion of saline solution (300 mL/h). Metoprolol was administered intravenously (range, 5-20 mg) to reduce the mechanical irritability of the heart until a heart rate of approximately 70 beats/min was obtained. Postoperatively, amoxicillin-clavulanic acid (7.5 mg/kg) was administered and for post-surgical analgesia fentanyl 25 μg transdermally for 3 days and meloxicam (0.4 mg/kg) intramuscularly daily at day 1 and 2. Animals were put to death with pentobarbitalsodium (200 mg/kg) intravenously, after having been heparinized to obtain an activated clotting time (ACT; Hemotec, Inc, Englewood, Colo) of at least 4 times the control value.

Surgery, Experimental Model, and Study Design

After a partial sternotomy, harvesting the left internal thoracic artery (LITA), partial heparinization (activated clotting time [ACT] > 200; not counteracted), and immobilization of the left anterior descending coronary artery (LAD; 1.6–1.9 mm OD) by a cardiac tissue stabilizer (Octopus Evolution AS Tissue Stabilizer; Medtronic Inc, Minneapolis, Minn), the bypass was constructed either with the connector as earlier described or by hand-suturing using an intracoronary arteriotomy shunt (Medtronic Inc, Minneapolis, Minn) and a running suture (Prolene 7-0; Ethicon, Somerville, NJ). Following construction, the coronary was ligated ±1.0 cm upstream with 3 medium hemoclips. Before chest closure, graft flow (mL/min) and pulsatility index ([maximum flow-minimum flow]/mean flow) was monitored for 1 hour with a transit time flow probe (VeriQ C; Medi-Stim ASA, Oslo, Norway), at a mean blood pressure of 90 mm Hg. Following ITA clamping for 30 seconds, the coronary peak hyperemic flow response was determined (45 minutes after construction, in duplicate, at an interval of 10 minutes) as the peak graft flow divided by the baseline flow.

A total of 33 connector-facilitated and 25 hand-sutured LITA-to-LAD anastomoses were constructed. The follow-up was completed for 56 pigs (1 pig of each subgroup died directly postoperatively). The safety of the technique was assessed by anastomotic hemostasis, graft flow measurement, angiography, and anastomotic healing (ie, effect of implant, vessel wall compression by the connector, and laser-punching of the LITA

Figure 2. The Trinity Clip before and after the design change

The Trinity Clip after the design change (left) is longer and 20% heavier compared to the connector before the design change (right).

and LAD; by histologic examination and scanning electron microscopy). The anastomoses were evaluated intraoperative (n=58) and postoperatively at 4 hours, 4, 10, 14, and 35 days (each subgroup per timeline n=2 anastomoses) and at 3 (n=10 connector, n=6 hand-sutured) and 6 months (n=12 connector, n=8 hand-sutured). Halfway the study, a design change of the connector was implemented to improve the mechanics of the connector in order to enhance hemostasis. The spring part of the connector was changed and ameliorated the stability of opening, closing, and compression of the connector (the spring of the connector is longer and 20% heavier; Figure 2). This design change was introduced after the first 15 connector-facilitated procedures (Group 1; 5 weeks [n=2]; 3 months [n=1]; 6 months [n=12]) and the connector with the new design facilitated the last 18 procedures (Group 2; 4 hours, 4, 10, and 14 days [each subgroup per timeline n=2]; 3 months [n=9]; 1 pig died directly postoperatively).

Follow-up Catheterization, Histology, and Scanning Electron Microscopy (SEM)

At follow-up, all anastomoses (n=56) were visualized by angiography (Philips Allura Xper FD20, Eindhoven, The Netherlands) and graded by 2 independent observers according to the FitzGibbon criteria.

One anastomosis per subgroup of each of the following timelines, 4 hours, 4, 10, 14, and 35 days (n=5 hand-sutured, n=5 connector), and additionally, all anastomoses at 3- and 6-month follow-up, were fixed in 4% formalin for histologic examination. The connector-facilitated anastomoses (n=28) were embedded in methyl methacrylate and the hand-sutured anastomoses (n=20) were embedded in paraffin, all were sectioned in transverse planes and stained with hematoxylin and eosin (H&E). Neointimal hyperplasia, adverse remodeling, and chronic inflammatory cell reaction were assessed (AnalySiS, Soft-Imaging Software GmbH, Münster, Germany).[2-5]

One anastomosis per subgroup of each of the following timelines, 4 hours, 4, 10, 14, and 35 days, was evaluated by SEM (n=5 hand-sutured, n=5 connector; Philips XL30LAB, FEI Europe, Eindhoven, The Netherlands) to study endothelialization of the non-intimal anastomotic surface.[4, 5]

Hemostasis

Hemostasis was quantified as either completely hemostatic, or oozing, or brisk leakage. Any self-limiting leakage was defined as oozing. If a stitch was necessary to obtain hemostasis, the leakage was defined as brisk.

Statistical Analysis

Data are presented as the mean ± standard deviation, or as noted otherwise. The difference between continuous variables was analyzed using the Student T-test and the differences between dichotomous variables were analyzed using the Fisher's exact test. P<0.05 was considered to indicate a significant difference.

RESULTS

Surgery

All procedures were performed by 1 investigator (D.S.; see Table 1 for the Operative Data). A faster construction time was found in the connector group compared to the hand-sutured group (P<0.01). In 3 procedures, a laser-punch failure (ie, incompletely lasering of the coronary wall) resulted in a successful re-do of the anastomosis distal to the initial anastomosis. One case occurred at the start of the study and was attributed to the learning curve. In 2 cases, it was due to a malfunctioning fixation clip, and these were excluded.

Table 1. Operative Data

	Connector	Suture	P =
LITA (mm, OD)	2.9 ± 0.3	3.0 ± 0.3	0.33
LAD (mm, OD)	1.8 ± 0.1	1.8 ± 0.1	0.90
Construction time (min)	3.2 ± 0.6 [a]	36 ± 6	<0.01
Flap retrieval rate (%)	97 (33/34) [b]	-	
Complete hemostasis (%)	94 (31/33)	80 (20/25)	0.11
Graft baseline flow (mL/min)	22 ± 5	22 ± 5	0.92
Pulsatility index at baseline	2.5 ± 1.0	2.5 ± 1.3	0.92
Graft flow at t=1 hrs (mL/min)	20 ± 6	22 ± 5	0.18
Pulsatility index at t=1 hrs	2.7 ± 0.9	2.8 ± 1.5	0.91
Peak hyperemic flow response	4.4 ± 1.0	4.6 ± 1.1	0.47

Data presented as mean ± standard deviation or % (n).

[a] Included insertion, positioning laser catheter and external fixation clip, vacuum suction, lasering, and closure of distal end of the graft.

[b] In 3 of 36 anastomoses, the coronary was not successfully laser-punched. In 2 of 3 laser-punch failures, a mechanical issue causing the laser-failure was found, and these were excluded from further analyses.

LAD, left anterior descending artery; LITA, Left internal thoracic artery; OD, outer diameter.

Brisk leakage was found in 6% (2/33) and in 20% (5/25) of the anastomoses in the connector and hand-sutured group, respectively; an extra stitch resulted in complete hemostasis. The 2 cases of brisk leakage in the connector group were found in the first 15 experiments, after which a design change of the connector was implemented to improve hemostasis. Following this change, leakage was not observed (0/18). Graft flow measurements were all comparable, suggesting full intraoperative patency in both groups (Table 1).

Follow-up and Angiography

Two animals (1 of the connector and 1 of the hand-sutured group) died directly post-operatively due to respiratory insufficiency and patent anastomoses were found. All hand-sutured anastomoses were fully patent (24/24). Of the connector-facilitated anastomoses, in Group 1 (before the design change), 1 of 15 anastomoses was occluded at 6 months (Table 2). However, the occlusion was due to competitive flow caused by a subtotal ligation (±60%) of the native proximal coronary artery. In Group 2 (after the design change), 4 of 17 anastomoses were occluded; 3 at 3 months and 1 occlusion was found at 14 days.

Table 2. Patency Data: Before and After Design Change of the Connector

	Connector			Suture
	Total	*Group 1*	*Group 2*	
Total patency (%)	84 (27/32) [a]	93 (14/15) [b]	76 (13/17)	100 (24/24)
Short-term patency (%)	90 (9/10)	100 (2/2)	88 (7/8)	100 (10/10)
Long-term patency (%)	82 (18/22) [c]	92 (12/13) [b, d]	67 (6/9) [e]	100 (14/14)

Patency is defined as: FitzGibbon grade A and B. Short-term is defined as: 0 - 35 days. Long-term is defined as: 3 and 6 months.

[a] p= 0.053 versus suture. [b] 1 occlusion at 6 months was found and in this particular case, the native proximal coronary artery was not fully occluded (subtotal occlusion ±60%), causing competitive flow. [c] p= 0.12 versus suture. [d] p= 0.48 versus suture. [e] p= 0.047 versus suture.

Group 1: Before the design change.

Group 2: After the design change.

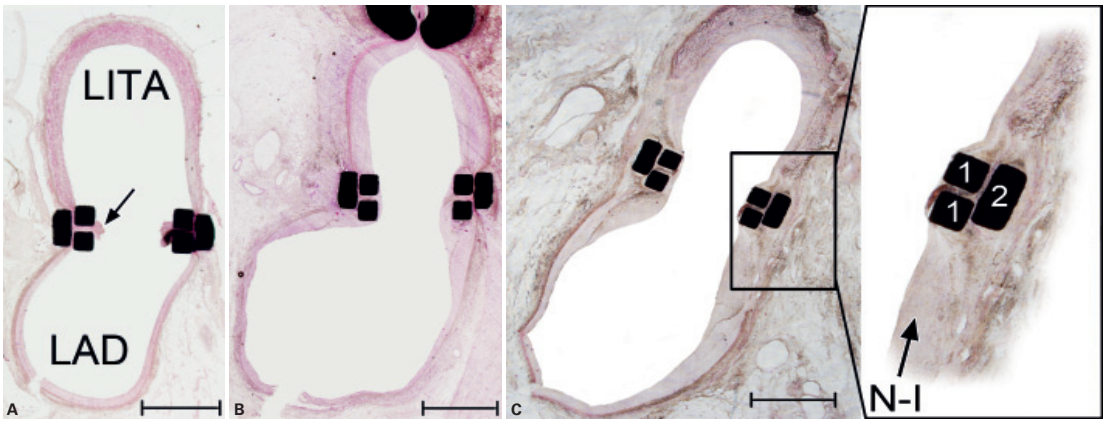

Figure 3. Histology of the Trinity Clip facilitated LITA-to-LAD anastomosis at different time-points postoperatively

Transverse sections, midanastomosis, H&E staining. Scale bar indicates 1 mm.

A: At 4 hours, the wall of both the LITA and LAD is compressed in between the forks and the extravascular band of the connector. A laser rim (*arrow*) of both the LITA and LAD is present on each lateral side and protrudes 0.1 mm.

B: At 10 days, the laser rim is retracted and the initial blood-exposed forks of the connector are completely covered by neointima. Note the hemoclip at the roof of the LITA, which ligates the 'cul de sac'.

C: At 6-month follow-up, the connector is covered by neointima (*N-I*), streamlining the anastomosis (magnified subsection). No medial necrosis, excessive intimal hyperplasia, or chronic inflammation was demonstrated over time.

(*1*) forks, (*2*) extravascular band.

Note, interruption of the inferior coronary wall caused by longitudinally opening of the coronary before inspection.

H&E: Hematoxylin and eosin stain; LAD: left anterior descending artery; LITA: left internal thoracic artery.

Histologic Examination

Healing and remodeling. All connector-facilitated anastomoses showed an inverted adventitia-adventitia apposition, with the adventitia of the graft on top of the adventitia of the coronary, which resulted in a blood-exposed edge of media and adventitia of both vessels, inside the anastomosis. The hand-sutured anastomosis showed predominantly an everted intima-intima apposition. At 4 hours, no acute laser-damage and minor deposition of platelets at the laser rim was found, with some pyknosis of smooth muscle cell nuclei at the compression site (Figure 3A). At 4 days, the laser rim was covered by a small platelet-rich thrombus, and at 10 days, the rim was retracted and completely covered by neointima (0.10 ± 0.07 mm), including the connector (Figure 3B). At that time, similarly, a layer of neointima covered the anastomotic line of the hand-sutured anastomosis (0.19 ± 0.03 mm).

At 35 days, 3, and 6 months (Figure 3C), both the connector and hand-sutured anastomoses were remodeled and fully covered by neointima (0.10 ± 0.02 versus 0.28 ± 0.07 mm; 0.07 ± 0.04 versus 0.20 ±

0.08 mm [P<0.01]; 0.08 ± 0.06 versus 0.26 ± 0.07 mm [P<0.01]; respectively, connector [without occluded anastomoses] versus hand-sutured). No pseudoaneurysm formation, no medial necrosis at the compression surface, and moreover, no excessive acute or long-term inflammation was demonstrated over time. The spring of the connector was completely encapsulated in connective scar- and repair tissue and incorporated in between the LITA and LAD, without erosion damage.

Anastomotic occlusion. Of the connector-facilitated anastomoses in Group 1, at 6 months, 1 anastomosis was occluded by gradual intimal hyperplasia formation caused by competitive flow (subtotal occlusion of native coronary). One additional anastomosis at 6 months showed a dissection of the LITA, originating proximally with a hematoma in between the intima and media, which had developed downstream toward the anastomosis, resulting in an approximately 50% occlusion.

In 1 of the 4 occluded anastomoses in Group 2, at 14 days, a thrombus occluded the anastomosis. At the toe, insufficient convergence of the forks due to asymmetric closure resulted in inadequate vessel wall compression. As a result, the laser-punched opening in the coronary wall shifted at the toe in relation to the lasered-opening of the graft, causing abnormal blood-exposed adventitial graft tissue, which was not seen in other anastomoses. In 3 anastomoses at 3 months, tilting of the connector in relation to the coronary artery was showed, plus a downward movement of the spring of the connector at the heel and an upward movement of the pins at the toe. This resulted in distortion of the connector and consequently the geometry of the target coronary at the site of the anastomosis, and presumably caused the occlusion of the 3 anastomoses.

Scanning Electron Microscopy

In the acute phase, a sharp laser-cut edge of both the LITA and the LAD with limited platelets attached to the rim and to the connector, and no endothelial laser-damage was seen (Figure 4A). After 10 days, the inner - initial nonintimal - surface was completely covered by a smooth layer of neointima, except for the medial inner surface of the pins (Figure 4B), while the prolene sutures in the hand-sutured anastomosis were fully endothelialized at 10-day follow-up. A continuous endothelial surface from the coronary artery over the connector and the rim into the LITA could be seen at 14 and 35 days.

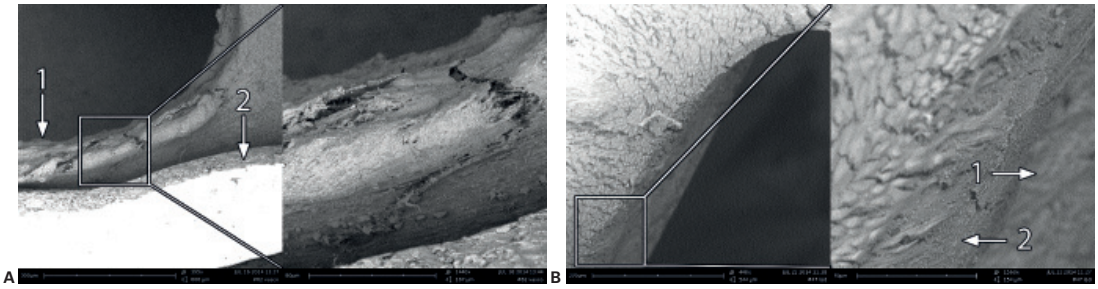

Figure 4. Scanning electron microscopy of the Trinity Clip facilitated LITA-to-LAD anastomosis at different points postoperatively

View from inside the LAD. The lasered coronary wall rim (1) and pin of the lower fork (2).

A: At 4 hours (395x magnification). The magnified (1440x) subsection demonstrates the sharp laser cut through the coronary (*1*) and limited fibrin and platelets coverage.

B: At 10 days (440x magnification). Complete endothelialization of the connector is demonstrated, except for the medial side of the fork (*2*). The magnified (1560x) subsection shows the process of endothelialization on this part of the fork; endothelial cells are migrating from the top of the fork toward the medial side, covering the circumference of the anastomotic orifice.

LAD: left anterior descending artery; LITA: left internal thoracic artery.

DISCUSSION

The principal findings are the following: the nonocclusive connector is feasible on small caliber coronary arteries and easy-to-use with a fast construction time without myocardial ischemia in the OPCAB porcine

model. The patency of the connector-facilitated anastomoses was inferior to the hand-sutured anastomoses (84% versus 100%) and was histologically related to distortion of the connector. However, a comparable initial anastomotic healing process was demonstrated and the patent anastomoses showed less intimal hyperplasia at the site of the connector compared to the hand-sutured anastomosis at 6 months (0.08 ± 0.06 versus 0.26 ± 0.07 mm, respectively; P<0.01).

Inferior Patency Rates and Implementation of the Design Change

After the first 15 consecutive connector-facilitated procedures, the design of the connector was changed to improve hemostasis; 2 cases of brisk leakage were found in the first 15 procedures (Group 1) and after the design change leakage was not observed (0/18, Group 2). However, in Group 2 (ie, the spring of the connector is longer and 20% heavier; Figure 2), 3 occlusions presumably due to distortion of the connector were found at 3 months (Table 2). We hypothesize that the increased weight and length (ie, increased lever arm) of the spring promotes external forces onto the anastomosis leading to increased mechanical stresses onto the small caliber and thin vessel walls (± 0.15 - 0.20 mm), which resulted in distortion of the connector, confirmed by histology, and subsequent occlusion of the anastomosis.

Group 1 showed superior patency results, with patent anastomoses at 5-week (n=2/2), 3-month (n=1) and 6-month (n=11/12) follow-up (Table 2). One anastomosis at 6 months was not patent, however, was due to competitive flow. In addition, all 3 anastomoses with a re-do anastomosis, due to a laser-punch failure, and, moreover, the 2 anastomoses requiring a hemostatic stitch, were part of Group 1 and showed, despite the extra maneuvers and manipulation, patent anastomoses at 6 months. Therefore, these results clearly suggest that the design change, in addition to the benefits for anastomotic hemostasis, had an adverse effect on the primary outcome, ie, anastomotic patency.

Key Features

Besides the failures encountered in this series, the anastomotic technique per se has potential to facilitate minimal access CABG. Compared to the single clinically available anastomotic device,[6-8] and other connectors which not (yet[9]) succeeded clinically,[10-14] the unique concept of nonocclusive anastomosis construction provides several interesting features. The first simple step, the connector-facilitated apposition of the graft to the coronary, is fast, bloodless, and performed with full sight, without blockage of instrumentation or a cumbersome activation system. In addition, it is reversible in case of malposition (ie, bail-out). The second step, the anastomotic opening by laser-punching, is standardized and reproducible with a sharply laser-cut oval-shaped orifice resulting in a geometry without impediment to flow. In contrast to other connectors, no separate incision into the graft or coronary is needed and the native coronary flow does not have to be interrupted.[6-12] The anastomosis is constructed without the potentially harming effects of temporary occlusion of the coronary or intracoronary shunting[15] and hence, there is no time-constraint related to myocardial ischemia. Finally, no standard extra hemostatic stitches[6-8] were required after the design change was implemented; all these features reduce coronary handling, conditioning, and manipulation, and thus simplify the off-pump bypass procedure, especially in a minimally invasive approach. Moreover, this controlled two-step approach results in a short learning curve. Moreover, in the absence of large application systems, this low-profile anastomotic system could reach all territories of the heart.

Future Perspective

Based on the results of this study, quality checks have been established incorporating in- and exclusion criteria for the connector and the lifespan of instruments (eg, external fixation clip). With this experience, a subsequent preclinical safety study will be initiated with a second-generation Trinity Clip, which will prevent distortion and displacement of the connector, either by stabilization of the complex of graft, connector, and coronary artery, or by removal or downsizing of the spring of the connector. Provided the technical limitations can be addressed, this concept of nonocclusive anastomotic construction could fill the missing link toward expansion of minimally invasive CABG.

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DISCLOSURES

David Stecher, Glenn Bronkers, Cornelis A.F. Tulleken, and Marc P. Buijsrogge are registered as co-inventors of patents regarding the ELANA technique, without financial benefits. Cornelis A.F. Tulleken holds shares in Corvasco Medical b.v., Utrecht, The Netherlands and is founder of the ELANA technique. All other authors declare no competing financial interests.

REFERENCES

1. Fishell TA, Virmani R. Intracoronary brachytherapy in the porcine model. A different animal. *Circulation* 2001;104:2388-90.
2. Stecher D, de Boer B, Tulleken CA, Pasterkamp G, van Herwerden LA, Buijsrogge MP. A new nonocclusive laser-assisted coronary anastomotic connector in a rabbit model. *J Thorac Cardiovasc Surg* 2013;145:1124-9.
3. Stecher D, van Slochteren FJ, Hoefer IE, et al. The nonocclusive laser-assisted coronary anastomotic connector in an off-pump porcine bypass model. *J Thorac Cardiovasc Surg* 2014;147:1390-7 e1392.
4. Stecher D, Agostoni P, Pasterkamp G, Hoefer IE, van Herwerden LA, Buijsrogge MP. Six-month healing of the nonocclusive coronary anastomotic connector in an off-pump porcine bypass model. *Innovations* 2014;9:130-6.
5. Stecher D, Bronkers G, Noest JOT, et al. Evaluation of a novel laser-assisted coronary anastomotic connector - the trinity clip - in a porcine off-pump bypass model. *J Vis Exp* 2014;93:e52127, doi:10.3791/52127.
6. Verberkmoes NJ, Wolters SL, Post JC, Soliman-Hamad MA, ter Woorst JF, Berreklouw E. Distal anastomotic patency of the Cardica C-Port(R) xA system versus the hand-sewn technique: A prospective randomized controlled study in patients undergoing coronary artery bypass grafting. Eur *J Cardiothorac Surg* 2013;44:512-9.
7. Balkhy HH, Wann LS, Arnsdorf S. Early patency evaluation of new distal anastomotic device in internal mammary artery grafts using computed tomography angiography. *Innovations* 2010;5:109-13.
8. Matschke KE, Gummert JF, Demertzis S, et al. The Cardica C-Port System: Clinical and angiographic evaluation of a new device for automated, compliant distal anastomoses in coronary artery bypass grafting surgery--a multicenter prospective clinical trial. *J Thorac Cardiovasc Surg* 2005;130:1645-52.
9. Suyker WJ, Buijsrogge MP, Suyker PT, Verlaan CW, Borst C, Grundeman PF. Stapled coronary anastomosis with minimal intraluminal artifact: the S2 Anastomotic System in the off-pump porcine model. *J Thorac Cardiovasc Surg* 2004;127:498-503.
10. Schaff HV, Zehr KJ, Bonilla LF, et al. An experimental model of saphenous vein-to-coronary artery anastomosis with the St. Jude Medical stainless steel connector. *Ann Thorac Surg* 2002;73:830–5.
11. Vicol C, Eifert S, Oberhoffer M, Boekstegers P, Reichart B. Mid-term patency after magnetic coupling for distal bypass anastomosis in coronary surgery. *Ann Thorac Surg* 2006;82:1452–6.
12. Martens S, Dietrich M, Doss M, Moritz A, Wimmer-Greinecker G. The Heartflo device for distal coronary anastomoses: clinical experiences in 60 patients. *Ann Thorac Surg* 2002;74:1139–43.
13. Suyker WJ, Borst C. Coronary connector devices: analysis of 1,469 anastomoses in 1,216 patients. *Ann Thorac Surg* 2008;85:1828–36.
14. Werker PM, Kon M. Review of Facilitated Approaches to Vascular Anastomosis Surgery. *Ann Thorac Surg* 1997;63:S122-7.
15. Gerosa G, Bottio T, Valente M, Thiene G, Casarotto D. Intracoronary artery shunt: an assessment of possible coronary artery wall damage. *J Thorac Cardiovasc Surg.* 2003;125:1160-2.

9

DISCUSSION AND CONCLUSIONS

DISCUSSION

The aim of this thesis was to develop and evaluate a new coronary anastomotic connector, based on an existing concept: the ELANA technique. This ELANA technology enables nonocclusive anastomosis construction with the most obvious advantage of not having to occlude the recipient artery. Proof of concept is shown in neurosurgery, but coronary bypass surgery is performed in a different environment with a moving target and small caliber vessels, often with low flow. The technique needed downsizing of both the connector ring and the laser catheter. A new design should ultimately enable a simplified and reliable connection of the graft to the coronary artery on the beating heart via a less or minimal invasive surgical approach. In addition, the connector should be easy-to-use, without additional sutures, and it should be applicable to remote and small caliber targets, inherently, resulting in low-flow bypasses.[1-4] To succeed in developing a coronary anastomotic connector, all the previous mentioned changes of the original ELANA connector design have to be fulfilled.

Part A – The Slide Connector

In Part A (Chapter 2), a first-generation ELANA-based prototype connector, the "Slide connector", was evaluated in an acute rabbit abdominal aortic-bypass model as an open feasibility concept study. With this prototype, the first step in the change of design was made: the connection of the mounted graft to the coronary artery was simplified by sutureless application. The Slide connector enabled easy-to-use, nonocclusive, and fast anastomosis construction with a 100% patency and a predictable and consistent intima–adventitia apposition. Several technical imperfections persisted, such as occasional failure to retrieve the flap with the laser catheter, the need for a sealant for anastomotic hemostasis, and sutures were still required for mounting the graft. Limitations of the model include the absence of evaluation on the beating heart and long-term anastomotic healing. A proof-of-concept is presented in an acute animal model, however, imperfections of the connector have to be addressed to show the feasibility for minimally invasive coronary artery bypass surgery.

Part B – The Clip Connector

In Part B (Chapters 3 and 4), an ameliorated second-generation ELANA-based prototype connector, the "Clip connector", was evaluated in an acute rabbit model and subsequently in a long-term porcine open sternotomy OPCAB model. The Clip connector incorporated the next steps toward a clinical device: the surgical sealant was eliminated, the technique was simplified by the ability of the connector to open and close, and laser-punching was optimized. However, mounting of the graft to the connector still requires sutures, which is time-consuming and increases the demands of manual dexterity.

The extra feature of this connector compared to the Slide connector was the ability to open, close, and reopen. This introduced a simplified and controlled method of 2-step coronary bypass grafting: first, nonocclusive prebounding of the graft to the coronary artery, and second, a laser-punched arteriotomy. As a consequence, an additional set of three improvements was obtained.

A "bail-out" approach was created for both malpositioning and a laser-punch failure. In case of connector malpositioning, the connector can be reopened and repositioned before the point of no return, which is the lasered-arteriotomy. In case the flap could not be retrieved directly by the laser catheter, a bail-out is feasible, with manual flap retrieval by reopening of the connector.

The third improvement is the cone-shaping of the laser catheter. This improved positioning and stabilization of the laser catheter into the connector with an enhanced laser-punch success rate as a consequence. In one out of 15 anastomoses a laser-punch failure occurred and this flap was subsequently successfully manually retrieved by reopening the Clip connector as a bail-out.

The Clip connector demonstrated its ease-of-use in both animal models, with a simple first step of nonocclusive prebounding of the vessel walls of graft and coronary artery; no need to seal the anastomosis and no separate incision into the target coronary.[5-8] The anastomotic construction was performed in a bloodless field, without time constraint. In contrast to most other coronary anastomotic connectors, coronary

conditioning by shunting or snaring was redundant.[5-8] These improvements resulted in reduced manipulation and increased simplicity, which are important aspects in the steps toward less invasive off-pump coronary artery bypass surgery.

The unconventional anastomosis construction, with 1) a laser-punched arteriotomy, 2) active compression of the vessel walls between the fork and ring of the connector, 3) apposition of the intima of the graft to the adventitia of the coronary artery, 4) the residual implant of the extravascular spring at the back of the connector, and 5) the intraluminal, blood-exposed fork, had no detriment on the long-term patency or remodeling of the anastomosis. Please note that the BENIS of the Clip connector was increased to 7.9 mm^2, compared to 4.4 mm^2 in the Slide connector and the dual antiplatelet therapy conformed to proposals for guidelines for postoperative care in conventional OPCAB surgery.[9] Moreover, after 10 days, the device was fully endothelialized and the anastomotic orifice tended to expand over time by retraction of the laser rim toward the maximal opening of the connector. The result at 6 months is limited intimal hyperplasia with an unrestricted flow (FFR, 0.93 ± 0.07). This period of follow-up is comparable with 1.5 – 3 years of human clinical follow-up.[10]

Initially, the anastomosis was relatively undersized (FFR, 0.82 ± 0.17). The increased protrusion of the tip of the cone-shaped laser catheter into the connector resulted in unwanted extension of the adventitial laser rim (a rim length of 0.63 ± 0.09 versus 0.11 ± 0.12 mm in a previous study without a cone-shaped catheter[11]). This resulted in a smaller anastomotic orifice than the intended 2 mm diameter. The extension of the adventitial rim applied to more than half of the total BENIS. The BENIS, however, is inherent to distal anastomotic connectors and is not per se detrimental.[1] Nevertheless, the tolerance to additional technical errors becomes smaller; in Chapter 3, the additional technical error of an asymmetrically lasered rim resulted in a fatal thrombotic occlusion. Consequently, this emerged for modifications to the laser catheter, which should ultimately result in 1) a relatively larger anastomotic orifice in relation to the target coronary artery, 2) a reduction in the intraluminal adventitial laser rim and thus in tissue BENIS, 3) an optimized laser-punch success rate, 4) a symmetric morphology of the laser-punched orifice, and 5) an oval-shaped configuration to target smaller coronary arteries. Furthermore, mounting of the graft with sutures should also be addressed, because it is time-consuming and increases the demand of dexterity. In addition, because most coronary bypasses are constructed within a coronary diameter range of 1.5 – 2.5 mm outer diameter, downsizing the anastomotic connector is of paramount importance. Moreover, the animal studies need controls, including a hand-sutured group, and an adequate sample size.

