

Review

Myocardial blood supply by left ventricle-to-coronary artery channel: An old idea revisited

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Abstract

Coronary artery disease is one of the most important causes of death in Western society. Attempts to revascularize the coronary artery by myocardial retroperfusion, direct revascularization from the left ventricle, and bypass surgery have finally led to percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) as standard treatment for coronary artery disease.

Direct revascularization from the left ventricle has already been studied in the late 1960s, but the idea was rejected because of a decrease in flow in combination with a failure of myocardial function. Recently, a left ventricle-to-coronary artery (LV–CA) stent has renewed interest as an alternative procedure when PTCA and CABG are no option. Animal studies showed a change in flow pattern from diastolic coronary inflow at baseline to systolic coronary inflow followed by diastolic regurgitive flow during direct ventricular sourcing, resulting in a coronary flow of 50–75% of baseline flow. Global myocardial function decreased in the same extent as the coronary flow suggesting perfusion–contraction matching. In a recent pilot study in the anaesthetized pig, direct revascularization after acute proximal coronary ligation resulted in sufficient blood supply to the outer layers of the myocardium, however, in the inner layers a metabolic disbalance occurred.

Incorporation of a valve-like mechanism to minimize the diastolic regurgitive flow may be necessary to improve the performance of the LV–CA stent. In addition, further research should be done in chronic ischemic animal models in which the effect of the collateral circulation on myocardial perfusion and performance is an important issue.

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1. Myocardial revascularization: a short historical view

Nowadays, coronary artery disease accounts for nearly half of the deaths in the developed world and 25% in the developing world [1,2]. Percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) are currently the standard methods for revascularization [3].

In the late nineteenth century, the necessity for coronary artery surgical procedures became evident by the observation of extensive minute vascular communications between normal coronary circulation and vascular supply of surrounding extracardiac structures, such as the pericardium [4]. Procedures like reversion of coronary sinus blood by arterIALIZING the coronary sinus, whereby coronary venous pressure was increased and reversing thebesian blood flows from the chambers back into the myocardium, and sympathectomy, which relieved the sensation of angina and produced a state of coronary vasodilation, were explored and became standard procedures for several years. Moreover, Beck suggested arterIALIZING the coronary sinus thereby attempting to create retroperfusion of the myocardium [4].

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Attempts to produce neovascularization and improve collateral circulation were also made by Beck and Leighninger who damaged the heart by inducing a sterile pericarditis [5]. Others tried to induce vascularization directly from the left ventricle by placing a T-tube in the myocardium [6] or by application of myocardial acupuncture [7], both techniques being pioneers of transmyocardial laser revascularization (TMLR). In addition, Vineberg implanted internal mammary arteries directly into the myocardium, believing the blood would be absorbed by the relatively large venous sinusoids [8]. This procedure was even used until the 1970s, often being effective in relieving angina.

Coronary artery bypass grafting, as we know it nowadays, has its origin already in 1910, when Carrel used an arterial graft to create a bypass between the aorta and the left coronary artery. Many groups using both arterial and venous grafts further studied bypass surgery in the 1950s. In 1954, Murray reported the first successful experimental bypass grafting, performed on beating dog hearts using carotid, axillary and internal mammary arteries directly onto coronary arteries. Six years later, Goetz and his coworkers performed the first right mammary artery-to-right coronary artery bypass in a human and in 1964 the first successful saphenous vein segment bypass operation was done by Garret, Dennis and DeBakey [4]. Bypass surgery with saphenous vein or internal mammary artery grafts finally became the standard of today.

2. Direct revascularization

The idea of creating direct myocardial blood supply from the left ventricle is originally from Wearn in 1928, who suggested that the thebesian vessels could supply blood to the myocardium directly from the ventricle via reversed blood flow [9]. Direct implantations of vessels in the myocardium was found to be helpful when Griffith and Bates accidentally perforated the left ventricle and tried to repair this by suturing part of the pectoral muscle together with the mammary arteries into the opening [10]. In 1946, Vineberg reported that he implanted a mammary artery directly into the myocardium, suggesting that the implanted artery would fill up the myocardial sinusoids [8].

