Outcome of long-term mechanical circulatory support

Quod bonum, faustum felixque est

Uitkomsten van langdurige mechanische circulatoire ondersteuning

Wat goed, voorspoedig en gelukkig is

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op
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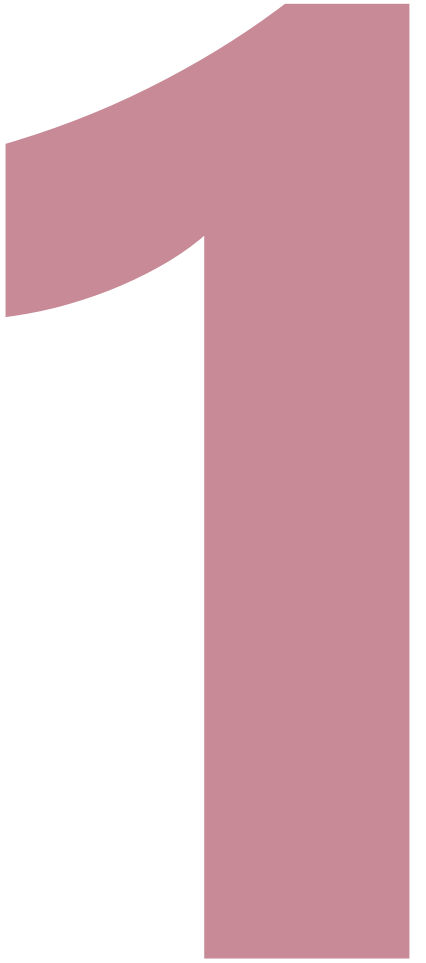
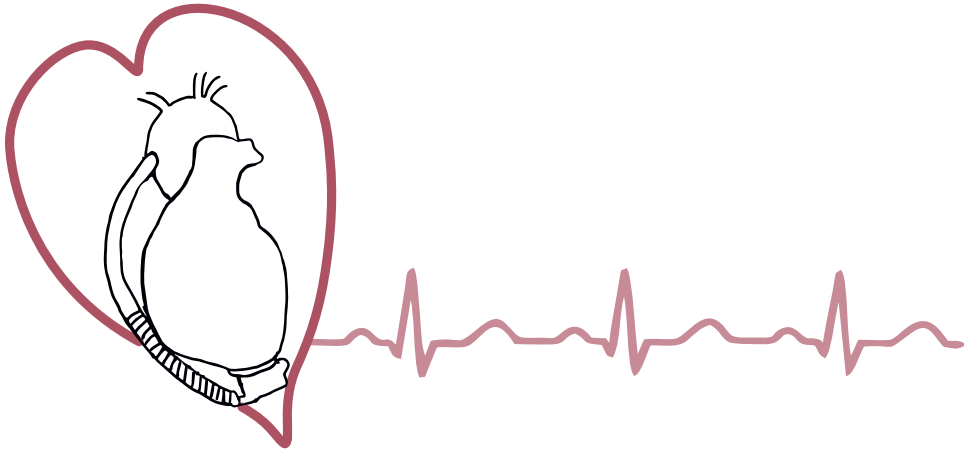
CHAPTER 1



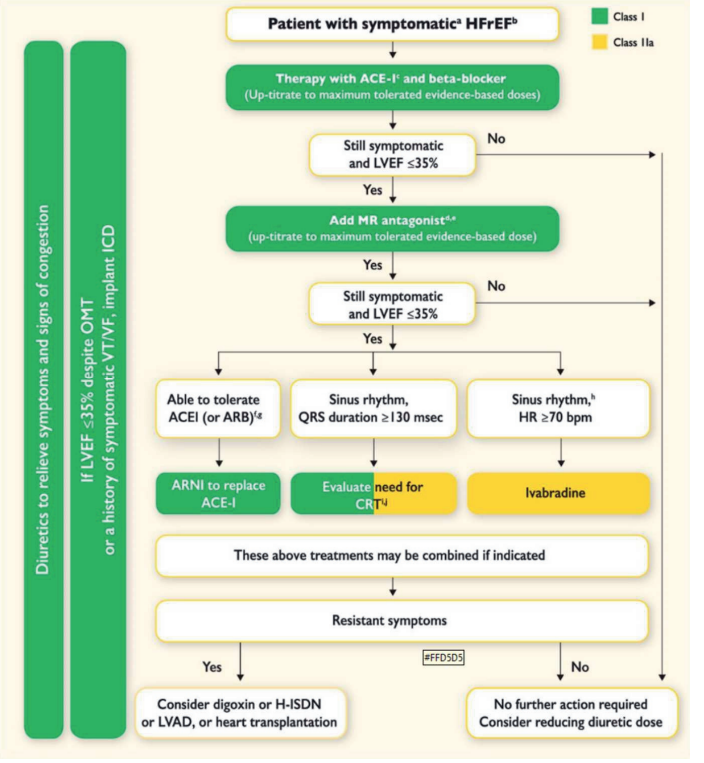
Introduction



Introduction

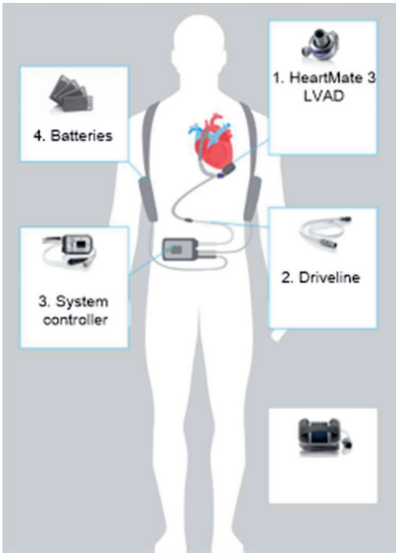
The clinical syndrome of heart failure is a growing pandemic, which affects at least 26 million people worldwide. [1] The mainstay of pharmacologic treatment in patients suffering from chronic heart failure with a reduced left ventricular ejection fraction is formed by beta blockers, inhibitors of the renin-angiotensin-aldosterone-axis (angiotensin converting enzyme (ACE) inhibitors/ angiotensin receptor blockers/ angiotensin receptor-neprilysin inhibitor and mineralocorticoid receptor antagonists) and sodium-glucose cotransporter 2 (SGLT2) inhibitors. [2,3] In addition, patients may be treated with an implantable cardioverter defibrillator, with or without cardiac resynchronization therapy, or Ivabradine according to current guidelines (Figure 1). [2]

Figure 1. Therapeutic algorithm for patients with symptomatic heart failure with reduced ejection fraction



If patients remain symptomatic despite these interventions, a heart transplantation or mechanical circulatory support (MCS) by a left ventricular assist device (LVAD, Figure 2) may be considered.

Figure 2. Continuous-flow left ventricular assist device, including the pump, driveline (connecting the pump to the system controller), system controller and batteries



Heart transplantation is an effective, but limited treatment due to the mismatch between the number of patients with advanced heart failure and the limited number of suitable donor hearts. [4,5] As a bridge to transplantation, patients may be treated with MCS. In the last decades, the use of MCS has increased substantially due to technological advancements. [6] This is partly related to the shortage of donor hearts but also to the improvement of clinical outcomes in these patients, together with the reimbursement to implant a LVAD as destination therapy. Destination therapy is performed in patients ineligible for heart transplantation. [7]

These factors have resulted in a generally longer treatment duration with MCS.

At the University Medical Center of Utrecht (UMCU), LVADs have been implanted since 1993, mostly as a bridge to transplantation. First implants consisted of pulsatile flow LVADs, which were larger pumps connected to the left ventricular apex by the inflow cannula and the outflow housing to the ascending aorta through a vascular prosthesis (Figure 3). [8]

Figure 3. First generation (pulsatile flow) left ventricular assist devices

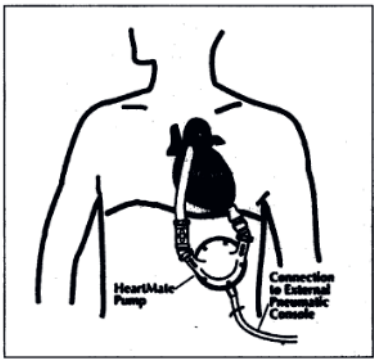


Figure 1 Schematic diagram of the HeartMate Implantable Pneumatic left ventricular assist device. The inflow canula is implanted in the left ventricular apex. The outflow graft is connected end to side to the ascending aorta. The transcutaneous driveline is connected to the external pneumatic console.

Since 2006, continuous-flow devices (HeartMate-II, HVAD and HeartMate 3) have been implanted that are associated with improved survival and durability in comparison to the pulsatile flow LVADs. [9,10] At present, over 400 continuous flow LVADs have been implanted at our center. A lot of experience was gained in the management of these patients, starting from the selection of the patient, the perioperative care and the management of complications associated with this therapy. [11-13] Because duration of MCS in patients in our center is longer than in most studies, we were able to study the long-term results of mechanical circulatory support.

Outline of this thesis

The aim of this thesis was to investigate the long-term outcome of end-stage heart failure patients treated with MCS. Different outcome parameters were analyzed, including the survival and adverse event rate at our center, as well as predictive analyses of specific adverse events.

In **Chapter 2,** we present an overview of the hemodynamic alterations related to continuous-flow LVADs, including the short-term and long-term effects on the right ventricle which is not supported in MCS. In addition, most prevalent adverse events associated with MCS are described, illustrated by a few clinical cases.

The experience gained with this therapy at the UMCU is presented in **Chapter 3.** The 5-year survival and adverse event rates (for example major bleeding, stroke, infections, ventricular tachycardia and right heart failure) are described for patients with extended MCS, which is necessitated by the shortage of donor hearts in the Netherlands.

The following 3 chapters focus on the prediction of specific adverse events that may occur in MCS. In general, these patients have an increased risk of bleeding and thrombotic events. [14,15] We aimed to predict these events, occurring after the peri-operative phase, by Cox regression analysis and describe the results in **Chapter 4**.

In collaboration with University of Utrecht Informatics department, a data mining based application for the prediction of bleeding in MCS patients was developed. This project had a dual purpose. First, we aimed to create an accurate model to predict a major bleeding in the near future at any moment during MCS. Second, the tool was made applicable to health care professionals less experienced in data mining. These two goals are intertwined into 'Autocrisp', presented in **Chapter 5.**

Another important adverse event related to durable MCS is the occurrence of right heart failure, which may occur early after LVAD implantation, but also during long-term support. [15]

Recently, the MCS academic research consortium updated the definition of all adverse events related to MCS. Late right heart failure (LRHF) is now defined as the need for implantation of a right ventricular assist device >30 days following LVAD implantation or the need for hospitalization >30days post-implant with the requirement of intravenous diuretics or inotropics for at least 72 hours in association with clinical signs of right sided congestion or hemodynamic compromise (e.g. renal failure, elevated lactate). [16] However, also outpatient MCS patients may show signs of right sided heart failure requiring increased doses of diuretics without the direct need for hospitalization. This should also to be included into the definition of LRHF as described in **Chapter 6**.

Another important clinical outcome is functional capacity. In addition to previous studies, which already identified an improved exercise capacity in patients after MCS, [17-20] we studied the serial results of cardio-pulmonary exercise tests (CPETs) at 6 and 12 months after implantation, which are presented in **Chapter 7**.

In **Chapter 8**, a review on the use of long-term MCS in The Netherlands is discussed. The indications, contra-indications, survival, adverse events and the organization of care for this special patient population is described.

Finally, in **Chapter 9**, the main findings of this thesis are described, along with future perspectives on this rapidly developing field of medicine.

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CHAPTER 2

2

Continuous-flow left ventricular assist device support in patients with advanced heart failure: points of interest for the daily management

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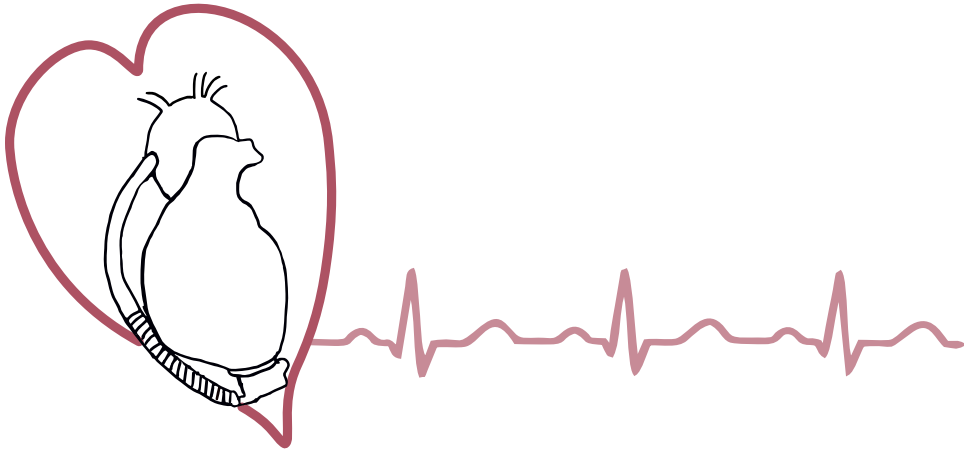

Abstract

Today, continuous-flow left ventricular assist devices (cf-LVADs) are implanted more often in patients with end-stage heart failure. Because of greater durability they can be implanted for an extended period of time. As a result of increased numbers of patients on cf-LVAD support, healthcare professionals should be aware of the potential complications inherent to this therapy. Both bleeding and thrombosis may occur, and also complications related either to the device itself or to the ensuing altered haemodynamics, valvular pathology, and rhythm disturbances such as ventricular tachycardias and fibrillation. Accurate clinical evaluation, together with an electrocardiogram and, if necessary, combined with an echocardiogram, is obligatory in these situations. This review summarizes common complications complemented by a few clinical cases.

Introduction

An increasing amount of patients develop end-stage heart failure, refractory to maximized medical therapy. Heart transplantation has been the only solution to improve both survival and quality of life of these patients. Due to the chronic shortage of donor hearts, only a fraction of patients receive this therapy. This growing discrepancy between supply and demand has driven the development of alternative therapies, such as mechanical circulatory support (MCS).

Many devices for MCS are available, which can be divided into short-term extracorporeal devices and long-term intracorporeal left ventricular assist devices (LVADs). The first generation of LVADs were pulsatile devices, providing adequate support for the heart but hampered by size and limited durability. Nevertheless, the REMATCH trial demonstrated the superiority of these devices compared with optimal medical therapy in patients with end-stage heart failure, 1 year after implantation.[1] Two years after implantation, however, the benefit dissipated mostly because of device malfunction.

More recently, continuous-flow LVADs (cf-LVADs) have been introduced, based on rotary pump technology. These are much smaller, quieter, and durable, potentially expanding the duration of mechanical support.

There are different types of cf-LVADs, of which the HeartMate-II (Thoratec Corp., Pleasanton, CA, USA) and the HeartWare HVAD (HeartWare Inc., Framingham, MA, USA) are mostly used today. An important difference between these two devices is the site of implantation of the pump. The HeartMate-II is implanted subdiaphragmatically, whereas the HeartWare, due to its smaller size, can be implanted in the pericardial cavity.

The current devices demonstrate much better outcome and fewer complications than the pulsatile devices.[2-4] Therefore, pulsatile devices are no longer used and will not be dealt with in this article.

Short-term survival after cf-LVAD implantation now approximates that of heart transplantation, and the functional capacity of patients on cf-LVAD support is reasonable, with values of ~50% of the predicted VO_2-max 3 months after implantation.[5–8]

In The Netherlands, LVADs are mainly implanted as a bridge to transplantation. In the USA, there is also approval for the use of LVADs as an alternative to heart transplantation in selected patients: destination therapy.

As a consequence of the increase in the number of patients with end-stage heart failure, together with the decreasing availability of donor hearts, more and more patients are supported for an extended period of time. [7,9] LVAD implantation results in improved haemodynamics and quality of life, allowing discharge from hospital and resumption of a relatively normal life. Because of the many potential complications, however, the patients require extensive medical care and follow-up. These complications include both thrombosis and bleeding, infections, right ventricular (RV) failure, valvular pathology, and rhythm disturbances. [10]

In this article we first present a few short cases of patients with various types of complications. Then, we elaborate on the most frequently seen complications in patients on cf-LVAD support.