Part C – The Trinity Clip Connector

Part C (Chapters 5 – 8) contains a comprehensive evaluation of the third-generation ELANA-based prototype connector, the "Trinity Clip connector". Several preclinical experimental models have been used: a human ex vivo atherosclerotic model, an acute porcine MIDCAB model, and a long-term porcine OPCAB model. Design modifications of the connector and the excimer laser catheter (now oval shaped) enabled a completely sutureless construction of the anastomosis onto clinically relevant, small caliber coronary arteries. The construction time was reduced from more than 30 minutes in the Clip connector (Chapter 3) to 3.2 minutes in the porcine OPCAB model, described for the Trinity Clip connector in Chapter 8. The reduced construction time is ascribed to the elimination of mounting sutures and the premounting of the laser catheter (Preface C).

In the preclinical assessment of the newly developed Trinity Clip connector, the following remaining questions have to be answered:

1) Is this laser-assisted anastomotic technique feasible in human diseased coronary arteries?
2) Does laser-punching induce arterial wall damage in small coronary targets?
3) Is the connector applicable via a minimal invasive approach in remote areas of the heart?
4) Is the connector feasible off-pump, onto small caliber coronary arteries and is the long-term patency comparable to the hand-sewn anastomoses?

In Chapter 6, the first question is addressed and we demonstrated the feasibility of the anastomotic

technique in human ex vivo diseased coronary arteries. However, severely atherosclerotic lesions caused malpositioning of the connector and one laser-punch failure. Similar to clinical practice, it is not recommended to graft a severely diseased coronary artery with the Trinity Clip. Another cause for malpositioning was observed if the coronary target was smaller than the intended diameter range of the connector, 1.4 – 1.6 mm inner diameter (= ID). To enhance the anastomotic success rate, the coronary segment should be more meticulously selected by measuring the ID on preoperative coronary angiography or intraoperative epicardial ultrasound (= ECUS) and by the assessment of disease status by tactile and visual inspection or ECUS.

The second question is answered in the second part of Chapter 6. We histologically evaluated the potential harming effects of exposing a small target vessel to the same levels of laser energy (10 mJ)[12] as used in previous studies on larger caliber coronary arteries.[11, 13, 14] On microscopic examination, it was showed that lasering does not induce coronary wall damage. However, the laser also punches the graft in the anastomosis construction with the Trinity Clip connector. This new construction method raises new questions regarding the effects of laser-punching on the grafts vessel wall. In Chapter 8, microscopic examination showed no excessive intimal hyperplasia of the graft in the long-term.

To answer the third question, an experimental pilot feasibility study in the porcine model was described in Chapter 7, which demonstrated the feasibility of the anastomotic technique in a total arterial MIDCAB approach. Via this approach, revascularization of the anterior, lateral, and inferoposterior regions of the heart proved to be feasible and a fast and standardized construction of a Y-graft was possible. The mounted and secured upright laser fulcrum was not a drawback in this setting, provided that the coronary target was center-positioned in relation to the access site so a collision of the fulcrum to the chest wall could be prevented. However, the reduced workspace hampered visualization during insertion of the connector into the coronary artery in absence of video-scopic assistance.

In a previous experiment, the feasibility of robot-assisted TECAB by using the Trinity Clip connector was demonstrated in an acute porcine model, but in this setting the laser fulcrum limited expediency.[15] In the TECAB setting, mounting the laser catheter, which is positioned via the graft into the connector, was very challenging. This was mainly due to the rather stiff and rigid laser catheter, which directed the surgeon, rather than that the surgeon directed the laser.

From this experience we conclude that dedicated application tools, more specifically a versatile applicator and a flexible laser catheter, and optimization of visualization by video-scopic assistance, are essential to succeed in minimally invasive anastomosis construction.

To answer the last question, in Chapter 8, we describe a preclinical safety study in which hand-sewn anastomoses and the Trinity Clip connector were evaluated on small caliber coronary arteries in a long-term porcine OPCAB model. The initial anastomotic healing process was similar in the hand-sutured anastomosis and the Trinity Clip connector. We found complete endothelialization of the nonintimal anastomotic surface within 14 days. The patency of the connector-facilitated anastomoses in the long-term was inferior to the hand-sewn anastomoses (82% versus 100%) and was histologically related to distortion of the connector. However, the patent connector-facilitated anastomoses showed less intimal hyperplasia at the anastomotic line compared to the hand-sutured anastomosis (at 6 months 0.08 ± 0.06 versus 0.26 ± 0.07 mm, respectively; $P<0.01$). This could be explained by a favorable healing reaction due to a less traumatic anastomosis construction. The inferior patency rate of the Trinity Clip connector may be related to a design change halfway of the study, which aimed at enhanced stability of the connector in order to improve hemostasis. After the design change the spring of the connector was longer and 20% heavier. The change was implemented after operation of the first 15 long-term animals, in which two cases of brisk leakage were observed but no device-related anastomotic occlusions. In the 18 experiments after the design change, no leakage was found, however, at three months, three occlusions were found due to distortion of the connector. We hypothesized that the increased weight and length of the spring promoted external forces onto the anastomosis, resulting in increased mechanical stress on the vessel wall and distortion of the anastomosis. This could lead eventually to gradual luxation of the connector, excessive intima hyperplasia, and finally occlusion of the bypass.

CONCLUSIONS

The studies in Part C of this thesis have shown that the Trinity Clip connector meets most of the requirements for "The Ideal Coronary Anastomotic Connector" in Chapter 1. However, essential specifics have to be ameliorated to adhere to the high standards for anastomotic connectors. If these have been addressed, the connector has conceivable potential to facilitate minimally invasive coronary artery bypass surgery.

Handling and Practical Use

The Trinity Clip is easy-to-use with a fast construction time and zero myocardial ischemia. The construction is safe, reliable, and reproducible on the beating heart, resulting in a standardized inverted adventitia-to-adventitia apposition, without anastomotic leakage (Chapter 8, Group 2). The applicability on the arrested heart is not extensively evaluated, but is feasible too, as long as the coronary artery is perfused. Moreover, histologic evaluation did not show laser-induced vessel wall damage in the acute phase or long-term follow-up (Chapter 6 and 8). However, in Chapter 8, distortion and tilting of the connector was observed at 3-month follow-up. Prevention of the latter, either by stabilization of the complex of graft, connector, and coronary artery, or by removal or downsizing of the spring of the connector, will further standardize the construction. With this, an enhanced durability and long-term effectiveness is anticipated on.

Compared to the single clinically available anastomotic device,[7, 16, 17] and other connectors, which not (yet[8]) succeeded clinically,[5, 6] the unique concept of nonocclusive anastomosis construction provides several interesting features. The first step, the connector-facilitated apposition of the graft to the coronary, is simple, fast, bloodless, and performed with full sight, without blockage of instrumentation or a cumbersome activation system, and results in a strong approximation resisting supraphysiologic pressures. In addition, it is reversible in case of malposition (ie, bail-out). The second step, laser-punching the anastomosis, is simple, standardized, and reproducible, with a sharply laser-cut oval-shaped orifice resulting in a geometry without impediment to flow (Chapter 8). So, no separate incision into the graft or coronary is needed and in contrast to other connectors, the native coronary flow does not have to be interrupted.[5-8, 16, 17] The anastomosis is constructed without the potentially harming effects of temporary occlusion of the coronary or intracoronary shunting,[18] and hence, there is no time-constraint related to myocardial ischemia. Finally, no standard extra hemostatic stitches are required[7, 16, 17]; all these features reduce coronary handling, conditioning, and manipulation, and thus simplify the off-pump bypass procedure, especially in a minimally invasive approach.

The low-profile anastomotic technique is feasible through a small workspace (eg, MIDCAB or robot-assisted TECAB). However, video-scopic assistance should be implemented and, additionally, dedicated versatile tools and a flexible, or even steerable laser catheter should be developed to further optimize the expediency of the minimally invasive procedure.

Consequently, the connector is demonstrated to accord to the conditions of "Handling and Practical Use". However, the long-term reliability and effectiveness have to be ameliorated and technical limitations in the minimally invasive application were encountered. The costs to manufacture the technology are currently high, but will go down substantially if manufactured systematically.

Vessel Wall Damage and BENIS

Anastomosis construction with the Trinity Clip resulted in minimal vessel wall damage during the construction. However, the non-compliant Trinity Clip provides active compression onto the vessel walls, which could result in necrosis and / or a chronic stimulating process of intimal hyperplasia formation. Though, the patent connector-facilitated anastomoses actually showed less intimal hyperplasia at the anastomotic line compared to the hand-sutured anastomosis (at 6 months 0.08 ± 0.06 versus 0.26 ± 0.07 mm, respectively; $P<0.01$; Chapter 8). This marked difference could be the result of the smaller anastomotic orifice in relation to the hand-sutured anastomosis. However, in Chapter 3 and 4, the Clip connector demonstrated a similar healing response with thin intimal coverage of the intraluminal connector on large coronary arteries (> 3 mm), supporting the data in

Chapter 8. Therefore, we hypothesize that these results suggest a favorable healing reaction of the connector-facilitated anastomosis compared to the hand-sewn, due to a less traumatic anastomosis construction. In the connector-facilitated nonocclusive anastomosis construction tissue trauma is minimized compared to the hand-sutured construction, which includes coronary snaring, a by hand incised arteriotomy, intracoronary shunting, and stitching. The introduction of the forks of the connector into the graft and coronary artery is likely to be less traumatic compared to approximately 12 separately placed stitches. The lasered-arteriotomy in both the graft and coronary artery does not induce damage to the surrounding vessel wall and seemed safe in the studies of this thesis (Chapter 6 and 8). In addition, emphasizing that the laser catheter is introduced through the distal free end of the graft, which is finally ligated and is not the actual functional conduit, stresses the fact that the necessity to manipulate the graft by laser introduction does not result in actual relevant intimal damage. However, in sequential grafting, the laser catheter is introduced through the actual blood-exposed graft, or a side-port (eg, side-branch), and thus exposed to potential damage by the introduction of the laser catheter. A histological study should assess its safety.

Finally, in addition to simplifying the off-pump minimally invasive procedure, an additional benefit of nonocclusive anastomosis construction is minimizing tissue trauma by the reduced handling, manipulation, and conditioning of the coronary artery, without the potential harming effects of coronary snares or intracoronary shunts.[18]

The introduction of a second fork into the bloodstream has increased the amount of material BENIS, 3.8 mm^2 in the Clip connector to 6.3 mm^2. However, by using the Trinity Clip connector, the vessel wall apposition is changed from an intima-to-adventitia to an adventitia-to-adventitia apposition, with in the latter only an edge of adventitia and media exposure. This is in favor of the tissue BENIS, 4.1 mm^2 in the Clip connector to 1.9 mm^2. Thus, the BENIS area is 8.2 mm^2, which is slightly higher than the reported BENIS score in the hand-sutured anastomoses, 1 – 6 mm^2.[19] As described earlier, presence of BENIS is not per se detrimental,[1] and the slightly higher score is presumably tolerated due to the minimal vessel wall damage associated with the anastomosis construction with the Trinity Clip. In addition, the nonintimal area inside the anastomosis is endothelialized within 14 days. This can direct the anticoagulation strategy with a more stringent dual antiplatelet therapy in, for example, the first 4 weeks after the operation. Moreover, histology did not show excessive acute or long-term inflammation over time (Chapter 3, 4, and 8), suggesting the proper biocompatibility of the connector (ie, titanium).

Patency

Chapter 8 did not show comparable long-term patency results for the Trinity Clip as found in the hand-sutured anastomoses (82% [18/22] versus 100% [14/14]). The inferior patency was histologically related to distortion and tilting of the connector. However, in the first part of the study before a design change was implemented, actually a comparable patency rate at 6 months was found (Group 1: 11 of 12 facilitated anastomoses were patent; 1 was occluded due to competitive flow). As mentioned before, we hypothesized that the design change (ie, the weight and length of the spring increased by 20%) led to distortion of the connector and subsequent occlusion of the bypass. Hence, following removal, or downsizing of the spring of the connector, an enhanced long-term patency is anticipated on.

Versatility

It is feasible to target remote regions of the heart by the Trinity Clip. In the absence of large and bulky application or deployment systems, and due to the controlled two-step approach with the simple maneuver of inserting the connector into the coronary artery, the low-profile anastomotic system will not hamper the bypass construction on these difficult to reach areas of the heart. However, as mentioned before in the section "Handling and Practical Use", dedicated tools such as a more flexible laser catheter and a versatile applicator, and video-scopic assistance are mandatory and will further simplify the anastomosis construction in minimal invasive approaches.

The ELANA-based connectors are applicable to distal (1.4 – 1.6 mm ID, the Trinity Clip) and proximal coronary targets (> 2.6 mm ID, the Clip connector) and safely accommodate a wall thickness up to 0.7 mm (unpublished data). Upsizing of the Trinity Clip will cover the coronary targets in between. However, further downsizing is technically not possible. Consequently, the connector does not fully accommodate the target range indicated in Chapter 1, ± 1.0 – 3.5 mm ID.

The Trinity Clip is versatile and compatible to different sizes and use of grafts. It has been showed that the use of venous grafts is feasible in ex vivo testing. Different approaches of grafting have been successfully evaluated (ie, side-to-side and end-to-side; single and Y-graft anastomosis), as well as sequential grafting. However, for this latter purpose, the graft is exposed to the potential damage by the laser catheter introduction. A histological study should address its safety.

To accommodate thicker vessel walls, the tip of the laser catheter can be modified. A study is warranted to systematically assess the ideal tip of the laser catheter in relation to various vessel wall thicknesses. Additionally, the anticipation on thicker vessel walls by the connector should also be addressed. A maximal vessel wall thickness for both graft and coronary target should be advised.

Finally, this anastomotic technology can be interchangeably used in any sequence preferred by the surgeon.

Atherosclerotic Coronary Arteries

The Trinity Clip enables anastomosis construction on healthy and atherosclerotic targets a hand-sutured anastomosis construction is reasonably feasible too. However, severely affected coronary arteries should be strictly avoided.

Final Consideration

In the chapters of this thesis, a journey into the development and preclinical evaluation of multiple ELANA-based prototypes has been described, toward the ultimate “destination”: an ideal coronary anastomotic connector. Unfortunately, the journey has not ended, the ultimate destination is not reached, yet.

Before clinical introduction, a subsequent experimental porcine OPCAB safety study is warranted with a second-generation, further finalized Trinity Clip connector. Distortion and displacement of the connector have to be prevented, preferably by removal or downsizing of the spring of the connector. For application in minimally invasive bypass surgery, the mounted complex of connector, graft, laser catheter, and fixation clip has to be easily guided and directed toward the remote areas of the heart. This can be achieved by developing a flexible laser catheter with a multi-angled applicator to open and insert the connector into the coronary target, guided by direct video-scopic assistance. Provided these technical limitations can be addressed, this technology could fill the missing link toward expansion of minimally invasive CABG.

Finally, this research project did not start with a finalized, cardio-surgical market ready product, but instead, it began with the original and unique concept used in neurosurgery. The amelioration and further development of the Trinity Clip technique toward a clinical acceptable connector, conforming to the historical excellent patency standards of the hand-sutured anastomosis, are behind the scope of this thesis. The trail has ended, but not the journey.

REFERENCES

1. Buijsrogge MP, Grundeman PF, Verlaan CW, Borst C. Unconventional vessel wall apposition in off-pump porcine coronary artery bypass grafting: low versus high graft flow. *J Thorac Cardiovasc Surg.* 2002;123:341-7.
2. Meyerson SL, Skelly CL, Curi MA, Shakur UM, Vosicky JE, Glagov S, et al. The effects of extremely low shear stress on cellular proliferation and neointimal thickening in the failing bypass graft. *J Vasc Surg.* 2001;34:90-7.
3. Berguer R, Higgins RF, Reddy DJ. Intimal hyperplasia. An experimental study. *Arch Surg.* 1980;115:332-5.
4. Hehrlein C, Chuang CH, Tuntelder JR, Tatsis GP, Littmann L, Svenson RH. Effects of vascular runoff on myointimal hyperplasia after mechanical balloon or thermal laser arterial injury in dogs. *Circulation.* 1991;84:884-90.
5. Carrel T, Englberger L, Keller D, Windecker S, Meier B, Eckstein F. Clinical and angiographic results after mechanical connection for distal anastomosis in coronary surgery. *J Thorac Cardiovasc Surg.* 2004;127:1632-40.
6. Filsoufi F, Farivar RS, Aklog L, Anderson CA, Chen RH, Lichtenstein S, et al. Automated distal coronary bypass with a novel magnetic coupler (MVP system). *J Thorac Cardiovasc Surg.* 2004;127:185-92.
7. Matschke KE, Gummert JF, Demertzis S, Kappert U, Anssar MB, Siclari F, et al. The Cardica C-Port System: clinical and angiographic evaluation of a new device for automated, compliant distal anastomoses in coronary artery bypass grafting surgery--a multicenter prospective clinical trial. *J Thorac Cardiovasc Surg.* 2005;130:1645-52.
8. Suyker WJ, Buijsrogge MP, Suyker PT, Verlaan CW, Borst C, Grundeman PF. Stapled coronary anastomosis with minimal intraluminal artifact: The S2 Anastomotic System in the off-pump porcine model. *J Thorac Cardiovasc Surg.* 2004;127:498-503.
9. Halkos ME, Cooper WA, Petersen R, Puskas JD, Lattouf OM, Craver JM, et al. Early administration of clopidogrel is safe after off-pump coronary artery bypass surgery. *Ann Thorac Surg.* 2006;81:815-9.
10. Fischell TA, Virmani R. Intracoronary brachytherapy in the porcine model: a different animal. *Circulation.* 2001;104:2388-90.
11. Stecher D, de Boer B, Tulleken CA, Pasterkamp G, van Herwerden LA, Buijsrogge MP. A new nonocclusive laser-assisted coronary anastomotic connector in a rabbit model. *J Thorac Cardiovasc Surg.* 2013;145:1124-9.
12. Biesbroek M, van Doormaal TP, van der Zwan A, Tulleken CA, Regli L, Heijnen HF, et al. The acute effect of increased laser energy during the excimer laser-assisted non-occlusive anastomosis procedure on the vessel wall of the recipient artery: a histopathological study. *Lasers Surg Med.* 2011;43:522-7.
13. Stecher D, van Slochteren FJ, Hoefer IE, Pasterkamp G, Tulleken CA, van Herwerden LA, et al. The nonocclusive laser-assisted coronary anastomotic connector in an off-pump porcine bypass model. *J Thorac Cardiovasc Surg.* 2014;147:1390-7 e2.
14. Stecher D, Agostoni P, Pasterkamp G, Hoefer IE, van Herwerden LA, Buijsrogge MP. Six-month healing of the nonocclusive coronary anastomotic connector in an off-pump porcine bypass model. *Innovations (Phila).* 2014;9:130-6; discussion 6.
15. Stecher D, van Herwerden LA, Pasterkamp G, Buijsrogge MP, Kiaii B. Robot-Assisted Endoscopic Construction of a LITA-to-LAD Anastomosis Facilitated by the Trinity Clip (ELANA Anastomotic Connector): An Experimental Case Report. Abstract. *Innovations.* 2014;9:178.
16. Balkhy HH, Wann LS, Arnsdorf S. Early patency evaluation of new distal anastomotic device in internal mammary artery grafts using computed tomography angiography. *Innovations (Phila).* 2010;5:109-13.

17. Verberkmoes NJ, Wolters SL, Post JC, Soliman-Hamad MA, ter Woorst JF, Berreklouw E. Distal anastomotic patency of the Cardica C-PORT(R) xA system versus the hand-sewn technique: a prospective randomized controlled study in patients undergoing coronary artery bypass grafting. *Eur J Cardiothorac Surg.* 2013;44:512-8; discussion 8-9.
18. Gerosa G, Bottio T, Valente M, Thiene G, Casarotto D. Intracoronary artery shunt: an assessment of possible coronary artery wall damage. *J Thorac Cardiovasc Surg.* 2003;125:1160-2.
19. Scheltes JS, van Andel CJ, Pistecky PV, Borst C. Coronary anastomotic devices: blood-exposed non-intimal surface and coronary wall stress. *J Thorac Cardiovasc Surg.* 2003;126:191-9.

10

FUTURE DEVELOPMENT

Challenges in Prototyping toward the Ideal Coronary Anastomotic Connector

This thesis describes a journey into the development and preclinical experimental evaluation of multiple ELANA-based prototype connectors, which were ameliorated and fine-tuned along the way. It started with a connector for large vessels (diameter > 3 mm), in an end-to-side configuration, with the need to suture and to use sealants for hemostasis. The concept evolved and finally ended in Part C of this thesis: the Trinity Clip connector. This third-generation prototype is suitable for small coronary arteries (diameter 1.4 - 1.6 mm), is easy-to-use without the need for surgical sealants, it offers a standardized construction while both the graft and recipient artery are laser-punched and no standard sutures are needed, and the technique is feasible on human diseased coronary arteries. However, unfortunately, the long-term patency for the connector-facilitated anastomoses, described in Chapter 8, was inferior to the hand-sewn. We hypothesized (Chapter 8) that the inferior patency rates were related to a design change halfway the study, which was realized to enhance the stability of the connector to improve hemostasis (in 2 of 15 cases leakage occurred). The design change resulted in a 20% increase of both the weight and length of the already quite bulky spring of the connector. After the design change, no leakage was observed in 18 consecutive cases, however, 3 occlusions were found at 3-month follow-up, due to distortion of the connector. Accordingly, we hypothesized that the increased weight and length (ie, increased lever arm) of the spring resulted in distortion of the connector (confirmed by histology) and subsequent occlusion of the bypass. Consequently, removal or downsizing of the spring of the connector could prevent displacement of the connector and presumably results in an enhanced patency.

To address the latter, first, we thought of ways to directly stabilize the complex of graft and connector in relation to the coronary artery, without a complete design change. In absence of viable direct solutions, a more rigorous path was taken, with ideas that result in a complete design change. The most obvious solution is to remove the spring after the anastomosis is constructed; in fact, the spring is abundant, to the extent that it provides active compression on both vessel walls. So, ideally, the spring is removed after the construction and the forks are fixated by it self or a small fixation mechanism. However, a technical solution did not come up, yet.

An “out-of-the-box” idea to remove the spring is a “hemoclip-prototype”, based on the Clip connector (Figure 1). This prototype has a less bulky extravascular residual implant. However, the action of the clip is irreversible, it is not possible to easily reopen it, and the technical translation toward the Trinity Clip design, including all its features, is too challenging.

Figure 1. The “hemoclip-prototype” ELANA connector

Another reasonable idea for downsizing the bulk of the spring is to bend the spring 90 degrees in relation to the forks, in such a way the spring is orientated in a flat, horizontal direction, instead of the upright vertical fulcrum, in its original state. However, the force applied onto the spring to open the forks by the applicator, is directed towards the forks, and in case the transition neck (ie, the part between the spring and forks) is turned 90 degrees, a length variation have to be compensated for. Technically this could be solvable, but it is very challenging to produce it accurately in such a way the vessel walls of both the graft and the coronary artery will not shift and cause an adventitial overlap. Please note, in fact, this is not really downsizing since the size of the spring will be identical. However, more important is the orientation of the bulk of the spring, which will be favorable in terms of stabilization of the anastomosis. This is an interesting and the most reasonable solution, if technically feasible.

Once a clinical acceptable solution is found, a long-term safety study has to be conducted, prior to clinical introduction.

Prototyping: A Concept to Potentially Improve the Anastomotic Technique

The Trinity Clip connector is suitable for coronary targets with an inner diameter (= ID) of 1.4 – 1.6 mm and it is not feasible to target smaller coronaries. Ideally, the connector should accommodate coronary targets of 1 mm diameter to cover the whole range of clinically relevant coronary targets. Moreover, in Chapter 6, another issue was frequently seen: malpositioning of the connector due to a target coronary artery with an inner diameter below the intended target range of the connector. The target range is based on the width of the connector, but also partly to the width of the 2 ends of the pins of the fork, which have to be inserted completely intraluminal, and not intramural. Correct positioning of the connector is of utmost importance, because, if malpositioned, there is not a straight surface for laser-tissue contact and that will most certainly result in a laser-punch error. Obviously, the site of the anastomosis construction has to be accurately targeted, so that the ID of the target is not too small. Different ideas to optimize correct intraluminal insertion of the fork in small targets up to 1 mm are thought of. One interesting idea is to use one upper and one lower pin, instead of the 2 forks (Patent "Blood Vessel Connectors", see Figure 7; Appendix 4). The pin is anchored onto the spring, it reaches to the toe of the anastomosis and loops back to the heel, where the sharp pin ends. This looped configuration resulted in the simple insertion of 1 pin into the lumen of the artery. However, the prototype is quite unstable due to the relatively long distance of the pin and did not result in a hemostatic anastomosis. But, the concept might have potential if stronger materials are used.

With the upcoming development of 3D printing, prototyping will be easier, faster, and different materials can be sequentially tested. In addition, miniaturizing will be simplified too. This will broaden the horizon for prototyping.

Low-Profile ELANA System for Minimally Invasive CABG: Flexible Laser Catheter and Optimizing Visibility

The feasibility of the Trinity Clip connector was demonstrated in a total arterial minimally invasive direct coronary artery bypass (MIDCAB) and in a robot-assisted total endoscopic coronary artery bypass (TECAB) approach in the porcine model. However, in the MIDCAB setting, the reduced workspace hampered visualization during insertion of the connector into the coronary artery. The insertion of the lower fork was directed away from the surgeon, directed distally, and therefore, the visibility was limited. This can be easily solved by the use of video-scopic assistance, which will enable the surgeon to have a detailed look at the site where the connector is introduced into the target coronary and will significantly optimize the procedure.

A second limitation was the 90-degree upstanding mounted-laser fulcrum (ie, the mounted complex of connector, graft, and laser catheter, fixated by the fixation clip [Chapter 7, Figure 1B]). The first 2 - 3 cm of the laser catheter is not bendable and thus, after mounting of the laser and during the insertion of the connector into the coronary target, this results in an upstanding fulcrum in a 90-degree angle in relation to the longitudinal plane of the coronary artery. It can cause problems in small workspaces during minimal invasive approaches. Therefore, to prevent collision of the laser fulcrum to the chest wall, in our experiments, coronary

targets on the anterolateral wall had to be center-positioned in relation to the thoracotomy. For targets on the inferoposterior wall or in a closed-chest approach, enough space (3 - 4 cm) between the chest wall and the target had to be created by using a heart positioner.

Further upward, the laser catheter is bendable to maximally 90 degrees, but it still is rigid and stiff and always moves back to its original curvature, hence limiting the surgeon during the procedure. Ideally, the laser catheter should be as flexible and manageable as a rope or an electricity cable, so it can be placed wherever the surgeon wants. In addition, the first rigid centimeters of the laser catheter, which is used for fixation of the complex by the fixation clip, can be made shorter. That will result in a lower fulcrum, which increases expediency. Lastly, with new technologies, the tip of the laser catheter could even be steerable to remotely fine-tune the movements during mounting of the laser catheter and insertion into the coronary artery.

For the robot-assisted TECAB procedure, a da Vinci robotic instrument was modified into an ELANA applier that was both applicable to the Trinity Clip as well as to the fixation clip. The video-scopic assistance of the robot was of great value, resulting in a 10-time magnification with incredible 3D detail of the anastomosis construction. The first step of the procedure, mounting of the laser via the graft into the connector, was easily done with the da Vinci robot. However, the rigid laser catheter produced lots of contra forces, which frequently resulted in dislocation of the laser catheter. A relatively simple maneuver became annoyingly difficult. The dexterity of the da Vinci robot was of great value, however, once the laser was mounted into the connector, the rigid laser catheter did not move gently along with the movements of the mounted connector fixated into the robotic arm, and again, resulted in dislocation of the laser catheter. So the laser catheter significantly limited expediency, and hence, similar as in the MIDCAB approach, a more flexible catheter will improve the procedure.

Consequently, the ultimate goal is to develop an ELANA system for totally endoscopic bypass procedures that consist of a low-profile unit of the mounted complex of connector, graft, flexible laser catheter, and fixation clip, that can be easily guided and directed toward the remote areas of the heart. Subsequently, a flexible, multi-angled applicator should be developed, which is used to open and insert the connector into the coronary target with direct video-scopic assistance. Thus, to succeed in (non-) robot-assisted totally endoscopic anastomosis construction and the less invasive (MIDCAB) procedures, dedicated versatile application tools are essentials for a successful anastomosis construction.

Versatility Extension

In this thesis, the Trinity Clip was demonstrated to be applicable in single grafting as well as Y-grafting. The versatility could potentially be further extended to sequential grafting. However, in the latter, the graft could potentially be damaged by the laser introduction, as described before. A histological study should address the potential presence of endothelial damage by the introduction of the laser and its subsequent temporary fixation by the fixation clip, to assess its safety.

Ex vivo testing has showed that the use of venous grafts is feasible with the Trinity Clip. However, due to the lack of a feasible venous animal model, this could not be further examined in vivo.