In 1956, Goldman channelled left ventricle (LV) blood through a carotid homograft into the myocardium [11]. Although occlusive narrowing of the graft was an unfavourable concomitant factor, blood could still reach the myocardium through spaces and new vessels that were formed around the occluded graft. Using a polyethylene tube instead of an arterial graft to overcome the extravascular pressures, thrombosis was found in all grafts and these tubes were poorly tolerated. One year later, Massimo and Buffi tried to make a connection from the left ventricle to the coronary circulation using a plastic T-tube, which should be more resistant against the extra vascular

compression. Although the tube was unobstructed in 80% of the cases, the ventricular end was often covered by endothelium [6].

A direct connection from the left ventricle to the left coronary artery was first created by Munro and Allen in 1968 and showed that during this kind of perfusion the coronary flow pattern changed from diastolic inflow to systolic inflow accompanied by diastolic regurgitive flow, because the coronary circulation is subjected to phasic oscillations of the left ventricular pressure and not the aortic pressure. However, as they found a decrease of coronary flow to one third of normal flow together with a failure of myocardial function it was concluded that this direct revascularization was unlikely to succeed [12].

Recently, direct ventricular revascularization has regained interest in cases where PTCA or classical bypass procedure are not an option and could be an alternative for patients with degenerated saphenous vein grafts, calcification of the aorta or a lack of suitable conduits or who have had reoperations [13]. In a chronic pig model, a transmyocardial device was implanted from the base of the left ventricle and connected to the left anterior descending coronary artery (LAD) by standard anastomosis techniques, resulting in 76% of normal coronary artery flow with 91% patency of the left ventricle-to-coronary artery (LV-CA) stent after 2 weeks implantation [14]. In a comparable acute study using dogs, direct ventricular blood supply resulted in approximately 45% of normal coronary blood flow [15]. Boekstegers et al. used the on-artery approach in pigs, which involves intraluminal implantation of the stent from the bottom of the LAD directly to the left ventricle and also found a coronary flow of 70% of baseline flow (Fig 1) [13].

To improve the net forward flow to the myocardial bed, the diastolic regurgitive flow should be diminished. Because the shunts in the studies of Tweden and Suehiro do not include a valve-like mechanism during diastole, substantial

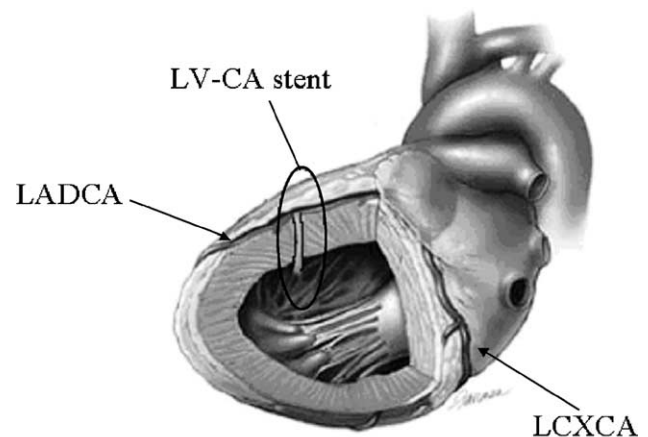


Fig. 1. Direct left ventricular blood supply by intraluminal implantation of the stent from the bottom of the LAD to the left ventricle (Percardia Inc., Merrimack, NIH).

backflow to the left ventricular cavity occurs (pressure sink). Boekstegers used a natural valve-like mechanism when he placed the LV–CA stent just below the coronary artery back wall, thereby creating a flap. This improved net forward coronary flow to 76% of baseline flow.

Recently, de Zeeuw et al. investigated whether augmentation of the coronary compliance during LV–CA shunting would improve net forward flow by enhancing forward flow in early diastole without reducing forward flow in systole [16]. Increased compliance was obtained by connecting a blind stump of the right internal thoracic artery (15 cm) to the distal LAD. Perfusion by the LV–CA stent changed the flow pattern from diastolic inflow during baseline to systolic inflow and diastolic regurgitative flow (Fig 2), resulting in a net forward LAD flow of $53 \pm 18\%$ of native flow. When epicardial coronary compliance was increased, systolic forward flow (53 ± 23 vs 37 ± 19 ml/min with normal compliance) was increased accompanied by a similar increase in diastolic regurgitant flow (-26 ± 20 vs -16 ± 16 ml/min). However, net forward coronary flow was unchanged and thus augmentation of coronary artery compliance did not improve stent performance (Fig 3).