Cases

A patient with a severe thrombotic complication

Seven months after implantation of a HeartMate-II because of a cardiomyopathy, a 23-year- old patient was admitted with cardiogenic shock and had to be resuscitated because of malfunction of the pump. During an emergency operation, a new LVAD was implanted, complicated by severe right-sided heart failure for which temporary mechanical support of the right ventricle was also needed. Malfunction of the first LVAD proved to be due to total thrombotic occlusion of the pump. Although the international normalized ratio (INR) at admission was adequate, in hindsight, anticoagulation was not optimally regulated in the days before this event.

A patient with a cerebrovascular accident

A 44-year-old patient with severe proximal three-vessel disease, for which the percutaneous coronary intervention (PCI) procedures were performed, received a HeartMate-II LVAD because of progressive haemodynamic deterioration due to a large anterior infarction, after which he rapidly improved.

He was reluctant to be put on the waiting list for heart transplantation. Two years after LVAD implantation he suffered a large cerebral ischaemic event resulting in aphasia and right-sided hemiparesis. His anticoagulation level had been adequate. Now, almost 2 years later, his hemiparesis has improved and he is able to cycle and walk, but he is still severely aphatic and still refuses a heart transplantation.

A patient with a ventricular tachycardia

A 58-year-old male, with a 4-year history of dilating cardiomyopathy for which he was treated with medication and CRT-D (cardiac resynchronization therapy with a defibrillator device), suffered from progressive heart failure and sustained ventricular tachycardias (VTs) for which amiodarone was instituted. This resulted in a significant reduction of sustained-VTs. Next, a HeartMate-II LVAD was implanted. The patient quickly recovered and was discharged from hospital. Four months later he was admitted because of a slow VT 148/min, which in retrospect had existed already for 2 weeks and was very difficult to terminate by electrical cardioversion in combination with amiodarone i.v. After this episode, quinidine was added to the amiodarone, which successfully diminished the ventricular arrhythmias.

Fourteen months after LVAD implantation, frequent slow VTs recurred, especially during slight exercise and changes in body posture, accompanied by complaints of hypotension. The VTs were probably triggered by mechanical pressure on the LV lateral wall by the inflow canula. Antiarrhythmic medication was further intensified, but, due to the severity of the complaints, the patient became bedridden until transplantation, 2 months later.

A patient with asystole

A 29-year-old patient who had already been on a cf-LVAD for 1 year because of autoimmune myocarditis presented with progressive right-sided heart failure after an episode of gastroenteritis. Further analysis by electrocardiogram (ECG) and echocardiogram revealed complete absence of both electrical and mechanical activity of the heart. Hypothetically, there was a recurrence of the severe autoimmune myocarditis destroying the myocardium, for which he was treated with immunosuppressive drugs. Diuretics were cautiously dosed to avoid excessive fluid overload, but at the same time the central venous pressure was kept high enough to allow for passive pulmonary perfusion in the Fontan-like situation. After 2 months the patient underwent heart transplantation. Histological examination of the explanted heart confirmed severe myocarditis with almost complete destruction of all cardiomyocytes.

Left ventricular assist device complications

Thrombosis and bleeding

Implantation of cf-LVADs results in a complex balance between pro- and anticoagulants, and patients are considered susceptible to both bleeding and thrombo-embolic complications.

As a result of the interaction of blood with the assist device there is a hypercoagulant state, requiring anticoagulation and antiplatelet therapy. While on this regimen, in trials with HeartMate-II, the risk of LVAD thrombosis was very low, being 0.02–0.03 events per patient-year. The risk for ischaemic stroke was 0.06–0.13 events/patient-year. [2,3]

Initially, the perioperative use of heparin may cause heparin-induced thrombocytopenia type II in ~10% of the patients, leading to either bleeding, thrombosis, or both. [11]
Another effect seen in patients with cf-LVAD is acquired von Willebrand syndrome type 2 which may lead to an increased risk of bleeding.[12–15] This complication is often seen already shortly after implantation. [16–18] Overall, bleeding of the gastrointestinal tract as well as nosebleeds are seen most often. [19]

Severe blood loss warrants temporary interruption of anticoagulation, combined with endoscopic or surgical intervention to stop the bleeding. [20]

Furthermore, as a consequence of the use of anticoagulants and antiplatelet therapy, ischaemic stroke may convert haemorraghically.

As bleeding was one of the most frequent adverse events observed in several trials, reduction of the anticoagulation regimen is advised by many centres, using a target INR of 1.5–2.5 in patients without other indications for oral anticoagulation. [2–4, 21–24]

Another related problem is haemolysis, probably induced by the high shear stress generated by the assist device, and noted by the patient due to the accompanying dark urine. This is supported by lower haptoglobin and higher free haemoglobin and lactate dehydrogenase (LDH) values in the blood. [25,26] Most of the time haemolysis is a temporary problem which subsides spontaneously after a few days. The specific trigger for these episodes is often not clear, but it is important to look for pump dysfunction or inflow/outflow occlusions.

Infections

Infectious complications remain one of the major challenges for long-term LVAD support. Recently, Hannan *et al*. formulated standardized definitions for infections in patients treated by a VAD. [27] In this new working formulation on VAD infections, three groups are distinguished: VAD-specific, VAD-related, and non-VAD-related infections. VAD-specific infections include pump and/or cannula infections, pocket infections, and driveline infections. VAD-related infections comprise infective endocarditis, bloodstream infections, and mediastinitis, whereas cholecystitis, urinary tract infection, and lower respiratory tract infection are examples of non-VAD-related infections.

In a recent retrospective study by Schaffer *et al*., the incidence of different types of infections was evaluated during a median time of support of 191 days in 133 patients (86 on a cf-LVAD).

[28] In agreement with previous reports, patients who received a cf-LVAD had significantly fewer infectious complications compared with those with pulsatile flow devices.

Of the VAD-specific infections, pocket infections occurred in 10% of the patients throughout the course. Moreover, it is clear that the type of cf-LVAD influences the risk for pocket infections. The HeartWare is implanted in the pericardial cavity and therefore is not characterized by a real pocket and as such is not liable to infection. [29] On the other hand, the HeartMate-II requires a subdiaphragmatic pocket for implantation, which can potentially become infected.

Driveline infections occurred more often than pocket infections, with 0.37–0.58 events per year of LVAD support, mainly seen after longer duration of support. [3,28] As driveline infections are related to movement at the exit site, good fixation is mandatory and patients should be thoroughly instructed in the care of the percutaneous lead. Moreover, they should be aware of the signs of infection, so that treatment can be instituted early.

In the case of a driveline infection, both local treatment with cleansing and systemic treatment with antibiotics is indicated, preferably driven by bacterial cultures. It is important to realize that VAD-related infections including bloodstream infections may lead to an additional increased risk for other types of complications, as inflammation shifts the haemostatic mechanisms in favour of thrombosis. [30]

Device-related complications

Complications may arise in any component of the portable controller, the percutaneous driveline, the inflow and outflow cannulae, batteries, and the cf-LVAD itself. Some of these complications trigger visual and auditory alarms during malfunction, which have to be interpreted, however, in combination with the clinical picture to exclude false alarms.

The pump speed may be too high for the available volume in the left ventricle, resulting in obstruction of the inflow cannula; this is called a suction event. [10] The LVAD will automatically reduce the pump speed temporarily, but an important sequela of suction is that it may trigger ventricular arrhythmias. One of the shortcomings of the device is that the displayed pump flow is not a measured flow, but a calculation related to the pump power and pump speed. In this way, pump obstructions may not always trigger an alarm as pump power increases, resulting in a normal or even high displayed pump flow. In these cases, clinical assessment of the patient, sometimes combined with a diagnostic right-sided heart catheterization, should provide important evidence for such an event.

Failure of the controller or power source is rare. The part of the LVAD outside the body that is most susceptible to damage is the cable between the device and the power source. This is related to chronic kinking or twisting occurring as ~0.03 events per patient-year. [4,31–33] Stringent fixation of the cable to the skin reduces the incidence of this damage.

Later on in the course after implantation, one of the implanted components may become malpositioned. This relates especially to the inflow cannula as a result of an increase in body weight and may lead to partial occlusion of this cannula. This subsequently diminishes adequate unloading of the left ventricle, leading to arrhythmias and RV failure. Surgical repositioning is often required in these cases.

Haemodynamic consequences/alterations in physiology

Short-term effects

The underlying disease leading to severe heart failure is often diffuse and involves both the left and right ventricle. However, a cf-LVAD only supports the left ventricle.
In clinical practice this usually results in enough lowering of RV afterload to warrant adequate flow to the left ventricle. However, intra- and post-operatively right-sided heart failure may be an important problem. In patients with pre-existing RV dysfunction and/or increased pulmonary vascular resistance, RV failure is more common.
Right ventricular failure is partly related to a leftward shift of the interventricular septum as a result of unloading of the left ventricle by the LVAD, resulting in dilatation of the right ventricle and dyssynchronous contraction. This problem may increase when the pump speed of the LVAD is raised too quickly after insertion of the device. Therefore, it is advised to optimize LVAD settings using perioperative echocardiography.

The importance of RV failure is that there may not be enough flow to the LVAD with ensuing low pump flow, potentially resulting in multiorgan failure. In this way, RV failure contributes substantially to the morbidity and mortality after LVAD implantation. [34]

Acute right-sided heart failure is defined as the need for a RVAD, 14 or more days of inotropic support after implantation, and/or inotropic support starting >14 days after implantation. It occurs in ~20% of the patients, as examined in the HM-II BTT clinical trial. [34,35]

To prevent right-sided heart failure, evaluation of the RV function and pulmonary vascular resistance is an important aspect in patient selection for LVAD therapy. For this, echocardiography and right-heart catheterization is used.

Several studies have been performed to assess risk factors for right-sided heart failure, though their predictive value is somewhat limited. [34,36] Optimization of RV function pre-operatively is generally advised by adequate dosing of i.v. diuretics to lower the central venous pressure to

≤15 mmHg, in combination with inotropics and/or vasodilating drugs, to increase cardiac output.

After implantation of the LVAD, RV failure is prevented by inhaled nitric oxide and/or inotropes in combination with adequate preload of the RV and gradually adjusted LVAD flow. [10]

Long-term effects

Some patients may develop chronic right-sided heart failure after LVAD implantation, accompanied by progression of the tricuspid regurgitation. Therefore, some centres advocate tricuspid valve repair during implantation of an LVAD. Pharmacological treatment of chronic RV failure comprises titration of diuretics, maintaining a delicate balance between reduction of oedema and sufficient preload for the left ventricle.

Clinical evaluation of a patient with a cf-LVAD is hampered by the change in physiology. As a result of the continuous flow, the systolic pressure remains fairly constant, while the diastolic pressure increases. This results in reduced pulsatility as compared with the physiological situation.[37] Therefore, palpation of the pulse is more difficult and often not possible at all. Measurement of blood pressure often requires special devices.

As a result of the increase in diastolic pressure, patients on cf-LVAD support may gradually develop arterial hypertension. Because pump output of continuous flow devices is directly related to afterload, hypertension must be controlled aggressively as well in order to avoid cerebrovascular events. Mean arterial blood pressure should be kept between 70 and 80 mmHg, using angiotensin-converting enzyme inhibitors and/or beta-blockers. [10]

Valvular pathology

By unloading the left ventricle by a continuous flow device, opening of the aortic valve is diminished or abolished. This may lead to some degree of degeneration, with regurgitation and/or fusion of the leaflets. [38–40]

Initially, moderate or severe aortic regurgitation was considered a contraindication for LVAD implantation because this creates a circulatory loop of flow to the ventricle instead of the systemic circulation, diminishing the efficiency of support, and the ventricular unloading.[38] Sometimes, the aortic valve needs to be repaired during the implantation procedure, for which many surgical techniques have been described, including total closure of the aortic annulus by a patch, or total or partial suture of the valve leaflets. [41,42] Other options such as biological or mechanical valve prosthesis are considered less appropriate, as they may become a potential source of thrombo-embolism due to the diminished opening of the valve during full support.

Later after cf-LVAD implantation, a tendency to develop aortic valve regurgitation is noted.[39,40] This '*de novo*' aortic regurgitation is supposedly induced by the LVAD and considered to have deleterious effects on pump efficiency and systemic output. Accordingly, up to 80% of patients without pre-operative valve regurgitation showed rapid development of mild to moderate aortic regurgitation following their LVAD implantation. [43] However, in clinical practice, the amount of aortic regurgitation in patients is limited, and yet has not shown much progression over time.

The mechanism involved in this LVAD-induced aortic regurgitation is still unknown. It is thought that the increased aortic transvalvular pressure associated with a permanently closed aortic valve could increase stress on the aortic valve, causing it to become incompetent. Once present, in patients with a permanently closed aortic valve, aortic regurgitation manifests mostly as a continuous flow towards the left ventricle, during diastole as well as systole. Otherwise, if the aortic valve is allowed to open, aortic regurgitation manifests during diastole. Remarkably, in a small number of patients, the aortic regurgitation manifests explicitly in the systolic phase of the cardiac cycle,[44] and probably would disappear at the opening of the aortic valve. The mechanism involved in this LVAD-related systolic aortic regurgitation is as yet unknown, but may involve a different mechanism associated with the dynamics of the aortic annulus or valve dynamics during support as a result of local turbulences in the ascending aorta. Either way, an increase in

the pump speed may initially compensate for the loss of systemic circulation; however, when aortic regurgitation becomes more severe, valve repair may eventually be inevitable.

Rhythm and conduction disturbances

As a diminished LV function is associated with ventricular arrhythmias, many patients eligible for mechanical support by cf-LVAD already have an implantable defibrillator (ICD) as primary or secondary prevention.

It would seem logical that unloading of the left ventricle by a cf-LVAD, by reducing wall stress, would result in a decrease in ventricular arrhythmias. However, in clinical practice, ventricular arrhythmias may still be present after cf-LVAD implantation or even progress over time. In a prospective study by Oswald *et al*., in patients who also had an ICD, 34% of the patients had an appropriate device intervention for a ventricular arrhythmia during a mean follow-up of 1 year.[45] So, ventricular arrhythmias in patients with a cf-LVAD should be treated like those in other patients using antiarrhythmic drugs with or without implantation of an ICD, taking into account the potential negative inotropic effect of several antiarrhythmics on the RV function. In the case of recurrent ventricular arrhythmias, potential reversible causes, such as suction events and suboptimal positioning of the inflow cannula, should be sought and, if possible, treated. This is important because ventricular arrhythmias can lead to suboptimal circulatory support.

In cases where a patient presents with newly developed RF failure, an ECG may be helpful in identifying a VT or even ventricular fibrillation as the cause, because it is difficult to palpate a pulse and ventricular arrhythmias can be deceptively well tolerated. Some patients have mild or even absent symptoms, although others become bedridden by the effect on the haemodynamics and decline in clinical condition.

Rarely, as described in the case of a patient presenting with RV failure based on asystole, the underlying disease leads to destruction of the myocardium including the conduction system.

Also in that case, mechanical support provides a situation compatible with life and an ECG identifies the cause of RV failure.

Implications for the future

Today, patients with refractory end-stage heart failure can be successfully treated by an LVAD. Where no short-term major improvements are to be expected in medical therapy, the coming years will certainly bring many new devices and developments in the field of MCS. As a consequence, the therapeutic goal of the LVADs may show a wide spectrum from bridge to transplant, to bridge to recovery, bridge to bridge, bridge to decision, and ultimately destination therapy in the near future.[46] With this therapy we are entering a whole new era in the treatment of patients with advanced heart failure. We have to prepare and educate for the treatment of patients without a palpable pulse or easily measurable blood pressure and know how to diagnose and handle the specific complications inherent in this kind of therapy.

The care of these complex patients is centralized in hospitals with extensive knowledge of advanced heart failure, heart transplantation, and MCS. This requires a large team consisting of specialized cardiothoracic surgeons, cardiologists, VAD nurses, and technicians with 24/7 coverage. The growing number of patients on long-term VAD support, however, means that more and more patients might be referred to local hospitals in the case of intercurrent problems. Therefore, it is important for cardiologists and other healthcare professionals to have insight into the clinical problems related to this therapy. As shown in the cases above, clinical observation can be deceptive, as severe arrhythmias may be tolerated well for quite some time. When a patient presents to the cardiologist, conventional clinical evaluation including laboratory tests and ECG may already indicate specific complications. Furthermore, echocardiography is an important diagnostic tool to evaluate ventricular dimensions and function as well as valvular competence. Specific evaluation of right-sided pressures can be achieved by right-sided catheterization, which should also include measurement of the cardiac output to check for the accuracy of the displayed pump flow.