Another extension of the technology is the application onto the aorta, as a proximal anastomotic connector. Multiple ex vivo feasibility experiments have been performed and demonstrated, by using the right increased laser energy settings and the right laser catheter tip configuration (ie, deeper tip for the thicker aortic wall), that laser-punching into the aorta is possible. However, since it is not possible to laser-punch a calcified area, these areas should be avoided. Epi-aortic ultrasound scanning could target a suitable laser-punch site. Finally, the clip connector should by upsized to accommodate the thicker vessel wall. In addition, previous experiments with a smaller sized connector (Chapter 3) have showed that the connector resists supra-physiologic pressure (300 mm Hg), and thus, suggests that the aortic pressure will not cause problems in terms of leakage of the anastomosis, especially if the spring of the connector is upsized too (ie, providing an increased compression force).

Envisioning the Future Ideal ELANA-Based Concept Connector

An ideal anastomotic technique to facilitate the distal coronary anastomosis construction is the ultimate wish for minimally invasive surgeons who want to expand single LITA-LAD MIDCAB or robot-assisted multivessel TECAB to complete myocardial revascularization via (non-) robotic total endoscopic approaches. Envisioning the future ideal ELANA-based concept, a small-sized low profile clip connector will consist of ultimate thin (ie, reducing BENIS) but strong pins of the fork, which are biodegradable and potentially drug-eluted with inhibitors of vascular smooth muscle cell proliferation.[1, 2] A particularly small sized mechanism enables opening and closing of the device and handling, to apply the connector. A flexible and steerable laser catheter, easily mounted into the connector and graft, can be freely maneuvered and the complex of connector, laser, and graft, directed as a lunar vehicle to remote areas of the heart. The 2 pins of the fork are initially positioned adjacent, against each other with limited space in between. With this, the connector can accommodate target coronaries with a minimal diameter below 1.4 mm (which is the current minimal coronary target ID of the Trinity Clip). The laser does not punch a part of the arterial tissue, but only incises an arteriotomy into the vessel walls of graft and coronary artery in one time. Subsequently, the pins of the fork expand laterally, resulting in a widely open orifice. Finally, the connector will be degraded and absorbed over time, without inducing excessive inflammatory reactions or intimal hyperplasia formation. This is a futurized concept and with the emerging technology of 3D-printing and biocompatible degradable material, this can be reality.

REFERENCES

1. Franzone A, Pilgrim T, Heg D, Roffi M, Tuller D, Vuilliomenet A, et al. Clinical Outcomes According to Diabetic Status in Patients Treated With Biodegradable Polymer Sirolimus-Eluting Stents Versus Durable Polymer Everolimus-Eluting Stents: Prespecified Subgroup Analysis of the BIOSCIENCE Trial. *Circ Cardiovasc Interv.* 2015;8.
2. Koppara T, Cheng Q, Yahagi K, Mori H, Sanchez OD, Feygin J, et al. Thrombogenicity and early vascular healing response in metallic biodegradable polymer-based and fully bioabsorbable drug-eluting stents. *Circ Cardiovasc Interv.* 2015;8:e002427.

APPENDIX 1

Summary

Chapter 1. Interestingly, the first reports of anastomosis constructions described techniques of connecting blood vessels without sutures, but with a "connector". So in fact, developing a coronary anastomotic connector, which is the aim of this research, is an old-fashioned idea. However, the current incentive is modernized. The desire for such a connector has derived from the communal wish of both patient and physician to minimize the trauma associated with the invasive approach for coronary artery bypass grafting (CABG) by operating via small sternal-sparing incisions. Conventional suturing of the anastomosis via less invasive approaches is technically very challenging and hence, automating the construction with a connector is the missing link toward expansion of minimally invasive CABG. The aim of the research in this thesis is to develop and evaluate a new coronary anastomotic connector based on the unique principles of the Excimer Laser-Assisted Nonocclusive Anastomosis (ELANA) technique. This interesting technology is used in neurosurgery and enables anastomosis construction without occlusion of the recipient artery. Downsizing of and modifications to the design of the concept (ie, both the connector ring and laser catheter) should ultimately enable a sutureless and reliable connection of the graft to the coronary artery and result in a comparable long-term patency as the conventional hand-sewn anastomosis. Moreover, the connector should enable a simplified construction of the anastomosis via a minimal invasive surgical approach on the beating heart ("off-pump") and be applicable to remote and small coronary targets.

PART A – THE SLIDE CONNECTOR

Chapter 2. A proof-of-concept of a first-generation ELANA-based prototype connector, the "Slide connector", was evaluated in an acute rabbit abdominal aortic-bypass model. With this prototype, the first step in the change of design was made: the connection of the mounted graft to the coronary artery was simplified by sutureless application. A total of 40 anastomoses were constructed on the abdominal aorta (3.5 mm diameter) of 10 rabbits. The Slide connector enabled easy-to-use, nonocclusive, and fast anastomosis construction with a 100% patency and a predictable and consistent intima–adventitia apposition. Several technical imperfections persisted, such as occasional failure to retrieve the flap with the laser catheter, the need for a sealant for anastomotic hemostasis, and sutures were still required for mounting the graft.

PART B – THE CLIP CONNECTOR

Chapter 3. The feasibility and anastomotic healing of an ameliorated second-generation ELANA-based prototype connector, the "Clip connector", was evaluated in an acute rabbit model and subsequently in a long-term porcine open sternotomy off-pump coronary artery bypass (OPCAB) model. This improved prototype incorporated the next steps toward a clinical device: the surgical sealant was eliminated, the technique was simplified by the ability of the connector to open and close, and laser-punching was optimized. However, the connector was suitable for relatively large coronary arteries (> 3 mm). In the rabbit model, all 18 anastomoses were patent and resisted supraphysiologic pressures (n = 12, 300 mm Hg). In the porcine model, 15 left internal thoracic artery (LITA) to left anterior descending artery (LAD) bypasses were evaluated intraoperative and at 4 hours, 4 and 10 days, 2, 3, and 5 weeks, and 6 months (each n = 2 anastomoses). Mounting of the graft to the connector still required stitching, which was time-consuming (27 ± 5 minutes). The connector enabled nonocclusive and relatively fast anastomosis construction (mean 7.7 ± 2.2 minutes). All, but 1 of 15 anastomoses (due to a technical error), were fully patent at follow-up. Histology and scanning electron microscopy (SEM) demonstrated complete endothelialization of the anastomoses at 10 days. At 6 months, no flow-limiting but streamline-covering intimal hyperplasia was shown with a fractional flow reserve of 0.93 ± 0.07.

Chapter 4. In this pilot study, the anastomotic healing of the Clip connector was extensively evaluated at 6 months in a porcine OPCAB model. A LITA-to-LAD bypass in two animals and a LITA-to-LAD and right internal thoracic artery to right coronary artery bypass in one animal were evaluated intraoperative and at 6 months. At follow-up, all anastomoses (n = 4) were fully patent (FitzGibbon grade A). SEM demonstrated

complete endothelial coverage of the anastomotic surface and histology showed minimal streamlining intimal hyperplasia. The in vivo IVUS and OCT acquisitions confirmed histologic findings. A 0.06 mm tissue coverage of the intraluminal part of the connector along the full circumference of the anastomosis was demonstrated with OCT. Furthermore, OCT acquired high-resolution, in vivo "near-histologic" images and it might have clinical implications as a follow-up assessment technique with assessment of connector and vessel wall apposition, anastomotic healing, and remodeling.

PART C – THE TRINITY CLIP CONNECTOR

Chapter 5. This protocol-based paper is supported by an online video of a third-generation ELANA-based prototype connector, the "Trinity Clip", which was further ameliorated toward clinical application. Design modifications of the connector and the laser catheter enabled a completely sutureless construction onto clinically relevant, small caliber coronary arteries with an inner diameter of 1.4 - 1.6 mm. The paper extensively outlined the procedural steps of the anastomotic construction in a porcine OPCAB model. Furthermore, multiple options were described for intraoperative, postoperative, and postmortem assessment of the anastomotic quality. Representative results were summarized and visually demonstrated.

Chapter 6. The feasibility of the Trinity Clip technique on human ex vivo diseased coronary arteries was demonstrated. In 13 of 38 anastomoses, the connector was mal-positioned; 3 due to a severely diseased coronary wall and 10 due to an inner diameter below the intended target range. The laser-punch success rate on coronary arteries with an early (mild) and advanced (severe) lesion was 100% (16/16) and 89% (8/9), respectively. Thus, severely atherosclerotic lesions caused malpositioning of the connector and one laser-punch failure. Hence, careful selection of the coronary, regarding the target inner diameter and disease status, will prevent construction failures. In the second part of this study, the potential harming effects of exposing a small target vessel to the same levels of laser energy as used in previous studies on larger caliber coronary arteries was histologically evaluated. It was showed that lasering does not induce coronary wall damage.

Chapter 7. In a pilot study, the feasibility of the Trinity Clip connector was demonstrated in a total arterial minimally invasive direct coronary artery bypass (MIDCAB) approach in the porcine model (n = 9 anastomoses, in 3 pigs). Via a small left lateral thoracotomy, revascularization of the anterior, lateral, and inferoposterior regions of the heart was feasible and a fast and standardized construction of a Y-graft was possible. However, the reduced workspace hampered visualization during insertion of the connector into the coronary artery. From this experience we conclude that dedicated application tools, more specifically a versatile applicator and a flexible laser catheter, and optimization of visualization by video-scopic assistance, are essential to succeed in minimally invasive anastomosis construction.

Chapter 8. In 58 pigs, 33 LITA-to-LAD bypasses were off-pump facilitated by the Trinity Clip, and 25 were hand-sutured, in a preclinical safety study. The anastomoses were evaluated at the short- (intraoperative and 4, 10, 14, 35 days) and long-term (90 and 180 days) follow-up to assess anastomotic healing and patency. A faster construction time was found and hemostasis tended to be better in the connector group compared to the hand-sutured group, whereas graft flow measurements were comparable. A similar initial anastomotic healing process as in the hand-sutured anastomosis was demonstrated, with complete endothelialization of the nonintimal anastomotic surface within 14 days. The long-term patency of the connector-facilitated anastomoses was inferior to the hand-sewn (82% versus 100%) and was histologically related to distortion of the connector. However, the patent connector-facilitated anastomoses showed less intimal hyperplasia at the anastomotic line compared to the hand-sutured anastomosis (at 6 months 0.08 ± 0.06 versus 0.26 ± 0.07 mm, respectively; $P<0.01$). The inferior patency rates may be related to a design change (ie, the spring of the connector was longer and 20% heavier) halfway the study, which aimed at enhanced stability of the connector in order to improve hemostasis. After the design change, no leakage was found. However, at 3 months 3 occlusions were found due to distortion of the connector. We hypothesized that the increased weight and

length (ie, increased lever arm) of the spring resulted in distortion of the anastomosis and finally occlusion of the bypass.

PART D – DISCUSSION AND FUTURE DEVELOPMENT

Chapter 9. The Trinity Clip was extensively evaluated in experimental studies and meets the following requirements for an ideal coronary anastomotic connector: it enables a simplified, fast, and standardized connection of the graft to the coronary artery on a beating heart. In addition, the connector is easy-to-use, is applicable to remote, small caliber targets, and is feasible on human diseased coronary arteries. However, long-term patency rates were inferior to the hand-sewn anastomosis, which may be related to a design change halfway the study resulting in distortion of the connector (confirmed by histology) and could potentially be improved by the removal or downsizing of the spring of the connector. In addition, the applicability via a minimal invasive approach is feasible. However, it should be optimized by dedicated application tools, more specifically a flexible laser catheter and versatile applicator, and optimization of visualization by video-scopic assistance. Provided the technical limitations can be addressed, this connector could fill the missing link toward expansion of minimally invasive CABG.

Chapter 10. This chapter outlines the future development and challenges in prototyping toward clinical application, including removal or downsizing of the spring of the connector. In addition, a concept to potentially improve the anastomotic technique regarding the insertion of the lower fork into the coronary artery is described as well as an outline of the limitations and desirable improvements for minimally invasive application of the anastomotic technique. Potential extension of the versatility of the technique is reviewed, including a proximal ELANA anastomotic connector. Finally, a future ideal ELANA-based concept connector is described.

APPENDIX 2

Samenvatting

Hoofdstuk 1. Opvallend is dat de historische eerste rapporten over het chirurgisch koppelen van twee bloedvaten (oftewel een "anastomose") technieken beschrijven zonder het gebruik van hechtingen, maar met behulp van een "connector". Dus in feite is het doel van dit onderzoek, het ontwikkelen van een connector, een ouderwets idee. Inmiddels is de doelstelling gemoderniseerd. De wens om een coronaire anastomose connector te ontwikkelen komt voort uit de gemeenschappelijke wens van de patiënt en de arts om het aanzienlijke chirurgische trauma te verminderen. Voor een kransslagader omleidingsoperatie (oftewel coronaire arteriële bypass graft, CABG) is namelijk een invasieve benadering nodig middels het openzagen van het borstbeen, maar is ook mogelijk via kleine, borstbeen-sparende incisies tussen de ribben door. Echter, het conventioneel hechten van de anastomose met de hand (de standaard techniek) op het kloppende hart via deze kleine incisies, dus minder of minimaal invasief, is technisch zeer moeilijk. Het versimpelen en automatiseren van de anastomose constructie met een connector is de ontbrekende schakel om minimaal invasieve bypass operaties wijdverspreid te laten slagen. Het doel van het onderzoek in dit proefschrift is dan ook om een coronaire anastomose connector te ontwikkelen welke gebaseerd is op de unieke eigenschappen van de Excimer Laser-Assisted Nonocclusive Anastomosis (ELANA) techniek. Deze technologie wordt gebruikt in de neurochirurgie en maakt het mogelijk een anastomose aan te leggen met behulp van een laser zonder het ontvangende vat af te sluiten (non-occlusief). Maar een coronaire bypass operatie vindt plaats in een geheel andere setting met een bewegend operatie vlak (het kloppende hart) en vaak op kleinere vaten. Door miniaturisering en verbetering moet deze techniek uiteindelijk in staat zijn om snel en gemakkelijk de graft (donor vat) en de coronair arterie te koppelen via een minimaal invasieve benadering op het kloppende hart, zonder gebruik te maken van hechtingen. Dit moet resulteren in een functioneel vrije doorgang van de anastomose op de lange termijn, welke vergelijkbaar is met de hand gehechte anastomose.

PART A – THE SLIDE CONNECTOR

Hoofdstuk 2. De toepasbaarheid van een eerste generatie prototype connector gebaseerd op de ELANA-techniek, de "Slide connector", was aangetoond op de abdominale aorta in een acuut konijnen model. Met dit prototype was de eerste stap gezet naar het uiteindelijk doel: de constructie is gesimplificeerd door een hechting loze connectie van de graft op de ontvangende arterie. Veertig anastomoses werden gemaakt op de abdominale aorta (3.5 mm diameter) van 10 konijnen. De connector maakte het mogelijk om non-occlusief, gemakkelijk en snel de anastomose aan te leggen met een 100% vrije doorgang en een voorspelbare en consistente constructie (intima van de graft tegen de adventitia van de ontvanger). Enkele technische onvolkomenheden moeten worden opgelost, zoals het in sommige gevallen falen van het laser-punchen, de noodzaak om een chirurgische lijm te gebruiken voor het lekvrij krijgen van de anastomose en het gebruik van hechtingen om de graft te bevestigen aan de connector.

PART B – THE CLIP CONNECTOR

Hoofdstuk 3. De toepasbaarheid en anastomose genezing van een tweede-generatie ELANA-gebaseerde prototype connector, de "Clip connector", was geëvalueerd in een acuut konijnen model en vervolgens in een varkens "off-pump" (zonder gebruik te maken van de hart-long machine) bypass model met een lange termijn follow-up. Het prototype was op meerdere punten verbeterd: er was geen lijm meer nodig, de techniek was verder gesimplificeerd doordat de connector geopend en gesloten kon worden, en het laser-punchen was verder geoptimaliseerd. Echter, de connector was nog steeds geschikt voor relatief grote vaten (> 3 mm). In het konijnen model waren alle 18 anastomoses patent en ze weerstonden supra-fysiologische drukken (n = 12, 300 mmHg). In het varkens model, 15 bypasses werden aangelegd tussen de linker arteria mammaria (LITA) en de linker coronair arterie (LAD), en de bypasses werden geëvalueerd intra-operatief en op 4 uur, 4 en 10 dagen, 2, 3 en 5 weken en 6 maanden. De graft werd nog steeds bevestigd met hechtingen op de connector, wat erg tijdrovend was (27 ± 5 minuten). De connector maakte het mogelijk om non-occlusief en relatief snel (7.7 ± 2.2 minuten) de verbinding aan te leggen tussen graft en coronair. Alle anastomoses waren volledig patent, behalve 1 van de 15 anastomoses door een technisch probleem. Histologie en elektronenmicroscopie

(SEM) lieten complete endothelialisatie zien van de anastomose op 10 dagen. Op 6 maanden, was er geen flow-limiterende, maar juist een gestroomlijnde bedekking met intima hyperplasie te zien met een fractionele flow reserve van 0.93 ± 0.07.

Hoofdstuk 4. In deze pilot studie was de anastomose genezing van de Clip connector uitgebreid geëvalueerd bij 6 maanden follow-up in een varkens off-pump bypass model. In 2 dieren werd een LITA-LAD bypass aangelegd en in 1 dier een LITA-LAD en een bypass van de rechter arteria mammaria op de rechter coronair arterie, welke intra-operatief en op 6 maanden follow-up geëvalueerd werden. Alle anastomoses waren volledig patent bij follow-up. SEM liet een volledige bedekking van de anastomose met endotheel zien en histologie gestroomlijnde minimale intima hyperplasie. De in vivo acquisities van optische coherentietomografie (OCT) en intravasculaire ultrasound bevestigden de histologische bevindingen. Over de hele circumferentie van de anastomose werd bedekking van de connector gezien met weefsel (0.06 mm). Tot slot, OCT leverde hoge-resolutie beelden op en heeft mogelijk klinische toegevoegde waarde als een follow-up techniek met bijvoorbeeld het beoordelen van de anastomose genezing en remodelering.

PART C – THE TRINITY CLIP CONNECTOR

Hoofdstuk 5. Dit is een protocol-gebaseerde paper welke gelinkt is aan een online video. Het beschrijft uitgebreid de stappen van de anastomose constructie met een derde-generatie ELANA-gebaseerde connector, de "Trinity Clip", welke verder verbeterd is richting de klinische toepassing. De connector en laser catheter hebben design modificaties ondergaan welke het mogelijk maken de constructie volledig hechting loos te volbrengen op kleine, klinisch relevante coronair arteriën (binnenste diameter, 1.4 - 1.6 mm). Tevens zijn er multipele mogelijkheden beschreven om intra-operatief, post-operatief en post-mortem de anastomose kwaliteit te beoordelen in een varkens off-pump bypass model. Tot slot zijn representatieve resultaten gedemonstreerd.

Hoofdstuk 6. De toepasbaarheid van de Trinity Clip techniek op zieke ex vivo humane coronair arteriën is gedemonstreerd. In 13 van 38 anastomoses was de connector verkeerd gepositioneerd in de coronair (niet volledig intraluminaal); in 3 gevallen kwam dit door een ernstig atherosclerotische vaatwand en in 10 gevallen doordat de binnenste diameter van de target coronair kleiner was dan de bedoelde target range. Het succes van laser-punchen van de coronairen met een milde en ernstige laesie was 100% (16/16) en 89% (8/9), respectievelijk. Dus, ernstige atherosclerotische laesies veroorzaakten het verkeerd inschuiven van de connector en 1 laser-punch failure. Daaruit werd geconcludeerd dat het belangrijk is om de target coronair nauwkeurig te selecteren met het oog op de binnenste diameter en ook de mate van atherosclerose, om zo constructie fouten te voorkomen. In het tweede deel van deze studie werden de mogelijk schadelijke effecten van het laseren op kleine vaten (een zelfde laser energie wordt gebruikt als op grotere vaten) histologisch geëvalueerd. De resultaten lieten zien dat het laseren geen vaatwand schade teweeg brengt.

Hoofdstuk 7. In deze pilot-studie werd de toepasbaarheid van de Trinity Clip in een totaal arterieel minimaal invasieve direct coronaire arteriële bypass (MIDCAB) benadering gedemonstreerd in een varkens model (n = 9 anastomoses, in 3 varkens). Via een kleine laterale thoracotomie links was revascularisatie van de anterieure, laterale en inferoposterieure regio's van het hart mogelijk. Tevens faciliteerde de connector een snelle en gestandaardiseerde Y-graft constructie. Echter, de beperkte werkruimte belemmerde het zicht tijdens de introductie van de connector in de coronair arterie in de afwezigheid van video-scopische ondersteuning. Derhalve, speciaal aangepaste veelzijdige instrumenten om de connector te hanteren, een flexibele laser catheter en optimalisatie van het zicht door video-scopische ondersteuning zijn essentieel om te slagen in de minimaal invasieve anastomose constructie.

Hoofdstuk 8. In 58 varkens werden 33 LITA-LAD (buitenste diameter LAD, 1.6 - 1.9 mm) bypasses met de Trinity Clip off-pump aangelegd en 25 werden hand-gehecht in een preklinische veiligheidsstudie. De anastomoses werden geëvalueerd op de korte- (intra-operatief en 4, 10, 14, 35 dagen) en lange termijn (90 en 180 dagen) om de anastomose genezing en patency te kunnen beoordelen. Een snellere constructie tijd werd gevonden voor de Trinity Clip en ook hemostase bleek beter te zijn, terwijl de intra-operatieve flow metingen vergelijkbaar waren. Initieel werd er een gelijkwaardige anastomose genezing gezien met complete endothelialisatie van de niet-intima oppervlaktes binnen 14 dagen. De patency van de connector-gefaciliteerde anastomoses op de lange termijn was inferieur aan de hand gehechte anastomoses (82% [18/22] versus 100% [14/14]) en was histologisch gerelateerd aan kanteling en verdraaiing van de connector. Niettemin, de patent connector-gefaciliteerde anastomoses lieten minimale intima hyperplasie zien welke minder was dan in de hand gehechte anastomoses (6 maanden, 0.08 ± 0.06 versus 0.26 ± 0.07 mm, respectievelijk; $P<0.01$). Het inferieure patency resultaat kon mogelijk gerelateerd worden aan een design verandering (de veer van de connector werd hierdoor 20% langer en zwaarder) halverwege de studie, welke geïmplementeerd werd om de hemostase te verbeteren. Na de design verandering werd er geen lekkage van de anastomoses meer gezien, echter wel 3 occlusies bij 3 maanden follow-up door kanteling en verdraaiing van de connector. De hypothese was dat de toegenomen lengte en gewicht van de connector resulteerde in verdraaiing van de connector, met vervolgens een occlusie van de bypass.

PART D – DISCUSSION AND FUTURE DEVELOPMENT

Hoofdstuk 9. De Trinity Clip is uitgebreid geëvalueerd in experimentele studies en voldoet aan de volgende voorwaarden voor een ideale coronaire anastomose connector: het simplificeert, versnelt en standaardiseert de anastomose constructie van de graft op de coronair op het kloppende hart. Daarnaast is de connector makkelijk in het gebruik, toepasbaar op moeilijk te bereiken, kleine coronairen en is het toepasbaar op humane zieke coronair arteriën. Echter, de lange termijn patency was inferieur aan de hand gehechte anastomose, wat mogelijk gerelateerd is aan de design verandering halverwege de studie met daarna verdraaiing van de connector (histologisch bevestigd; Hoofdstuk 8). Dit zou verbeterd kunnen worden door het verwijderen of het kleiner maken van de veer van de connector. Daarnaast is de techniek toepasbaar via minder invasieve benaderingen, echter, zou verder geoptimaliseerd moeten worden door speciaal aangepaste veelzijdige instrumenten om de connector te hanteren, een flexibele laser catheter en optimalisatie van het zicht door video-scopische ondersteuning. Deze zijn essentieel om te slagen in de minimaal invasieve anastomose constructie. Aangenomen dat de technische limitaties van de connector opgelost kunnen worden, dan zou deze connector de ontbrekende schakel kunnen zijn om minimaal invasieve bypass operaties wijdverspreid te kunnen laten slagen.

Hoofdstuk 10. Dit hoofdstuk staat stil bij de toekomstige ontwikkeling en de ondervonden uitdagingen in prototypering richting klinische toepassing. Daarnaast wordt er een concept beschreven om de techniek te verbeteren door het inschuiven van de onderste vork van de connector in de coronair arterie te vergemakkelijken. Verder worden de limitaties en wenselijke verbeterpunten binnen de minimaal invasieve toepassing geresumeerd. Tot slot wordt beschreven of de toepassing van de techniek verbreed kan worden met onder meer de toepassing als proximale connector.

APPENDIX 3

Abbreviations and Acronyms

BENIS	Blood-Exposed Non-Intimal Surface
CABG	Coronary Artery Bypass Graft
CE	Conformité Européenne
CFR	Coronary Flow Reserve
CPB	Cardiopulmonary Bypass
Cx	Circumflex
DF	Diastolic Filling
ELANA	Excimer Laser-Assisted Nonocclusive Anastomosis
FDA	Food and Drug Administration
FFR	Fractional Flow Reserve
ICS	Intercostal Space
ID	Inner Diameter
IH	Intimal Hyperplasia
ITA	Internal Thoracic Artery
IVUS	Intravascular Ultrasound
LAD	Left Anterior Descending Artery
LIMA	Left Internal Mammary Artery
LITA	Left Internal Thoracic Artery
MIDCAB	Minimally Invasive Direct Coronary Artery Bypass
OCT	Optical Coherence Tomography
OD	Outer Diameter
OM	Obtuse Marginal
PCI	Percutaneous Coronary Intervention
PDA	Posterior Descending Artery
PHFR	Peak Hyperemic Flow Response
PI	Pulsatility Index
PLcx	Posterolateral Circumflex branch
RCA	Right Coronary Artery
RIMA	Right Internal Mammary Artery
RITA	Right Internal Thoracic Artery
SEM	Scanning Electron Microscopy
TECAB	Total Endoscopic Coronary Artery Bypass
TTFM	Transit Time Flow Measurements

APPENDIX 4

Patent 1: Blood Vessel Connectors and Methods for Blood Vessel Connection

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(54) **BLOOD VESSEL CONNECTORS AND METHODS FOR BLOOD VESSEL CONNECTION**

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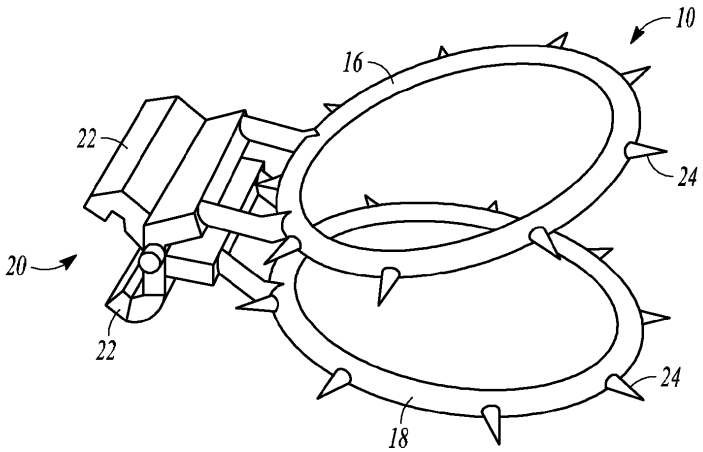
A61B 17/11 (2006.01)

(52) **U.S. Cl.**
CPC ***A61B 17/11*** (2013.01); *A61B 2017/1107* (2013.01)
USPC **606/153**

(57) **ABSTRACT**

Various embodiments of the present disclosure include an apparatus comprising a clip which includes a first side including a first ring configured to pass over an end of a first vessel, the first ring configured to engage the first side with the first vessel, and a second side coupled to the first side, the second side including a second ring configured to pass over an end of a second vessel, the second ring being configured to engage the second side with the second vessel. The first and second sides, when in a closed position, are configured to maintain the first and second vessels in substantially end-to-end contact.