3. Decrease in coronary flow is correlated with changes in myocardial function

The effect of graded occlusion of the LAD on the myocardium is studied in many different animal models. Using a porcine model, a 90 min 30% or 70% blood flow reduction in the LAD resulted in a 6% and 16% decrease in

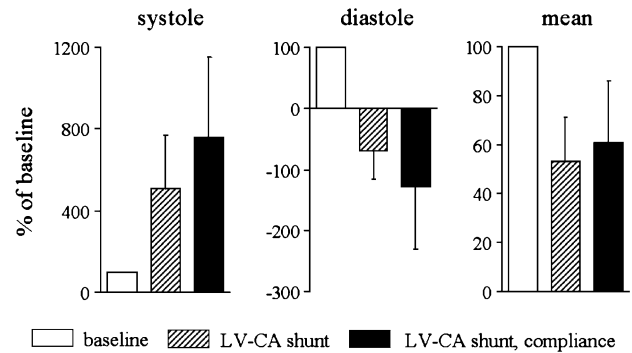


Fig. 3. Systolic, diastolic, and mean mid-LAD flow presented as percentage of baseline, measured during baseline (native blood supply, open bars), during direct left ventricular sourcing with normal compliance (hatched bars) and with increased compliance (closed bars). LAD flow was measured just distal from the LV–CA stent by transit time flow probes. Data are presented as means \pm SD. Note that when the epicardial compliance was increased both systolic and diastolic mid-LAD flow increased, however, net forward flow remained unchanged.

systolic segment shortening (SS), respectively [17]. In addition, Vatner found no change in myocardial function when blood flow was decreased by $6\% \pm 1\%$ in a study using dogs with acute graded stenosis in the LAD or one of its major branches, but 20% coronary flow reductions of blood flow impaired myocardial function significantly [18]. The impact of graded coronary occlusion on myocardial performance cannot be translated unambiguously to changes in coronary blood supply by a LV–CA stent, because in the former condition coronary flow is predominantly diastolic, whereas the latter condition is predominantly systolic.

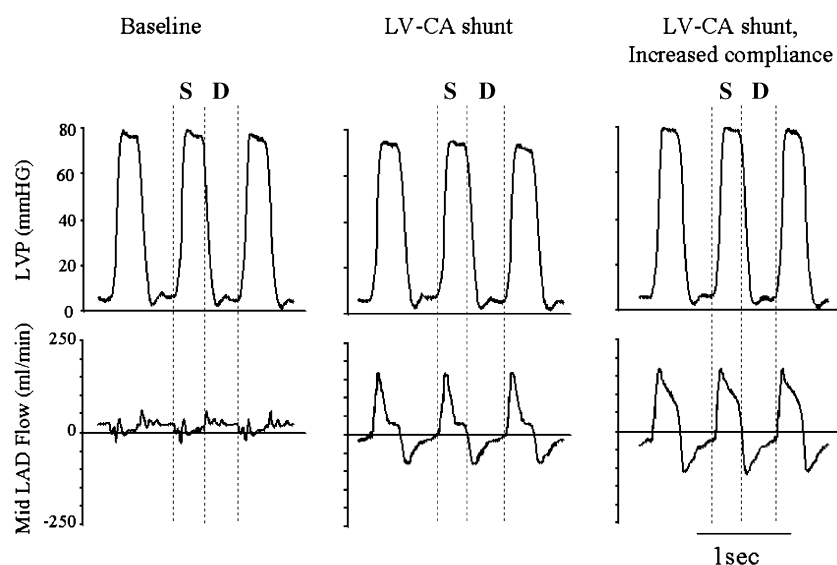


Fig. 2. Representative recording of mid-LAD flow during native blood supply and during direct left ventricular sourcing with normal and increased epicardial compliance. Top graphs show the left ventricular pressure (LVP, mm Hg), bottom graphs show the mid-LAD flow (ml/min). S, systole; D, diastole. End-diastole was defined as the onset of rapid increase in left ventricular pressure, whereas end-systole was defined at the maximal rate of decrease in left ventricular pressure. Note that during left ventricular sourcing a huge systolic inflow followed by diastolic regurgitative flow occurred.