Although LVADs offer excellent survival and quality of life, this therapy remains extremely costly. Hopefully both the initial costs and readmissions for complications will decrease, resulting in costs per annum approaching those of haemodialysis.[46]

So, in conclusion, due to the growing number of patients with advanced heart failure, together with the shortage of suitable donor hearts and the evolving technological developments, MCS by LVADs will play an ever-increasing role in the near future. However, we have to learn more with regard to optimal patient selection and timing of implantation and the care of these patients in the long-run, especially in relation to the device-specific complications. The lack of need for immunosuppressive therapy might be a real advantage over heart transplantation and, as short-term prognosis after LVAD implantation is now already approximating that of heart transplantation, very soon LVAD implantation may be judged to be a worthy alternative to heart transplantation.

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CHAPTER 3

3

Outcome of mechanical circulatory support at the University Medical Centre Utrecht.

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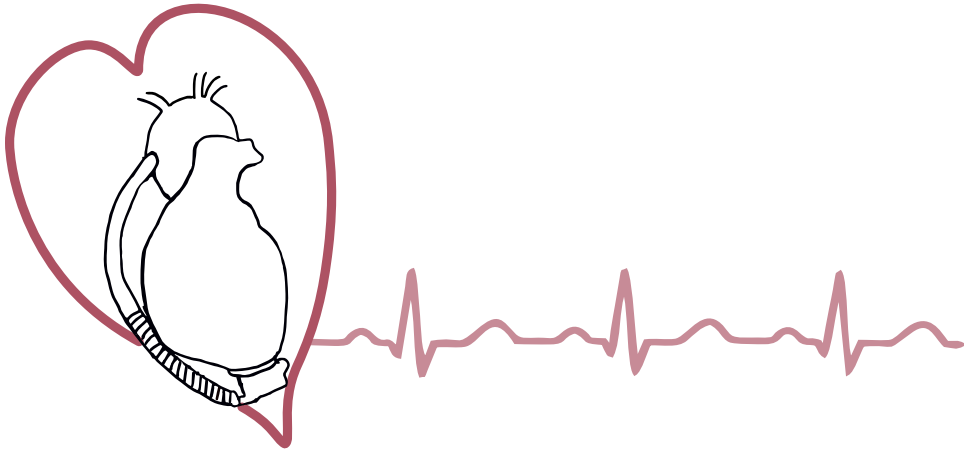


Abstract

Background The prevalence of heart failure (HF) is increasing substantially and, despite improvements in medical therapy, HF still carries a poor prognosis. Mechanical circulatory support (MCS) by a continuous-flow left ventricular assist device (cf-LVAD) improves survival and quality of life in selected patients. This holds especially for the short-term outcome, but experience regarding long-term outcome is growing as the waiting time for heart transplantation is increasing due to the shortage of donor hearts. Here we present our results from the University Medical Centre Utrecht.

Methods Data of all patients with a cf-LVAD implant between March 2006 and January 2018 were collected. The primary outcome was survival. Secondary outcomes included adverse events defined according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) definitions, described per patient year.

Results A total of 268 patients (69% male, mean age 50±13 years) received a cf-LVAD. After a median follow-up of 542 (interquartile range 205-1044) days, heart transplantation had been performed in 82 (31%) patients, the cf-LVAD had been explanted in 8 (3%) and 71 (26%) had died. Survival at 1, 3 and 5 years was 83%, 72% and 57%, respectively, with heart transplantation, cf-LVAD explantation or death as the end-point. Death was most often caused by neurological complications (31%) or infection (20%). Major bleeding occurred 0.51 times and stroke 0.15 times per patient year.

Conclusion Not only short-term results but also 5-year survival after cf-LVAD support demonstrate that MCS is a promising therapy as an extended bridge to heart transplantation. However, the incidence of several major complications still has to be addressed.

What's new?

- This is the first study investigating the long-term outcome of mechanical circulatory support (MCS) in The Netherlands.
- The 1-, 3- and 5-year survival on MCS was 83%, 72% and 57%, respectively. These results support its use as an extended bridge to heart transplantation, as necessitated by the shortage of donor hearts in our country.
- Survival in the period 2006-2012 did not differ from that in 2013-2017.
- Adverse events in terms of major bleeding and stroke occurred 0.51 and 0.15 times per patient year, respectively.

Background

The prevalence of heart failure (HF) is increasing substantially in Western countries. In the Netherlands already 1.3% of the total population (227,300 patients) suffer from HF. This percentage will certainly grow in the coming decades owing to the aging population and better treatment of heart disease in general [1,2].

Despite a substantial improvement in prognosis resulting from the use of beta blockers, ACE inhibitors/angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors , aldosterone antagonists, implantable cardioverter defibrillators and resynchronisation therapy, HF still carries a poor prognosis with a 1-year mortality of 26% in patients below the age of 75 years and 56% for those aged above 75 [3].

In patients with end-stage HF refractory to optimal medical therapy, heart transplantation is 'the gold standard' [4, 5]. However, because of the severe shortage of donor hearts, only few patients may benefit from this procedure. It is not to be expected that the number of donor hearts will increase substantially, so alternative treatment options need to be considered. Long-term mechanical circulatory support (MCS) by continuous-flow left ventricular assist devices (cf-LVADs) has demonstrated improved life expectancy and quality of life in these patients and may hold promise for the future as a realistic alternative to heart transplantation [6-10]. On the other

hand, management of patients on long-term cf-LVADs is still very laborious owing to well-known adverse events, such as infection, bleeding, thrombosis and device malfunction [11].

In our centre cf-LVADs have been implanted since 2006, initially the HeartMate II (HM-II, Abbott, St. Paul, MN, USA), from 2010 the HVAD (Medtronic, Framingham, MA, USA) and, since the end of 2015, the HeartMate 3 (HM 3, Abbott) [12].

Previously, only relatively short-term results of cf-LVAD implantations in the Netherlands have been published [13, 14]. As the duration of MCS is growing, partly caused by the shortage of donor hearts, this study was performed to provide insight into the long-term outcome in terms of survival and adverse events. Furthermore, we were interested whether the clinical situation of patients before cf-LVAD implantation has changed over the years with respect to Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile.

Methods

Study population

Data of all patients in whom the HM-II, HM 3 or the HVAD was implanted at the University Medical Centre Utrecht between March 2006 and January 2018 (end of study) were collected in a central database. The database included baseline clinical characteristics and all adverse events defined according to the INTERMACS definitions [15]. Adverse events were described for the total population. The institutional ethics board approved the study.

cf-LVAD implantation and anticoagulation

cf-LVADs were implanted via a median sternotomy using extracorporeal circulation on the beating heart. In the absence of bleeding, heparin was started within 48 h after surgery if drainage during 3 consecutive hours post-implant did not exceed 50 ml/h. A vitamin K antagonist was started after drain removal and heparin was stopped when the INR reached the lower limit of the therapeutic range as described for each cf-LVAD type below.

A thrombocyte aggregation inhibitor was started after 48 h, in general aspirin 100 mg/day. From March 2006 until August 2009, in HM-II patients warfarin was titrated to an INR of 2-2.5, 7 days after implantation. The INR range was reduced to 1.5-2.0 due to a substantial incidence of bleeding, as reported in the literature [16]. From December 2011 the INR range was increased again to 1.8-2.5 because of increased thrombo-embolic complications. For the HVAD and HM 3, target INR was 2.5-3.5 and 2.0-3.0, respectively, according to the manufacturer's advice.

Outcome

The primary outcome of the study was survival on cf-LVAD support until a pre-specified end-point, i.e. death, device explantation, heart transplantation or the end of the study. Secondary outcomes included all adverse events defined according to INTERMACS.

Definition of adverse events

All adverse events were defined according to the INTERMACS definitions. Major bleeding was defined as suspected internal or external bleeding, resulting in death, re-operation, hospitalisation and/or transfusion of red blood cells (within the first 7 days after the implantation requiring transfusion ≥ 4 units of packed red blood cells, or any transfusion beyond 7 days postoperatively). Neurological complications included a transient ischaemic attack and ischaemic/haemorrhagic strokes. Major infection was defined as a clinical infection accompanied by pain, fever, drainage and/or leukocytosis, treated by antimicrobial agents (non-prophylactic).

Major haemolysis included biochemical signs of haemolysis (free plasma haemoglobin >200 mg/l or lactate dehydrogenase >625 U/l), accompanied by at least one of the following symptoms: haemoglobinuria, anaemia, hyperbilirubinaemia and/or pump malfunction. Minor haemolysis comprised asymptomatic biochemical abnormalities.

Major device malfunction included pump thrombosis, high-urgency transplantation, pump replacement, pump explantation, breach of driveline or death. Minor device malfunction included inadequately functioning external components which required repair or replacement.

Right heart failure (RHF) was defined as symptoms and signs of persistent right ventricular

dysfunction [central venous pressure >18 mmHg with a cardiac index <2.3 l/min/m^2 in the absence of elevated left atrial/pulmonary capillary wedge pressure (> 18 mmHg), tamponade, ventricular arrhythmias or pneumothorax] requiring implantation of a right ventricular assist device, inhaled nitric oxide or inotropic therapy for > 1 week at any time after cf-LVAD implantation.

Statistical analysis

We used SAS software (SAS Institute, Cary, NC, USA) for statistical analysis. Kaplan-Meier survival estimation was applied for survival analysis of the entire cohort, and as specified by INTERMACS profile at baseline. Differences in survival were considered statistically significant if the log-rank test showed a *p*-value <0.05. Comparison of dichotomous variables between implantations from 2006 to 2012 and from 2013 to 2017 was performed by chi-square test or Fisher's exact test. Continuous variables were compared by the Mann-Whitney U test. In patients who died, the cause of death was retrospectively verified by one researcher and categorised according to the annual INTERMACS reports. Rate of complications was described per patient year.

Results

Baseline

From March 2006 until January 2018, 268 patients underwent cf-LVAD implantation [69% male, mean age 50 (±13) years]. In 59% of patients HM-II was implanted, 98.5% of devices as a bridge to transplantation, the remaining 1.5% as destination therapy. Follow-up was completed for all 268 patients for a median period of 542 [interquartile range (IQR): 205–1044] days, resulting in a total experience of 510 patient years (mainly determined by 380 patient years for HM-II).

The clinical profile before cf-LVAD implantation was most often INTERMACS 2 (42%) or 3 (27%), implying a progressive decline on inotropic support and stable but inotrope dependent, respectively. Furthermore, 19% of the patients were on temporary MCS prior to cf-LVAD implantation, mostly by central or peripheral extracorporeal life support, so were originally

INTERMACS 1 but stabilised on temporary MCS. Baseline characteristics for the total cohort and per device type are summarised in Table 1.

Table 1. Characteristics of the overall population of patients with a continuous-flow left ventricular assist device (cf-LVAD) as well as per type of cf-LVAD

	Total	**HM-II**	**HVAD**	**HM 3**
	N (%)	N (%)	N (%)	N (%)
Total	268 (100)	159 (59)	71 (27)	38 (14)
Age (years, mean ± SD)	50 ± 13	48 ± 13	54 ± 12	51 ± 14
Gender–male	185 (69)	109 (69)	52 (73)	24 (63)
Aetiology of cardiomyopathy				
Dilated	146 (54.5)	97 (61)	27 (38)	22 (57.9)
Hypertrophic	5 (1.9)	4 (2.5)	1 (1.4)	0 (0)
Ischaemic	69 (25.7)	35 (22)	27 (38)	7 (18.4)
Myocarditis	11 (4.1)	9 (5.7)	2 (2.8)	0 (0)
Peri-partum	3 (1.1)	2 (1.3)	1 (1.4)	0 (0)
Toxic	7 (2.6)	6 (3.8)	0 (0)	1 (2.6)
Congenital	1 (0.4)	1 (0.6)	0 (0)	0 (0)
Other	26 (9.7)	5 (3.1)	13 (18.3)	8 (21.1)
INTERMACS profile				
1 Critical cardiogenic shock without MCS	10 (3.7)	6 (3.8)	3 (4.2)	1 (2.6)
1* Critical cardiogenic shock with MCS	52 (19.4)	24 (15.1)	23 (32.4)	5 (13.2)

2 Progressive decline on inotropic support	112 (41.8)	75 (47.2)	20 (28.2)	17 (44.7)
3 Stable but inotrope dependent	71 (26.5)	43 (27)	18 (25.4)	10 (26.3)
4 Resting symptoms at home on oral therapy	22 (8.2)	10 (6.3)	7 (9.9)	5 (13.2)
6 Exertion limited	1 (0.4)	1 (0.6)	0 (0)	0 (0)

HM-II HeartMate II, HM 3 HeartMate 3, INTERMACS Interagency Registry for Mechanically Assisted Circulatory Support; MCS mechanical circulatory support

The INTERMACS profile prior to the cf-LVAD implantation has changed over time. Since 2013, patients in higher INTERMACS profiles received implants more frequently than in the first few years. Statistical analysis was performed to compare survival of patients receiving implants between 2006 and 2012 with those between 2013 and 2017. Patients in whom a cf-LVAD was implanted between 2006 and 2012 were significantly younger (p<0.001) and more frequently in INTERMACS profile 2 (p=0.008) than those receiving implants between 2013 and 2017 (Electronic Supplementary Material, Table 1).

Supplementary table 1.

Characteristics of the total population and per timeframe (2006-2012 and 2013-2017)

	Total	**2006-2012**	**2013-2017**	**p-value**
	N (%)	N (%)	N (%)	
Total	268 (100)	109 (41)	159 (59)	
Age (Mean ± SD)	50 (13)	47 (13)	53 (13)	< 0.001
Gender–male	185 (69)	77 (71)	108 (68)	0.636

Etiology of cardiomyopathy				
Dilated	146 (54.5)	59 (54)	90 (57)	0.689
Hypertrophic	5 (1.9)	31 (28)	39 (25)	0.474
Ischemic	69 (25.7)	2 (2)	3 (2)	0.672
Myocarditis	11 (4.1)	7 (6)	4 (3)	0.128
Peri-partum	3 (1.1)	3 (3)	0 (0)	0.066
Toxic	7 (2.6)	5 (5)	2 (1)	0.124
Congenital	1 (0.4)	0 (0)	1 (1)	1.000
Other	26 (9.7)	2 (2)	20 (13)	0.002
INTERMACS profile				
1 Critical cardiogenic shock without MCS	10 (3.7)	6 (6)	4 (3)	0.561
1* Critical cardiogenic shock with MCS	52 (19.4)	23 (21)	29 (18)	0.325
2 Progressive decline on inotropic support	112 (41.8)	56 (51)	56 (35)	0.008
3 Stable but inotrope dependent	71 (26.5)	22 (20)	49 (31)	0.053
4 Resting symptoms home on oral therapy	22 (8.2)	2 (2)	20 (13)	0.002
6 Exertion limited	1 (0.4)	0 (0)	1 (1)	1.000
Device				
HM-II	159 (59.3)	98 (90)	61 (38)	<0.001
HVAD	71 (26.5)	11 (10)	60 (38)	<0.001
HM 3	38 (14.2)	0 (0)	38 (24)	<0.001

MCS=mechanical circulatory support; HMII= HeartMate II; HM3= HeartMate 3.

Primary outcome

Seventy-one (26%) patients (44 HM-II, 24 HVAD and 3 HM3) died after cf-LVAD implantation after a median of 216 (IQR: 20-807) days. Death was most often caused by neurological complications (22 patients) or infections (14 patients) (Table 2).