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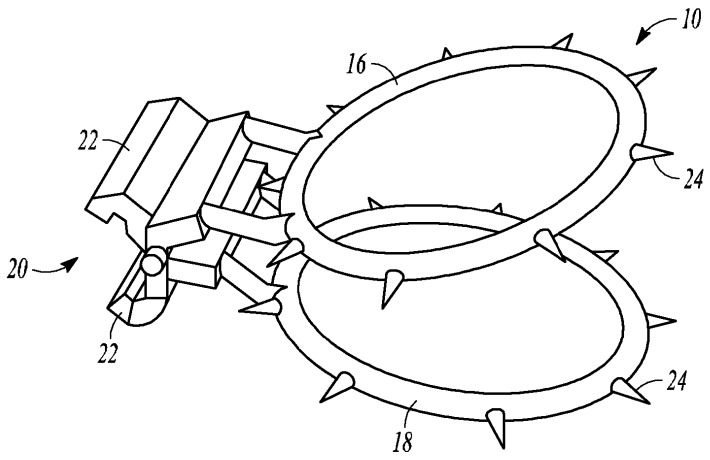

FIG. 1A

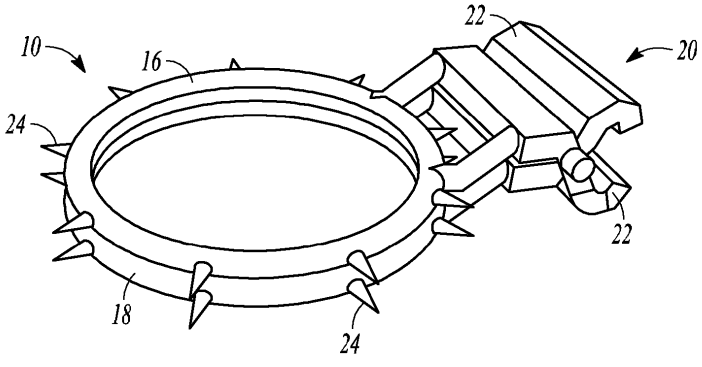

FIG. 1B

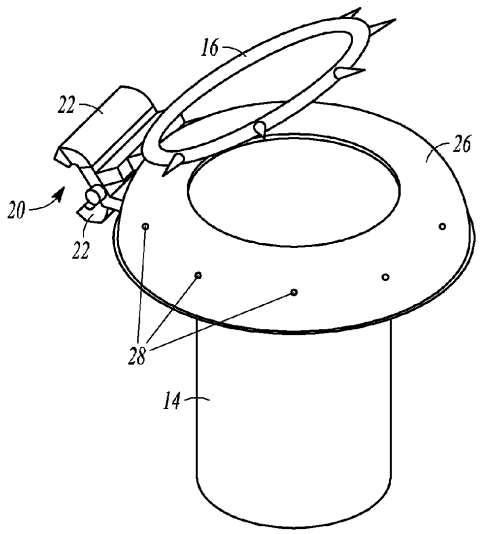

FIG. 1C

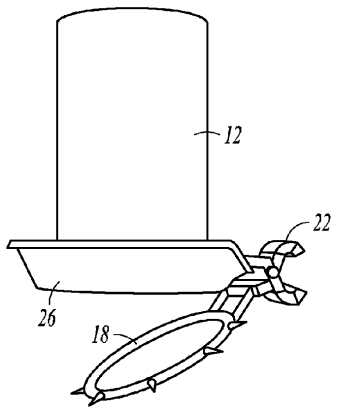

FIG. 1D

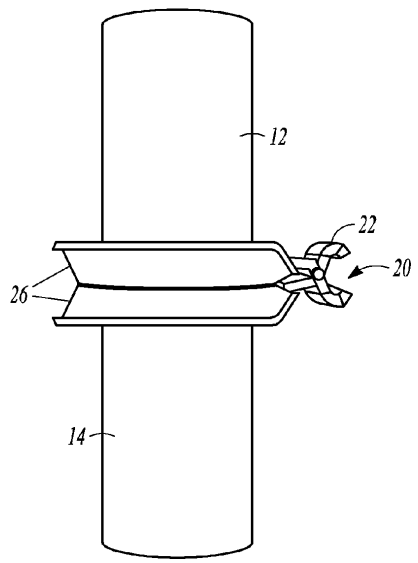

FIG. 1E

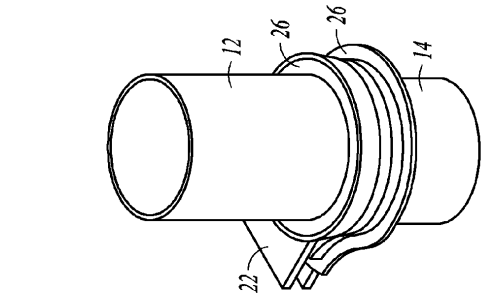

FIG. 2C

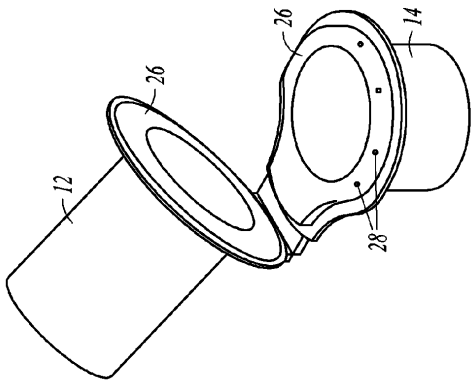

FIG. 2B

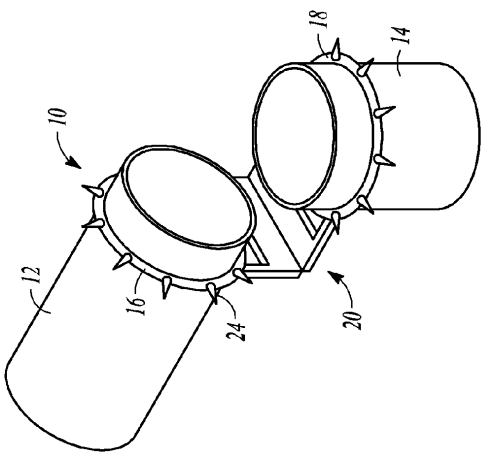

FIG. 2A

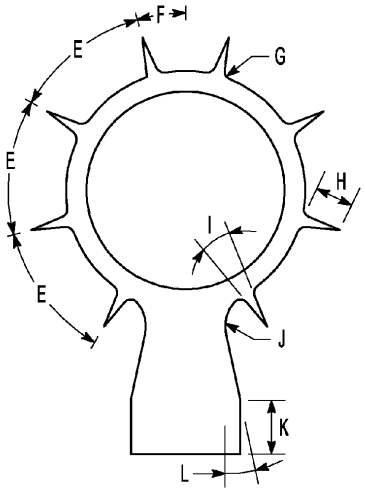

FIG. 3A

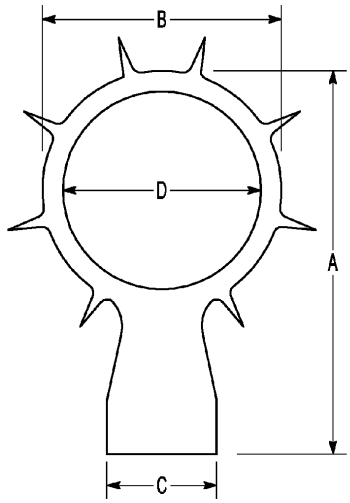

FIG. 3B

NUMERAL	DIMENSION (mm)
A	5.7
B	3.5
C	1.6
D	2.96
E	45°
F	15°
G	R 0.1
H	0.5
I	13.2°
J	R 0.6
K	0.81
L	12.6°

FIG. 3C

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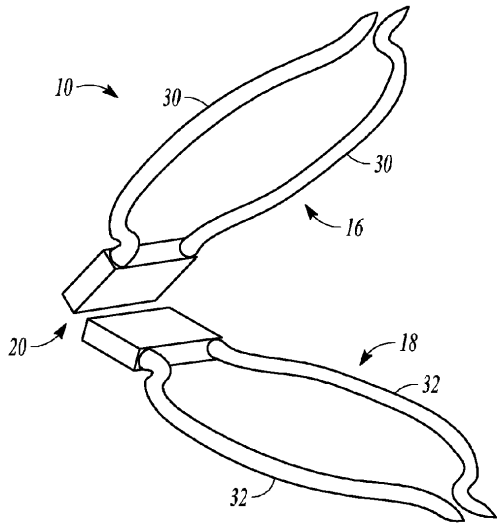

FIG. 4A

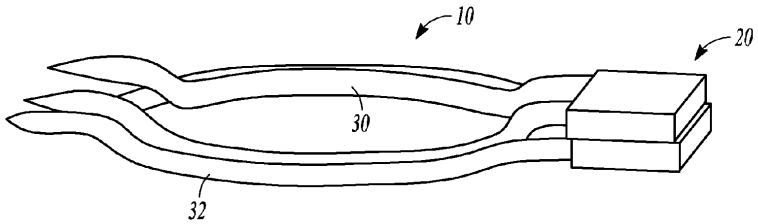

FIG. 4B

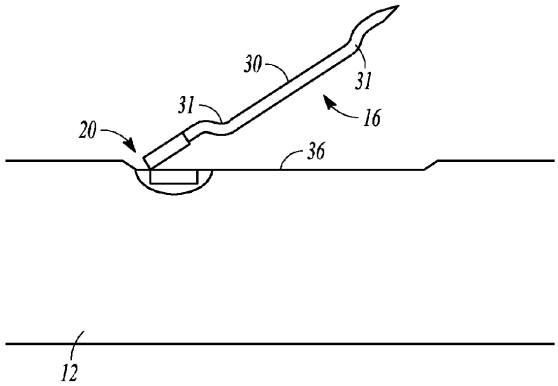

FIG. 5D

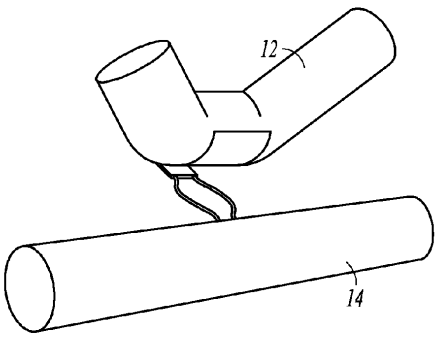

FIG. 5E

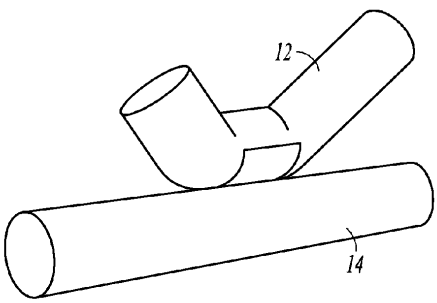

FIG. 5F

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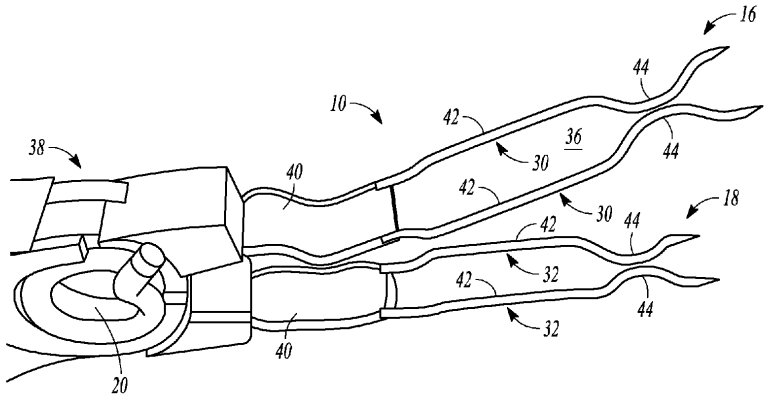

FIG. 6A

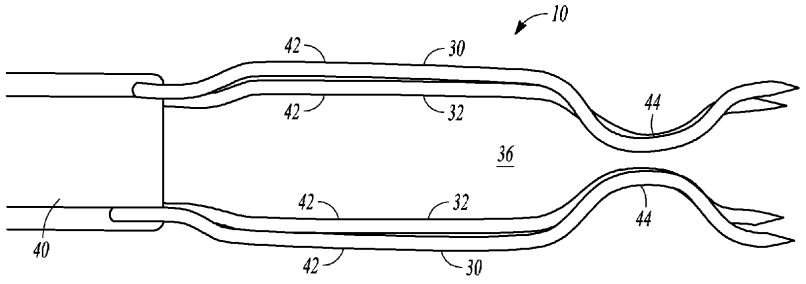

FIG. 6B

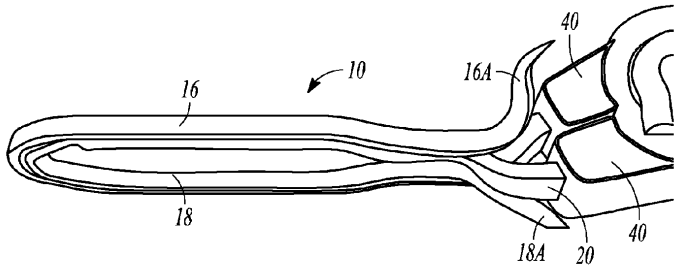

FIG. 7A

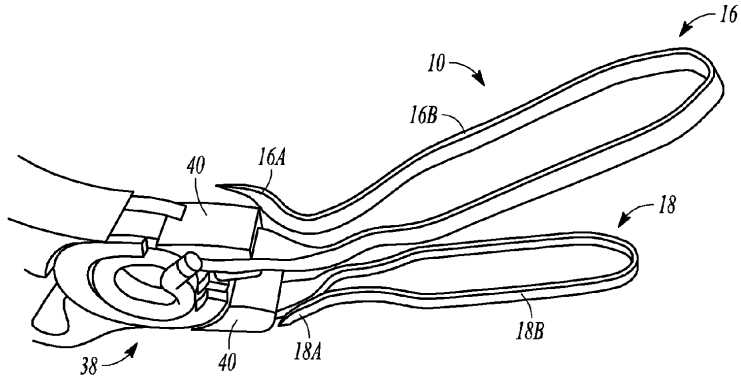

FIG. 7B

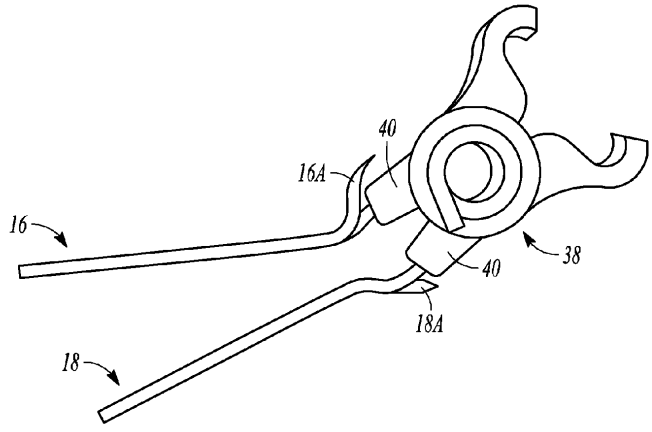

FIG. 7C

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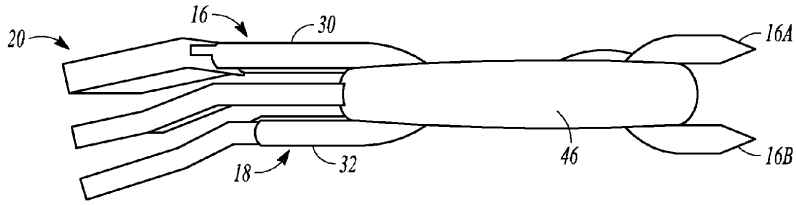

FIG. 8A

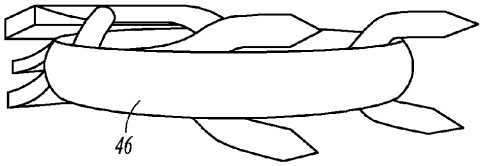

FIG. 8B

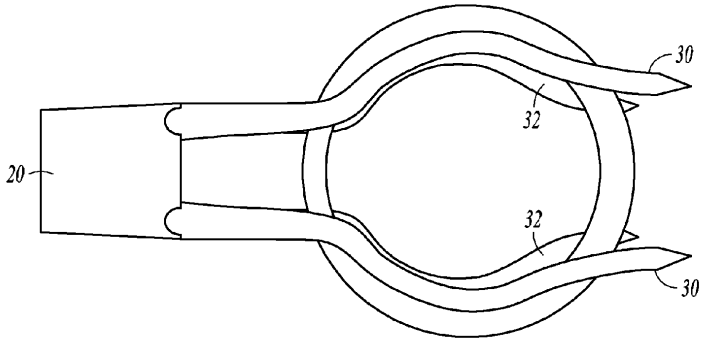

FIG. 8C

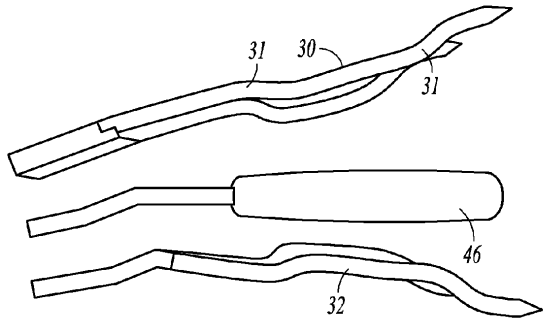

FIG. 8D

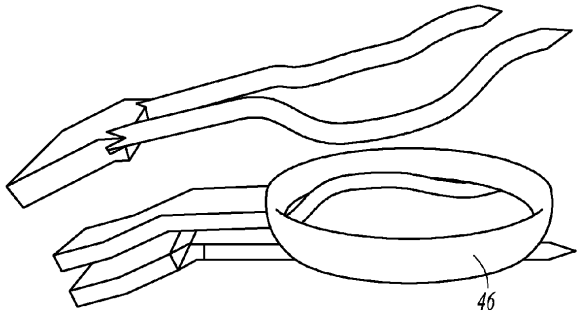

FIG. 8E

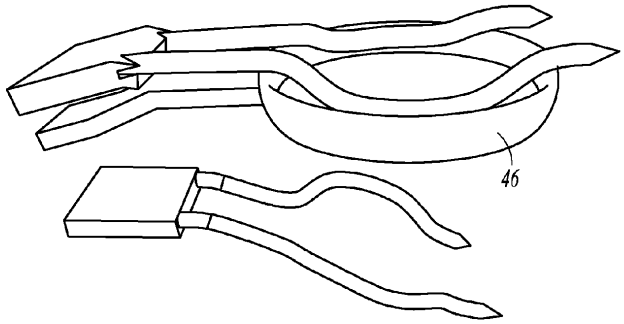

FIG. 8F

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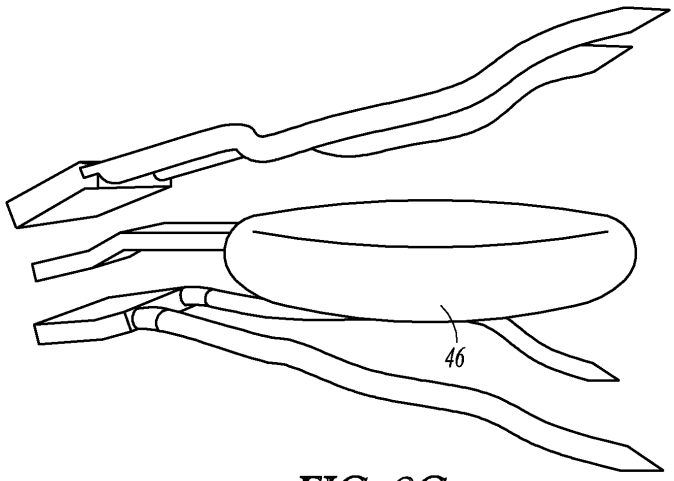

FIG. 8G

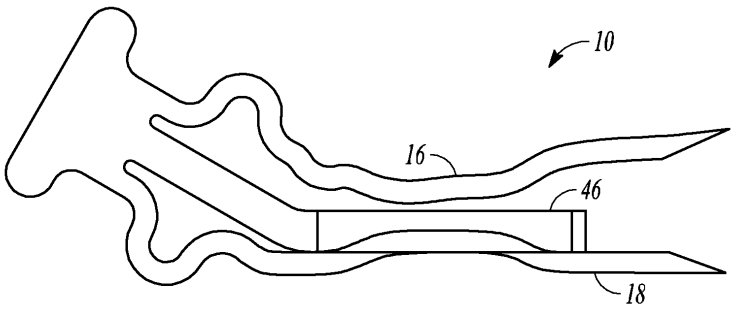

FIG. 8H

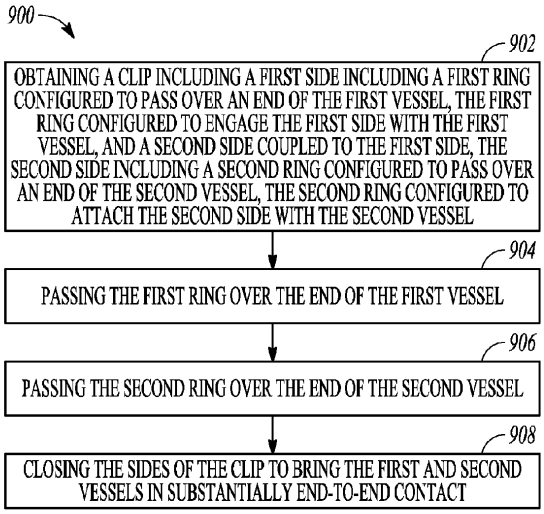
900
902
OBTAINING A CLIP INCLUDING A FIRST SIDE INCLUDING A FIRST RING CONFIGURED TO PASS OVER AN END OF THE FIRST VESSEL, THE FIRST RING CONFIGURED TO ENGAGE THE FIRST SIDE WITH THE FIRST VESSEL, AND A SECOND SIDE COUPLED TO THE FIRST SIDE, THE SECOND SIDE INCLUDING A SECOND RING CONFIGURED TO PASS OVER AN END OF THE SECOND VESSEL, THE SECOND RING CONFIGURED TO ATTACH THE SECOND SIDE WITH THE SECOND VESSEL
904
PASSING THE FIRST RING OVER THE END OF THE FIRST VESSEL
906
PASSING THE SECOND RING OVER THE END OF THE SECOND VESSEL
908
CLOSING THE SIDES OF THE CLIP TO BRING THE FIRST AND SECOND VESSELS IN SUBSTANTIALLY END-TO-END CONTACT

FIG. 9A

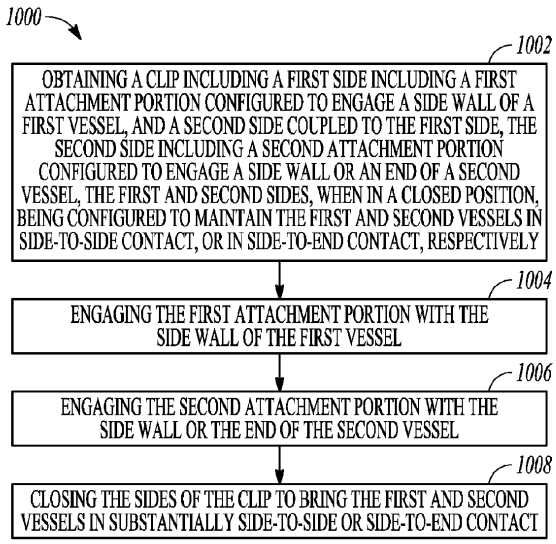
1000
1002
OBTAINING A CLIP INCLUDING A FIRST SIDE INCLUDING A FIRST ATTACHMENT PORTION CONFIGURED TO ENGAGE A SIDE WALL OF A FIRST VESSEL, AND A SECOND SIDE COUPLED TO THE FIRST SIDE, THE SECOND SIDE INCLUDING A SECOND ATTACHMENT PORTION CONFIGURED TO ENGAGE A SIDE WALL OR AN END OF A SECOND VESSEL, THE FIRST AND SECOND SIDES, WHEN IN A CLOSED POSITION, BEING CONFIGURED TO MAINTAIN THE FIRST AND SECOND VESSELS IN SIDE-TO-SIDE CONTACT, OR IN SIDE-TO-END CONTACT, RESPECTIVELY
1004
ENGAGING THE FIRST ATTACHMENT PORTION WITH THE SIDE WALL OF THE FIRST VESSEL
1006
ENGAGING THE SECOND ATTACHMENT PORTION WITH THE SIDE WALL OR THE END OF THE SECOND VESSEL
1008
CLOSING THE SIDES OF THE CLIP TO BRING THE FIRST AND SECOND VESSELS IN SUBSTANTIALLY SIDE-TO-SIDE OR SIDE-TO-END CONTACT

FIG. 9B

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BLOOD VESSEL CONNECTORS AND METHODS FOR BLOOD VESSEL CONNECTION

CLAIM OF PRIORITY

[0001] This patent application claims the benefit of priority to Tulleken et al, U.S. Provisional Patent Application Ser. No. 61/586,073, entitled "Blood Vessel Connectors and Methods for Blood Vessel Connection", filed on Jan. 12, 2012 (Attorney Docket No. 3481.017PRV), which is hereby incorporated by reference herein in its entirety.

FIELD

[0002] The present subject matter relates to the field of surgery, including methods for fusing or otherwise connecting body tissues, such as blood vessels. In particular, the invention is useful during vascular surgery for creating anastomoses and for vascular reconstruction.

BACKGROUND

[0003] Fusion of body tissues for repairing tissues, including when closing surgical openings, as well as for creating new connections of tissue, such as an anastomosis for vascular bypass, has been an important concern of surgeons since surgical procedures were first used.

[0004] In vascular surgery, anastomoses need to be made to join vessels with other vessels or open volumes through which blood can flow. Such tissue connections should be made blood-tight, and be able to withstand the pressures and forces acting on them in vivo.

[0005] The creation of a fluid or blood-tight (hemostatic) and mechanically stable connection such as for an anastomosis takes considerable time, skill, and care and is prone to complications. Even slight misalignment, asymmetric tension, introduction of foreign material, or wrong tissue types may trigger bodily responses, such as thrombogenesis, coagulation, or scar formation, which may have a detrimental effect on the patency (i.e., the ability to let fluids pass) of a connection, or cause immediate or delayed leakage of vessels or vessel damage, later followed by dehiscence, pseudo aneurysm, or anastomotic aneurysm formation.

[0006] In most cases, tissue joints such as the ones required in an anastomosis are created when the surgeon sutures or staples tissues, such as vessel wall tissues, together. Tissue soldering, tissue welding, and the use of adhesives have also been discussed, but the first two methods are not widely used, while adhesives are generally only used in combination with sutures, clips, or mechanical closures.

[0007] A common concern associated with the use of adhesives, especially when connecting blood vessels, is that the adhesive may enter the bloodstream leading to blockage and other complications. In addition, using adhesives alone to join body tissues can result in mechanically unsafe connections or connections with insufficient patency. The tissues to be joined can be under a different tension during surgery than in vivo, or can be subject to varying tensions, which can result in the weakening or breaking of an adhesive bond between the tissues or a change in the form of a connection. Although methods of using adhesives to connect a graft to an unoccluded recipient vessel were described decades ago (see, U.S. Pat. No. 3,805,793 to Wright, which was issued in 1974), adhesives are generally not used by themselves in surgical procedures for the reasons stated above, despite the apparent advantages that adhesives seem to offer, in particular, ease of application.

[0008] In many clinical applications, it is advantageous to perform anastomosis without occluding the recipient vessel. This becomes particularly important when the recipient vessel involved performs a vital function. In generally sensitive or critical organs such as the brain and the heart, occluding a recipient vessel even temporarily is often disadvantageous. A technique commonly referred to as the ELANA (Excimer Laser Assisted Nonocclusive Anastomosis) technique, is used in clinical practice to create an anastomosis without occluding the recipient vessel (see also, U.S. Pat. No. 5,964,750 (Tulleken et al.)). This technique is, for example, used by neurosurgeons in bypass surgery.

[0009] There exists a need in the art for an improved method for attaching body vessels to each other. More specifically, there exists a need for attaching body vessels in so-called "end-to-end", "end-to-side", or "side-to-side" fashions. There is also a need for an improved anastomotic surgery aid for forming connections between body vessels.

SUMMARY

[0010] In general, the present invention addresses the above-described needs by providing improved methods for attaching body vessels to each other as well as for improved anastomotic surgery aids.

[0011] In one aspect, an apparatus comprises a clip which includes a first side including a first ring configured to pass over an end of a first vessel, the first ring configured to engage the first side with the first vessel; and a second side coupled to the first side, the second side including a second ring configured to pass over an end of a second vessel, the second ring configured to engage the second side with the second vessel, the first and second sides, when in a closed position, being configured to maintain the first and second vessels in substantially end-to-end contact.

[0012] In another aspect, an apparatus comprises a clip including a first side including a first attachment portion configured to engage a side wall of a first vessel; and a second side coupled to the first side, the second side including a second attachment portion configured to engage a side wall or an end of a second vessel, the first and second sides, when in a closed position, being configured to maintain the first and second vessels in side-to-side contact, or in side-to-end contact, respectively.

EXAMPLES

[0013] To better illustrate the apparatus and methods disclosed herein, a non-limiting list of examples is provided here:

[0014] 1. An apparatus comprising a clip including a first side including a first ring configured to pass over an end of a first vessel, the first ring configured to engage the first side with the first vessel; and a second side coupled to the first side, the second side including a second ring configured to pass over an end of a second vessel, the second ring configured to engage the second side with the second vessel, the first and second sides, when in a closed position, being configured to maintain the first and second vessels in substantially end-to-end contact.

[0015] 2. The apparatus of example 1, wherein the second side of the clip is hinged to the first side of the clip.

[0016] 3. The apparatus of example 1 or example 2, wherein the first and second sides are biased to a closed position.

[0017] 4. The apparatus of any one of examples 1-3, wherein the first or second ring is configured to engage the respective first or second side of the clip to a folded-over portion of the respective first or second vessel end.

[0018] 5. The apparatus of any one of examples 1-4, wherein a first or second side of the clip includes respective first or second attachment features configured to attach the first or second side of the clip with the first or second vessel.

[0019] 6. The apparatus of example 5, wherein the first or second attachment features include points configured to puncture a wall of the respective first or second vessel, thereby to attach the first or second side of the clip with the respective first or second vessel.

[0020] 7. The apparatus of any one of the examples 1-6,

[0021] wherein the first side of the clip and the second side of the clip are hinged to each other to be movable between the closed position and an open position,

[0022] wherein in the closed position the first ring and second ring are arranged mutually parallel, wherein in the open position the first ring and second ring are arranged at an angle with respect to each other.

[0023] 8. The apparatus of example 7, wherein the clip comprises a biasing mechanism biasing the first and second side of the clip to the closed position.

[0024] 9. A method for facilitating connection of first and second vessels, the method comprising obtaining a clip including a first side including a first ring configured to pass over an end of the first vessel, the first ring configured to engage the first side with the first vessel, and a second side coupled to the first side, the second side including a second ring configured to pass over an end of the second vessel, the second ring configured to attach the second side with the second vessel; passing the first ring over the end of the first vessel; passing the second ring over the end of the second vessel; and closing the sides of the clip to bring the first and second vessels in substantially end-to-end contact.

[0025] 10. The method of example 9, further comprising folding a portion of the end of the first or second vessel over the first or second ring; and attaching the first or second ring to the folded-over portion of the first or second end, respectively.