In animal models in which direct revascularization is studied, myocardial function was measured in addition to coronary flow [13,15]. The 30% flow reduction found in the study by Boekstegers was accompanied by a 29% decrease in systolic segment shortening. Moreover, similar results were found by Suehiro, who showed a 55% decrease in pressure-segment length area together with a 54% decrease in coronary flow indicating perfusion–contraction matching. These parameters are limited as these are global measurements and do not distinguish between subepicardium and subendocardium. Therefore regional parameters are important to study the effect, which is affirmed by the myocardial perfusion results. Microsphere data showed that the residual coronary flow was distributed disproportionately among the inner and outer myocardial layers. The subendocardium obtained less than 40%, while the subepicardium obtained over 60% of total residual coronary flow [13]. Thus, subendocardium will be more affected than subepicardium and decrease in global function is most likely caused by decrease in subendocardial flow. Regarding the study of Boekstegers, perfusion level of the subepicardial layers near the mid-LAD was even 80% of baseline, which should be sufficient to maintain myocardial contractility [13].

4. Myocardial metabolism during ischemia

What are the metabolic sequelae of hypoperfusion? This question is of interest as during LV–CA stent perfusion an imbalance of supply and demand may develop.

The heart strongly depends on aerobic metabolism and thus oxygen and substrates to preserve its viability and contractile function, as anaerobic metabolism can only

provide 7% of the energy production that is required to maintain normal contractile function. Free fatty acid (FFA) oxidation accounts for 67% of the energy supply of the heart, while the remainder is acquired by the oxidation of lactate and glucose [19]. Different substrates will be used, dependent on their plasma concentration. Under normal circumstances, when both oxygen and substrates are sufficiently supplied, acetyl coenzyme A (acetyl CoA) is the key product in myocardial energy production. In the mitochondria it can be formed from 1) FFA (β -oxidation) or 2) pyruvate, converted from lactate or glucose in the cytosol.

When blood supply to the myocardium is insufficient, an imbalance between the amount of oxygen and substrates supplied to the heart and the amount needed to perform normal function is created, termed ischemia. Under these anaerobic circumstances, β -oxidation, citric acid cycle and electron transport chain cannot take place (Fig 4). Several studies have shown that during ischemia differences exist in metabolism between the subepicardium and subendocardium, resulting in a more rapid depletion of energy stores in the subendocardium compared to the subepicardium, in analogue to the perfusion differences found with microspheres [20–22]. These differences in metabolism can be explained by several reasons. First, during ischemia the subendocardium is underperfused in comparison to the subepicardium [22–24]. This underperfusion of the subendocardium, causing more severe ischemia, might be due to the mechanism of transmural steal. Second, wall stress is higher in the subendocardium than in the outer layers of the myocardium, resulting in uneven depletion of energy stores [25,26]. Third, a greater intrinsic metabolism in the endocardium has been found in excised myocardium

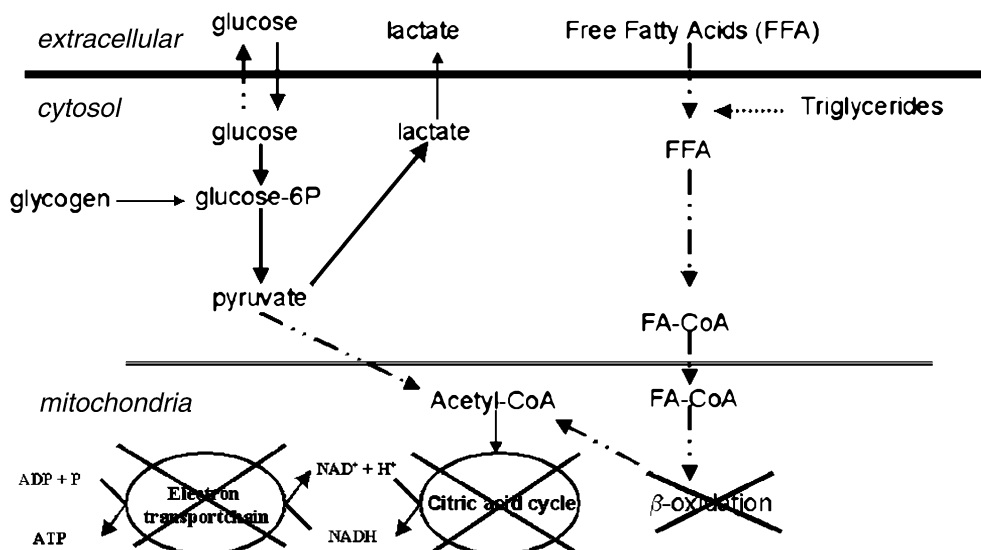


Fig. 4. Metabolism of the heart during ischemia. During anaerobic metabolism the electron transport chain, citric acid cycle and β -oxidation are blocked. Under these conditions formation of NADH only occurs during glycolysis.