Table 2. Cause of death, also divided into peri-operative and late mortality

Cause of death	**Number of patients (%)**	**<= 30 days postoperative**	**> 30 days postoperative**
Multi-organ failure	4 (5.6%)	2 (9.5%)	2 (4%)
RV failure	7 (9.9%)	1 (4.8%)	6 (12%)
Device malfunction	7 (9.9%)	0 (0%)	7 (14%)
Neurological	22 (31%)	4 (19%)	18 (36%)
Infection	14 (19.7%)	5 (23.8%)	9 (18%)
Other	17 (23.9%)	9 (42.9%)	8 (16%)
Total mortality	71 (100%)	21 (29.6%)	50 (70.4%)

RV failure therapy-refractory right ventricular failure leading to death

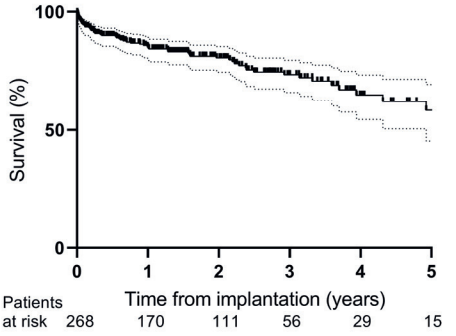
Device malfunction includes technical failure of the pump itself and pump thrombosis. Neurological causes of death include haemorrhagic or ischaemic stroke. Infection comprises systemic infections, non-responsive to the applied treatment. Other causes of death include multifactorial and unknown causes of death, for example in patients in whom no autopsy was performed

Device malfunction was the cause of death in 7 patients, pump thrombosis in 5 cases and technical failure in 2. Eighty-two (31%) patients underwent a heart transplantation, after a median duration of 674 (IQR: 394-1028) days on cf-LVAD-support. Explantation of the cf-LVAD was possible in 8 (3%) patients after a median period of 529 (IQR: 351-670) days. In these 8 patients, myocarditis and peri-partum cardiomyopathy were the most common aetiologies. In one patient with dilated cardiomyopathy in whom the cf-LVAD was initially explanted following

the recovery of left ventricular function, a new device had to be implanted after 144 days due to recurrent HF.

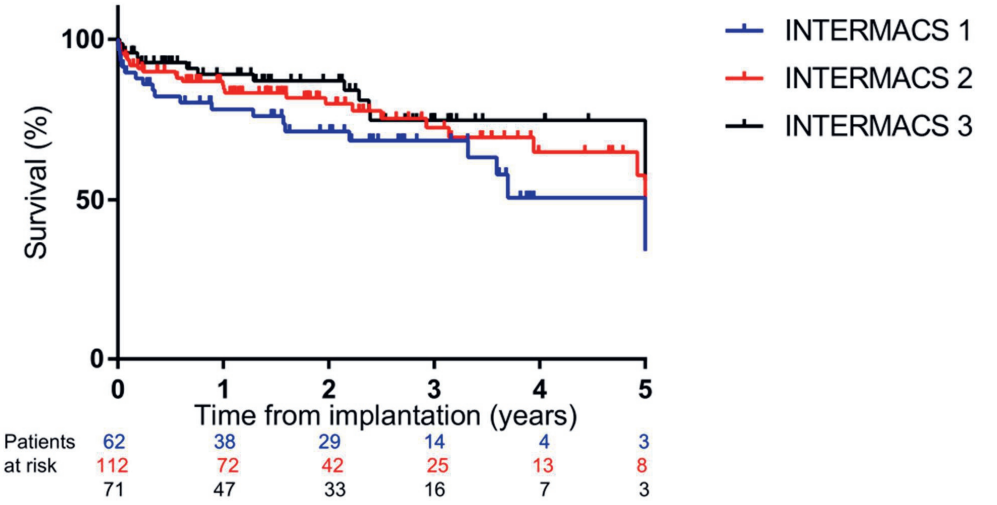
Survival after 1, 3 and 5 years was 83%, 72% and 57%, respectively (Fig. 1).

Figure 1 Kaplan Meier survival curve. *Dotted line* 95% confidence interval



There was a trend towards worse survival in patients with INTERMACS profile 1 in comparison to INTERMACS profile 2 or 3, though not significantly different (Fig. 2, p=0.24).

Figure 2. Kaplan Meier survival curve, stratified by INTERMACS profile



Neither did survival differ significantly between implants in 2006-2012 in comparison to implants in 2013-2017 (p=0.44). Because patients receiving implants between 2006 and 2012 were significantly younger and more frequently in INTERMACS 2 in comparison to 2013-2017, correlation between survival and these variables was analysed. Both age and INTERMACS profile 2 were not associated with mortality in this cohort [hazard ratio (HR) 0.98 (95% confidence interval, CI, 0.96-1.01), p=0.123 and HR 0.91 (95% CI 0.55-1.50), p=0.702, respectively].

Secondary outcomes

Beside localised infections not specifically related to the MCS, such as urinary tract infections and pneumonias, the three most commonly encountered adverse events were major bleeding, ventricular tachycardia and minor haemolysis with corresponding event rates of 0.51, 0.35 and 0.26 per patient year, respectively, as shown in Table 3.

Table 3 Complications (event rate per patient year) for the total cohort (*n*=268)

Clinical data		**Complications**	**Events**	**Event rate**
Patient years – total	510	Cardiac arrhythmia – SVT	129	0.25
Patient years – HM-II	380	Cardiac arrhythmia – VT	180	0.35
Patient years – HVAD	99	Device malfunction – major	50	0.1
Patient years – HM 3	30	Device malfunction - minor	83	0.16
30-day mortality (%)	7.8	Haemolysis – major	76	0.15
90-day mortality (%)	11.2	Haemolysis – minor	131	0.26
Hospitalisation (days, mean ±SD)	50±36	Hepatic dysfunction	68	0.13
Postoperative data		Hypertension	8	0.02
ICU stay (days, mean ±SD)	11±12	Major bleeding – ENT	15	0.03
Ventilator (days, mean ±SD)	5.5±9.7	Major bleeding – GI	72	0.14
Inotropics (days, mean ±SD	5.8±7.2	Major bleeding – other	174	0.34
		Major infection - exit site	82	0.16
		Major infection – pocket	15	0.03
		Major infection – sepsis	103	0.2
		Haemorrhagic stroke	25	0.05
		Ischaemic stroke	51	0.1
		Neurological dysfunction – TIA	30	0.06
		Pericardial fluid effusion	41	0.08
		Renal dysfunction – acute	50	0.1
		Renal dysfunction – chronic	4	0.01
		Respiratory failure	76	0.15
		Right heart failure	116	0.23

SVT supraventricular tachycardia, VT ventricular tachycardia, major bleeding – ENT major bleeding in the ear-nose-throat region, major bleeding – GI major gastro-intestinal bleeding, TIA transient ischaemic attack

Strokes (haemorrhagic and/or ischaemic) occurred 0.15 times per patient year. RHF occurred 0.23 times per patient year, most often (65%) within the first month after implantation. In 29

patients, RHF developed beyond 30 days after implantation, of whom 8 (28%) also suffered from early RHF.

Discussion

This analysis of 268 patients, resulting in clinical experience of 510 patient years, describes the 5-year outcome of cf-LVAD patients in a Dutch population, in whom the device was initially implanted as a bridge to transplantation. Survival at 1, 3 and 5 years was 83%, 72% and 57%, respectively, in this selected group of end-stage HF patients. This denotes its use as an extended bridge to heart transplantation, although still with considerable morbidity.

Interpretation of findings

Previously, only a few smaller single-centre studies were performed regarding long-term results of cf-LVAD support. Takeda et al. presented their results in 140 patients, showing a survival rate of 83%, 75% and 61% after 1, 3 and 5 years, respectively [17]. We now confirmed these results in a larger population. In the most recent annual INTERMACS report, survival rates at 1, 3 and 5 years were 83%, 63% and 46%, respectively [18]. With regard to the pre-operative condition, it is known that patients in INTERMACS profiles 1-3 have worse survival rates, especially INTERMACS profile 1 [15, 18]. Our study confirmed the relationship between the initial poor state and the trend towards worse survival of patients in INTERMACS profile 1, in comparison to INTERMACS profile 2 or 3, despite prior stabilisation on short-term MCS, although this was not statistically significant.

Generally, in MCS patient selection is of utmost importance for the outcome. Stewart et al. studied the use of the INTERMACS classification to identify ambulatory patients with advanced HF who may benefit from a cf-LVAD. In that study, patients in INTERMACS profile 4 had a higher mortality rate and needed MCS more often compared to patients in INTERMACS profile 5-7 [19]. In addition, the ROADMAP trial concluded that patients in INTERMACS 4 have better survival, functional capacity and improved quality of life when treated with a cf-LVAD in comparison to

optimal medical management. [20]
Furthermore, prediction of RHF is important, because this is related to worse survival. Recently, the EUROMACS-RHF risk score was developed, which can be used to predict early RHF. [21] Unfortunately, little is known about risk factors for late RHF, which needs further research in the setting of long-term MCS.

Technical improvements in the HM 3, using a magnetically levitating environment, revealed fewer haemocompatibility-related adverse events (e.g. pump thrombosis) in comparison to HM-II at 2 years, as concluded in the MOMENTUM 3 trial. However, the rate of bleeding events was comparable in both groups [22-24]. A personalised anticoagulation regimen could decrease the individual risk for bleeding and thrombosis. Furthermore, the risk for infection could be decreased by the use of cf-LVAD with smaller (or no) external components including the driveline, which is the most frequently encountered location for VAD-related infections.

Strengths and limitations
This is the largest single-centre study reporting on 5-year outcome in cf- LVAD patients in whom the device was implanted as a bridge to transplantation, reflecting the Dutch results of long-term MCS. Complications were recorded prospectively and systematically in a central database. Patient follow-up was complete in our own centre, minimising the risk of missing data.

However, the single-centre design may indicate that our results cannot be extrapolated directly to other centres. Furthermore, in nearly all patients the cf-LVAD was implanted as a bridge to transplantation. In general these patients appear to have a more favourable outcome in comparison to those receiving this device as destination therapy [15, 18, 25]. Finally it has to be realised that our results are mainly based on the HM-II LVAD, as almost 60 % of patients received this device.

Conclusion

In our experience, based on 268 cf-LVADs, the use of cf-LVADs for end-stage HF demonstrated a survival of 57% after 5 years, proving relatively good long-term results. These results support the use of such devices as an extended bridge to heart transplantation, necessitated by the shortage of donor hearts. However, several important adverse effects need to be tackled by further technical improvements. Also risk stratification before cf-LVAD implantation in individual patients is essential. Presently we are only on the verge of acquiring this knowledge [26, 27]. The assessment of a personal risk model could improve individualised therapy, for example the anticoagulation regimen, which is now generally the same for each type of device and for every patient.

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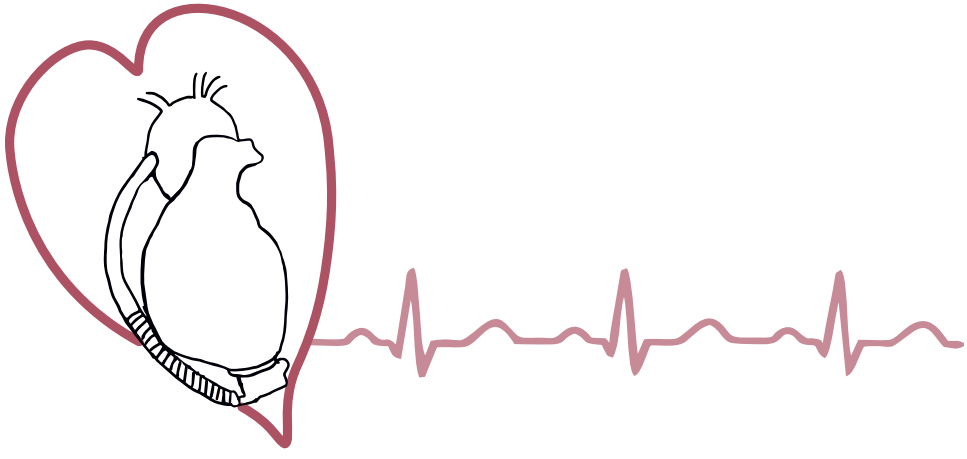
CHAPTER 4

4

Clinical factors associated with bleeding and thrombosis in long-term mechanical circulatory support, after the perioperative phase.

Submitted



Abstract

Bleeding and thrombosis are major factors related to outcome after mechanical circulatory support (MCS). This retrospective study including 270 MCS patients (147 HeartMate-II, 72 HVAD and 51 HeartMate 3) of the University Medical Centre Utrecht focused on the post-30 days hemorrhagic and thrombotic event rates. To quantify the contribution of patient and procedure characteristics, univariate and multivariable Cox proportional hazard analyses were performed. Kaplan-Meier analysis estimated event-free survival and characteristics of frequently affected patients were identified. 94 patients experienced bleeding (0.29 events per patient-year (EPPY)), 65 patients thrombosis (0.16 EPPY) and 35 had both during a median of 1.96 years. Multivariable analysis indicated the use of intravenous heparin (hazard ratio (HR) 6.2; 95% confidence interval (95% CI) 3.31 to 11.62), a history of hypertension (HR 2.3;95% CI 1.11-4.55), age (years, HR 1.03; 95% CI 1.00 to 1.05), and days on the intensive care unit (HR 1.03;95% CI 1.01 to 1.05) to be associated with bleeding. Older patients had bleedings earlier and more frequently during MCS. A history of atrial fibrillation increased the risk of thrombosis (HR 2.01;95% CI 1.13 to 3.42), while previous major cardiac surgery lowered the risk (HR 0.37;95% CI 0.16 to 0.85). The interaction between comorbidities and bleeding/thrombosis advocates personalized anticoagulation to reduce these events.

Introduction

In patients with advanced heart failure, mechanical circulatory support (MCS) with continuous flow left ventricular assist devices (cf-LVAD) results in improved survival rates of approximately 82% at 1 year and 72% at 2 years. [1,2] Nowadays, as a result of the shortage of donor hearts, improved technical aspects and implantation as destination therapy, patients are generally supported for a much longer period. Therefore adverse events, like infection, bleeding and neurologic dysfunction are becoming more and more important. [3]

Thrombotic events, like transient ischemic attack (TIA), ischemic stroke or pump thrombosis, may result from the interaction between the pump and blood. This has a huge impact on mortality as well as on clinical course and quality of life. [4]

Bleeding is the second most encountered adverse event, after infections, occurring in approximately 35% of patients, both in the early postoperative period and later in the course. [5] Apart from hemorrhagic stroke, most bleedings (gastro-intestinal or other localized bleedings) do not impact mortality, though lead to substantial morbidity. [6,7]

Bleedings are related to the use of anticoagulation with coumarins, in combination with platelet inhibitors and the interaction of the pump and the blood, so called hemocompatibility, resulting in the acquired von Willenbrand syndrome. [8] This combined anticoagulation and platelet dysfunction results in an increased risk of bleeding.[9]

The delicate balance between bleeding and thrombosis has already become apparent through the changes in anticoagulants over time. [10] In addition, the risk of adverse events, including bleeding and neurologic events, differ over time. [5] Risk factors identified for bleeding after discharge for MCS implantation with a HeartMate-II (HM-II) device, were an age >65 years, lower pre-operative hematocrit, ischemic etiology and female gender. Female gender has been identified as a risk factor in more studies, although this could not be confirmed in all. [9, 11-13] As a result of technical development, the HeartMate 3 (HM 3) has led to an improved survival free from disabling stroke and less pump replacements or reoperation for malfunction, like pump thrombosis and

driveline failure, in comparison to its predecessor the HM-II. [14] Also bleedings occurred less frequently in HM 3 versus HM-II, but still had an incidence of 0.61 events per patient year (EPPY). Therefore, a better understanding of the risk factors for hemorrhagic and thrombotic events is paramount for an improvement of long-term outcome.

The purpose of this study was to analyze the incidence of hemorrhagic and thrombotic events and its risk factors involved, after the perioperative period in MCS patients, thereby excluding surgery related adverse events, which probably have another etiology. This study was performed in patients, initially implanted as a bridge to transplantation (BTT), but eventually supported for an extended period as a result of the shortage of donor hearts.

Materials & Methods

Study sample and data collection

Data of all patients who received a cf-LVAD (HM-II, HM 3 (Abbott, St. Paul, MN, USA) or HVAD (Medtronic, Framingham, MA, USA)) at our center between 2006 and 2019 were collected in a central database. The database included pre-implant demographics, past medical history and clinical status as well as postoperative adverse events. Adverse events were defined according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) criteria. [15] After the peri-operative phase, anticoagulation consisted of a vitamin K antagonist with target International Normalized Ratio (INR) according to the manufacturer of the device, combined with Carbasalaatcalcium 100mg once daily. In case the vitamin K antagonist was switched to intravenous heparin in the week before a thrombotic/hemorrhagic event (for any reason, like elective coloscopy/any surgery, thrombotic/hemorrhagic event), it was registered.