[0026] 11. The method of example 10, wherein the first or second side of the clip includes respective first or second attachment features, the first or second attachment features including points configured to puncture a wall of the first or second vessel.

[0027] 12. The method of example 11, wherein the wall is a wall of the first or second folded-over portion, and wherein the method further comprises inserting the points into the wall to attach the first or second ring to the folded-over portion of the first or second vessel end, respectively.

[0028] 13. The method of any one of examples 9-12, wherein the first and second sides of the clip are biased to a closed position, and wherein the method further comprises closing the sides of the clip to maintain the first and second vessels in substantially end-to-end contact.

[0029] 14. An apparatus comprising a clip including a first side including a first attachment portion configured to engage a side wall of a first vessel; and a second side coupled to the first side, the second side including a second attachment portion configured to engage a side wall or an end of a second vessel, the first and second sides, when in a closed position, being configured to maintain the first and second vessels in side-to-side contact, or in side-to-end contact, respectively.

[0030] 15. The apparatus of example 14,

[0031] wherein the first side of the clip and the second side of the clip are movable with respect to each other between the closed position and an open position,

[0032] wherein in the closed position the first attachment portion and second attachment portion are arranged mutually parallel,

[0033] wherein in the open position the first attachment portion and second attachment portion are arranged at an angle with respect to each other.

[0034] 16. The apparatus of any one of examples 14-15, wherein the first and second sides are biased to the closed position.

[0035] 17. The apparatus of any of examples 14-15, wherein the clip comprises a biasing mechanism biasing the first and second side of the clip to the closed position.

[0036] 18. The apparatus of any one of examples 14-16, wherein the first or second attachment portion includes at least one fork or point configured to puncture the side wall or end of the respective first or second vessel, thereby to engage the first or second side of the clip with the side wall or end of the respective first or second vessel.

[0037] 19. The apparatus of any one of examples 14-16, wherein the first or second attachment portion includes a pair of forks for insertion into the side wall of the first or second vessel.

[0038] 20. The apparatus of example 19, wherein the pair of forks defines an outline that stretches or supports a portion of the side wall disposed between the inserted forks.

[0039] 21. The apparatus of any of examples 18-20, wherein the fork is a two-prong fork.

[0040] 22. The apparatus of any of examples 14-17, wherein the first attachment portion comprises a first fork with two prongs, and wherein the second attachment portion comprises second fork with two prongs.

[0041] 23. The apparatus of example 22, wherein each fork has a curved section where the prongs are outwardly curved with respect to each other.

[0042] 24. The apparatus of example 23, wherein, in the closed position, the curved sections of the first and second fork are nested into each other.

[0043] 25. The apparatus of example 22, wherein each fork has a rectilinear section where the prongs are substantially parallel to each other.

[0044] 26. The apparatus of example 25, wherein, in the closed position, the rectilinear sections of the forks are nested into each other.

[0045] 27. The apparatus of any of examples 21-26,

[0046] wherein the prongs of the fork have a pointed distal end to puncture a vessel, and

[0047] wherein the fork has a first prong section, a second prong section arranged between the first prong section and the distal ends of the prongs, and a third prong section, which is arranged between the second prong section and the distal ends of the prongs and extends up to the distal ends of the prongs,

[0048] wherein the distance between the prongs is, in the second section, smaller than in the first section, and

[0049] wherein in the third prong section, viewed in the direction of the distal ends, the prongs diverge with respect to each other.

[0050] 28. The apparatus of example 27, wherein the distance between the distal ends of the prongs corresponds to the maximum distance between the prongs in the first section.

[0051] 29. The apparatus of any of examples 14-18,

[0052] wherein the first attachment portion includes a first loop having a first leg, a second leg and a reverse bend connecting the first and second leg and extending 180°,

[0053] wherein the first leg extends from an end of the loop coupled to the second side to the reverse bend, and

[0054] wherein the second leg extends from the reverse bend to a free end of the loop which is pointed to puncture a vessel.

[0055] 30. The apparatus of examples 29,

[0056] wherein the second attachment portion includes a second loop having a first leg, a second leg and a reverse bend connecting the first and second leg and extending 180°,

[0057] wherein the first leg extends from an end of the loop coupled to the second side to the reverse bend, and

[0058] wherein the second leg extends from the reverse bend to a free end of the loop which is pointed to puncture a vessel.

[0059] 31. Apparatus of example 30, wherein, in the closed position, the first and second loop are nested into each other.

[0060] 32. Apparatus of any of examples 29-31, wherein the first or second loop has an U-shaped configuration.

[0061] 33. The apparatus of any one of examples 14-32, wherein the first attachment portion on the first side of the clip lies at least partially within the second attachment portion on the second side of the clip when the clip is in the closed position.

[0062] 34. The apparatus of any one of examples 14-33, wherein the first attachment portion on the first side of the clip lies at least partially on top of the second attachment portion on the second side of the clip when the clip is in the closed position.

[0063] 35. The apparatus of any one of examples 14-34 further comprising a hinge coupling the first side to the second side of the clip.

[0064] 36. The apparatus of example 35, wherein the hinge is formed integrally with the clip, the hinge including a deformable material that biases the first and second sides to the closed position, or holds the first and second sides in a desired position.

[0065] 37. The apparatus of any one of examples 14-36, further comprising a retainer member interposable between the first and second sides of the clip, the retainer member being configured to engage with a side of the clip to open or close a connection between the first and second vessels.

[0066] 38. The apparatus of example 37, wherein the retainer member includes a ring structure that can allow the passage of blood through the center of the ring structure at least when the connection is closed.

[0067] 39. The apparatus of example 38, wherein, on the one hand, the ring structure and, on the other hand, at least a part of the first attachment portion or the second attachment portion are, in closed position, nested into each other.

[0068] 40. The apparatus of any of examples 38-39, further comprising a second retainer member, such as a second ring structure, interposable between the first and second sides of the clip, the second retainer member being configured to engage with a side of the clip to open or close a connection between the first and second vessels.

[0069] 41. A method for facilitating connection of first and second vessels, the method comprising obtaining a clip including a first side including a first attachment portion configured to engage a side wall of a first vessel, and a second side coupled to the first side, the second side including a second attachment portion configured to engage a side wall or an end of a second vessel, the first and second sides, when in a closed position, being configured to maintain the first and second vessels in side-to-side contact, or in side-to-end contact, respectively; engaging the first attachment portion with the side wall of the first vessel; engaging the second attachment portion with the side wall or the end of the second vessel; and closing the sides of the clip to bring the first and second vessels in substantially side-to-side or side-to-end contact.

[0070] 42. The method of example 41, wherein the first and second sides of the clip are biased to a closed position, and wherein closing the sides of the clip includes maintaining the first and second vessels in substantially side-to-side or side-to-end contact.

[0071] 43. The method of example 41 or example 42, wherein the first or second attachment portion includes points or at least one fork configured to puncture the side wall or end of the respective first or second vessel, and wherein the method further includes inserting the points or the at least one fork into the side wall or end of the first or second vessel thereby to engage the first or second side of the clip with the respective side wall or end of the first or second vessel.

[0072] 44. The method of any one of examples 41-43, wherein the first or second attachment portion includes a pair of forks for piercing the side wall of the first or second vessel, the pair of forks defining an outline that can stretch or support a portion of the side wall disposed between the forks when the forks are embedded in the side wall of the first or second vessel; and wherein the method further comprises inserting the pair of forks into the side wall of the respective first or second vessel, and supporting or stretching a portion of the side wall disposed between the inserted forks.

[0073] 45. The method of any one of examples 42-44, wherein the clip includes a retainer member interposable between the first and second side soft the clip, the retainer member being configured to engage with a side of the clip to open or close a connection between the first and second vessels, the method further comprising opening or closing at least one of the sides of the clip to open or close the connection.

[0074] 46. The method of any one of examples 42-45, further comprising forming a hole in the side wall of the first or second vessel.

[0075] These and other examples and features of the present apparatus and methods will be set forth in part in the following Detailed Description. The Summary and the Examples are intended to provide non-limiting examples of the present subject matter. It is not intended to provide an exclusive or exhaustive explanation. The Detailed Description is included to provide further information about the present subject matter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0076] Embodiments are illustrated by way of example and not limitation in the figures of the accompanying drawings. In the drawings, which are not necessarily drawn to scale, like numerals may describe similar components in different views. Like numerals having different letter suffixes may represent different instances of similar components. The

drawings illustrate generally, by way of example, but not by way of limitation, various embodiments discussed in the present document.

[0077] FIGS. **1**A-**1**E show aspects of an anastomosis clip, according to example embodiments.

[0078] FIGS. **2**A-**2**C show aspects of a method for facilitating connection of first and second vessels, according to example embodiments.

[0079] FIGS. **3**A-**3**C show aspects of an anastomosis clip, according to example embodiments.

[0080] FIG. **4**A-**4**D show aspects of an anastomosis clip, according to example embodiments.

[0081] FIGS. **5**A-**5**F show aspects of a method for facilitating connection of first and second vessels, according to example embodiments.

[0082] FIGS. **6**A-**6**B show aspects of an anastomosis clip, according to example embodiments.

[0083] FIGS. **7**A-**7**C show aspects of an anastomosis clip, according to example embodiments.

[0084] FIGS. **8**A-**8**H show aspects of an anastomosis clip, according to example embodiments.

[0085] FIGS. **9**A-**9**B are block flow diagrams depicting aspects of methods for facilitating connection of first and second vessels, according to example method embodiments.

DETAILED DESCRIPTION

[0086] The following detailed description includes references to the accompanying drawings, which form a part of the detailed description. The drawings show illustrations in accordance with example embodiments. These example embodiments, which are also referred to herein as "examples," are described in enough detail to enable those skilled in the art to practice the present subject matter. The embodiments may be combined, other embodiments may be utilized, or structural changes may be made without departing from the scope of what is claimed. The following detailed description is, therefore, not to be taken in a limiting sense.

[0087] The accompanying figures illustrate generally an example anastomosis clip. In some examples, the anastomosis clip can be used to connect two vessels together. In further examples, the anastomosis clip can be used to connect two vessels substantially end to end, as shown for example in FIG. **1**E. The anastomosis clip can be used to connect various vessels together. The vessels may be connected in occlusive or non-occlusive manner. In some examples, the anastomosis clip can be used in a bypass procedure.

[0088] Referring now to FIGS. **1**A-**1**E, an example anastomosis clip **10** includes two rings **16** and **18** coupled together by a hinge shown generally by numeral **20**. In some examples, the hinge **20** includes opposed gripping formations **22** that allow the rings **16** and **18** to be manipulated by a suitable applicator (not shown). The applicator may have jaws that can engage with the gripping formations **22** to open and close the clip, for example. In some examples described herein, at least one of the sides of the clip, and in some cases both sides, is biased to a closed position. In some examples, the hinge **20** of the anastomosis clip **10** is biased to a closed position (FIG. **1**B). In some examples, the gripping formations **22** can be squeezed together against the bias by an applicator to move the rings **16** and **18** apart (FIG. **1**A). In some examples, biasing mechanisms or features can include or use springs or spring-like elements, clamps, "memory" steel or deformable material, and manual clip-closing systems. In some examples, the rings **16** and **18** can be held in a closed or open position by deformation of material included in the hinge **20** or biasing mechanism.

[0089] In an example, the rings **16** and **18** have attachment features in the form of points **24** extending radially outwardly from the rings **16** and **18**. In some examples, the points **24** are configured to puncture the vessel wall, such as, for instance, the folded-over vessel wall **26** of one or more of the vessels to be joined (FIGS. **1**B-**1**C). In some examples, the points **24** puncture the vessel wall completely such that ends of the points **24** can be seen at exit puncture marks **28** (FIG. **1**C). In some examples, the points do not puncture the vessel wall completely. In an example, the rings **16** and **18** have eight points **24**, although it is contemplated that the rings include more or less than eight points, or no points (i.e. a smooth ring), or that the rings have different numbers of points from one another. The surface of the rings may be roughened to provide a textured surface. The points or roughened surface can assist in avoiding slippage of the connected vessels or avoid slippage of the vessels relative to the rings. The points can also improve the stability of the connected vessels leading to improved hemastosis. Some points **24** might be configured to extend in different directions or angles relative a plane or axis of the ring. In some examples, the points **24** include different point configurations of features, for example a pin configuration, or a hook configuration, or one or more teeth, or a hardened surface (for example, diamond), or may include biocompatible or bio-absorbable material.

[0090] Reference is now made to FIGS. **2**A-**2**C of the accompanying drawings. FIG. **2**A shows two vessel ends **12** and **14** in contact with the anastomosis clip **10**, with one vessel end placed through each of the rings **16** and **18** of the anastomosis clip **10**. FIG. **2**B shows the ends of the vessels **12** and **14** being folded over, shown generally at **26**, with the points of one of the rings penetrating through the vessel wall at **28** to attach the ring of the anastomosis clip **10** with the vessel wall. This connection can avoid slippage. FIG. **2**C shows each vessel wall folded over and attached to the corresponding ring of the anastomosis clip **10**, with the anastomosis clip **10** in the closed position to connect the vessels **12** and **14** substantially end-to-end. Since both vessel walls are folded an intima to intima contact is facilitated. This can be important in surgical procedures. In some examples, the anastomosis clip **10** (and the hinge **20** thereof) is sufficient to maintain the vessels **12** and **14** in end-to-end contact without the need of separate fasteners, such as sutures, for instance. However, in other examples, it is contemplated that one or more additional fasteners can be used with the anastomosis clip.

[0091] FIGS. **3**A-**3**B show an example of a side of the anastomosis clip **10** of FIGS. **1**A-**2**C. Each side of the anastomosis clip **10** can be identical, in some examples. In other examples, the sides of the anastomosis clip can differ in shape, size, or configuration. A circular shape is shown for both rings in the accompanying drawings, but other shapes for the rings individually or collectively are possible. The overall or greatest size of a clip **10** can range from a couple of millimeters to a couple of centimeters. Although some dimensions are specified in relation to the clip **10** shown in FIGS. **3**A-**3**B, in various examples, the sides of the clip **10** can have different dimensions, for instance, to fit the vessels intended to be attached. In some examples, the anastomosis clip has the dimensions indicated in the table appearing in FIG. **3**C. The numerals listed in that table are marked in FIGS. **3**A-**3**B.

[0092] FIGS. **4**A-**4**D generally depict an example anastomosis clip **10**. The clip can include two sides **16** and **18** coupled together. In an example, the two sides are hinged together shown generally at **20**. In some examples, the hinge **20** of the anastomosis clip **10** is biased to a closed position. In some examples, the clip **10** can include gripping formations and can be manipulated with a suitable applicator, for example in similar manner to the clip **10** described above. In some examples, the present clip **10** includes one or more biasing mechanisms or features, for example biasing mechanisms or features of the type described above.

[0093] In some examples, at least one of the sides **16** and **18** of the clip includes an attachment portion configured to attach the side to a corresponding vessel. In some examples, the attachment portion includes attachment features such as forks **30** and **32** configured to pierce the vessel wall. While each side is shown with a two-prong (or paired) fork, it is contemplated that the sides of the anastomosis clip **10** include differently configured attachment features. FIGS. **5**A-**5**F show an example procedure for joining two vessels **12** and **14** together. In some examples, an anastomosis clip **10**, as shown, can be used to connect the two vessels. In some examples, the two-pronged forks **30** and **32** are pushed through the walls of a donor and recipient vessel and then the clip **10** is closed. In further examples, the anastomosis clip **10** can be used to connect two vessels side to side. The anastomosis clip **10** can be used to connect various vessels together, including, but not limited to vessels in the brain. In some examples, the anastomosis clip can be used in a bypass procedure.

[0094] FIGS. **5**A-**5**D show a first side **18** of the anastomosis clip attached to a first vessel **12** (for instance, a donor vessel). The forks **32** of the first side **18** of the clip **10** have been inserted into the wall of the vessel **12** and therefore the side **18** and the forks **32** are not directly visible in these views. On insertion into the wall of the vessel **12**, the outwardly curved configuration of the forks **32** serves to stretch the wall of the vessel **12** somewhat. The stretched wall defines a substantially planar or level surface **36** in the vessel wall. The planar or level surface **36** can facilitate the ability to cut an incision or a hole in, or a flap from, the vessel wall using a laser catheter, a puncher or scissors, for example. The region **36** is generally bounded by the contours of the underlying forks **32** and the wall of the vessel is stretched or at least supported in that region.

[0095] If desired, a laser catheter (or other device) can be passed through the first vessel **12** to align a tip of the laser catheter with the surface **36** and to cut through the wall of the first vessel lying within that region. Instead of a laser other devices may be used like punchers or scissors to create an incision or hole in, or flap from, the vessel wall. The laser catheter can be of conventional type. Appropriate cuts by the laser form a hole in the vessel wall allowing the passage of blood. In some examples, a hole is not formed in the region **36** until the two vessels **12** and **14** have first been joined together in the following manner.

[0096] Referring to FIG. **5**D, the clip **10** can be placed in an open position such that a second side **16** of the clip which includes the forks **30** is moved away from the wall of the vessel **12**. The standing configuration of the forks **30** in an open clip **10** can facilitate entry of the forks into an adjacent vessel wall, but depending on the configuration of the forks **30**, or the overall configuration of the clip **10**, or the configuration of the sides **16** and **18**, the need to open the clip **10** to join one side to another vessel may not always be required. For example, sharp ends of the forks may stand proud of the clip even in a closed position such that the sharp ends are free to be inserted, by sliding action of the clip along the vessel wall, into the vessel wall.

[0097] Now referring to FIG. **5**E, the second side **16** of the anastomosis clip is then connected with a second vessel **14** (for instance, a recipient vessel) by inserting the forks **30** into the wall of the vessel **14**. Once attached, the anastomosis clip **10** can be placed in the closed position to abut the sides of the first and second vessels together, as shown in FIG. **5**F.

[0098] In the event a hole has already been formed in the first vessel **12** (as described above), the laser catheter (or other device) can then be used to cut a second hole in the side of the second vessel **14** to allow fluid to pass between the first and second vessels **12** and **14** through the now-aligned holes in their sides. If a hole has not previously been formed in the first vessel **12**, the laser catheter (or other device) can then be used at this time to cut a "joint" hole in abutting sides of both of the first and second vessels **12** and **14** to allow fluid to pass between the first and second vessels through the "joint" hole. In some examples, the anastomosis clip **10** in the closed position connects the vessels side-to-side, and can disconnect the vessels in the open position. In some examples, the anastomosis clip **10** (and the hinge **20** thereof) is sufficient to maintain the vessels in side-to-side contact without the need of separate fasteners, such as sutures, for instance.

[0099] However, in other examples, it is contemplated that one or more additional fasteners can be used with the anastomosis clip.

[0100] The sides and/or forks of the clip **10** can assume different configurations or be of different sizes relative to one another. For example, and with reference to FIG. **4**D, the forks **30** and **32** can have an open ring shape in plan outline, with the diameter of the outer open ring of the forks **32** being larger than the diameter of the inner open ring of the forks **30**. This configuration allows an attachment feature on one side of the clip **10** (inserted, for example, into a recipient vessel) to nest within, or at least partially lie inside, an attachment feature on the other side of the clip **10** (inserted, for example, into a donor vessel). In some examples, one side or attachment feature of the clip **10** can lie within the other side or attachment feature of the clip **10** in a "side-by-side" general configuration when the clip **10** is closed. As will be seen at **31** in the side view of FIG. **5**D, the contours of the forks **30** are configured or bent out of plane as appropriate to allow such nesting. The nesting configuration can improve fixation of the vessel walls to each other and allow improved hemostasis. In some examples, the rings or attachment features are of similar size and assume an overlapping or "ring-on-ring" general configuration when the clip **10** is closed.

[0101] FIGS. **6**A-**6**B generally depict an example anastomosis clip **10**. The clip can include two sides **16** and **18** coupled together by means of an applicator shown generally at **38**. In an example, the two sides **16** and **18** can be held and manipulated using opposed jaws **40** of the applicator **38**. The sides **16** and **18** can move about a pivot axis **20** defined by the applicator **38**. In some examples, the sides of the clip **10** are biased to a closed position by the applicator **38**. In some examples, the jaws **40** are detachable from the applicator **38** and, in some examples, the sides **16** and **18** are detachable from the jaws **40**. In some examples, the clip **10** or applicator **38** can include one or more biasing mechanisms of features of the type described above.

[0102] One or both sides **16** and **18** include attachment features configured to attach the side to a corresponding vessel. In the examples illustrated in FIGS. **6**A-**6**B, attachment features are provided on both sides and include forks **30** and **32** configured to pierce the vessel wall. The forks **30** and **32** are two-pronged and assume a "bull-horn" configuration as shown. An example function of the bull horn is to match the puncture holes to the size of maximum lateral size of the metal ring in order to avoid extra stretch of the vessel wall, which potentially can reduce the chance of vessel damage during device positioning. Other configurations are possible. In some examples, the bull-horn forks are configured to assume a "side-by side" (FIG. **6**B) configuration, or in some examples a "ring-on-ring" configuration, when the clip **10** is closed.

[0103] It will be appreciated that the substantially parallel, rectilinear portions **42** of the bull-horn forks **30** and **32** do not stretch the walls of the vessel as much as the rounder ring-shaped forks of the example clip **10** discussed further above, when inserted into the walls of a vessel. The narrower or straighter fork configuration can allow easier entry of the forks into the walls of a corresponding vessel.

[0104] As shown in FIGS. **6**A-**6**B, distal portions **44** of the opposed forks **30** and **32** are shaped inwardly to define a substantially enclosed region **36** lying within the forks **30** and **32**. The region **36** can, in similar manner to that described above, be used to provide a supported area for joining the walls of abutting vessels in "side-to-side" manner, or the end of a vessel to the wall of another vessel in "end-to-side" manner. While each side of the clip **10** is shown with a two-prong fork, it is contemplated that the sides of the anastomosis clip **10** include differently configured attachment features.

[0105] In some examples, a clip **10** includes a fork-ring combination such that a first side of the clip **10** includes attachment features (such as the example forks **30** and **32** of FIGS. **4**A-**6**B), while a second side of the clip **10** includes a ring formation so that vessels can be joined in "side-to-end" manner. The second side of the clip may include a "closed ring" of the type shown in FIGS. **1**A-**3**C, or in some examples may include an "open ring" forked configuration of the type shown in FIGS. **4**A-**6**B (or any of the other examples described further below). In some examples, the second or "ring" side of the clip is used to secure a folded-over portion of an end of a vessel against the walls of another vessel which has been pierced and secured by the first or "forked" side of the clip. When closed, the clip **10** holds the two vessels together. A laser catheter or other device can be used to form a hole in the wall of the second vessel to allow passage of blood from the open end of the one vessel through the wall of the other vessel. As desired or appropriate, either side of the clip **10** can include attachment features or rings of any of the example embodiments described herein.

[0106] FIGS. **7**A-**7**C generally depict an example anastomosis clip **10**. The illustrated example clip **10** is of a general "paper-clip" configuration and includes two legs or loops that define (when the clip **10** is open) sides **16** and **18** of the clip **10** (FIG. **7**C). In some examples, the legs of the sides **16** and **18** assume a nesting "side-by-side" configuration when the clip **10** is closed (FIG. **7**A), while in some examples, the legs of the sides **16** and **18** lie one on top of another in a "ring-on-ring" configuration when the clip **10** is closed. Various combinations are possible. Each side of the clip **10** has only one vessel penetration pin or tip, in one example. In some examples, the other aspects of the clip operate in similar manner to other examples described in this specification.

[0107] In some examples, the sides **16** and **18** of the clip are joined together by a central hinge portion **20** formed integrally with the material of the clip **10**, similar again to the structure of a paper-clip. In some examples, the sides **16** and **18** of the clip can be urged apart manually. In some examples, the sides **16** and **18** can be urged apart by an operator using the jaws **40** of an applicator **48** which engage with areas of the hinge portion **20** (FIGS. **7**B-**7**C). In some examples, as the clip **10** is opened, the hinge portion **20** is deformed and the restorative force generated by the deformed material biases the sides **16** and **18** back into a closed position of the clip **10** (FIG. **7**A). Other biasing mechanisms or features are possible, such as those described further above. In some examples, the deformed hinge portion **20** does not bias the clip but is sufficient to hold the clip in a desired position. In some examples, the hinge portion **20** is formed separately from the clip **10**.

[0108] In some examples, a leg of each side **16** and **18** of the clip terminates at a proximal end in a curved, sharp portion indicated respectively by numerals **16**A and **18**A in FIGS. **7**A-**7**C. The distal ends (i.e. away from the applicator) of each side **16** and **18** of the clip form hoops, similar again to a paper-clip. In some examples, the sharp portions **16**A and **18**A are carried by respective straight pin portions of the legs marked **16**B and **18**B in FIG. **7**B. When the sides **16** and **18** of the clip **10** are moved apart (FIGS. **7**B-**7**C), the sharp legs can more easily be inserted into the walls of respective donor and recipient vessels, for example. The sides **16** and **18** of the clip **10** can then be moved or released to hold the walls of the joined vessels together. In some examples, the entry of a single leg alone into each vessel results in only one point of entry in each vessel being formed accordingly. Reduction of entry points can be less traumatic to the vessel wall and can provide an advantage for the operator in being able to focus on one entry point only when inserting the clip. In some examples, the legs of the sides **16** and **18** assume round, oval, rectilinear, or other shapes or configurations in outline or cross-section. The legs may be of different sizes with respect to one another.

[0109] FIGS. **8**A-**8**H generally depict an example anastomosis clip **10**. This example clip is sometimes referred to as a "trinity" clip in that it can comprise three parts: two sides **16** and **18**, and a retainer member **46**. In some examples, the clip nevertheless operates in similar manner to other examples described in this specification, and can provide the same advantages. The shape of the sides and/or forks of the clip can be as shown in the example drawings in FIGS. **8**A-**8**H or can have the bull horn configuration or paper clip configuration or a combination of the configurations for each side, ring, or fork. In some examples, a retainer member **46** is interposed, or at least interposable, between the sides **16** and **18** of the clip **10**. The retainer member **46** can allow a donor vessel connection and a recipient vessel connection to be opened or closed independently of each other. One side **16** of an installed clip **10** acting, for instance, against the retainer member **46** to close a donor vessel connection (with or without closing bias), can be left intact (i.e. in closed position) while the other side **18** of the clip can be opened or moved away from the retainer member **46** to open, for instance, a recipient vessel connection. The thus-opened recipient connection can be closed again, as desired, without disturbing the donor connection on the other side of the clip **10**. The independent

opening and closing of connections can allow improved fixation and stability of a surgical site while allowing more control of blood flow, the introduction of catheters, and so forth.

[0110] Turning again to FIGS. **8**A-**8**H, an example anastomosis clip **10** includes two sides **16** and **18** coupled together. In some examples, the two sides are hinged together shown generally at **20**. In some examples, the hinge **20** of the clip **10** is biased to a closed position. In some examples, the clip **10** includes formations or mechanisms so that one or more of the sides **16** and **18** can be manipulated, with or without associated movement of the retainer member **46**. In some examples, the sides **16** and **18** of the clip **10** can be manipulated with an applicator. In some examples, the clip **10** can include one or more biasing mechanisms or features, including for example the biasing mechanisms of features described further above.

[0111] In some examples, each of the sides **16** and **18** includes attachment features configured to attach each of the sides to a corresponding vessel. In some examples, the attachment features include forks **30** and **32** configured to pierce the vessel wall. While each side is shown with a two-prong (or paired) fork, it is contemplated that the sides of the anastomosis clip **10** include differently configured attachment features. In some embodiments, the ends of the forks **30** and **32** are sharp to pierce the vessel wall. In some examples, the retainer member **46** is fixed to the clip, or may be attached to or form part of the hinge **20**. In some examples, the retainer member **46** is free and unattached to the clip. A clip kit including a clip **10** (as described in any of the examples above) and a separate retainer member **46** (configured to be interposable between the sides) may be provided. In some examples, the retainer member includes a ring structure, including for example a structure substantially as shown in FIGS. **8**A-**8**H. Other configurations, structures and shapes of retainer member **46** are possible. The configurations, structures and shapes of the retainer member may be selected to cooperate with the attachment features of the clip, or the size of the vessels to be joined, for example. In some examples, an attachment feature of one or both sides **16** and **18** of the clip **10** is shaped or bent (for example, at **31** in FIG. **8**H) so that at least a portion of the attachment feature lies within the retainer member **46** when the clip **10** is closed. The sides **16** and **18** of the clip **10** may, in conjunction with the retainer member **46** or independently thereof, form "side-by-side" or "ring-on-ring" configurations of the type described above when brought together. Each or both of the sides **16** and **18** of the clip **10** may include one or more of the example rings and attachment features described herein, or variants thereof. In some examples, a second or more retainer members **46** are provided. For example, a clip **10** may include two ring structures **46** interposed between the sides **16** and **18** of the clip **10**, and hence comprise four parts.