[27], resulting in a more rapid depletion of the sub-endocardium energy stores independent of blood flow and wall stress.

5. Microdialysis technique: a method to demonstrate anaerobic metabolism

Microdialysis, a technique that has its origin in neuroscience, is an accurate way to measure regional myocardial substances. This technique is based on diffusion of interstitial substances through a semi-permeable membrane located at the end of a microdialysis catheter (Fig 5). An isotonic perfusion fluid, similar to the extra cellular fluid, is pumped through the microdialysis probe via an inlet tube and fluid from the outflow of the probe (dialysate) is collected for later analysis. The concentration gradient between the interstitium and the perfusion fluid initiates diffusion of molecules from the fluid to the probe and vice versa. Dependent on the cut-off of the membrane, molecules smaller than the pore size of the membrane can only perfuse through the membrane.

An advantage of this technique is that regional interstitial concentrations can be measured without producing severe damage to the myocardium. Other advantages of this technique are the possibilities to measure several substances simultaneously and manipulation of pharmacological systems without having systemic effects [28]. Moreover, the measurements are semi-continuous as dialysate samples are collected over a certain period. Nowadays, microdialysis is increasingly used in studies for

myocardial metabolism, perfectly suitable to detect at different locations in the same organ, e.g. subendocardium and subepicardium or ischemic area versus non-ischemic area.

6. Myocardial metabolism during direct ventricular sourcing

The influences of the systolic instead of the diastolic perfusion in the different layers of the myocardium can be shown by studying transmural perfusion, but also by studying the metabolism in each layer, as glucose and lactate levels are indications for aerobic or anaerobic metabolism.

In a pilot study in our laboratory, a LV–CA stent was placed transmurally in the lateral wall of the LV and connected to the proximal LAD via an arterial graft in an acute porcine model. Measurements were obtained at baseline (native LAD flow was the unique coronary blood supply), when the LV–CA stent was fully patent in competition with the native LAD and when the proximal LAD was acutely occluded and the perfusion was exclusively from the LV–CA stent. Subepicardial and subendocardial interstitial lactate and glucose concentrations were measured during the 3 conditions by collecting dialysate samples for 10 min (each condition lasted 10 min), using microdialysis technique. During native blood supply or when the LV–CA stent was additionally opened no changes in dialysate lactate or glucose levels were found in either the subepicardium or subendocardium. When blood supply was provided solely by the LV–CA

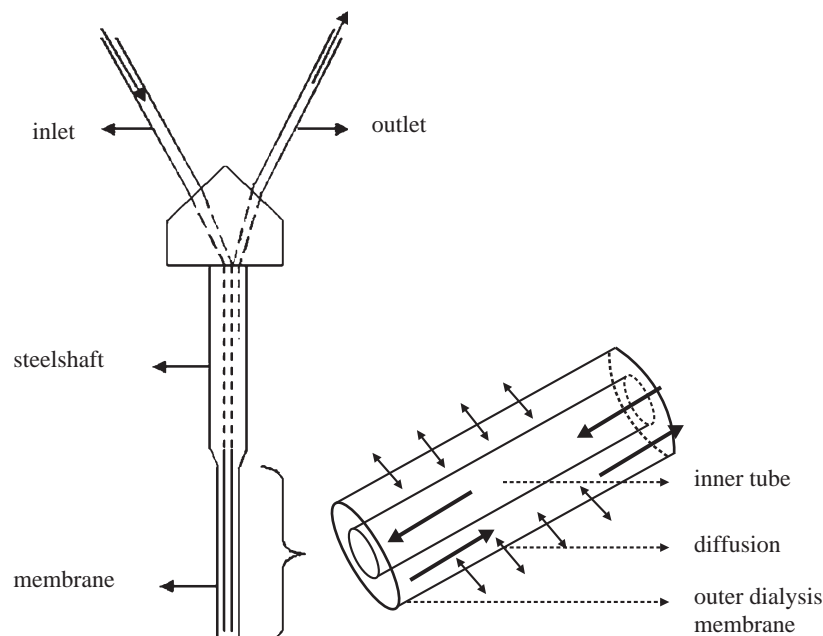


Fig. 5. Schematic drawing of a microdialysis probe (CMA/20, Carnegie Medicine, AB, Sweden) designed for dialysis experiments in moving soft tissues such as muscle, skin and adipose tissue. Diffusion between the extracellular fluid (ECF) and the perfusion fluid takes place in the outer dialysis membrane.