Follow-up was completed for all patients from the time of implantation until death, heart transplantation, explantation of the cf-LVAD or end of study date (i.e. 31-12-2018).This study was approved by our local institutional review board.

End points

The primary end point of the study was the occurrence of either a thrombotic or hemorrhagic event during MCS, after the initial 30 days postoperatively, thereby excluding surgery-related complications. Secondary end points were ischemic stroke, confirmed pump thrombosis, hemorrhagic stroke, major gastro-intestinal hemorrhagic and major 'other' bleeding. The event rate of all end points is described in EPPY.

Definition of adverse events

Ischemic stroke was defined as a new, temporary or permanent, neurologic deficit ascertained by a standard neurological examination and included both TIA (defined as an acute event, resolving within 24 hours with no evidence of infarction) and ischemic stroke (defined as an acute event with infarction on an imaging study).

Pump thrombosis was defined as an obstructive thrombus within the device or its conduits with clinical symptoms of pump failure or requirement of thrombolytic or surgical intervention, confirmed by autopsy or pump analysis after replacement.

Major bleeding was defined as a suspected internal or external bleeding, resulting in death, re-operation, hospitalization and/or transfusion of red blood cells. Major bleeding was sub classified as gastro-intestinal bleeding or 'other' bleeding (including epistaxis and anemia).

Hemorrhagic stroke was defined as a neurologic deficit associated with matching abnormalities on an imaging study. Disability resulting from a stroke was defined by a modified Rankin score of 4 or 5. [14] A modified Rankin score of 4 means that patients are not able to attend to their own bodily needs without assistance and are unable to walk unassisted. If patients require nursing care and are bedridden, it is scored 5 on the modified Rankin scale. Additionally, mortality due to a stroke (modified Rankin score 6) was registered [16]

Statistical analysis

Kaplan-Meier analysis was performed using GraphPad Prism (version 8.3 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com) to analyze the freedom from event rate over time for different groups, with difference tested using a log-rank test. Age was

dichotomized at 60 years, as only 23 (9%) were aged > 65 years at the time of implantation. Cox proportional hazards models were used to determine the univariate association between the hazard of a thrombotic or hemorrhagic adverse event and each of the demographic, pre- and peri-operative covariates and the use of heparin intravenously prior to the event, stratified by the type of device. Subsequently, clinical variables (i.e. baseline parameters and the duration of ICU and hospitalization) together with the use of intravenous heparin in the week before the event, entered the multivariable Cox model. Laboratory results were excluded as these are unlikely related to events beyond the early postoperative period. Significant predictors, identified by the multivariable Cox analysis, are reported.

Furthermore, patient characteristics were compared between patients who suffered once from a bleeding or thrombotic event versus twice or more during MCS. Continuous variables were compared by non-parametric test and dichotomous variables by chisquare or Fisher's exact test, as appropriate. Statistical analyses were performed using SPSS version 25.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp).

Results

Baseline characteristics of patients are shown in Table 1.

Table 1. Baseline demographics (n=270)

Characteristics	
Gender – male, *n* (%)	180 (67)
Age (years), median (25th-75th percentile)	53.1 (43.9-60.9)
Type – HM-II, *n* (%)	147 (54.4)
Type – HVAD, *n* (%)	72 (26.7)
Type – HM3, *n* (%)	51 (18.9)
End point – death, *n* (%)	57 (21)
End point – heart transplantation, *n* (%)	92 (34)
End point – explantation, *n* (%)	8 (3)
End point – ongoing (at end study), *n* (%)	113 (42)
Body mass index, kg/m^2, median (25th-75th percentile)	23.6 (21.8-26.5)

Previous history	
Ischemic cardiomyopathy, *n* (%)	73 (27)
Hypertension, *n* (%)	25 (9.3)
Pulmonary hypertension, *n* (%)	103 (38.1)
TIA/stroke, *n* (%)	23 (8.5)
COPD, *n* (%)	13 (4.8)
Diabetes, *n* (%)	34 (12.6)
Atrial fibrillation, *n* (%)	67 (24.8)
Pacemaker/Internal Cardioverter Defibrillator, *n* (%)	152 (56.3)
Previous major cardiac surgery	49 (18.1)
CABG, *n* (%)	18 (6.7)
Valvular surgery, *n* (%)	16 (5.9)
Other, *n* (%)	18 (6.7)
Clinical parameters pre-operative	
INTERMACS 1 without temporary circulatory support, *n* (%)	7 (2.6)
INTERMACS 1 with temporary circulatory support, *n* (%)	49 (18.1)
INTERMACS 2, *n* (%)	112 (41.5)
INTERMACS 3, *n* (%)	79 (29.3)
INTERMACS 4-6, *n* (%)	23 (8.5)
Laboratory results pre-operative	
BUN (mg/dL), median (25th-75th percentile)	30 (22-40)
Kreatinin (mg/dL), median (25th-75th percentile)	1.28 (1.00-1.58)
eGFR < 60ml/min/m2, *n* (%)	122 (45.2)
Bilirubin total (mg/dL), median (25th-75th percentile)	1.29 (0.88-2.05)
AST (U/L), median (25th-75th percentile)	41 (26-67)
ALT (U/L), median (25th-75th percentile)	55 (26-116)
Hemoglobin (g/dL), median (25th-75th percentile)	12.2 ± 2.3
Hematocrit (%), median (25th-75th percentile)	38 (33-42)
Thromobocytes, 1000/mm^3	209 (30-619)
Details cf-LVAD implantation	
Aortic valve replacement concomittant, *n* (%)	5 (1.9)
Tricuspid or mitral valve intervention concomittant, *n* (%)	41 (15.2)

Other concomittant, *n* (%)	35 (13)
CPB time (min), median (25th-75th percentile)	113 (95-135)
Packed red cells (units), median (25th-75th percentile)	0 (0-2)
Hospitalization	
Intensive care unit stay (days), median (25th-75th percentile)	6 (4-12)
Total duration hospitalization (days), median (25th-75th percentile)	44 (33-58)
Time to censor	
Death (days), median (25th-75th percentile)	469 (164-1090)
Heart transplantation (days), median (25th-75th percentile)	777 (429-1286)
Explantation (days), median (25th-75th percentile)	529 (346-688)
Ongoing dd 31-12-2018 (days), median (25th-75th percentile)	809 (407-1338)

AST= aspartate aminotransferase; ALT= alanine aminotransferase; BUN=blood urea nitrogen; CABG = coronary artery bypass graft; cf-LVAD = continuous flow left ventricular assist device; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; eGFR = estimated glomerular filtration rate; INTERMACS= Interagency Registry for Mechanically Assisted Circulatory Support

294 patients received a cf-LVAD between 2006 and 2019 at our center, of which 24 were excluded from this study because of death (22 patients, 7.5%) or heart transplantation (2 patients, 0.7%) within 30 days after the implantation. So, in total, 270 patients (67% male, mean age 50.7±12.8 years) were included in this analysis with a median time of follow-up of 1.96 (interquartile range (IQR): 0.96-3.4) years, resulting in a total experience of 628 patient-years. Thrombotic events occurred in 65 patients (24%, 0.16 EPPY) after a median of 307 (IQR: 124-789) days, mostly ischemic stroke or TIA. Six of them had both an ischemic stroke/TIA and a pump thrombosis (Table 2).

Table 2. Incidence of bleeding and thrombotic events from 30 to 90 and 30 to 365 days after implantation

Event	Events (Event per patient-year) from 30-90 days postoperatively	Events (Events per patient-year) from 30-365 days postoperatively
Hemorrhagic events		
Major bleeding – GI	8 (0.19)	41 (0.18)
Major bleeding – other	19 (0.44)	32 (0.14)
Hemorrhagic stroke	2 (0.05)	13 (0.06)
Thrombotic events		
Ischemic stroke	5 (0.12)	21 (0.09)
TIA	4 (0.09)	17 (0.08)
Pump thrombosis	4 (0.09)	14 (0.06)

GI=gastro-intestinal; TIA=transient ischemic attack

Almost half (43%) of ischemic neurologic events were TIAs, 14% of ischemic strokes resulted in disability and 10% were fatal.

In total, 94 patients (35%) suffered a hemorrhagic event (0.29 EPPY), after a median LVAD support of 296 (IQR: 70-642) days. 27 patients had bleedings at different locations and most (39%) bleedings were gastro-intestinal. Hemorrhagic strokes had a high mortality rate, 16 of 23 patients (70%) died because of this adverse event.

Thirty-five patients (13%) had both a thrombotic and a hemorrhagic event during MCS, of which the majority (71%) was female and approximately one third had atrial fibrillation (AF) before cf-LVAD implantation. In these patients, the following adverse events occurred at least once: 26 (74%) patients had a TIA/ischemic stroke, 10 (29%) a hemorrhagic stroke, 14 (40%) a gastro-intestinal bleeding, 24 (69%) a major 'other' bleeding and 16 (46%) a pump thrombosis.

Intravenous heparin was prescribed when INR was below the target range. In 10% of cases, the postoperative course after cf-LVAD implantation did not tolerate the initiation of a vitamin K

antagonist and patients were still on intravenous heparin. In 7% of cases intravenous heparin was used to bridge the cessation of the vitamin K antagonist for a planned procedure. In the majority (83%) intravenous heparin was prescribed during an unplanned admission because of an adverse event.

Freedom from hemorrhage and thrombosis

To analyze the freedom from hemorrhage and thrombosis, Kaplan Meier analysis was performed, for all patients and per gender and age categories. Results are seen in Figure 1-3, showing no differences between males and females for both events (p=0.244 resp. p=0.281).

Figure 1. Freedom from thrombosis and bleeding for the total cohort

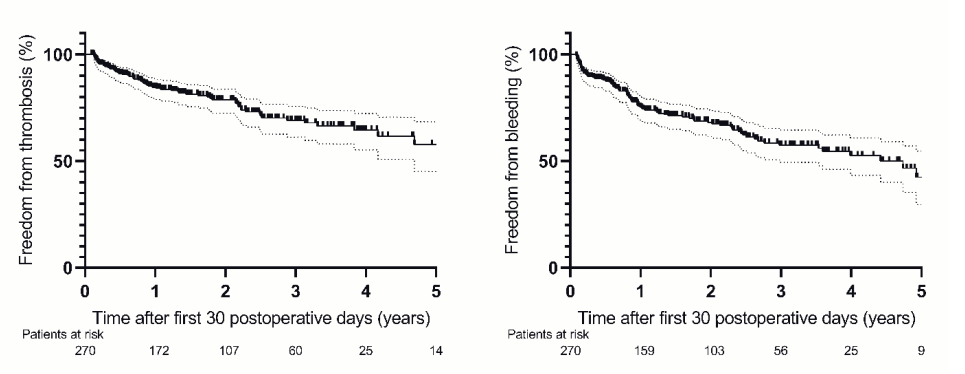


Figure 2. Freedom from thrombosis and bleeding, stratified by gender

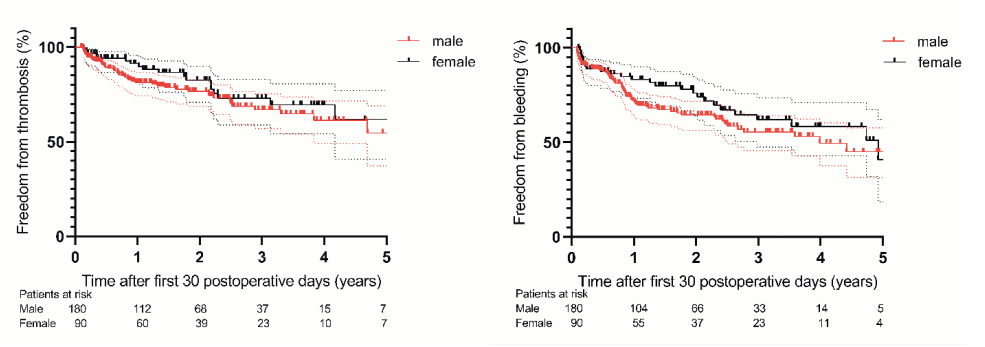
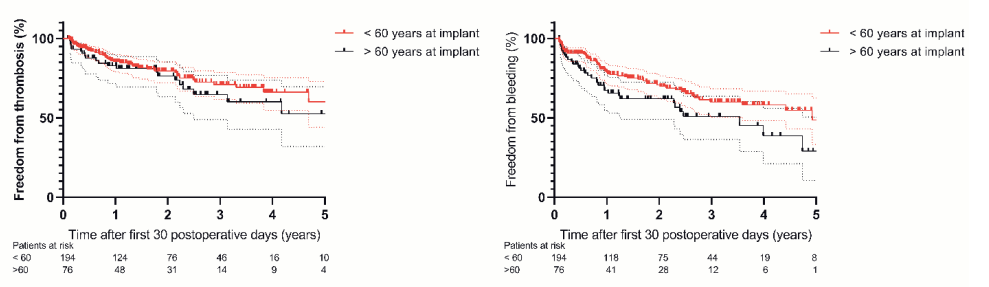


Figure 3. Freedom from thrombosis and bleeding, stratified by age (below/above 60 years at implant)



Hemorrhagic complications occurred earlier in patients aged above 60 years at implantation than in younger patients (p=0.036), but this did not apply to thrombotic events (p=0.451).

Risk factors associated with hemorrhagic and thrombotic events

Univariate correlates for thrombosis were the use of intravenous heparin prior to the event (HR 6.93;95% CI 2.97 to 16.15), a history of AF (HR 2.16;95% CI 1.28 to 3.63) and previous major cardiac surgery (HR 0.44;95% CI 0.20 to 0.96). Closer analysis revealed that some patients suspected of having a pump thrombosis were treated with intravenous heparin. Therefore, intravenous heparin was excluded from the multivariable analysis. Using standard multivariable analysis, a history of atrial fibrillation (HR 2.01; 95% CI 1.13 to 3.42) was a significant predictor of thrombosis while previous major cardiac surgery resulted in a lower risk of thrombosis (HR 0.37; 95% CI 0.16 to 0.85), as shown in Table 3.

Table 3. Univariate and multivariable risk factors for thrombotic events, stratified by type of device

	Univariate risk factors		**Significant multivariable risk factors**	
Variable	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
Gender – male	0.77 (0.45-1.33)	0.357		
Age, years	1.01 (0.99-1.03)	0.390		
Body mass index, kg/m^2	1.00 (0.95-1.05)	0.935		
Etiology – ischemic	0.77 (0.44-1.36)	0.375		
History of hypertension	0.91 (0.67-2.28)	0.841		
Previous stroke/TIA	0.74 (0.27-2.03)	0.551		
Diabetes mellitus	0.71 (0.32-1.55)	0.383		
History of AF	2.16 (1.28-3.63)	0.003	2.01 (1.13-3.42)	0.017
Previous major cardiac surgery	0.44 (0.20-0.96)	0.039	0.37 (0.16-0.85)	0.019
BUN, mg/dL	1.00 (0.99-1.01)	0.808		
Kreatinin, mg/dL	0.96 (0.62-1.50)	0.858		
Bilirubin, mg/dL	0.89 (0.66-1.20)	0.447		
AST, U/L	1.00 (0.999-1.001)	0.807		
ALT, U/L	1.00 (0.999-1.001)	0.759		
Pre-op temporary MCS	0.65 (0.33-1.29)	0.216		
ICU stay (days)	0.98 (0.96-1.01)	0.158		
Hospitalization (days)	1.00 (0.99-1.01)	0.497		
DAPT	0.74 (0.23-2.41)	0.622		
INR prior to event	0.91 (0.73-1.14)	0.415		
Intravenous heparin	6.93 (2.97-16.15)	<0.001		

AF= atrial fibrillation; AST= aspartate aminotransferase; ALT= alanine aminotransferase; BUN=blood urea nitrogen; DAPT= dual antiplatelet therapy; HR=hazard ratio; ICU=intensive care unit; INR=international Normalized Ratio; MCS=mechanical circulatory support; TIA = transient ischemic attack

Significant preoperative univariate factors related to bleeding were a history of AF (HR 1.95;95% CI 1.25 to 3.03), history of hypertension (HR 1.79;95% CI 0.95 to 3.4), age (years, HR 1.03;95% CI

1.01 to 1.05), and the blood urea nitrogen (BUN) and creatinine level (in mg/dL; HR 1.02;95% CI 1.01 to 1.03 and 1.88;95% CI 1.35 to 2.60, respectively), as shown in Table 3. Postoperative variables included the use of intravenous heparin prior to the event (HR 6.55;95% CI 3.78 to 11.36) and the duration of admission on the intensive care unit in days (ICU; HR 1.02;95% CI 1.01 to 1.04).