[0112] As with the examples described above, installation of the clip **10** can proceed as follows. The clip **10** is opened (or otherwise manipulated when closed, depending on the overall configuration of the clip **10**, or its respective sides **16** and **18** and attachment features, and so forth) so that one side **16** of the clip **10** is inserted into the wall of a first vessel (such as a donor vessel), and the other side **18** of the clip is inserted into the wall of a second vessel (such as a recipient vessel). The clip **10** can be used as appropriate to form end-to-end, side-to-side, or end-to-side vessel connections. In a side-to-side vessel connection, for example, the retainer member **46** lies in use between the outer surfaces of the walls of the adjoining vessels and defines a reaction surface against which the sides **16** and **18** of the clip **10** (inserted within the corresponding vessel wall) can push or engage the vessel walls to close a corresponding vessel connection. This arrangement is shown for example in schematic sectional outline in FIG. **8**H. The vessel walls have been omitted in this view in the interest of clarity, but it will be appreciated that the "upper" side **16** of the clip can be moved (as desired) towards or away from the retainer member **46** and independently of the "lower" side **18** of the clip **10**, which can do the same. Once the clip **10** has been installed in the vessel walls, a hole can be formed (by a laser catheter or other device, for example) to pass though through the walls of the adjoining vessel walls and through the center of the retainer member **46**. In some examples, the pins or forks on a side **16** or **18** of the clip **10** are first advanced into a donor vessel. The clip **10** is closed and the donor vessel wall is captured between the retainer member (e.g. ring **46**) of the clip and the pins in the donor vessel wall. A hole can be formed or burned by advancing a laser catheter (or other device, for example) via the distal end of the donor vessel. Then the other side of the clip (**18** or **16**, respectively—lower part of the clip **10** in the view)can be opened while donor vessel (which has already been holed) is held in place by the retainer member **46**. Now the pins or forks on the other side of the clip **10** can be introduced into a recipient vessel and clip **10** can be closed. Now the catheter (or other device) can be positioned again and will form or burn a hole in the recipient vessel. Again the retainer member **46** will give stability to the recipient vessel and the introduced pins or forks. The shape of the clip sides **16** and **18**, the pins or forks, and the retainer member **46**, can be configured in such a way that the vessel walls are pushed on top of each other so that good connection is facilitated.

[0113] Some embodiments of the present inventive subject matter include methods for facilitating connection of first and second vessels. One such embodiment is illustrated in FIG. **9**A. In some embodiments, a method **900** includes: at element **902**, obtaining a clip including a first side including a first ring configured to pass over an end of the first vessel, the first ring configured to engage the first side with the first vessel, and a second side coupled to the first side, the second side including a second ring configured to pass over an end of the second vessel, the second ring configured to attach the second side with the second vessel; at element **904**, passing the first ring over the end of the first vessel; at element **906**, passing the second ring over the end of the second vessel; and, at element **908**, closing the sides of the clip to bring the first and second vessels in substantially end-to-end contact.

[0114] In some examples, the method **900** further comprises folding a portion of the end of the first or second vessel over the first or second ring; and attaching the first or second ring to the folded-over portion of the first or second end, respectively. The first or second side of the clip may include respective first or second attachment features, the first or second attachment features including points configured to puncture a wall of the first or second vessel.

[0115] In some examples, the wall is a wall of the first or second folded-over portion, and the method **900** further comprises inserting the points into the wall to attach the first or second ring to the folded-over portion of the first or second vessel end, respectively.

[0116] The first and second sides of the obtained clip may be biased to a closed position, and the method **900** may further comprise closing the sides of the clip to maintain the first and second vessels in substantially end-to-end contact.

[0117] With reference to FIG. **9**B, a method **1000** includes: at element **1002**, obtaining a clip including a first side including a first attachment portion configured to engage a side wall of a first vessel, and a second side coupled to the first side, the second side including a second attachment portion configured to engage a side wall or an end of a second vessel, the first and second sides, when in a closed position, being configured to maintain the first and second vessels in side-to-side contact, or in side-to-end contact, respectively; at element **1004**, engaging the first attachment portion with the side wall of the first vessel; at element **1006**, engaging the second attachment portion with the side wall or the end of the second vessel; and, at element **1008**, closing the sides of the clip to bring the first and second vessels in substantially side-to-side or side-to-end contact.

[0118] In some examples, the first and second sides of the obtained clip are biased to a closed position, and wherein closing the sides of the clip includes maintaining the first and second vessels in substantially side-to-side or side-to-end contact.

[0119] The first or second attachment portion may include points or at least one fork configured to puncture the side wall or end of the respective first or second vessel, and wherein the method further includes inserting the points or the at least one fork into the side wall or end of the first or second vessel thereby to engage the first or second side of the clip with the respective side wall or end of the first or second vessel.

[0120] In some examples, the first or second attachment portion includes a pair of forks for piercing the side wall of the first or second vessel, the pair of forks defining an outline that can stretch or support a portion of the side wall disposed between the forks when the forks are embedded in the side wall of the first or second vessel. The method **1000** may further comprise inserting the pair of forks into the side wall of the respective first or second vessel, and supporting or stretching a portion of the side wall disposed between the inserted forks.

[0121] In some examples, the obtained clip includes a retainer member interposable between the first and second side soft the clip, the retainer member being configured to engage with a side of the clip to open or close a connection between the first and second vessels, the method further comprising opening or closing at least one of the sides of the clip to open or close the connection. The method **1000** may further comprise forming a hole in the side wall of the first or second vessel.

Additional Notes

[0122] The patent or application file, including the file of related applications, may contain at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0123] The above detailed description includes references to the accompanying drawings, which form a part of the detailed description. The drawings show, by way of illustration, specific embodiments in which the invention can be practiced. These embodiments are also referred to herein as "examples." Such examples can include elements in addition to those shown or described. However, the present inventors also contemplate examples in which only those elements shown or described are provided. Moreover, the present inventors also contemplate examples using any combination or permutation of those elements shown or described (or one or more aspects thereof), either with respect to a particular example (or one or more aspects thereof), or with respect to other examples (or one or more aspects thereof) shown or described herein.

[0124] All publications, patents, and patent documents referred to in this document are incorporated by reference herein in their entirety, as though individually incorporated by reference. In the event of inconsistent usages between this document and those documents so incorporated by reference, the usage in the incorporated reference(s) should be considered supplementary to that of this document; for irreconcilable inconsistencies, the usage in this document controls.

[0125] In this document, the terms "a" or "an" are used, as is common in patent documents, to include one or more than one, independent of any other instances or usages of "at least one" or "one or more." In this document, the term "or" is used to refer to a nonexclusive or, such that "A or B" includes "A but not B," "B but not A," and "A and B," unless otherwise indicated. In this document, the terms "including" and "in which" are used as the plain-English equivalents of the respective terms "comprising" and "wherein." Also, in the following claims, the terms "including" and "comprising" are open-ended, that is, a system, device, article, or process that includes elements in addition to those listed after such a term in a claim are still deemed to fall within the scope of that claim. Moreover, in the following claims, the terms "first," "second," and "third," etc. are used merely as labels, and are not intended to impose numerical requirements on their objects.

[0126] Method examples described herein can be machine or computer-implemented at least in part. Some examples can include a computer-readable medium or machine-readable medium encoded with instructions operable to configure an electronic device to perform methods as described in the above examples. An implementation of such methods can include code, such as microcode, assembly language code, a higher-level language code, or the like. Such code can include computer readable instructions for performing various methods. The code may form portions of computer program products. Further, in an example, the code can be tangibly stored on one or more volatile, non-transitory, or non-volatile tangible computer-readable media, such as during execution or at other times. Examples of these tangible computer-readable media can include, but are not limited to, hard disks, removable magnetic disks, removable optical disks (e.g., compact disks and digital video disks), magnetic cassettes, memory cards or sticks, random access memories (RAMs), read only memories (ROMs), and the like.

[0127] The above description is intended to be illustrative, and not restrictive. For example, the above-described examples (or one or more aspects thereof) may be used in combination with each other. Other embodiments can be used, such as by one of ordinary skill in the art upon reviewing the above description. The Abstract is provided to comply with 37 C.F.R. §1.72(b), to allow the reader to quickly ascertain the nature of the technical disclosure. It is submitted with the understanding that it will not be used to interpret or limit the scope or meaning of the claims. Also, in the above Detailed Description, various features may be grouped together to streamline the disclosure. This should not be interpreted as intending that an unclaimed disclosed feature is essential to any claim. Rather, inventive subject matter may lie in less than all features of a particular disclosed embodiment. Thus, the following claims are hereby incorporated into

the Detailed Description, with each claim standing on its own as a separate embodiment, and it is contemplated that such embodiments can be combined with each other in various combinations or permutations. The scope of the invention should be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled.

1. An apparatus comprising a clip including:

a first side including a first ring configured to pass over an end of a first vessel, the first ring configured to engage the first side with the first vessel; and

a second side coupled to the first side, the second side including a second ring configured to pass over an end of a second vessel, the second ring configured to engage the second side with the second vessel, the first and second sides, when in a closed position, being configured to maintain the first and second vessels in substantially end-to-end contact.

2. The apparatus of claim **1**, wherein the second side of the clip is hinged to the first side of the clip.

3. The apparatus of claim **1** wherein the first and second sides are biased to a closed position.

4. The apparatus of any ones of claim **1**, wherein the first or second ring is configured to engage the respective first or second side of the clip to a folded-over portion of the respective first or second vessel end.

5. The apparatus of claim **1**, wherein a first or second side of the clip includes respective first or second attachment features configured to attach the first or second side of the clip with the first or second vessel.

6. The apparatus of claim **5**, wherein the first or second attachment features include points configured to puncture a wall of the respective first or second vessel, thereby to attach the first or second side of the clip with the respective first or second vessel.

7. The apparatus of e claim **1**, wherein the first side of the clip and the second side of the clip are hinged to each other to be movable between the closed position and an open position, wherein in the closed position the first ring and second ring are arranged mutually parallel, wherein in the open position the first ring and second ring are arranged at an angle with respect to each other.

8. The apparatus of claim **7**, wherein the clip comprises a biasing mechanism biasing the first and second side of the clip to the closed position.

9. A method for facilitating connection of first and second vessels, the method comprising:

obtaining a clip including:

a first side including a first ring configured to pass over an end of the first vessel, the first ring configured to engage the first side with the first vessel, and

a second side coupled to the first side, the second side including a second ring configured to pass over an end of the second vessel, the second ring configured to attach the second side with the second vessel;

passing the first ring over the end of the first vessel;

passing the second ring over the end of the second vessel; and

closing the sides of the clip to bring the first and second vessels in substantially end-to-end contact.

10. The method of claim **9**, further comprising:

folding a portion of the end of the first or second vessel over the first or second ring; and

attaching the first or second ring to the folded-over portion of the first or second end, respectively.

11. The method of claim **10**, wherein the first or second side of the clip includes respective first or second attachment features, the first or second attachment features including points configured to puncture a wall of the first or second vessel.

12. The method of claim **11**, wherein the wall is a wall of the first or second folded-over portion, and wherein the method further comprises inserting the points into the wall to attach the first or second ring to the folded-over portion of the first or second vessel end, respectively.

13. The method of claim **9**, wherein the first and second sides of the clip are biased to a closed position, and wherein the method further comprises closing the sides of the clip to maintain the first and second vessels in substantially end-to-end contact.

14. An apparatus comprising a clip including:

a first side including a first attachment portion configured to engage a side wall of a first vessel; and

a second side coupled to the first side, the second side including a second attachment portion configured to engage a side wall or an end of a second vessel, the first and second sides, when in a closed position, being configured to maintain the first and second vessels in side-to-side contact, or in side-to-end contact, respectively.

15. The apparatus of claim **14**,

wherein the first side of the clip and the second side of the clip are movable with respect to each other between the closed position and an open position,

wherein in the closed position the first attachment portion and second attachment portion are arranged mutually parallel,

wherein in the open position the first attachment portion and second attachment portion are arranged at an angle with respect to each other.

16. The apparatus of claim **14**, wherein the first and second sides are biased to the closed position.

17. The apparatus of claim **14**, wherein the clip comprises a biasing mechanism biasing the first and second side of the clip to the closed position.

18. The apparatus of claim **14**, wherein the first or second attachment portion includes at least one fork or point configured to puncture the side wall or end of the respective first or second vessel, thereby to engage the first or second side of the clip with the side wall or end of the respective first or second vessel.

19. The apparatus of claim **14**, wherein the first or second attachment portion includes a pair of forks for insertion into the side wall of the first or second vessel.

20. The apparatus of claim **19**, wherein the pair of forks defines an outline that stretches or supports a portion of the side wall disposed between the inserted forks.

21. The apparatus of claim **18**, wherein the fork is a two-prong fork.

22. The apparatus of claim **14**, wherein the first attachment portion comprises a first fork with two prongs, and wherein the second attachment portion comprises second fork with two prongs.

23. The apparatus of claim **22**, wherein each fork has a curved section where the prongs are outwardly curved with respect to each other.

24. The apparatus of claim **23**, wherein, in the closed position, the curved sections of the first and second fork are nested into each other.

25. The apparatus of claim **22**, wherein each fork has a rectilinear section where the prongs are substantially parallel to each other.

26. The apparatus of claim **25**, wherein, in the closed position, the rectilinear sections of the forks are nested into each other.

27. The apparatus of claim **21**,

wherein the prongs of the fork have a pointed distal end to puncture a vessel, and

wherein the fork has a first prong section, a second prong section arranged between the first prong section and the distal ends of the prongs, and a third prong section, which is arranged between the second prong section and the distal ends of the prongs and extends up to the distal ends of the prongs,

wherein the distance between the prongs is, in the second section, smaller than in the first section, and

wherein in the third prong section, viewed in the direction of the distal ends, the prongs diverge with respect to each other.

28. The apparatus of claim **27**, wherein the distance between the distal ends of the prongs corresponds to the maximum distance between the prongs in the first section.

29. The apparatus of claim **14**,

wherein the first attachment portion includes a first loop having a first leg, a second leg and a reverse bend connecting the first and second leg and extending 180°,

wherein the first leg extends from an end of the loop coupled to the second side to the reverse bend, and

wherein the second leg extends from the reverse bend to a free end of the loop which is pointed to puncture a vessel.

30. The apparatus of claims **29**,

wherein the second attachment portion includes a second loop having a first leg, a second leg and a reverse bend connecting the first and second leg and extending 180°,

wherein the first leg extends from an end of the loop coupled to the second side to the reverse bend, and

wherein the second leg extends from the reverse bend to a free end of the loop which is pointed to puncture a vessel.

31. Apparatus of claim **30**, wherein, in the closed position, the first and second loop are nested into each other.

32.-**46**. (canceled)

* * * * *

APPENDIX 5

Patent 2: Catheter Apparatus and Method

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(19) **United States**

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Van Thoor et al. (43) **Pub. Date: Sep. 12, 2013**

(54) **CATHETER APPARATUS AND METHOD**

(76) Inventors: **Alexander Cornelis Elisabeth Van Thoor**, Utrecht (NL); **David Stecher**, Utrecht (NL); **Diederick Marco Keizer**, Utrecht (NL)

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(22) Filed: **Mar. 7, 2012**

Publication Classification

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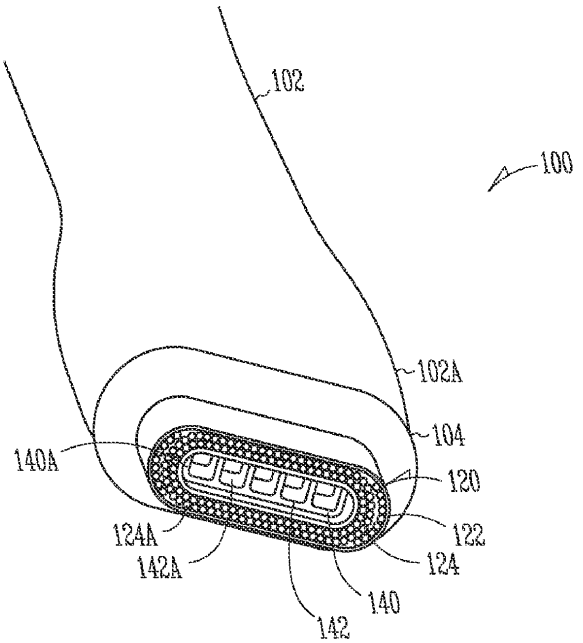
A61B 18/20	(2006.01)
A61B 17/32	(2006.01)

(52) **U.S. Cl.**

USPC **606/15**; 606/170; 606/14

(57) **ABSTRACT**

In some examples, a catheter apparatus, configured to cut through a vessel wall, includes an elongate body including a distal end. A cutting device, configured to selectively cut a hole in the vessel wall, is disposed at the distal end of the elongate body. The cutting device includes a substantially ring-shaped cutting portion including a first dimension and a second dimension, wherein the first dimension is greater than the second dimension. The gripping device, disposed at the distal end of the elongate body, is configured to grip the vessel wall to maintain the cutting device proximate the vessel wall during cutting of the hole in the vessel wall. The gripping device is further configured to retain a portion of the vessel wall removed during cutting of the vessel wall. In some examples, a method includes using a catheter apparatus to cut through a vessel wall.



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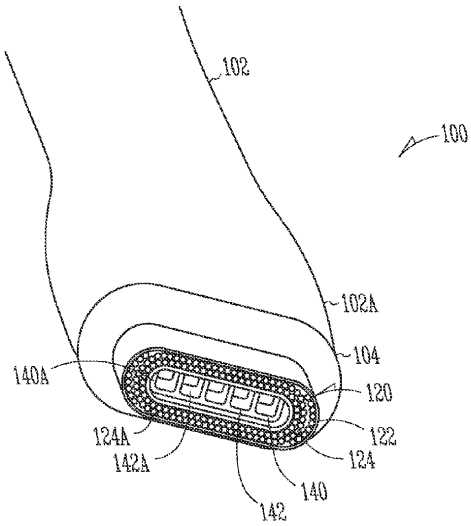

Fig. 1

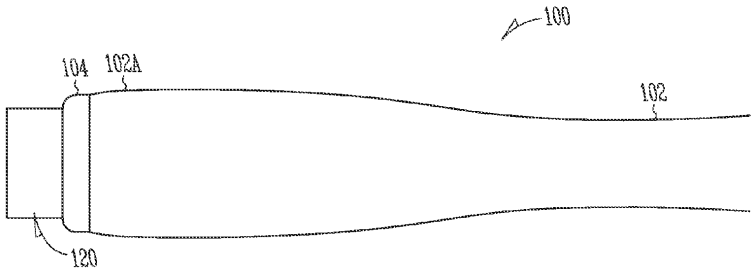

Fig. 2

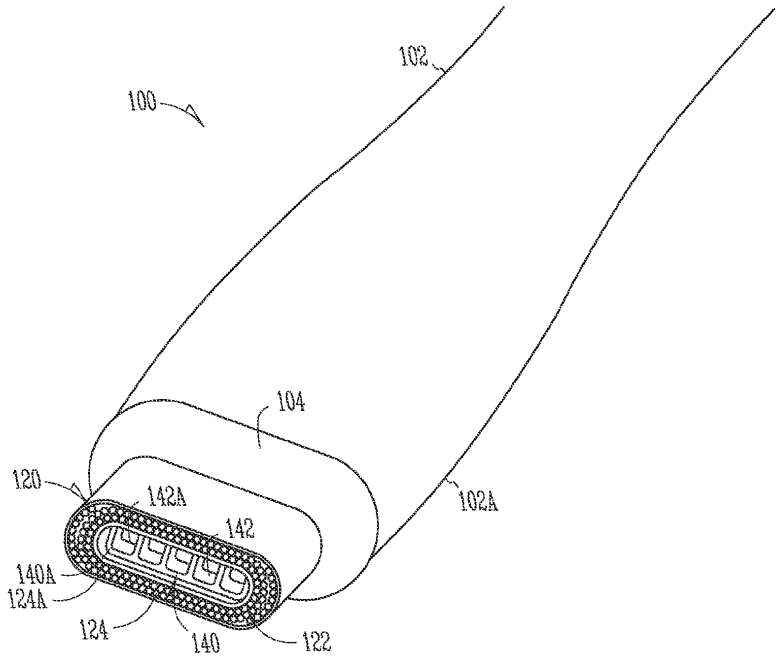

Fig. 3

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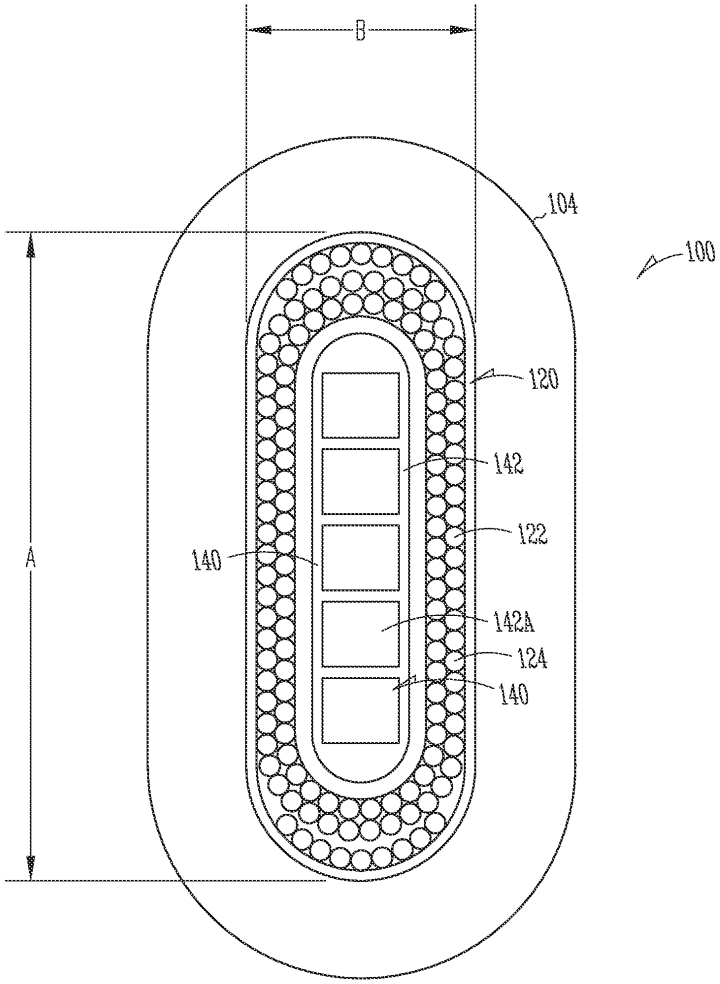

Fig. 4

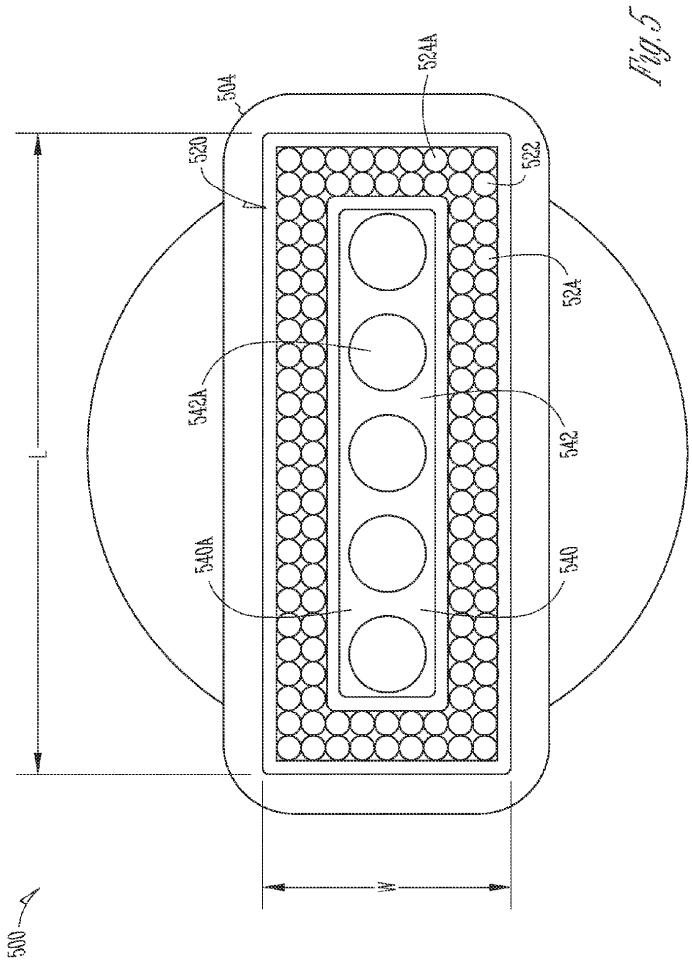
Fig. 5
504
524A
520
522
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542A
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540A
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L
W
500

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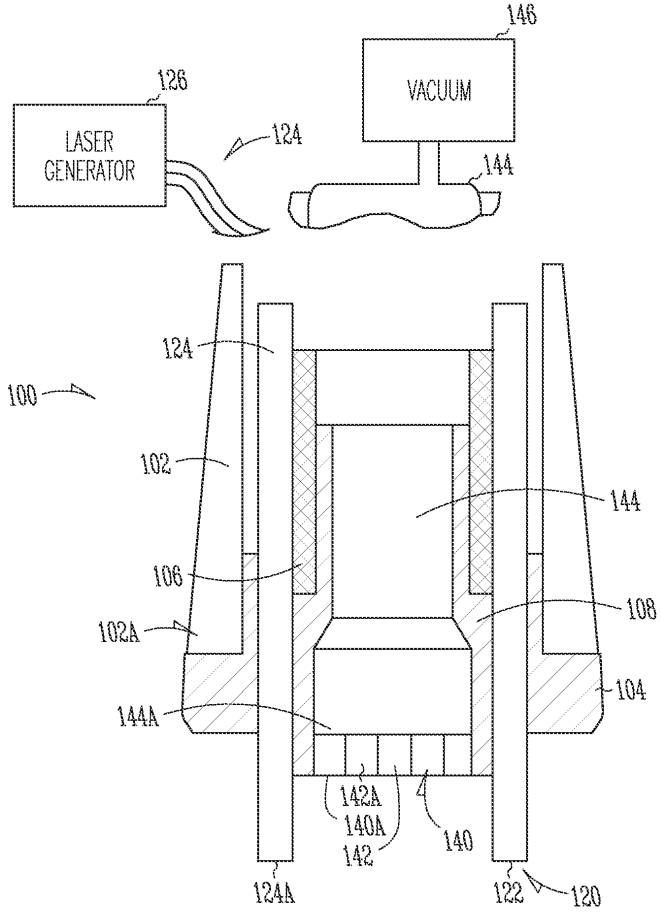

Fig. 6

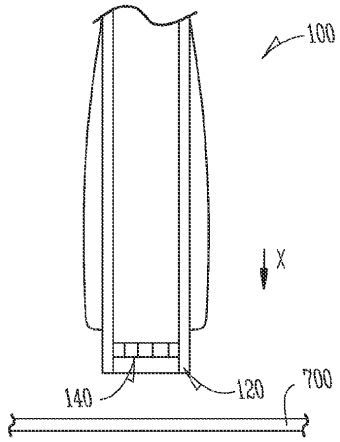

Fig. 7A

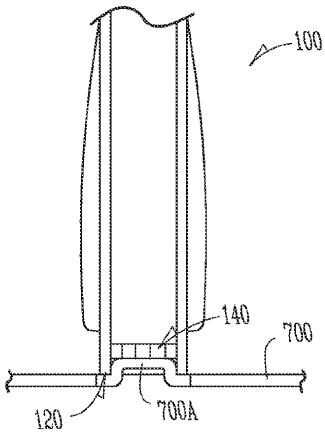

Fig. 7B

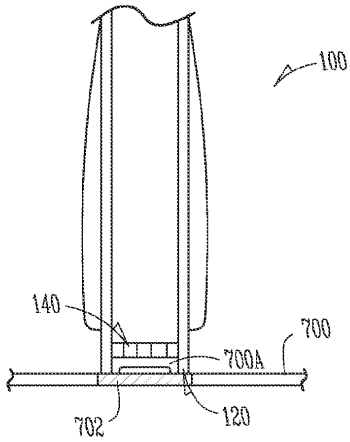

Fig. 7C

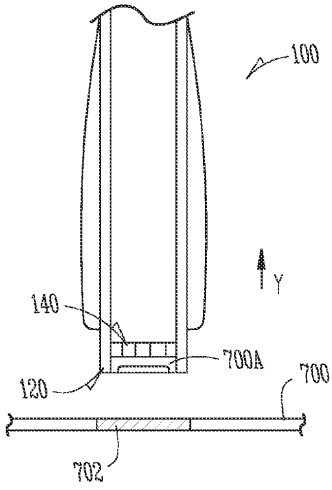

Fig. 7D

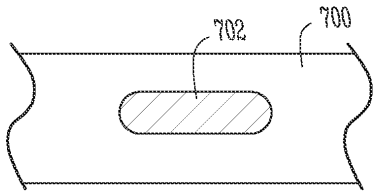

Fig. 8A

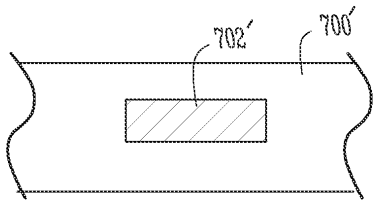

Fig. 8B

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CATHETER APPARATUS AND METHOD

TECHNICAL FIELD

[0001] Various embodiments described herein relate to apparatuses, systems, and methods associated with anastomosis.

BACKGROUND

[0002] Anastomosis, in the medical field, is a connection between two channels, for instance, blood vessels. Such connections can be made between sides of respective vessels, between ends of respective vessels, or between an end of a vessel and a side of another vessel. In various anastomosis procedures, a hole is formed in one or both of the vessels. Such anastomosis procedures can be used in various surgical procedures, such as, for instance, bypass procedures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0003] In the drawings, which are not necessarily drawn to scale, like numerals may describe similar components in different views. Like numerals having different letter suffixes may represent different instances of similar components. The drawings illustrate generally, by way of example, but not by way of limitation, various embodiments discussed in the present document.

[0004] FIG. **1** shows a perspective view of a distal end of an example catheter apparatus according to an embodiment of the invention.

[0005] FIG. **2** shows a side view of an example catheter apparatus according to an embodiment of the invention.