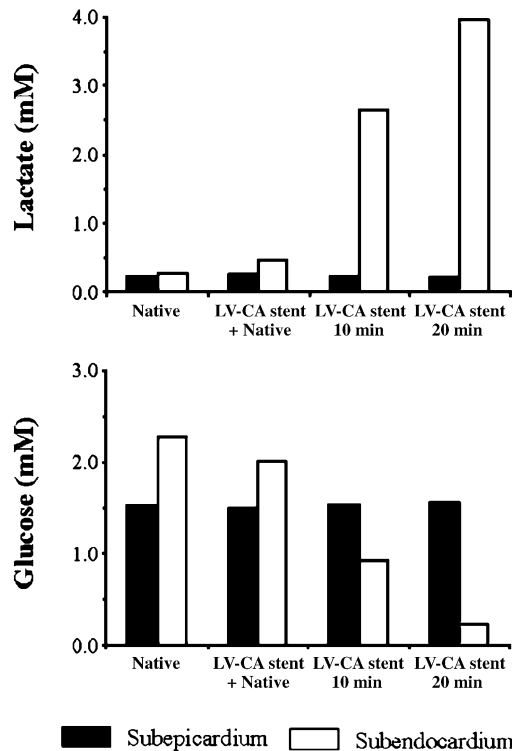


Fig. 6. Result of a pilot study done in our laboratory. Purpose of the experiment was to determine regional myocardial metabolism using the microdialysis technique during baseline (native LAD flow was the unique coronary blood supply), when the LV-CA stent was fully patent in competition with the native LAD and when the proximal LAD was acutely occluded and the perfusion was exclusively from the LV-CA stent. Panel A, regional interstitial lactate (mM) concentrations in the subepicardium and subendocardium of the area perfused by the LV-CA stent during the 3 conditions. Panel B, regional interstitial glucose (mM) concentrations in the subepicardium and subendocardium of the area perfused by the LV-CA stent during the 3 conditions.

stent, dialysate lactate and glucose levels still remained unchanged in the subepicardium.

However, in the subendocardium, acute direct left ventricular sourcing resulted in a 10- to 14-fold increase in dialysate lactate levels after 10 and 20 min, respectively, compared to baseline (2.659 and 3.968 mM vs 0.275 at baseline). In addition, a decrease in subendocardial glucose levels after 10 and 20 min left ventricular sourcing was found, 60% and 90% compared to baseline values, respectively (Fig 6). These results suggest that in the anesthetized pig, direct revascularization after acute proximal coronary ligation results in sufficient blood supply to the outer layers of the myocardium, however, in the inner layers a metabolic disbalance occurs, indicating subendocardial ischemia.

7. Summary

Recently the LV-CA stent has regained interest as alternative treatment when standard procedures like coro-

nary artery bypass and PTCA are insufficient. Previous studies have shown that direct left ventricular perfusion results in a decrease of the coronary artery flow to 50–76% of native flow distal to a total ligation in an acute animal model. Pilot studies have shown that systolic blood supply is sufficient to perfuse the subepicardial layers, whereas the subendocardial layers show a metabolic imbalance. These results suggest that the LV-CA stent can be a beneficial device for patients with chronic hypoperfusion to save the epicardium, because an endocardial infarction may already exist in general. To understand the consequences of systolic myocardial perfusion further research should be executed to determine myocardial metabolism using microdialysis.

When a mechanism will be found to reduce regurgitive flow in the LV-CA stent, it will further broaden the clinical applications. In addition, studies should also be performed in an animal model with myocardial ischemia or hypoperfusion, because it is unknown what the effect is of ischemia-induced collaterals on LV-CA stent performance. Moreover, the data must be confirmed in chronic models to study the maintenance of the patency of the LV-CA stent.

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