Standard multivariable Cox proportional hazard analysis revealed the use of intravenous heparin (HR 6.20;95% CI 3.31 to 11.62, p<0.001), a history of hypertension (HR 2.25;CI 1.11 to 4.55, p=0.024), an older age at implantation (in years, HR 1.03;CI 1.00 to 1.05, p=0.031) and longer duration on the ICU (in days, HR 1.03; CI 1.01 to 1.05, p=0.010) to be independent significant predictors of bleeding (Table 4).

Table 4. Univariate and significant multivariable risk factors for bleeding, stratified by type of device

	Univariate risk factors		**Significant multivariable risk factors**	
Variable	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
Gender – male	0.78 (0.50-1.22)	0.279		
Age, years	1.03 (1.01-1.05)	0.006	1.03 (1.00-1.05)	0.031
Body mass index, kg/m^2	1.02 (0.98-1.07)	0.256		
Etiology – ischemic	0.95 (0.61-1.51)	0.841		
History of hypertension	1.79 (0.95-3.4)	0.072	2.25 (1.11-4.55)	0.024
Previous stroke/TIA	0.66 (0.27-1.64)	0.370		
Diabetes mellitus	1.20 (0.68-2.13)	0.523		
History of AF	1.95 (1.25-3.03)	0.003		
Previous major cardiac surgery	1.03 (0.61-1.72)	0.925		
BUN, mg/dL	1.02 (1.01-1.03)	<0.001		
Kreatinin, mg/dL	1.88 (1.35-2.60)	<0.001		
Bilirubin, mg/dL	1.06 (0.85-1.33)	0.597		
AST, U/L	1.00 (0.996-1.00)	0.114		

ALT, U/L	1.00 (0.998-1.00)	0.179		
Pre-op temporary MCS	0.73 (0.42-1.26)	0.257		
ICU stay (days)	1.02 (1.01-1.04)	0.003	1.03 (1.01-1.05)	0.010
Hospitalization (days)	1.01 (1.00-1.01)	0.133		
DAPT	0.32 (0.04-2.29)	0.255		
INR prior to event	0.96 (0.86-1.06)	0.424		
Intravenous heparin	6.55 (3.78-11.36)	<0.001	6.20 (3.31-11.62)	<0.001

AF= atrial fibrillation; AST= aspartate aminotransferase; ALT= alanine aminotransferase; BUN=blood urea nitrogen; DAPT= dual antiplatelet therapy; HR=hazard ratio; ICU=intensive care unit; INR=international Normalized Ratio; MCS=mechanical circulatory support; TIA = transient ischemic attack

Multiple hemorrhagic and/or thrombotic events

In total, forty-three patients (16%) had two or more bleeding events during MCS. They were significantly older (mean age 57.2 ± 9.1 years) at the time of implantation in comparison to patients who experienced a bleeding once (n=51, mean age 50.8 ± 10.6 years, p=0.001) or no bleeding at all (n=176, mean age 49.1 ± 13.7 years, p<0.001). All other baseline, peri-operative and postoperative parameters did not differ between these groups, neither did the duration of support and the timing of the first event differ (Supplemental Table 1).

Supplementary table 1. Bleeding events, occurring once versus twice or more during MCS

Variable	**1 event (n=51)**	**2 or more events (n=43)**	**p-value**
Age, years (mean±SD)	50.8 ± 10.6	57.2 ± 9.1	0.001
Gender, male (*n* (%))	63 (64.7)	33 (76.7)	0.204
Body surface area, m^2 (mean±SD)	1.99 ± 0.28	1.92 ± 0.24	0.293
Body mass index, kg/m^2 (mean±SD)	25.8 ± 4.6	24.4 ± 4.2	0.184
MCS type – HVAD (*n* (%))	19 (37)	12 (28)	0.337
MCS type - HM-II (*n* (%))	26 (51)	27 (63)	0.250
MCS type - HM3(*n* (%))	6 (12)	4 (9)	0.75

INTERMACS 1 (*n* (%))	14 (27.5)	6 (14)	0.111
INTERMACS 2 (*n* (%))	22 (43)	18 (41.9)	0.901
INTERMACS 3 (*n* (%))	14 (27.5)	14 (32.5)	0.59
INTERMACS 4-6 (*n* (%))	1 (2)	5 (11.6)	0.09
Temporary support (*n* (%))	13 (25.5)	4 (9.3)	0.042
Etiology ischemic (*n* (%))	12 (23.5)	15 (34.9)	0.225
History of atrial fibrillation (*n* (%))	14 (27.5)	16 (37.2)	0.312
History of hypertension (*n* (%))	5 (9.8)	6 (14)	0.533
Previous stroke/TIA (*n* (%))	3 (5.9)	2 (4.7)	1.000
History of diabetes (*n* (%))	8 (15.7)	6 (14)	0.814
Pre-op ICD/pacemaker (*n* (%))	32 (62.7)	36 (83.7)	0.024
Blood urea nitrogen, mg/dL (mean±SD)	36.8 ± 24.8	40.5 ± 26.3	0.205
Kreatinin, mg/dL (mean±SD)	1.38 ± 0.62	1.57 ± 0.67	0.091
CPB time, min (mean±SD)	116 ± 28	132 ± 42	0.057
ICU stay, days (mean±SD)	12.4 ± 14.5	14.5 ± 16.9	0.701
Hospitalization, days (mean±SD)	53.8 ± 32.3	54.4 ± 35.6	0.773
Duration of MCS, days (mean±SD)	974 ± 707	1005 ± 735	0.951
N of days to event (mean±SD)	522 ± 562	360 ± 390	0.121
INR prior to event (mean±SD)	3.4 ± 2.3	2.93 ± 1.21	0.822

BUN=blood urea nitrogen; MCS=mechanical circulatory support; HM= HeartMate; INTERMACS= Interagency Registry for Mechanically Assisted Circulatory Support; TIA=transient ischemic attack; ICD=implantable cardioverter defibrillator; CPB=cardiopulmonary bypass time; ICU=intensive care unit; N=number; INR= International Normalized Ratio

Multiple thrombotic events occurred in 27 patients (10%). Only ischemic etiology of heart failure could be correlated to these events (Supplemental Table 2).

Supplementary table 2. Thrombotic events, occurring once versus twice or more during MCS

Variable	**1 event (n=38)**	**2 or more events (n=27)**	**p-value**
Age, years (mean±SD)	51 ± 12.6	53.4 ± 10.5	0.549
Gender, male (*n* (%))	28 (74)	18 (67)	0.54
Body surface area, m^2 (mean±SD)	1.96 ± 0.26	1.93 ± 0.22	0.822
Body mass index, kg/m^2 (mean±SD)	24.9 ± 5	24.3 ± 2.8	0.946
MCS type – HVAD (*n* (%))	11 (28.9)	8 (29.6)	0.952
MCS type - HM-II (*n* (%))	25 (65.8)	19 (70.4)	0.697
MCS type - HM3 (*n* (%))	2 (5.3)	0	0.507
INTERMACS 1 (*n* (%))	9 (23.7)	5 (18.5)	0.618
INTERMACS 2 (*n* (%))	14 (36.8)	13 (48.1)	0.362
INTERMACS 3 (*n* (%))	11 (28.9)	7 (25.9)	0.788
INTERMACS 4-6 (*n* (%))	4 (10.5)	2 (7.4)	1.000
Temporary support (*n* (%))	7 (18.4)	3 (11.1)	0.503
Etiology ischemic (*n* (%))	6 (15.8)	11 (40.7)	0.024
History of atrial fibrillation (*n* (%))	12 (31.6)	10 (37)	0.647
History of hypertension (*n* (%))	1 (2.6)	4 (14.8)	0.151
Previous stroke/TIA (*n* (%))	3 (7.9)	1 (3.7)	0.636
History of diabetes (*n* (%))	5 (13.2)	2 (7.4)	0.690
Pre-op ICD/pacemaker (*n* (%))	25 (65.8)	17 (63)	0.814
BUN, mg/dL (mean±SD)	34.6 ± 23.1	33.2 ± 19.2	0.984
Kreatinin, mg/dL (mean±SD)	1.33 ± 0.49	1.32 ± 0.56	0.531
CPB time, min (mean±SD)	109 ± 24	122 ± 32	0.113
ICU stay, days (mean±SD)	8.8 ± 8.3	9.3 ± 11.7	0.773
Hospitalization, days (mean±SD)	54 ± 32	54 ± 36	0.501
Duration of MCS, days (mean±SD)	1140 ± 651	1020 ± 549	0.506
N of days to event (mean±SD)	537 ± 535	416 ± 373	0.690
INR prior to event (mean±SD)	2.8 ± 1.8	2.5 ± 0.8	0.714

BUN=blood urea nitrogen; MCS=mechanical circulatory support; HM= Heart Mate; INTERMACS= Interagency Registry for Mechanically Assisted Circulatory Support; TIA=transient ischemic attack;

ICD=implantable cardioverter defibrillator; CPB=cardiopulmonary bypass time; ICU=intensive care unit; INR= International Normalized Ratio

Discussion

In this study, including 270 patients with a HM-II, HVAD or HM 3 cf-LVAD, risk factors for bleeding and thrombosis after the initial postoperative phase were identified, together with characteristics of patients who suffered multiple events.

We observed that any use of intravenous heparin (instead of a vitamin K antagonist) identifies a patient at risk of bleeding and atrial fibrillation doubles the risk of thrombosis.

This implies that intravenous heparin should be prescribed with caution. Moreover, regulation of the heparin ratio during intravenous heparin in this category of patients is challenging, which was also described in a review concerning anticoagulation in percutaneous MCS. [17] Because of these negative effects of intravenous heparin, other anticoagulants might be considered. So far however, no good alternatives have been identified. [18,19] It is therefore extra important to carefully assess whether bridging of anticoagulation is indicated at all, especially for planned interventions.

Furthermore, age has also proven to be an important risk factor for the occurrence of hemorrhagic events after the initial 30 days postoperatively. In addition, older patients are more likely to be affected earlier and more frequently during MCS. Our study confirms earlier results, [11, 20] but emphasizes the impact of age on the frequency and timing of bleeding. This might advocate the need for a different anticoagulation regimen in older patients.

In this study, we observed that previous major cardiac surgery results in a lower risk of thrombotic events after the first month after MCS implantation, which might seem counterintuitive. It has also been observed in an INTERMACS analysis on the occurrence of strokes after MCS, which showed a significant lower risk for early strokes in patients with a major cardiac operation in the history. [21] In contrast, the study by Frontera et al., revealed similar amount of previous cardiac surgery in patients with an early and late stroke versus patients

without stroke. [4] Our results suggest that cardiac surgery prior to MCS was probably performed in patients with less risk factors for thrombosis in general.
Furthermore, pre-operative atrial fibrillation in our study was independently associated with thrombotic events after cf-LVAD implantation. This was reported before in a study by Stulak et al. but could not be confirmed in a recent meta-analysis. [22,23] The different findings on the role of AF might be related to different outcome definitions and confounding variables including age. [23] In addition, anticoagulant regimens might differ between centers, have changed over time and per type of device. For example, in HM-II patients, target INR was temporarily decreased as a result of increased bleeding events, but later on increased again because of higher incidence of thrombosis. [24]

Presently, anticoagulation regimens are generally equal for all patients, with target INR based on the advice of the manufacturer of the devices combined with platelet inhibition. However, with this regimen, some patients suffer multiple and/or significant thrombotic and/or hemorrhagic events, while others are spared. Many mechanisms affecting the coagulable state in MCS have been identified. [8,9]
On individual basis, these mechanisms might differ and/or change over time, resulting in either an increased risk of bleeding or thrombosis. Ideally therefore, anticoagulant regimens after MCS, in future, should be individualized to the specific patient needs and the present findings may help to substantiate this.

Limitations
There are some inherent limitations to this study. First, results are based on a single center experience. Second, the majority of devices are second generation pumps. Approximately half of the devices were HM-II, the device that is associated with a higher incidence of strokes and bleeding events in comparison to the HM 3. However, incidence rates of the adverse events in our study approximate those of the HM 3, as reported in the MOMENTUM 3 trial and are therefore probably translatable to the presently used devices. [13] This relatively low incidence of adverse effects may be related to the characteristics of our study population, which consisted of

BTT patients. In contrast, approximately 60% of patients in the MOMENTUM 3 trial received MCS as destination therapy and were on average 6 years older at implantation.

Conclusions

The use of intravenous heparin identifies a patient at high risk of bleeding after MCS, resulting in a 6-fold increase after the perioperative period. Furthermore, age has shown to be an important factor in the prediction, frequency and timing of hemorrhagic events in MCS and preoperative atrial fibrillation is associated with thrombosis. These risk factors for bleeding and thrombosis may be used for individually targeted anticoagulant regimens to optimize anticoagulation aiming at a better long-term outcome.

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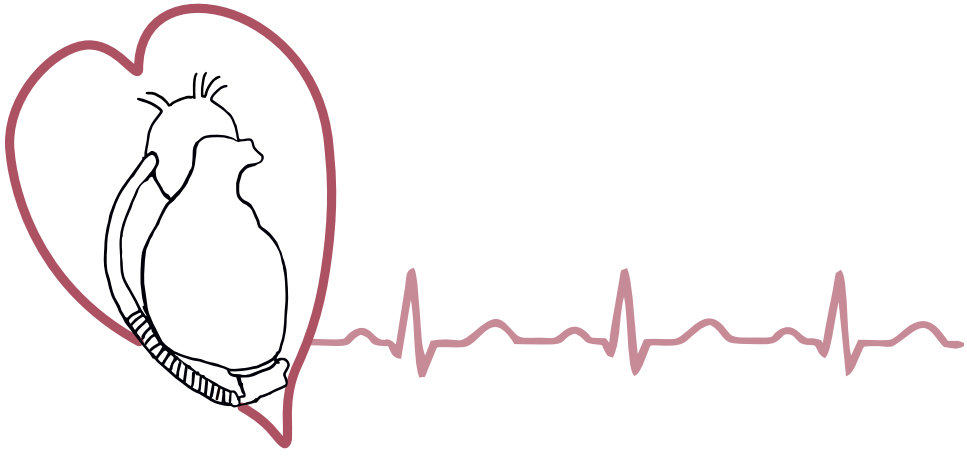
CHAPTER 5

A Data Mining-based Cross-Industry Process for Predicting Major Bleeding in Mechanical Circulatory Support.

Submitted



Abstract

Background Over a third of patients, treated with mechanical circulatory support (MCS) for end-stage heart failure, experience major bleeding. Currently, the prediction of a major bleeding in the near future is difficult because of many contributing factors.

Objectives Predictive analytics using data mining could help calculating the risk of bleeding, however its application is generally reserved for experienced researchers on this subject. We propose an easy applicable data mining tool to predict major bleeding in MCS patients.

Methods All data of electronic health records of MCS patients in the University Medical Centre Utrecht were included. Based on the cross-industry standard process for data mining (CRISP-DM) methodology, an application named Auto-Crisp was developed. Auto-Crisp was used to evaluate the predictive models for a major bleeding in the next 3, 7 and 30 days after the first 30 days postoperatively following MCS implantation. The performance of the predictive models are investigated by the area under the curve (AUC) evaluation measure.

Results In 25.6% of 273 patients, a total of 142 major bleedings occurred during a median follow-up period of 542 (IQR 205–1044) days. The best predictive models assessed by Auto-Crisp had AUC values of 0.792, 0.788, and 0.776 for bleedings in the next 3, 7, and 30 days, respectively.

Conclusion The Auto-Crisp-based predictive model created in this study had an acceptable performance to predict major bleeding in MCS patients in the near future. However, further validation of the application is needed to evaluate Auto-Crisp in other research projects.