[0006] FIG. **3** shows a perspective view of a distal end of an example catheter apparatus according to an embodiment of the invention.

[0007] FIG. **4** shows an end view of a distal end of an example catheter apparatus according to an embodiment of the invention.

[0008] FIG. **5** shows an end view of a distal end of an example catheter apparatus according to an embodiment of the invention.

[0009] FIG. **6** shows a cross-sectional view of an example catheter apparatus according to an embodiment of the invention.

[0010] FIGS. **7**A-**7**D show simplified cross-sectional views of an example catheter, according to an embodiment of the invention, being used to cut through a vessel wall.

[0011] FIG. **8**A shows a hole cut through a vessel wall using the catheter apparatus of FIG. **4**.

[0012] FIG. **8**B shows a hole cut through a vessel wall using the catheter apparatus of FIG. **5**.

DETAILED DESCRIPTION

[0013] In the following detailed description, reference is made to the accompanying drawings that form a part hereof and in which are shown, by way of illustration, specific embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention. Other embodiments may be utilized and structural, logical, and electrical changes may be made.

[0014] Referring to FIGS. **1**-**4**, in some examples, a catheter apparatus **100** is configured to cut through a vessel wall. The catheter apparatus **100** can be used in various procedures including, but not limited to, anastomosis procedures in which two vessels are fluidly coupled to one another. In some examples, a hole can be cut in the side of one of the vessels (for instance, with end-to-side anastomosis techniques) or in the sides of both of the vessels (for instance, in side-to-side anastomosis techniques). Such anastomosis procedures can be used in various bypass procedures. In some examples, such anastomosis procedures can be used to join blood vessels in various areas of the body, including, but not limited to, in and around the brain, the heart, and the kidneys. Such anastomosis procedures can also be used for joining two tubular structures other than blood vessels, such as intestines, for instance.

[0015] In some examples, the catheter apparatus **100** includes an elongate body **102**. In some examples, the elongate body **102** is configured for use in surgery. That is, the elongate body **102** can be formed from one or more biocompatible materials that can be relatively easily sterilized. In addition, the elongate body **102** can be formed from one or more flexible materials. In some examples, the elongate body **102** includes a tubular body. The elongate body **102** can include a distal end **102**A configured for insertion within the body. In some examples, the distal end includes a widened portion **104** at or near the distal end **102**A. In some examples, the widened portion **104** is sized to be at least as wide as the width (or diameter) of the vessel through which the catheter apparatus **100** is intended to be guided. By sizing the widened portion **104** at least as wide as the width of the vessel, the widened portion **104** can function to center the distal end **102**A of the catheter apparatus **100** within the vessel to aid in guiding the catheter apparatus **100** through the vessel and positioning it for cutting of the vessel wall. In other examples, the widened portion **104** can be sized to be smaller than the width (or diameter) of the vessel through which the catheter **100** is intended to be guided to allow for greater ease of insertion and guiding of the catheter apparatus **100** within the vessel than if the widened portion **104** were sized as wide or wider than the vessel. In some examples, as described in greater detail herein, the widened portion **104** is sized to correspond with a ring, a clip, or another device used in an anastomosis procedure to inhibit the catheter apparatus **100** from being inserted too far into the vessel to lessen the likelihood of potentially accidentally cutting a portion of a vessel that was not intended to be cut. Although shown as separate from the elongate body **102**, in some examples, the widened portion **104** can be integrally formed with the elongate body **102**.

[0016] In some examples, the catheter apparatus **100** includes a cutting device **120** disposed at the distal end **102**A of the elongate body **102**. In some examples, the cutting device **120** extends beyond the distal end **102**A. In other examples, the cutting device **120** can be flush with or recessed within the distal end **102**A. In various examples, the cutting device **120** can extend beyond, be flush with, or be recessed within the widened portion **104**. The cutting device **120**, in some examples, includes a substantially ring-shaped cutting portion **122** configured to selectively cut a hole in the vessel wall. In some examples, the ring-shaped cutting portion **122** includes a first dimension and a second dimension, wherein the first dimension is greater than the second dimension.

[0017] In some examples, the widened portion **104** of the catheter apparatus **100** is sized to correspond with a ring, a clip, or another device used in an anastomosis procedure to inhibit the catheter apparatus **100** from being inserted too far into the vessel to lessen the likelihood of potentially accidentally cutting through a portion of a vessel that was not

intended to be cut through. In examples in which the cutting device **120** extends beyond the distal end **102**A, the cutting device **120** or the ring, clip, or other device can be sized to allow the cutting device **120** to fit through the ring, clip, or other device while the widened portion **104** can be sized to be larger than the ring, clip, or other device such that the catheter device **100** is inhibited from passing through the ring, clip, or other device, thereby inhibiting the catheter apparatus **100** from being inserted too far into the vessel to lessen the likelihood of potentially accidentally cutting something (such as a portion of a vessel) that was not intended to be cut. In examples in which the cutting device **120** is flush with or recessed within the distal end **102**A, the widened portion **104** being sized to be larger than the ring, clip, or other device functions in a similar manner to inhibit the catheter device **100** from passing through the ring, clip, or other device to lessen the likelihood of potentially accidentally cutting something (such as a portion of a vessel) that was not intended to be cut. If the catheter apparatus **100** were able to be passed through the ring, clip, or other device, the cutting device **120** could potentially be placed in proximity of another structure (such as another portion of the vessel being cut or a portion of another vessel) and could potentially at least partially cut or damage the structure.

[0018] In some examples, the catheter apparatus **100** includes a gripping device **140** disposed at the distal end **102**A of the elongate body **102**. The gripping device **140** can be configured to grip the vessel wall to maintain the cutting device **120** proximate the vessel wall during cutting of the hole in the vessel wall. In some examples, the gripping device **140** can be disposed within and surrounded by the substantially ring-shaped cutting portion **122**. In further examples, the gripping device **140** encompasses substantially the entire area within the substantially ring-shaped cutting portion **122**. In other examples, the gripping device **140** can be disposed outside the substantially ring-shaped cutting portion **122**. In still further examples, the gripping device **140** can be disposed both within and outside of the substantially ring-shaped cutting portion **122**. The gripping device **140**, in various examples, is configured to retain a portion of the vessel wall removed during cutting of the vessel wall. That is, with the substantially ring-shaped cutting portion **122**, the cutting device **120** cuts or ablates a similarly sized and shaped ring-shaped portion from the vessel wall, which leaves a free portion of the vessel wall (substantially corresponding to the size and shape of the interior of the substantially ring-shaped cutting portion **122**) now unattached to the vessel wall, which the gripping device **140** can retain after cutting of the blood vessel and remove from within the body of the patient.

[0019] In some examples, the gripping device **140** includes a vacuum gripping device **140** that creates a suction force to grip and retain the portion of the vessel wall. In some examples, the gripping device **140** can include a cover **142** at a distal end **140**A of the gripping device **140** to inhibit unwanted objects from being sucked into the end of the gripping device **140**. For instance, in some examples, the cover **142** can be configured to inhibit the cut-out portion of the vessel wall from being sucked into the gripping device **140**. In some examples, the cover **142** can be configured to hold the vessel wall in a particular position with respect to the cutting device **120** during cutting of the vessel wall. For instance, maintaining the vessel wall in the particular position can, among other things, facilitate proper dimensioning of the hole to be cut by inhibiting the vessel wall from being sucked too far into the gripping device **140** (and potentially making a larger than intended hole in the vessel wall) or moving excessively during cutting (and potentially leading to a hole being formed with improper dimensions).

[0020] The cover **142**, in some examples, can include one or more holes **142**A to allow the suction force of the gripping device **140** to grip the portion of the vessel wall while, at the same time, inhibiting the portion of the vessel wall (or other objects larger than the one or more holes **142**A in the cover **142**) from being sucked into the distal end **140**A of the gripping portion **140**. The cover **142** shown in FIGS. **1** and **3** includes a grid-like pattern of substantially square-shaped holes **142**A. However, in other examples, the cover can include differently configured holes (circular, for instance), a screen, protrusions or abutments extending within the distal end **140**A, or other structures or configurations capable of inhibiting objects from being taken in by the gripping device **140**. In some examples, the gripping device **140** is recessed with respect to the ring-shaped cutting portion **122**, such that, when the gripping device **140** grips the vessel wall, a portion of the vessel wall is drawn within the recess (for instance, to abut the cover **142**). Such a configuration allows for several advantages, including, but not limited to increasing the likelihood that the vessel wall is in close proximity to the ring-shaped cutting portion **122** for cutting of the vessel wall and allowing the portion removed to be retained within the recess, for instance, to decrease the likelihood of the portion separating from the gripping device **140** if, for instance, the distal end of the catheter apparatus **100** brushes against a vessel wall, a clip, a surgical instrument, or any other object prior to removing the catheter apparatus **100** from the body of the patient. Separation or dislodgement of the portion from the gripping device **140** could lead to the portion being released into the bloodstream, which could lead to various issues including, for instance, vessel obstruction or blockage.

[0021] Referring now to FIG. **5**, in some examples, a catheter apparatus **500** is configured to cut through a vessel wall and can be similar to the catheter apparatus **100** described herein. In some examples, the catheter apparatus **500** includes an elongate body similar to the elongate body **102** described herein. In some examples, the elongate body **502** includes a tubular body. The elongate body can include a distal end configured for insertion within the body. In some examples, the distal end includes a widened portion **504** at or near the distal end. In some examples, the widened portion **504** is sized to be at least as wide as the width (or diameter) of the vessel through which the catheter apparatus **500** is intended to be guided. By sizing the widened portion **504** at least as wide as the width of the vessel, the widened portion **504** can function to center the distal end of the catheter apparatus **500** within the vessel to aid in guiding the catheter apparatus **500** through the vessel and positioning it for cutting of the vessel wall. In other examples, the widened portion **504** can be sized to be smaller than the width (or diameter) of the vessel through which the catheter **500** is intended to be guided to allow for greater ease of insertion and guiding of the catheter apparatus **500** within the vessel than if the widened portion **504** were sized as wide or wider than the vessel. In some examples, as described in greater detail herein, the widened portion **504** is sized to correspond with a ring, a clip, or another device used in an anastomosis procedure to inhibit the catheter apparatus **500** from being inserted too far into the vessel to lessen the likelihood of potentially accidentally cutting a portion of a vessel that was not intended to be cut.

Although shown as separate from the elongate body, in some examples, the widened portion **504** can be integrally formed with the elongate body.

[0022] In some examples, the catheter apparatus **500** includes a cutting device **520** disposed at the distal end of the elongate body. In some examples, the cutting device **520** extends beyond the distal end. In other examples, the cutting device **520** can be flush with or recessed within the distal end. In various examples, the cutting device **520** can extend beyond, be flush with, or be recessed within the widened portion **504**. The cutting device **520**, in some examples, includes a substantially ring-shaped cutting portion **522** configured to selectively cut a hole in the vessel wall. In some examples, the ring-shaped cutting portion **522** includes a first dimension and a second dimension, wherein the first dimension is greater than the second dimension. In some examples and in a manner similar to that described herein with respect to the widened portion **104** of the catheter apparatus **100**, the widened portion **504** of the catheter apparatus **500** is sized to correspond with a ring, a clip, or another device used in an anastomosis procedure to inhibit the catheter apparatus **500** from being inserted too far into the vessel to lessen the likelihood of potentially accidentally cutting through a portion of a vessel that was not intended to be cut through.

[0023] In some examples, the catheter apparatus **500** includes a gripping device **540** similar to the gripping device **140** described herein. The gripping device **540** can be configured to grip the vessel wall to maintain the cutting device **520** proximate the vessel wall during cutting of the hole in the vessel wall. In some examples, the gripping device **540** can be disposed within and surrounded by the substantially ring-shaped cutting portion **522**. In further examples, the gripping device **540** encompasses substantially the entire area within the substantially ring-shaped cutting portion **522**. In other examples, the gripping device **540** can be disposed outside the substantially ring-shaped cutting portion **522**. In still further examples, the gripping device **540** can be disposed both within and outside of the substantially ring-shaped cutting portion **522**. The gripping device **540**, in various examples, is configured to retain a portion of the vessel wall removed during cutting of the vessel wall. That is, with the substantially ring-shaped cutting portion **522**, the cutting device **520** cuts or ablates a similarly sized and shaped ring-shaped portion from the vessel wall, which leaves a free portion of the vessel wall (substantially corresponding to the size and shape of the interior of the substantially ring-shaped cutting portion **522**) now unattached to the vessel wall, which the gripping device **540** can retain after cutting of the blood vessel and remove from within the body of the patient.

[0024] In some examples, the gripping device **540** includes a vacuum device that creates a suction force to grip and retain the portion of the vessel wall. In some examples, the gripping device **540** can include a cover **542** at a distal end **540**A of the gripping device **540** to inhibit unwanted objects from being sucked into the end of the gripping device **540**. For instance, in some examples, the cover **542** can be configured to inhibit the cut-out portion of the vessel wall from being sucked into the gripping device **540**. In some examples, the cover **542** can be configured to hold the vessel wall in a particular position with respect to the cutting device **520** during cutting of the vessel wall. For instance, maintaining the vessel wall in the particular position can, among other things, facilitate proper dimensioning of the hole to be cut by inhibiting the vessel wall from being sucked too far into the gripping device **540** (and potentially making a larger than intended hole in the vessel wall) or moving excessively during cutting (and potentially leading to a hole being formed with improper dimensions).

[0025] The cover **542**, in some examples, can include one or more holes **542**A to allow the suction force of the gripping device **540** to grip the portion of the vessel wall while, at the same time, inhibiting the portion of the vessel wall (or other objects larger than the one or more holes **542**A in the cover **542**) from being sucked into the distal end **540**A of the gripping portion **540**. The cover **542** shown in FIG. **5** includes a circular holes **542**A. However, in other examples, the cover can include differently configured holes (differently shaped, for instance), a screen, protrusions or abutments extending within the distal end **540**A, or other structures or configurations capable of inhibiting objects from being taken in by the gripping device **540**. In some examples, the gripping device **540** is recessed with respect to the ring-shaped cutting portion **522**, such that, when the gripping device **540** grips the vessel wall, a portion of the vessel wall is drawn within the recess (for instance, to abut the cover **542**). Such a configuration allows for several advantages, including, but not limited to increasing the likelihood that the vessel wall is in close proximity to the ring-shaped cutting portion **522** for cutting of the vessel wall and allowing the portion removed to be retained within the recess, for instance, to decrease the likelihood of the portion separating from the gripping device **540** if, for instance, the distal end of the catheter apparatus **500** brushes against a vessel wall, a clip, a surgical instrument, or any other object prior to removing the catheter apparatus **500** from the body of the patient. Separation or dislodgement of the portion from the gripping device **540** could lead to the portion being released into the bloodstream, which could lead to various issues including, for instance, vessel obstruction or blockage.

[0026] Referring now to FIGS. **1-5**, the ring-shaped cutting portion **122**, **522** can take different shapes in various examples. For instance, the ring-shaped cutting portion **122** can include an elliptical ring shape with the first dimension being a major axis of the elliptical ring shape and the second dimension being a minor axis of the elliptical ring shape. In further examples, the ring-shaped cutting portion **122** includes a flattened elliptical ring shape or a "racetrack" shape, as shown in FIGS. **1-4**. As shown in FIG. **4**, the flattened elliptical ring-shaped cutting portion **122** can include a first dimension A and a second dimension B, with the first dimension A being greater than the second dimension B. In other examples, as shown in FIG. **5**, the substantially ring-shaped cutting portion **522** of the cutting device **520** can include a rectangular ring shape, with a first dimension including a length L and a second dimension including a width W. In still further examples, other shapes for the substantially ring-shaped cutting portion are contemplated, such as circular, square-shaped, diamond-shaped, triangular, hexagonal (or any polygonal shape), or the like.

[0027] Referring specifically to FIGS. **4** and **5**, in some examples, the size of the ring-shaped cutting portion **122**, **522** can be determined according to the vessel or vessels to be cut using the ring-shaped cutting portion **122**, **522**. That is, the first dimension A, L and/or the second dimension B, W can be chosen to correspond to the size of one or more of the vessels that are to be cut using the cutting device **120**, **520**. In some examples, sizing of the substantially ring-shaped cutting portion **122**, **522** includes sizing the first dimension A, L to correspond to a size of a first vessel to be cut with the cutting

device **120**, **520**. In some examples, sizing of the substantially ring-shaped cutting portion **122**, **522** includes sizing the second dimension B, W to correspond to a size of a second vessel to be cut with the cutting device **120**, **520**. For instance, the first dimension or the major axis A of the flattened elliptical ring-shaped cutting portion **122** can be chosen to correspond to a flow surface of the largest recipient vessel to be cut using the cutting device **120**, and/or the second dimension or the minor axis B of the flattened elliptical ring-shaped cutting portion **122** can be chosen to correspond to a diameter of the smallest recipient vessel to be cut using the cutting device **120**. In another example, the first dimension or the length L of the rectangular ring-shaped cutting portion **522** can be chosen to correspond to a flow surface of the largest recipient vessel to be cut using the cutting device **520**, and/or the second dimension or the width W of the rectangular ring-shaped cutting portion **522** can be chosen to correspond to a diameter of the smallest recipient vessel to be cut using the cutting device **520**. In some examples, the first and second dimensions A, L, B, W the ring-shaped cutting portion **122**, **522** can be sized and shaped to match a surface area of an anastomosis to a surface area of the recipient vessel, such that the flow surface area of the recipient vessel and the anastomosis surface area is substantially equal to or larger than the flow surface area of the recipient vessel. For instance, the first and second dimensions A, L, B, W the ring-shaped cutting portion **122**, **522** can be sized and shaped to allow cutting of a hole in a vessel that is substantially equal to (or larger than) the flow surface of the recipient vessel. In this way, stenosis in the recipient vessel can be inhibited. In other examples, the size of one or more of the first and second dimensions A, B, L, W can be sized according to other aspects or dimensions of the one or more vessels to be cut with the cutting device **120**, **520**.

[0028] Referring again to FIGS. **1-5**, the cutting device **120**, **520**, in various examples, can include different forms of cutting mechanisms. In some examples, the cutting device **120**, **520** can include a laser cutting device **120**, **520** configured to cut through the vessel wall. In some examples, the laser cutting device **120**, **520** includes a plurality of optical fibers **124**, **524** each including an end **124**A, **524**A. The ends **124**A, **524**A of the optical fibers **124**, **524**, in some examples, are arranged to define the substantially ring-shaped cutting portion **122**, **522**. For instance, with respect to the example shown in FIGS. **1-4**, the ends **124**A of the optical fibers **124** are arranged to define a substantially planar flattened ellipse to form the flattened elliptical ring-shaped cutting portion **122**. With respect to the example shown in FIG. **5**, the ends **524**A of the optical fibers **524** are arranged to define a substantially planar rectangle to form the rectangular ring-shaped cutting portion **522**. In some examples, the substantially ring-shaped cutting portion **122**, **522** is configured to emit a laser distally from the catheter apparatus **100**, **500**.

[0029] Referring now to FIG. **6**, an example of the catheter apparatus **100** is shown. Although shown and described with respect to the catheter apparatus **100**, it should be understood that the description of FIG. **6** can apply to at least some examples of the catheter apparatus **500**, as shown and described herein. In some examples, the cutting device **120** can include a laser generator **126** configured to produce the laser energy to be emitted by the ends **124**A of the optical fibers **124**. In some examples, a proximal end of each optical fiber **124** is coupled to the laser generator **126** with the optical fibers **124** running from the laser generator **126**, through the elongate body **102**, and terminating at the substantially ring-shaped cutting portion **122**. In this way, the laser generator **126** can produce a laser which can propagate through the optical fibers **124** and be emitted from the ends **124**A of the optical fibers **124**. In some examples, the laser is emitted from the ends **124**A of the optical fibers **124** which are arranged to form the ring-shaped cutting portion **122** in order to cut or ablate a hole in a vessel wall or other structure. In some examples, various other types of cutting devices **120** are contemplated, including, but not limited to, a scalpel, a punch, a bi/mono polar cutting device, a radiofrequency cutting device, or an ultrasonic cutting device.

[0030] In some examples, the optical fibers **124** are disposed immediately within the elongate body **102**. The optical fibers **124** can be arranged within the elongate body **102** in various ways, including, but not limited to a continuous ring, a segmented ring, or a single bundle of optical fibers. In some examples, the catheter apparatus **100** includes an inner tube **106**, for instance disposed within the optical fibers **124**. The inner tube **106** can provide additional structure to the catheter apparatus **100**. The inner tube **106**, in some examples, can define, or at least partially define, an inner lumen **144** of the catheter apparatus **100**.

[0031] In some examples, the catheter apparatus **100** includes an end portion **108** disposed at the distal end **102**A of the elongate body **102**. The end portion **108** can provide, in some examples, a relatively rigid structure for the end of the catheter apparatus **100**. In some examples, the end portion **108** partially defines the inner lumen **144** and provides a nozzle **144**A for the vacuum gripping device **140** disposed at the distal end **102**A of the elongate body **102**. In some examples, the gripping device **140** is configured to create a suction force between the nozzle **144**A and the vessel wall to grip the vessel wall. The vacuum gripping device **140** includes a vacuum source **146** coupled to the nozzle **144**A. In some examples, the vacuum source **146** is coupled to a proximal portion of the inner lumen **144** of the catheter apparatus **100** to fluidly couple the vacuum source **146** with the nozzle **144**A to allow the suction force to be created at the nozzle **144**A with operation of the vacuum source. In this way, operation of the vacuum source **146** allows the gripping device **140** to selectively grip the vessel wall to be cut and also to retain the portion of the vessel wall removed after cutting. The nozzle **144**A, in some examples, is disposed within and surrounded by the substantially ring-shaped cutting portion **122** of the cutting device **120**. In some examples, the nozzle **144**A can be configured to inhibit the cut-out portion of the vessel wall or unwanted objects from being sucked into the end of the gripping device **140** without requiring the cover **142** to be used (although it should be noted that the cover **142** can be used even with the nozzle **144**A being configured to inhibit the cut-out portion of the vessel wall or unwanted objects from being sucked into the end of the gripping device **140**). For instance, an interior surface of the nozzle **144**A can be substantially conically-shaped to inhibit the cut-out portion of the vessel wall or unwanted objects from being drawn too far into the end of the gripping device **140**. In further examples, the interior surface of the nozzle **144**A can include other shapes to inhibit the cut-out portion or other objects from being drawn too far into the end of the gripping device **140**.

[0032] In some examples, the cover **142**, although shown as being substantially flat in FIG. **6**, can be differently shaped. For instance, the cover **142**, when viewed in cross section, can be slanting or sloping, substantially pyramidal, substantially

conical, substantially spherical, wave-shaped, or zig-zag-shaped. In some examples, the cover **142** can be attached to the end portion **108**. For instance, the cover **142** can be integrally formed with the end portion **108**. In some examples, the cover **142** is separately formed but attached to the end portion **108** in some manner including, but not limited to a snap fit, a friction fit, an adhesive, welding (for instance, ultrasonic welding), a threaded connection, or some other manner of attachment.

[0033] FIGS. **7**A-**7**D show a simplified depiction of the catheter apparatus **100** cutting through a vessel wall **700**. Although shown and described with respect to the catheter apparatus **100**, it should be understood that the description of FIGS. **7**A-**7**D can apply to at least some examples of the catheter apparatus **500**, as shown and described herein.

[0034] Referring to FIGS. **7**A-**7**D, the catheter apparatus **100** can be used to cut through the vessel wall **700** in the context of anastomosis, for instance. It is noted that the depiction is simplified at least in part because the catheter apparatus **100** is shown merely with the vessel wall **700** to be cut. That is, the catheter apparatus **100** is not shown disposed within a vessel. In at least some example anastomosis procedures, the catheter apparatus **100** would be disposed within a vessel for cutting of the vessel wall **700**. Also, only one vessel wall **700** is shown and no other vessel or vessel wall is shown attached to the vessel wall **700**. In at least some example anastomosis procedures, the vessel wall **700** would be attached (for instance, clipped, sutured, or otherwise affixed) to a portion (for instance, a vessel wall or an end of another vessel) during cutting of the vessel wall **700**.

[0035] In some examples, in use, the catheter apparatus **100** is advanced along arrow X toward the vessel wall **700** to be cut, as shown in FIG. **7**A. Once positioned proximate the vessel wall **700**, the gripping device **140** can be used to grip the vessel wall, as shown in FIG. **7**1B. In some examples, the gripping device **140** actually draws in a portion **700**A of the vessel wall **700** into the recess of the gripping device **140** with respect to the cutting device **120**. In some examples, gripping the vessel wall **700** includes creating the suction force between the nozzle **144** (see FIG. **6**) of the gripping device **140** and the vessel wall **700**. In further examples, the gripping device **140** includes a vacuum gripping device **140** for creating the suction force to grip the vessel wall.

[0036] As shown in FIG. **7**C, the vessel wall **700** can then be cut using the cutting device **120** disposed at the distal end of the catheter apparatus **100**. In some examples, the cutting device **120** can include the substantially ring-shaped cutting portion **122** similar to that described herein in which the first dimension is greater than the second dimension of the substantially ring-shaped cutting portion **122** (see FIG. **4**). The gripping device **140** can be disposed within and surrounded by the substantially ring-shaped cutting portion **122** of the cutting device **120**. The cutting device **120** can be configured to cut the vessel wall **700** along the substantially ring-shaped cutting portion **122** to form a hole **702** in the vessel wall **700**. In some examples, cutting the vessel wall **700** includes emitting a laser distally from the substantially ring-shaped cutting portion **122**, with the laser being configured to cut through or ablate the vessel wall **700**. As shown in FIG. **7**1), once a portion **700**A is cut from the vessel wall **700**, the portion **700**A can be retained by the catheter apparatus **100** using the gripping device **140**. In this way, the portion **700**A of the vessel wall **700** can be removed with movement of the catheter apparatus **100** in the direction of arrow Y and removal of the catheter apparatus **100** from the body of the patient.

[0037] Depending upon the shape of the cutting portion of the cutting device, variously shaped holes can be formed in the vessel wall using the catheter apparatuses **100**, **500** described herein and used, for instance, as shown in FIGS. **7**A-**7**D. For instance, referring to FIGS. **4** and **8**A, using the catheter apparatus **100** including the substantially flattened elliptical ring-shaped cutting portion **122**, a substantially flattened elliptical hole **702** can be formed in the vessel wall **700**, with dimensions of the hole **702** substantially corresponding to the dimensions (the major axis A and the minor axis B) of the substantially flattened elliptical ring-shaped cutting portion **122**. In another example, referring to FIGS. **5** and **8**B, using the catheter apparatus **500** including the rectangular ring-shaped cutting portion **522**, a rectangular hole **702'** can be formed in a vessel wall **700'**, with dimensions of the hole **702'** substantially corresponding to the dimensions (the length L and the width W) of the rectangular ring-shaped cutting portion **522**. In other examples, cutting portions including different shapes are contemplated herein.

[0038] Referring again to FIGS. **1**-**5**, the example catheter apparatuses described herein are advantageous in several respects. For instance, while previous catheter shapes were prone to creating stenosis in a recipient artery, the shapes of the substantially ring-shaped cutting portions **122**, **522** allow for the creation of a flow surface (a hole in a vessel wall) that is substantially equal to (if not larger than) the flow surface of the recipient vessel so that the likelihood of creating a stenosis in the recipient vessel is lessened. Moreover, in some examples, the shapes of the substantially ring-shaped cutting portions **122**, **522** (and the corresponding gripping devices **140**, **540**) are configured to facilitate maneuvering of the catheter apparatuses **100**, **500** within the desired vessels and successful cutting of the vessel wall and capturing of the portion removed from the vessel wall. That is, the elliptical or flattened elliptical ring-shaped cutting portion **122**, with the major axis A being greater than the minor axis B, and the rectangular ring-shaped cutting portion **522**, with the length L being greater than the width W, enable movement of the respective catheter apparatuses **100**, **500** through the desired vessels by sizing the dimensions A, B, L, W of the ring-shaped cutting portions **122**, **522** to correspond with the vessels to be cut. Also, the shape of the ring-shaped cutting portions **122**, **522** (and the corresponding shapes of the gripping portions **140**, **540**), with the first dimensions A, L being greater than the second dimensions B, W, allows for an increased cutting and gripping surface area for each catheter apparatus **100**, **500** in relation to the size constraints of the vessels with which the catheter apparatuses **100**, **500** are to be used. Because of the increased surface areas of the ring-shaped cutting portions **122**, **522** and the gripping devices **140**, **540**, the likelihood of a clean cut by the ring-shaped cutting portions **122**, **522** is increased and the gripping of the vessel wall, initially, and retention of the removed portion is facilitated. Although described with respect to substantially elliptical and rectangular ring-shaped cutting portions **122**, **522** (and corresponding gripping devices **140**, **540**), it should be understood that other shapes optimizing the available cutting and gripping surface areas are contemplated herein.

Additional Notes and Examples

[0039] Example 1 can include subject matter (such as an apparatus, a system, a method, a means for performing acts,

or a machine-readable medium including instructions that, when performed by the machine, cause the machine to perform acts) that can comprise a catheter apparatus configured to cut through a vessel wall. The catheter apparatus can comprise: an elongate body including a distal end; a cutting device disposed at the distal end of the elongate body, the cutting device including a substantially ring-shaped cutting portion including a first dimension and a second dimension, wherein the first dimension is greater than the second dimension, wherein the cutting device is configured to selectively cut a hole in the vessel wall; and a gripping device disposed at the distal end of the elongate body, the gripping device configured to grip the vessel wall to maintain the cutting device proximate the vessel wall during cutting of the hole in the vessel wall, the gripping device further configured to retain a portion of the vessel wall removed during cutting of the vessel wall.