Graphical abstract

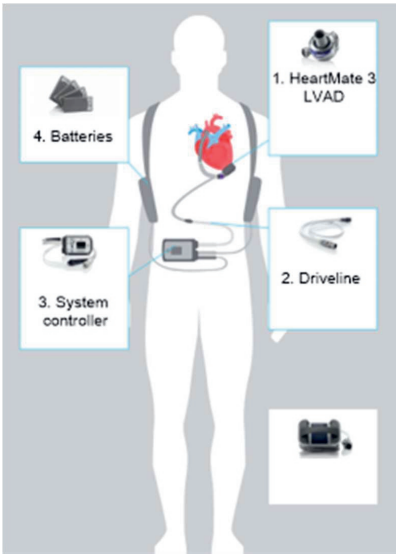
An easy applicable data mining tool to predict major bleeding in patients treated with mechanical circulatory support (MCS).

Over a third of MCS patients experience major bleeding. Currently, the prediction of major bleeding in the near future is difficult because of many contributing factors. We developed an easy appicable tool, based on the cross-industry standard process for data mining (CRISP-DM), named Auto-Crisp. Auto-Crisp was used to evaluate the predictive models for a major bleeding in the next 3, 7 and 30 days after the first 30 days postoperatively following MCS implantation, investigated by the area under the curve (AUC) evaluation measure.

Introduction

Patients with refractory advanced (end-stage) heart failure may be treated with mechanical circulatory support (MCS) by a continuous-flow left ventricular assist device (cf-LVAD), which is inserted into the heart and takes over left ventricular heart function (Figure 1).

Figure 1. Continuous-flow left ventricular assist device (cf-LVAD), including all parts of the device



1. *HeartMate 3 (HM 3) LVAD*
2. *Driveline, connecting the HM 3 to the system controller*
3. *System controller, which senses the function of the LVAD and controls the power*
4. *Batteries*

These devices are implanted as a bridge to heart transplantation, bridge to candidacy (for example to evaluate the reversibility of organ failure) or destination therapy (if heart transplantation is contra-indicated). [1-4]

As a result of the shortage of donor hearts and the use as destination therapy, the duration of

MCS has increased in the recent years. The use of cf-LVADs has potential disadvantages in terms of adverse events, affecting a substantial percentage of the patients, both in short-term and long-term support. For example, bleeding occurs in 35% of the patients. [4] Bleedings are most frequently located in the gastro-intestinal tract, often requiring blood transfusion and readmission. [5-7] Also bleedings located elsewhere, for example intracranial hemorrhage, result in significant morbidity and an increased risk of mortality. [8,9] The occurrence of bleeding is associated with the use of anticoagulation, which is required to prevent thrombosis, provoked by the foreign material. Anticoagulation consists of a vitamin K antagonist, mostly in combination with a thrombocyte aggregation inhibitor. Furthermore, after cf-LVAD implantation, bleeding risk is increased because the majority of patients have an acquired coagulopathy disorder, caused by several factors including platelet dysfunction and an impaired function of the von Willenbrand factor.[10,11]

Current knowledge on the risk of bleeding during MCS is based on baseline and perioperative data using 'conventional' regression methods. [12,13] Pre-operative risk factors for bleeding after discharge include an age above 65 years old, female gender, ischemic etiology and the lowest quartile hematocrit (<31%). [14]

However, the risk of bleeding differs over time. [15] In addition, it has been observed that some patients require recurrent hospitalization for gastro-intestinal bleedings, while others are admitted once. [16] Therefore, an accurate prediction of a bleeding in the short term at any moment during MCS is required to optimize the outcome. Identification of a patient 'at risk' could result in closer monitoring and/or change in the anticoagulation regimen to limit or even prevent the actual occurrence of bleeding. At present, no predictive models are available to accompany this. As the risk of a bleeding changes over time, we may overlook a (number of) risk factor(s). The addition of data collected during follow-up might improve the predictive performance. Furthermore, using data mining can contribute in the identification of risk factors. [17] Cross-industry standard process for data mining (CRISP-DM) is a standard approach which will help to translate the research question into data mining tasks, to select appropriate data transformations and data mining techniques, and to provide means for evaluating the effectiveness of the results. [18,19] However, for most healthcare professionals, this method remains

a major challenge due to limited knowledge on data mining. We propose a data mining-based approach according the CRISP-DM methodology to predict a future major bleeding in MCS patients, excluding the initial postoperative phase.

Methods

In this section, the study data is introduced and the methodology of this study is described in summary. In the appendix, detailed information and background information on the application, named Auto-Crisp, is described.

Study data

Data of all patients who received a cf-LVAD at the University Medical Centre of Utrecht between 2006 and 2018 were collected from their electronic health records (EHRs). These comprise laboratory results, medication and baseline data registered in the local EHRs and results of all International Normalized Ratio (INR) values from the anticoagulation clinics during MCS (the latter was available in 77 patients). The ethics committee of the University Medical Centre Utrecht approved this study.

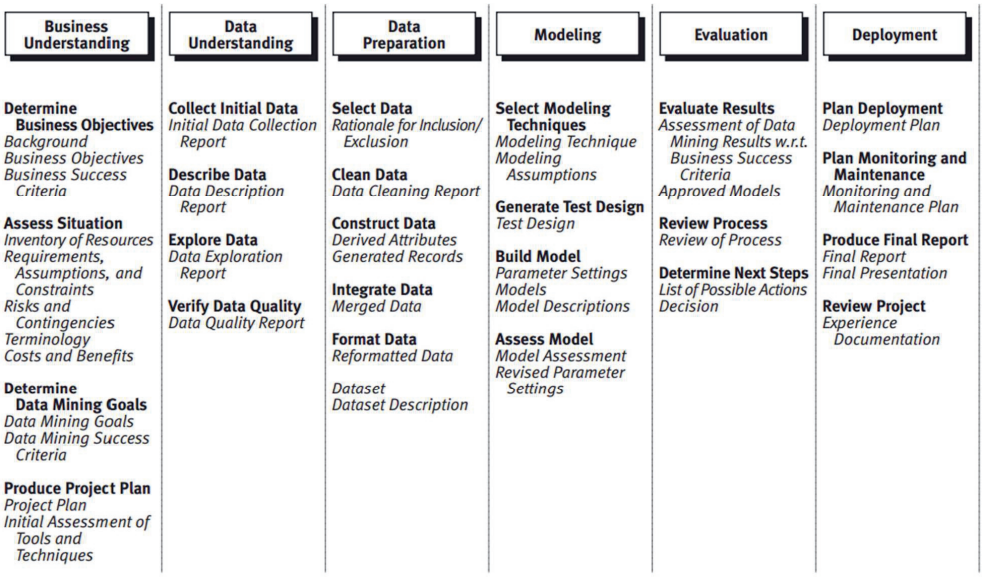
EHRs contain heterogeneous data originating from multiple sources. To address this, we distinguished medical data into the following types: time point data, time interval data, baseline data and event data. Time point data contain data about a dynamic variable at one time point (e.g. INR), whereas time interval data contain data about a time period of a dynamic variable (e.g. medicine X from March to June). Baseline data include static variables without a temporal aspect (e.g. sex). Lastly, event data are time point data which contain the events to be predicted, also known as class labels (e.g. mortality or, in this study, major bleeding). The end point of the study was the occurrence of a major bleeding, that occurred beyond 30 days after the implantation of the cf-LVAD, thereby excluding surgery-related bleedings, as these probably have another etiology. Major bleeding was defined according to the definition of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS): an episode of

suspected internal or external bleeding that results in death, re-operation, hospitalization and/or transfusion of red blood cells. [1]

Auto-Crisp

CRISP-DM is a widely used open standard process model with which a data mining project is built. As shown in Figure 2, CRISP-DM consists of 6 steps: business understanding, data understanding, data preparation, modeling, evaluation, and deployment.

Figure 2. CRISP-DM methodology



CRISP-DM consists of 6 steps, which are shown as column heading: business understanding, data understanding, data preparation, modeling, evaluation, and deployment. In each column, the tasks related to the steps are described.

In business understanding, the project plan is produced, following the objective of the study, inventory of the resources and the determination of the data mining goals. Data understanding is the step in which initial data are collected, a description report is provided, data are explored and the quality of the data is verified. Then, data are prepared by the selection of data, data cleaning, construction, integration and formatting of the data. In the modeling step, the modeling techniques are selected, a test design is generated and the model is built. Thereafter, the models are evaluated and the process is reviewed. The deployment step comprises the production of the final report and monitoring and maintenance of the plan.

Auto-Crisp guides users through these steps of the data mining project, providing sensible defaults for each step and automating most processes that have no or little influence. However it still provides some design choices. To enable the use of this application for other researchers, the complete source code is available at https://github.com/Susannefelix/AutoCrisp.

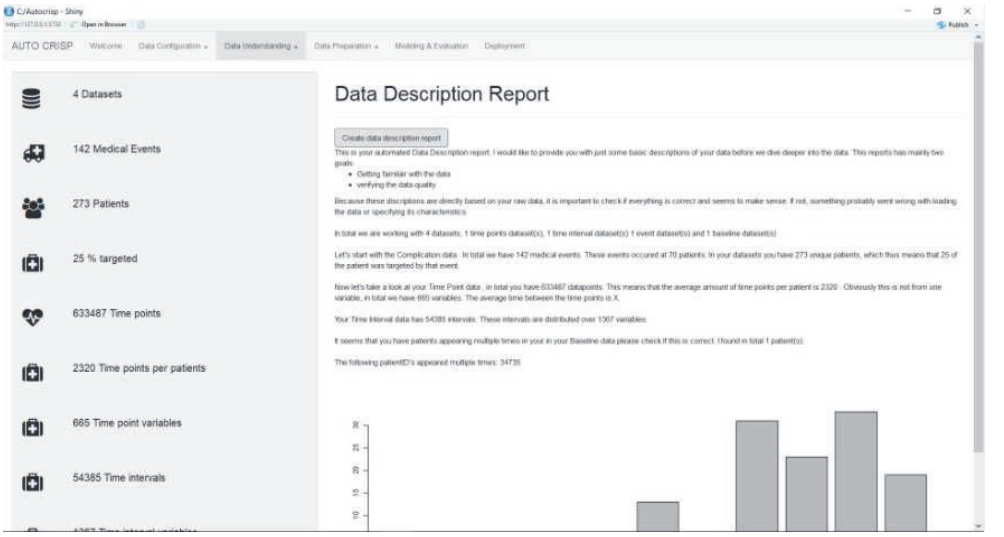
After the modeling step, the output of the built model is depicted in a confusion matrix out of which the sensitivity and specificity, the positive and the negative predictive values are visualized. Furthermore, a receiver operating characteristic (ROC)-curve is used with corresponding area under the curve (AUC) to assess the performance of the model. We report on the best functioning model in different settings, i.e. prediction of bleeding in several time frames, identified from any moment during MCS after the first 30 postoperative days. For the occurrence of a major bleeding at t_i and within 3, 7 and 30 days, an AUC of 0.5-0.6 was interpreted as a poor diagnostic value, 0.6-0.7 as fair, 0.7-0.8 as acceptable, 0.8-0.9 as excellent and 0.9-1 as outstanding. [30]

Results

Between 2006 and 2018, 273 patients (69% male) received a cf-LVAD. Follow-up was completed for all patients for a median period of 542 (IQR: 205 - 1044) days. In total 633,487 time points were included, on average 2,320 laboratory values per patient. The time interval dataset

consisted of 54,385 time intervals and thus an average of 1,367 medications were registered per patient. During a total follow-up period of 510 patient years (ie. the duration of support in years per patient, multiplied by the number of patients), 142 bleedings beyond 30 days after cf-LVAD implantation occurred. Major bleeding affected 25.6% of the patients, of which 76% were male with a mean age of 52.3 years old. In Auto-Crisp, an overview of these descriptive data is shown (Figure 3).

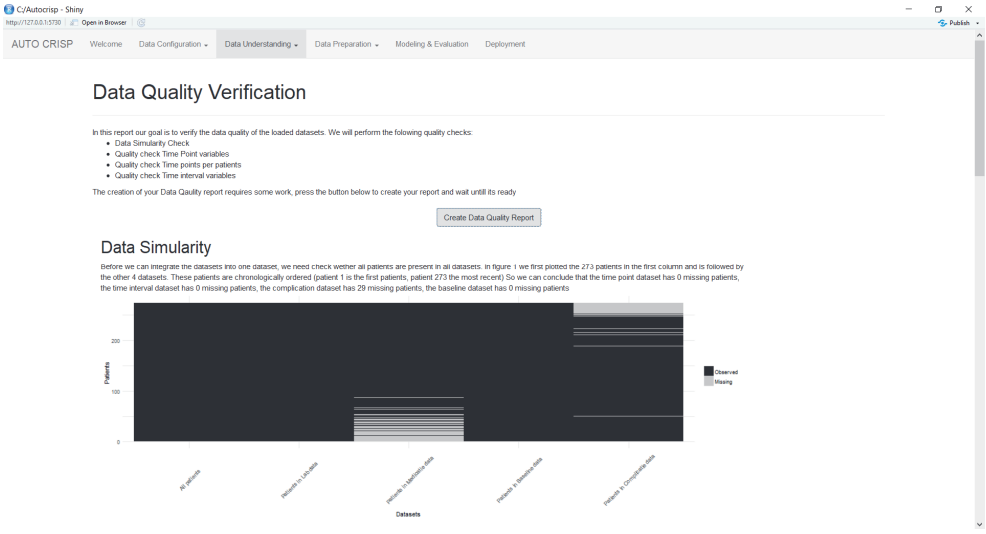
Figure 3. Data description report



The data description report reveals an overview of the descriptive statistics from the different datasets

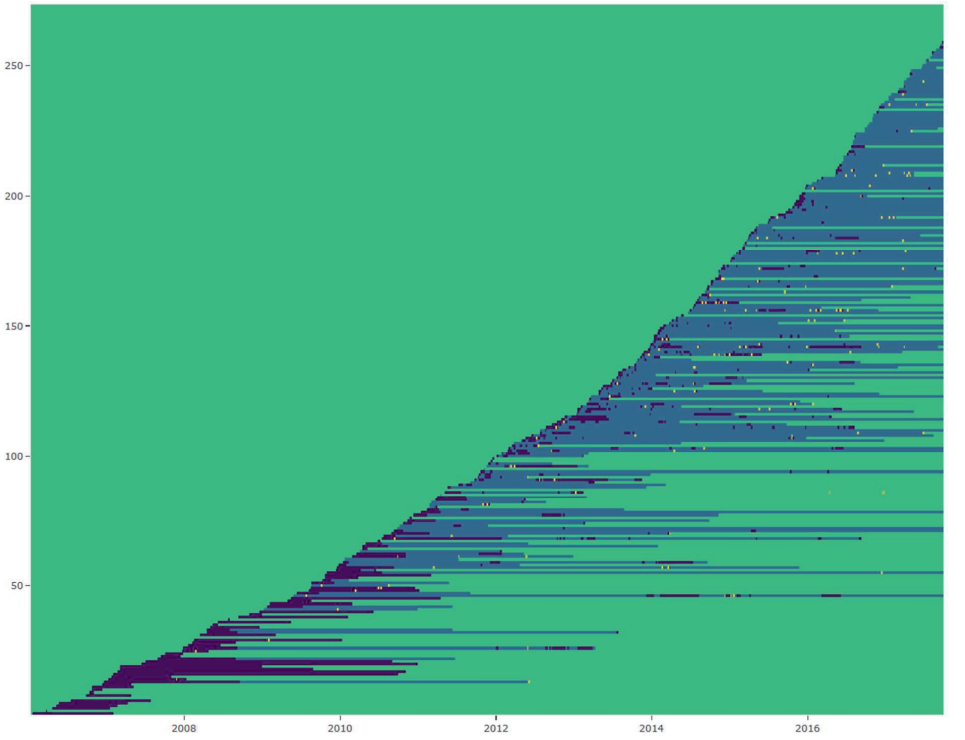
Insight is given concerning the quality of the data, including the amount of missing data and, in this study, an illustrative overview of the duration of MCS together with the duration of anticoagulation and the occurrence of a bleeding (Figure 4 and 5).

Figure 4. Data quality verification



The data quality verification tab reveals information on the completeness of the datasets, for example if all patients are represented in each dataset

Figure 5. The use of oral anticoagulation and events



A graphical overview to visualize the use of anticoagulation during the study period and the moment(s) of a bleeding event. Purple: inclusion in cohort, no oral anticoagulation. Blue: inclusion in cohort, use of oral anticoagulation. Yellow: bleeding complication.