[0040] Example 2 can include or use, or can optionally be combined with the subject matter of Example 1 to include or use a catheter apparatus, wherein the cutting device includes a laser cutting device configured to cut through the vessel wall.

[0041] Example 3 can include or use, or can optionally be combined with the subject matter of Example 2 to include or use a catheter apparatus, wherein the laser cutting device includes a plurality of optical fibers each including an end, the ends of the optical fibers arranged to define the substantially ring-shaped cutting portion.

[0042] Example 4 can include or use, or can optionally be combined with the subject matter of Examples 1-3 to include or use a catheter apparatus, wherein the substantially ring-shaped cutting portion is configured to emit a laser distally from the catheter apparatus.

[0043] Example 5 can include or use, or can optionally be combined with the subject matter of Examples 1-4 to include or use a catheter apparatus, wherein the substantially ring-shaped cutting portion includes an elliptical ring shape, wherein the first dimension includes a major axis and the second dimension includes a minor axis.

[0044] Example 6 can include or use, or can optionally be combined with the subject matter of Example 4 to include or use a catheter apparatus, wherein the elliptical ring shape of the substantially ring-shaped cutting portion includes a flattened elliptical ring shape.

[0045] Example 7 can include or use, or can optionally be combined with the subject matter of Examples 1-6 to include or use a catheter apparatus, wherein the substantially ring-shaped cutting portion includes a rectangular ring shape, wherein the first dimension includes a length and the second dimension includes a width.

[0046] Example 8 can include or use, or can optionally be combined with the subject matter of Examples 1-7 to include or use a catheter apparatus, wherein the gripping device includes a vacuum device including a nozzle disposed at the distal end of the elongate body, the vacuum device configured to create a suction force between the nozzle and the vessel wall to grip the vessel wall.

[0047] Example 9 can include or use, or can optionally be combined with the subject matter of Example 8 to include or use a catheter apparatus, wherein the nozzle is disposed within and surrounded by the substantially ring-shaped cutting portion of the cutting device.

[0048] Example 10 can include or use, or can optionally be combined with the subject matter of Example 8 to include or use a catheter apparatus, wherein the vacuum device includes a vacuum source coupled to the nozzle.

[0049] Example 11 can include or use, or can optionally be combined with the subject matter of Examples 1-10 to include or use a catheter apparatus, wherein the elongate body includes a tubular body.

[0050] Example 12 can include, or can be combined with the subject matter of one or any combination of Examples 1-11 to optionally include, subject matter (such as an apparatus, a method, a means for performing acts, or a machine-readable medium including instructions that, when performed by the machine, cause the machine to perform acts) that can comprise a catheter apparatus configured to cut through a vessel wall. The catheter apparatus can comprise: an elongate body including a distal end; a laser cutting device disposed at the distal end of the elongate body, the laser cutting device including a substantially elliptical ring-shaped cutting portion, including a major axis and a minor axis, wherein the cutting device is configured to selectively cut a hole in the vessel wall; and a vacuum device including a nozzle disposed at the distal end of the elongate body, the nozzle is disposed within and surrounded by the substantially elliptical ring-shaped cutting portion of the laser cutting device, the vacuum device configured to create a suction force between the nozzle and the vessel wall to grip the vessel wall and to maintain the laser cutting device proximate the vessel wall during cutting of the hole in the vessel wall, the vacuum device further configured to retain a portion of the vessel wall removed during cutting of the vessel wall.

[0051] Example 13 can include or use, or can optionally be combined with the subject matter of Example 12 to include or use a catheter apparatus, wherein the laser cutting device includes a plurality of optical fibers each including an end, the ends of the optical fibers arranged to define the substantially elliptical ring-shaped cutting portion.

[0052] Example 14 can include or use, or can optionally be combined with the subject matter of Examples 12-13 to include or use a catheter apparatus, wherein the substantially elliptical ring-shaped cutting portion includes a flattened elliptical ring shape.

[0053] Example 15 can include or use, or can optionally be combined with the subject matter of Examples 12-14 to include or use a catheter apparatus, wherein the substantially elliptical ring-shaped cutting portion is configured to emit a laser distally from the catheter apparatus.

[0054] Example 16 can include, or can be combined with the subject matter of one or any combination of Examples 1-15 to optionally include, subject matter (such as an apparatus, a method, a means for performing acts, or a machine-readable medium including instructions that, when performed by the machine, cause the machine to perform acts) that can comprise a method of cutting through a vessel wall. The method can comprise: gripping the vessel wall using a gripping device disposed at a distal end of a catheter apparatus; cutting the vessel wall using a cutting device disposed at the distal end of the catheter apparatus, the cutting device including a substantially ring-shaped cutting portion including a first dimension and a second dimension, wherein the first dimension is greater than the second dimension, the gripping device being disposed within and surrounded by the substantially ring-shaped cutting portion of the cutting device, the cutting device cutting the vessel wall along the substantially ring-shaped cutting portion to form a hole in the vessel wall; and retaining a portion of the vessel wall removed

during cutting of the hole in the vessel wall, the portion of the vessel wall retained using the gripping device.

[0055] Example 17 can include or use, or can optionally be combined with the subject matter of Example 16 to include or use a method, wherein cutting the vessel wall includes emitting a laser distally from the substantially ring-shaped cutting portion, the laser being configured to cut through the vessel wall.

[0056] Example 18 can include or use, or can optionally be combined with the subject matter of Examples 16-17 to include or use a method, wherein the cutting device includes a substantially flattened elliptical ring-shaped cutting portion configured to cut a substantially flattened elliptical hole in the vessel wall, wherein the first dimension includes a major axis and the second dimension includes a minor axis.

[0057] Example 19 can include or use, or can optionally be combined with the subject matter of Examples 16-18 to include or use a method, wherein the cutting device includes a rectangular ring-shaped cutting portion configured to cut a rectangular hole in the vessel wall, wherein the first dimension includes a length and the second dimension includes a width.

[0058] Example 20 can include or use, or can optionally be combined with the subject matter of Examples 16-19 to include or use a method, wherein gripping the vessel wall includes creating a suction force between a nozzle of the gripping device and the vessel wall, the gripping device including a vacuum device.

[0059] Example 21 can include or use, or can optionally be combined with the subject matter of Examples 16-20 to include or use a method, including sizing the substantially ring-shaped cutting portion of the cutting device to correspond to a vessel to be cut.

[0060] Example 22 can include or use, or can optionally be combined with the subject matter of Example 21 to include or use a method, wherein sizing the substantially ring-shaped cutting portion includes sizing the first dimension to correspond to a size of a first vessel to be cut with the cutting device.

[0061] Example 23 can include or use, or can optionally be combined with the subject matter of Example 22 to include or use a method, wherein sizing the substantially ring-shaped cutting portion includes sizing the second dimension to correspond to a size of a second vessel to be cut with the cutting device.

[0062] Example 24 can include or use, or can optionally be combined with the subject matter of Examples 21-23 to include or use a method, wherein sizing the substantially ring-shaped cutting portion includes sizing the second dimension to correspond to a size of a second vessel to be cut with the cutting device.

[0063] These non-limiting examples can be combined in any permutation or combination.

[0064] The above detailed description includes references to the accompanying drawings, which form a part of the detailed description. The drawings show, by way of illustration, specific embodiments in which the invention can be practiced. These embodiments are also referred to herein as "examples." Such examples can include elements in addition to those shown or described. However, the present inventors also contemplate examples in which only those elements shown or described are provided. Moreover, the present inventors also contemplate examples using any combination or permutation of those elements shown or described (or one or more aspects thereof), either with respect to a particular example (or one or more aspects thereof), or with respect to other examples (or one or more aspects thereof) shown or described herein.

[0065] In the event of inconsistent usages between this document and any documents incorporated by reference, the usage in this document controls.

[0066] In this document, the terms "a" or "an" are used, as is common in patent documents, to include one or more than one, independent of any other instances or usages of "at least one" or "one or more." In this document, the term "or" is used to refer to a nonexclusive or, such that "A or B" includes "A but not B," "B but not A," and "A and B," unless otherwise indicated. In this document, the terms "including" and "in which" are used as the plain-English equivalents of the respective terms "comprising" and "wherein." Also, in the following claims, the terms "including" and "comprising" are open-ended, that is, a system, device, article, or process that includes elements in addition to those listed after such a term in a claim are still deemed to fall within the scope of that claim. Moreover, in the following claims, the terms "first," "second," and "third," etc. are used merely as labels, and are not intended to impose numerical requirements on their objects.

[0067] The above description is intended to be illustrative, and not restrictive. For example, the above-described examples (or one or more aspects thereof) may be used in combination with each other. Other embodiments can be used, such as by one of ordinary skill in the art upon reviewing the above description. The Abstract is provided to comply with 37 C.F.R. §1.72(b), to allow the reader to quickly ascertain the nature of the technical disclosure. It is submitted with the understanding that it will not be used to interpret or limit the scope or meaning of the claims. Also, in the above Detailed Description, various features may be grouped together to streamline the disclosure. This should not be interpreted as intending that an unclaimed disclosed feature is essential to any claim. Rather, inventive subject matter may lie in less than all features of a particular disclosed embodiment. Thus, the following claims are hereby incorporated into the Detailed Description, with each claim standing on its own as a separate embodiment, and it is contemplated that such embodiments can be combined with each other in various combinations or permutations. The scope of the invention should be determined with reference to the appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A catheter apparatus configured to cut through a vessel wall, the catheter apparatus comprising:

an elongate body including a distal end;

a cutting device disposed at the distal end of the elongate body, the cutting device including a substantially ring-shaped cutting portion including a first dimension and a second dimension, wherein the first dimension is greater than the second dimension, wherein the cutting device is configured to selectively cut a hole in the vessel wall; and

a gripping device disposed at the distal end of the elongate body, the gripping device configured to grip the vessel wall to maintain the cutting device proximate the vessel wall during cutting of the hole in the vessel wall, the

gripping device further configured to retain a portion of the vessel wall removed during cutting of the vessel wall.

2. The catheter apparatus of claim **1**, wherein the cutting device includes a laser cutting device configured to cut through the vessel wall.

3. The catheter apparatus of claim **2**, wherein the laser cutting device includes a plurality of optical fibers each including an end, the ends of the optical fibers arranged to define the substantially ring-shaped cutting portion.

4. The catheter apparatus of claim **1**, wherein the substantially ring-shaped cutting portion is configured to emit a laser distally from the catheter apparatus.

5. The catheter apparatus of claim **1**, wherein the substantially ring-shaped cutting portion includes an elliptical ring shape, wherein the first dimension includes a major axis and the second dimension includes a minor axis.

6. The catheter apparatus of claim **5**, wherein the elliptical ring shape of the substantially ring-shaped cutting portion includes a flattened elliptical ring shape.

7. The catheter apparatus of claim **1**, wherein the substantially ring-shaped cutting portion includes a rectangular ring shape, wherein the first dimension includes a length and the second dimension includes a width.

8. The catheter apparatus of claim **1**, wherein the gripping device includes a vacuum device including a nozzle disposed at the distal end of the elongate body, the vacuum device configured to create a suction force between the nozzle and the vessel wall to grip the vessel wall.

9. The catheter apparatus of claim **8**, wherein the nozzle is disposed within and surrounded by the substantially ring-shaped cutting portion of the cutting device.

10. The catheter apparatus of claim **8**, wherein the vacuum device includes a vacuum source coupled to the nozzle.

11. The catheter apparatus of claim **1**, wherein the elongate body includes a tubular body.

12. A catheter apparatus configured to cut through a vessel wall, the catheter apparatus comprising:

an elongate body including a distal end;

a laser cutting device disposed at the distal end of the elongate body, the laser cutting device including a substantially elliptical ring-shaped cutting portion, including a major axis and a minor axis, wherein the cutting device is configured to selectively cut a hole in the vessel wall; and

a vacuum device including a nozzle disposed at the distal end of the elongate body, the nozzle is disposed within and surrounded by the substantially elliptical ring-shaped cutting portion of the laser cutting device, the vacuum device configured to create a suction force between the nozzle and the vessel wall to grip the vessel wall and to maintain the laser cutting device proximate the vessel wall during cutting of the hole in the vessel wall, the vacuum device further configured to retain a portion of the vessel wall removed during cutting of the vessel wall.

13. The catheter apparatus of claim **12**, wherein the laser cutting device includes a plurality of optical fibers each including an end, the ends of the optical fibers arranged to define the substantially elliptical ring-shaped cutting portion.

14. The catheter apparatus of claim **12**, wherein the substantially elliptical ring-shaped cutting portion includes a flattened elliptical ring shape.

15. The catheter apparatus of claim **12**, wherein the substantially elliptical ring-shaped cutting portion is configured to emit a laser distally from the catheter apparatus.

16. A method of cutting through a vessel wall, the method comprising:

gripping the vessel wall using a gripping device disposed at a distal end of a catheter apparatus;

cutting the vessel wall using a cutting device disposed at the distal end of the catheter apparatus, the cutting device including a substantially ring-shaped cutting portion including a first dimension and a second dimension, wherein the first dimension is greater than the second dimension, the gripping device being disposed within and surrounded by the substantially ring-shaped cutting portion of the cutting device, the cutting device cutting the vessel wall along the substantially ring-shaped cutting portion to form a hole in the vessel wall; and

retaining a portion of the vessel wall removed during cutting of the hole in the vessel wall, the portion of the vessel wall retained using the gripping device.

17. The method of claim **16**, wherein cutting the vessel wall includes emitting a laser distally from the substantially ring-shaped cutting portion, the laser being configured to cut through the vessel wall.

18. The method of claim **16**, wherein the cutting device includes a substantially flattened elliptical ring-shaped cutting portion configured to cut a substantially flattened elliptical hole in the vessel wall, wherein the first dimension includes a major axis and the second dimension includes a minor axis.

19. The method of claim **16**, wherein the cutting device includes a rectangular ring-shaped cutting portion configured to cut a rectangular hole in the vessel wall, wherein the first dimension includes a length and the second dimension includes a width.

20. The method of claim **16**, wherein gripping the vessel wall includes creating a suction force between a nozzle of the gripping device and the vessel wall, the gripping device including a vacuum device.

21. The method of claim **16**, comprising sizing the substantially ring-shaped cutting portion of the cutting device to correspond to a vessel to be cut.

22. The method of claim **21**, wherein sizing the substantially ring-shaped cutting portion includes sizing the first dimension to correspond to a size of a first vessel to be cut with the cutting device.

23. The method of claim **22**, wherein sizing the substantially ring-shaped cutting portion includes sizing the second dimension to correspond to a size of a second vessel to be cut with the cutting device.

24. The method of claim **21**, wherein sizing the substantially ring-shaped cutting portion includes sizing the second dimension to correspond to a size of a second vessel to be cut with the cutting device.

* * * * *

APPENDIX 6

List of Publications and Presentations

LIST OF PUBLICATIONS (THIS THESIS)

- Stecher D, de Boer B, Tulleken CA, Pasterkamp G, van Herwerden LA, Buijsrogge MP.
  A New Nonocclusive Laser-Assisted Coronary Anastomotic Connector in a Rabbit Model
  Journal of Thoracic and Cardiovascular Surgery 2013 Apr;145(4):1124-9

- Stecher D, van Slochteren F, Hoefer IE, Paterkamp G, Tulleken CA, van Herwerden LA, Buijsrogge MP.
  The Nonocclusive Laser-Assisted Coronary Anastomotic Connector in an Off-Pump Porcine Bypass Model
  Journal of Thoracic and Cardiovascular Surgery 2014 Apr;147(4):1390-7

- Stecher D, Agostoni P, Pasterkamp G, Hoefer IE, van Herwerden LA, Buijsrogge MP.
  6-Month Healing of the Nonocclusive Coronary Anastomotic Connector in an Off-Pump Porcine Bypass Model
  Innovations 2014 Mar-Apr;9(2):130-6

- Stecher D, Bronkers G, Noest JO, Tulleken AF, Hoefer IE, van Herwerden LA, Pasterkamp G, Buijsrogge MP.
  Evaluation of a Novel Laser-Assisted Coronary Anastomotic Connector – the Trinity Clip – in a Porcine Off-Pump Bypass Model
  Journal of Visualized Experiments 2014 Nov;(93):e52127

- Stecher D, Bronkers G, Vink A, Homoet-van der Kraak PH, Helthuis J, Pasterkamp G, Buijsrogge MP.
  A Laser-Assisted Anastomotic Technique – Feasibility on Human Diseased Coronary Arteries
  Innovations. Accepted - revision pending

- Stecher D, Bronkers G, Hoefer IE, Pasterkamp G, Buijsrogge MP.
  Total Arterial MIDCAB Facilitated by the Trinity Clip Connector
  Innovations. Accepted - revision pending

- Stecher D, Bronkers G, Tulleken CA, Hoefer IE, van Herwerden LA, Pasterkamp G, Buijsrogge MP.
  The Laser-Assisted Coronary Anastomotic Connector – The Trinity Clip – in a Preclinical Safety Study
  Submitted

OTHER PUBLICATIONS

- Noort WA, Feyen D, Van Den Akker F, Stecher D, Chamuleau SA, Sluijter JP, and Doevendans PA.
  Mesenchymal stromal cells to treat cardiovascular disease: strategies to improve survival and therapeutic results
  Panminerva Medica 2010 Mar;52(1):27-40

- Noort WA, Oerlemans MI, Rozemuller H, Feyen D, Jaksani S, Stecher D, Naaijkens B, Martens AC, Bühring HJ, Doevendans PA, and Sluijter JP.
  Human versus porcine mesenchymal stromal cells: phenotype, differentiation potential, immunomodulation and cardiac improvement after transplantation
  Journal of Cellular Molecular Medicine 2012 Aug;16(8):1827-1839

LIST OF PRESENTATIONS

2015 International Society for Minimally Invasive Cardiothoracic Surgery
Oral and poster presentation
Berlin, Germany
Poster finalist award

2015 Dutch Association of Cardiothoracic Surgery
Oral presentation
Utrecht, The Netherlands

2014 American Heart Association Scientific Sessions
Oral presentation
Chicago, IL, USA

2014 International Society for Minimally Invasive Cardiothoracic Surgery
Oral presentation (2x)
Boston, MA, USA

2013 International Society for Minimally Invasive Cardiothoracic Surgery
Oral presentation
Prague, Czech Republic
ISMICS President's Award - Best full-length oral presentation

2013 Dutch Association of Cardiothoracic Surgery
Oral presentation
Utrecht, The Netherlands

2013 American Association for Thoracic Surgery
Oral presentation
Minneapolis, MN, USA

2012 Symposium of Experimental Research of Surgical Specialties (SEOHS)
Oral presentation
Amsterdam, The Netherlands
Best abstract session

2012 Dutch Association of Cardiothoracic Surgery
Oral presentation
Utrecht, The Netherlands
Award - Best full-length oral presentation

2012 European Association for Cardio-Thoracic Surgery - Techno College
Live surgical demonstration
Barcelona, Spain

2012 International Society for Minimally Invasive Cardiothoracic Surgery
Oral presentation
Los Angeles, CA, USA

APPENDIX 7

Dankwoord

Iedereen die mij geholpen heeft met het in dit proefschrift beschreven onderzoek wil ik graag bedanken en in het bijzonder de volgende personen:

Professor van Herwerden, "streng maar rechtvaardig", zei mijn moeder altijd over haar zelf, en dat kan ik ook over u zeggen. Zoals ik het ondervonden heb bent u iemand die zegt wat hij denkt, zonder de woorden voorzichtig te verpakken. Dit kon ik erg waarderen omdat het altijd duidelijk was. Uw kritische opmerkingen werden ruim gecompenseerd door de complimenten voor geaccepteerde papers, praatjes en geslaagde experimenten en betrokkenheid bij presentaties in binnen- en buitenland, met zelfs plaatsvervangende zenuwen bij een live operatie op de EACTS. Dat u halverwege mijn onderzoek met emeritaat bent gegaan heeft niets afgedaan aan de supervisie die je als promovendus mag verwachten van de promotor. U zei heel kort na uw emeritaat: ik mag nog 5 jaar gebruik maken van mijn rechten als hoogleraar en daarmee jouw promotor zijn, dus wel een beetje opschieten! De steun en support bij het afronden van het proefschrift en de gastvrijheid bij u thuis daar zal ik u altijd dankbaar voor zijn.

Professor Pasterkamp, beste Gerard, onze tweewekelijkse onderzoekmeetings afgewisseld bij ELANA of bij jou op de kamer waren altijd snel business doen, geen gejammer, en vervolgens nog even bijkletsen, potje tafelvoetbal met oude, leerzame en grappige anekdotes. Jouw no-nonsense houding en het altijd bereid zijn hulp te bieden zijn goud waard.

Dr. Buijsrogge, beste Marc, je bent een mentor pur sang. Door jou heb ik vakinhoudelijk veel geleerd, maar ook op het persoonlijke vlak, over mijzelf. Met jouw vertrouwen heb ik veel chirurgische ervaring kunnen opdoen in het lab. Jij hebt mij alles gegund en altijd de credits gegeven. Complimenteus en in de 1-op-1-tjes leerzame, opbouwende kritiek. Elke presentatie ben jij van de partij geweest, zo lang je geen dienst had. Die betrokkenheid is fantastisch. Ook nadat je een nacht had geopereerd of gewoon op je vrije dag, kwam je toch nog even mee doen met een operatie met een nieuw prototype op het lab. Je betrokkenheid komt ook terug in de tig revisies van papers, het telkens beter willen maken, overzicht houden met de zogenaamde legendarische helikopter-view, je bekende uitspraak "keep it stupid simple" en op de hotel kamer nog even een generale repetitie van een van de presentaties; dit heeft ervoor gezorgd dat ik mij ontwikkeld heb in het schrijven en presenteren. Jouw onuitputtelijke energie, altijd scherpe en kritische blik, niet te zuinige humor, maakt niet uit welk moment van de dag of hoeveel uur je geslapen hebt en de voor iedereen herkenbare keiharde aanstekelijke galmende lach, maken jou tot een "one of a kind" persoon. De ontelbare slappe lach momenten, dinertjes, borreltjes, evaluatie-momentjes, kereltje-gozertje-ventje emailtjes, idiote foto's, kreeft, oesters, porterhouse, boven mijn budget wijn traktaties, Zinfandel, Chardonnay, truc met de kurk in de fles, IPA's, per ongeluk belanden in de ghetto van Chicago met enkele doodsangst momentjes, pinda's-spetterende hot-shots ontmoeten, road trip Boston-Plymouth-Provincetown, put your hands on the dashboard, op 1 been staan en het alfabet van achter naar voren, door een barre sneeuwstorm en een halve meter sneeuw eindelijk in de Starbucks aankomende per ongeluk een ice coffee bestellen (en mij gewoon uitlachen met z'n lekkere warme cappuccino) en ga zo maar door…. dit alles ga ik nooit vergeten. Mede door jou is mijn promotie tijd onvergetelijk geworden en hier zal ik je altijd dankbaar voor zijn.

Professor Tulleken, de founder van de ELANA techniek. U heeft mij geleerd om te opereren door een microscoop en vervolgens heeft u mij meerdere malen geprobeerd over te halen neurochirurg te worden, maar tot op heden staat de hartchirurgie nog steeds bovenaan. U bent altijd positief. Zo positief dat u altijd wel iets goeds ziet in mislukte experimenten, soms tot enige irritatie van mij. Terwijl ik zat te balen was u enorm positief: "een experiment is pas geslaagd als er iets mis gaat, daar leer je van". Fantastisch mooie eigenschap. U bent voor mij een enorme inspiratie geweest met uw volhardende, onuitputtelijke drift naar innovatie en out-of-the-box vindingrijkheid. U zei mij dat ik een homo ludens ben, maar u bent een homo ludens pur sang. Om maar een voorbeeld te noemen, op uw zeventigste heeft u compleet autodidactisch 3d-software onder

de knie gekregen waaruit al de prachtige animaties in mijn papers en de animatie films in mijn presentaties uit voort zijn gekomen. Voor wat u heeft betekent voor de neurochirurgie heb ik enorm veel ontzag. Het is een grote eer met u samengewerkt te hebben.

Glenn Bronkers, mijn paranimf en mijn rechter (en soms ook linker) hand. Je geduld, enorme passie voor het project, inzicht, vindingrijkheid en behulpzaamheid hebben een enorme indruk op mij achtergelaten. Wij delen een eigenschap wat voor ons beide nogal belangrijk is: genieten van het leven en met name genieten van lekker eten en drinken. Als ik je weer zag in de vroege ochtend was het altijd: "Leeft het varken nog? Ja, top! Luister, wat ik gister gegeten heb..." Altijd stond je voor me klaar, en nog steeds. Top collega en goede vriend, ondanks jouw uitlatingen als Utrechter over Amsterdam… Hoop dat wij elkaar nooit uit het oog gaan verliezen.

Cees Verlaan, jij hebt mij, naast Marc, de kneepjes van de off-pump bypass chirurgie op varkens geleerd. Je jarenlange ervaring als experimenteel cardio-, vaat- en algemeen-chirurg heb jij fantastisch overgebracht aan menig promovendus en het gehele team fantastische biotechnici. Je geniale uitspraken, goede humeur, grappen, verhalen en passie voor het vak maakten de talloze uren samenwerken met jou tot een waar genot. Je bent een top kerel.

Sander van Thoor, master mind, wiskundig en natuurkundig genie. Nou dat zijn wel weer genoeg complimenten. Zal nooit vergeten wat je altijd zei als ik eens om 18:00 uur naar huis ging: "zo, middagje vrij genomen? Part-timer!". Bedankt voor al je hulp, het gezelschap houden in het lab tot de late uurtjes, het serveren van knakworstjes in die zelfde uurtjes, je hulp bij alle berekeningen op hoger niveau, maken van test-opstellingen, eerste hulp bij laser-instellingen en natuurlijk je gezelligheid. Daarnaast zei je altijd, "niks te danken, als je me maar noemt in je boekje". Dus bij deze Sander, en met volle overtuiging: dank je!

Rik Mansveld Beck en Niklank Noest, technisch genieën. Enorm eigenwijs, maar oh zo handig vingerwerk. Bedankt voor de fijne samenwerking, het vertalen van abstracte ideeën naar tekeningen, naar devices en hulpstukken. Soms hebben jullie heel wat te verduren gekregen van ons clinici. Zonder jullie handigheid waren we nooit zover gekomen.

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De inmiddels flink geslonken groep CTC promovendi: Frederiek de Heer, Linda de Heer, Jesper Hjortnaes, Jerson Martina, Paul Riem Vis, Sabrina Siregar, Hanna Talacua en Marcelle Uiterwijk (en de nieuwe versterking Kirolos Alfy Jacob natuurlijk). Fijne groep ambitieuze mensen. Zullen elkaar hopelijk nog de rest van ons leven vaak genoeg treffen.

De PA's, arts-assistenten en chirurgen van de afdeling Cardio-thoracale Chirurgie, bedankt voor jullie interesse en steun in met name het laatste jaar waarin ik begonnen ben in de kliniek en ik ondertussen nog dit proefschrift aan het afronden was. Mooie club harde werkers. Blij dat ik onderdeel mag uitmaken van dit geweldige team.

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Irfan, dank voor jouw geloof in mij en je eeuwige steun. Mis je.

Vincent, mijn grote broer, beste vriend en paranimf. Jij weet bijna alles van mijn onderzoek, volgt het op de voet, volgt mij ook naar Berlijn om mijn presentatie bij te wonen, is altijd geïnteresseerd en komt met goede ideeën. Dank dat je er echt altijd voor mij bent.

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Sharon, als laatste mijn liefste.
Jij hebt mij ongelofelijk gesteund, je staat altijd voor mij klaar en geeft mij de ruimte om te knallen. Jouw zorgzaamheid en vrolijkheid hebben mij door de zware dagen heen getild en jouw intelligentie en talent om situaties te doorgronden hebben mij veel advies gegeven. Door jou ben ik mijzelf beter gaan leren kennen. Als een abstract was goedgekeurd voor een presentatie of een paper geaccepteerd dan zorgde jij altijd weer voor een heerlijk champagne-momentje samen. Samen vieren we het leven, door dik en dun. Op nog vele champagne-momentjes! Hou van jou!

APPENDIX 8

Curriculum Vitae

David Stecher was born in Naarden, The Netherlands, July 17, 1984. He completed high school at the Casparus College in Weesp. In 2002, after being differed from medical school by *numerus fixus*, he started his study Biomedical Sciences at the University of Amsterdam. Following his Bachelors of Science, he subsequently applied for the Selective Utrecht Medical Masters at the University Medical Center Utrecht (UMCU). He was selected for the 4-year masters program where he was trained to become both a medical doctor and clinical researcher. His scientific graduation thesis was conducted at the Department of Experimental Cardiology on the basic science of tissue engineering, in which human mesenchymal stromal cells were compared to porcine, regarding their phenotype and differentiation potential. In 2010, he graduated as a medical doctor and clinical researcher at the UMCU. Directly afterward, he started his PhD at the Department of Cardiothoracic Surgery and Experimental Cardiology at the UMCU. During his PhD, he was trained in microsurgical techniques, off-pump surgery and minimally invasive bypass surgery. The developments in the ELANA technique, in collaboration with the Department of Neurosurgery, resulted in 2 patents (all currently pending). During these years, he was involved in the education of Biomedical Sciences students in device development and presented his scientific work at major international conferences through oral presentations and a live surgical demonstration. Furthermore, he interned at the Robotic Coronary Artery Bypass project of the London Health Sciences Centre, London Ontario, Canada. In 2014, after 4 years of research, he started as a clinical resident not in training (ANIOS), at the Department of Cardiothoracic Surgery of the UMCU. David lives together with his partner Sharon Kniest in Amsterdam.