The hemoglobin level was lower in the patients with a bleeding in comparison to the total population, while the creatinin and the INR was higher in patients with a bleeding, though not significantly different (P = 0.36 and P = 0.25 respectively). The level of lactate dehydrogenase (LD) showed a peak approximately two weeks prior to the bleeding event, though had a broad standard deviation, as a result of very high LD-levels in a few patients.

Data preparation

A plot of the time interval data set (medication) showed an increase in the mean amount of medication prescribed from 2011. The mean number of medications per patient prior to this period was too low to represent the truth, as in general the mean number of medication has not changed over the years. The low number of medication prior to 2011 was probably related to the limited digital medication prescription. Therefore, these medication files were excluded.

We cleaned the data by excluding the data of seven days following the bleeding event, because these are not relevant in predicting the event and result in noise of the model. In Table 1, the AUC-values of the model are shown, both with and without cleaning the data as described.

Table 1. AUC-values of the model in predicting a major bleeding >30 days after cf-LVAD implantation, with and without the data 7 days after the bleeding event

Setting	Full window	Cleaned dataset
1: 0	.799	.824
2: 1-3	.779	.792
3: 1-7	.779	.788
4: 1-30	.769	.776

Feature extraction and selection

In Auto-Crisp different feature extraction methods can be selected (see the Appendix for a detailed explanation). In this study, the Summary technique achieved the highest AUC in most settings, where for example the frequent sequential pattern mining method did not improve the accuracy of the model despite its complex approach (Table 2). [27]

Table 2. Feature extraction

Setting	Last value	Statistics	Summary	TVA	PatternMining
1: 0	.824	.817	.830	.820	.820
2: 1-3	.792	.785	.780	.787	.828
3: 1-7	.788	.799	.796	.777	.794
4: 1-30	.776	.803	.796	.780	.721
Baseline	.594	.582	.664	.595	Not applicable

TVA: trend-based approximation

For feature selection, both boruta and recursive feature elimination (RFE) did not improve the AUC, while both were very time consuming. [28] Therefore, we did not exclude any features.

Modeling

Despite unbalanced datasets in this study, where only 2% of the data were from patients with a major bleeding, none of the data sampling techniques revealed improvement of the AUC-level of the model. The random forest classifier provided the best performance in comparison to logistic regression and decision tree (Table 3).

Table 3. Classifier algorithm

Setting	random forest	naïve Bayes	decision tree	logistic regression	support vector machine
1: 0	.824	.690	.501	.793	.772
2: 1-3	.792	.773	.494	.787	.701
3: 1-7	.788	.773	.524	.754	.657
4: 1-30	.776	.770	.490	.705	.708

The overall accuracy of the best predictive model of a major bleeding in the next 3, 7 and 30 days correspond to an AUC-level of 0.792, 0.788 and 0.776, respectively.

Discussion

In MCS patients, the substantial amount of adverse events are still the Achilles heel of this therapy. Amongst the adverse events, bleeding has been shown to be related to both the use of anticoagulation and acquired coagulopathies in these patients. However, the prediction of a major bleeding over time is difficult. In this study, including all available data out of the EHR, we evaluated predictive factors for a major bleeding after the first postoperative phase. By implementing data mining, based on the CRISP-DM methodology into a semi-automated tool called Auto-Crisp, we demonstrated acceptable prediction of a major bleeding in a MCS patient from any moment following the first thirty days after implantation. The models developed were applicable for risk assessment in several time frames, with a maximum of thirty days. [30] This is a promising tool with a relatively easy applicability, even for clinicians and healthcare professionals. Auto-Crisp contains automated steps in the data mining process, though does reveal insight into the quality of the data at different steps in an intuitive manner. As well, as a result of the automated steps, it is less time consuming. Further validation of the application is needed to evaluate Auto-Crisp in other research projects.

The prediction of a bleeding in the near future could result in a change of the anticoagulation regimen. For example, target INR could be decreased or platelet inhibition interrupted, weighing the risk of thrombosis on the contrary. Recently, an analysis was performed on the safety of a lower target INR range in patients implanted with the newest device (HeartMate 3, HM 3), as the HM 3 had already demonstrated to have less thrombo-embolic complications in comparison with its predecessor, the HM II. [31] Using a lower target INR did not result in thrombo-embolic events over 6 months in a small number of HM 3 patients (n=15), major bleeding in only 1 patient. [32] In addition, a lower dose of Aspirin (81 instead of 325mg) did not change the rates of bleeding or thrombosis during 2-year follow-up of HM 3 patients. [33-34]
However, for the individual patient identified as a patient 'at risk' of major bleeding, all

contributing factors should be taken into account to make the decision to lower the intensity of the anticoagulation. [35]

Because EHRs usually have sparsely sampled data, resulting in a lot of missing data points, imputation of the data is useful to evaluate as much data as available. In this study, there was no significant effect of the type of imputation technique in terms of the accuracy of the model. However, some parameters might be underexposed because of their disproportional measurements. This might be the explanation of the competitive results of the AUC-level between the random forest classifier algorithm and the 'conventional' logistic regression analysis.

Furthermore, the completeness of the data is of utmost importance. There is an international registry in which all baseline, periprocedural and adverse event data are registered for all MCS patients. This registry is suitable for analyzing patterns in adverse events, for example. [36,37] However, individual prediction of a specific (type of) adverse events is difficult due to a lot of missing data.

In MCS patients, the addition of (continuous) functional data of the pump, e.g. power, flow and speed, might contribute to the ability to predict certain adverse events, for example pump thrombosis (then, power is increased and flow diminished). Currently, the actual values of these data are continuously visualized on the screen of the controller of the LVAD and data of a longer period are administered by the manufacturer. If the temporal changes of these data will be collected and visualized, e.g. by an application, it might detect pump thrombosis at an early stage. [38] For future perspectives, the integration of risk models into the EHR could identify a patient at risk of an adverse event, ideally resulting in an intervention to prevent or limit the consequences.

Conclusion

Auto-Crisp is an application that enables data mining for healthcare professionals with less experience in data mining. Using Auto-Crisp, a model was created to predict major bleeding in MCS patients in the near future with acceptable accuracy. We proposed validation and further development of Auto-Crisp to provide the application of data mining for healthcare professionals with less experience in data science.

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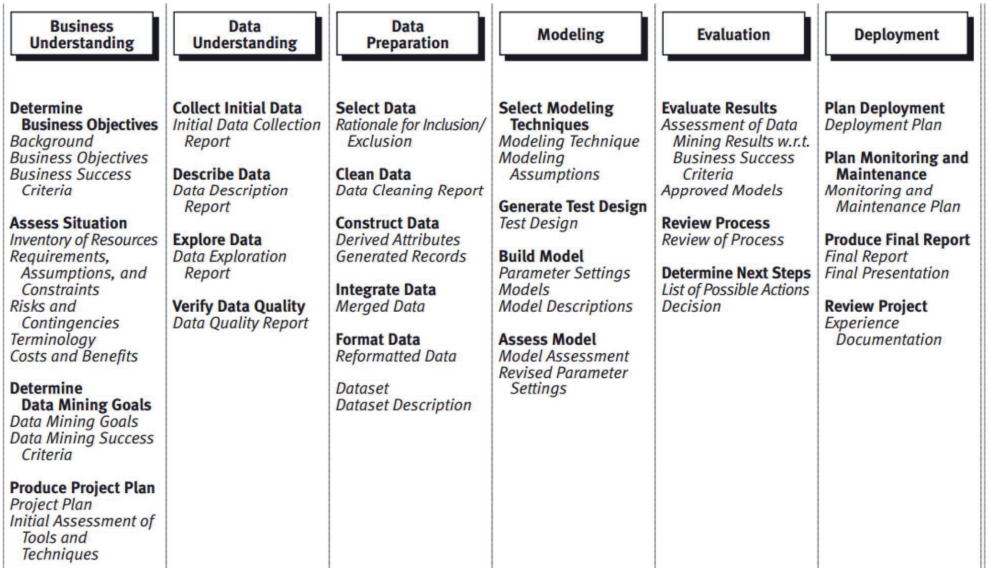
Chapter 5: Appendix – methodology



5

Business understanding

The objective of this study was to predict a major bleeding in the near future in a patient on MCS by a data mining technique. Data were derived from the intensive care unit and the general hospital electronic health records (EHRs), as well as the results of the International Normalized Ratio (INR) from the anticoagulation clinics in the outpatient setting.

The development of our proposed application, named Auto-Crisp, to enable data mining for healthcare professionals with less experience in data science was based on the cross-industry standard process for data mining (CRISP-DM) methodology. The main steps of this methodology are data understanding, data preparation, modeling and evaluation.

Data understanding

After initial data collection, different types of data (i.e. time point, time interval, baseline and event data) are imported. In the data description report, an overview of the number of patients, the number of data per data type and the prevalence of the end point is shown (Figure 3).

The quality of the data is verified in the next tab of the application. First, data similarity is illustrated by a figure in which the total number of patients is shown, together with the number of patients identified in the other data sets (Figure 4). Time point data, in this study laboratory results, are visualized first by a 2-dimensional plot with the number of variables on the X-axis and the number of patients on the Y-axis. However, the factor time is not included in this plot. Therefore, an additional 3-dimensional plot is built, in which the user of Auto-Crisp can hover to retrieve the exact amount of time points for a specific variable in a specific patient. Furthermore, for time interval data (medication) a plot in which the time of inclusion in the study, the duration of medication (here, anticoagulation) and the moment of adverse event(s) is shown (Figure 5). Exploration of the data refers to the first insight into the content of the data. A Kaplan-Meier curve is depicted, in which the patients at risk at a certain moment are shown. As well, a figure for time point data shows the mean value (+/- standard deviation or standard error) of a time point value (laboratory result) at the time of an adverse event and the time before and after an adverse event. The number of days before and after the event can be changed by the user, and the mean can be presented as a mean per moment or a rolling mean. A rolling mean is the mean of three consecutive days surrounding the selected moment. The final task in this step comprises a correlation matrix, giving a correlation coefficient between -1 and 1 per correlation. In Auto-Crisp, correlations between all variables are analyzed by Cramer's V, Interclass correlation or Pearson's correlation test, depending on the type of variable (nominal or continuous).

Data preparation

The main objective of data preparation is to create a feature space that represents data in a way that classification algorithms can learn from it most effectively and predict the class labels of a test set most accurately. To reduce the dimensionality of time series, they can be structured in instance-based and feature-based classification. [20] Instanced-based classification is based on dimension reduction by using similarity measures between the time series. Most often, this method is used in studies with frequent measurements, e.g. on the intensive care unit. [21] Because only the minority of our data are from the intensive care unit, we used the feature-based classification. In feature-based classification, the simplest method is summarizing window frames by the rolling mean. These window frames can be created with a fixed or flexible size and can be either overlapping or non-overlapping and slide along with a specified time interval (e.g. each hour, day etc.). The model is trained to predict the probability of event occurrence for that time interval. In this study, we structured the data on a slight modification of this approach. As EHRs are irregularly sampled, sliding the window on a regular interval would result in a lot of missing data. Instead of time dependence, we suggest to slide the window with the occurrence of a new time point. Auto-Crisp therefore provides the opportunity to set the class label by specifying the number of days prior to the event that should be considered as the positive label. For example, specifying the minimum at 1 and maximum at 7 means the model will be trained to predict the event occurrence in the following week while if one would specify both minimum and maximum at 0, it would mean that it considers events at the end of the window frame as positive events Including data collected after the event would potentially lead to noise into the model. Therefore, Auto-Crisp offers the capability to specify the amount of days after the event that should be excluded.

Handling missing data can be distinguished in either deletion or data imputation. Deletion of data results in the loss of a large amount of data, which is disastrous in a data mining project. By data imputation missing values are replaced with substituted values. Data imputation methods affect classifiers performance and because our goal is to predict event most reliably, the most used methods are implemented in Auto-Crisp. [22] Mean replacement is the simplest data

imputation method, where each missing value is replaced by the mean of that variable. Due to its simplicity it does not require any extensive computation and is therefore very efficient but it suffers from the fact that it treats objects the same and does not take the condition of that object into account. Methods that do take the condition of the object into account are considered to be more accurate. Possibly the most used method is called multivariate imputation via chained equations (MICE) (Multivariate Imputation via Chained Equations), which uses a fully conditional specification method to predict the missing value. [23]

The next task in the preparation of data concerns feature extraction. Feature extraction is a process that transforms a high dimensional data into a lower dimensional feature space through the application of mapping. The first technique used in this study, is the use of last values as features. The method described by Nanopoulos et al ('statistics') is our second used technique, and uses the first and second order features (the first order features base their calculation on the actual values of the time series whereas the second order features are based on the difference of nearby values). [24] Furthermore, the 'summary' method uses the results of different formulas using parts of the slope in a window frame for feature extraction (Figure 1. Appendix). [25] Esmael et al developed another technique: trend-based approximation (TVA), by addition of a trend approximation to the time series. To generate this trend-based approximation, a least squares linear model is fitted to the window frame. For each variable a separate attribute and trend feature is created. [26] Finally, the process of frequent sequential pattern mining by Batal et al, includes a modeling algorithm within the feature extraction, as shown in Figure 2. Appendix. [27]

Modeling

The objective of the modeling phase is to develop a prediction model based on the prepared data that best reflects the truth. Auto-Crisp will automate most processes that have no or little influence, however it still provides some design choices to be made. Of importance is to create an optimum in the complexity of the model, known as the Bias-Variance tradeoff (Figure 3. Appendix). A very flexible model can perfectly predict the events in the train data but results in a very poor performance on new data. To counter this challenge, a test set is commonly used in

machine learning to test how well the developed model performs. On the other hand, a simple model leads to a high bias and thus a high training and test error. Although a test error gives a far more reliable assessment of the model, it still suffers from a few disadvantages. First, by splitting the data set into a train and test set, it loses information from the test data to learn from. Secondly, the model is only tested once on a subset of the data, which might randomly vary a bit from the real world representation. To counter the above two challenges, we included K-fold cross-validation into Auto-Crisp. Cross-validation is done by randomly partitioning the data into *K* equal subsamples, in which a single subsample is used as a test set and *K*-1 subsamples as the training data. By iterating this process *K* times, all *K* subsamples are used exactly once as a test set. The final predictive performance of the model is then estimated by averaging over the *K*-folds. Sliding overlapping windows are used as the main structure in our prepared data. Because windows overlap each other, randomly partitioning the data would be incorrect as parts of the training data will also be included in test data. To address this problem, instead of randomly dividing the data sets, we split the data set in a sequential order. In order to create an accurate model, feature selection and data sampling is applied on the train set.

Feature selection is the process of identifying and removing redundant features from the data set that do not contribute to the predictive performance. Feature selection techniques are categorized in filter and wrapper methods. These methods are a form of subset selection to rank variables on importance. Two frequently used wrapper methods are recursive feature elimination (RFE) and boruta. [28] By RFE, the worst performing feature for each iteration is excluded from the model. It creates a new model with the remaining features and then ranks all features in the order of elimination. The boruta algorithm is a wrapper method built around a random forest. It firstly creates so called shadow features which are random features unrelated to the class label. Secondly, a random forest model is built and all features are ranked on importance by calculating the mean decrease accuracy. By running different iterations, features lower than the best shadow features are removed. If it reaches a specified limit of iterations or all features are confirmed or rejected, it returns the selected features.

Data sampling can mainly be categorized into oversampling and undersampling. With undersampling we randomly select a subset of the over populated class to balance the dataset.

With oversampling we randomly duplicate the minority class to make it more balanced. The disadvantage of oversampling is that since it replicates observations, it potentially overfits the data resulting in a lower accuracy. Therefore, we consider a third method, in this study, called Random Over Sampling Estimate (ROSE). ROSE is a bootstrapped-based oversampling method, which synthetically generates data that provide a better estimate of the original data. [29]

The final step in the creation of a model is the analysis of classification algorithms, comprising logistic regression, naive Bayes, support vector machine (SVM), decision tree and random forest. Logistic Regression is a traditional prediction model that can be used as a classification algorithm; it is often used in healthcare research, and has the advantage that, as the training set size grows, its outputs tend to correspond to well-calibrated probabilities. Naive Bayes is a closely related technique that regularizes the input implicitly by assuming predictors are uncorrelated conditionally on the label. This can be useful in situations in which the correlations among predictors are unstable, causing overfitting. SVMs are penalized linear classifiers in an implicit nonlinear projection of the original data. They allow for a very flexible class of nonlinear prediction models, and have some advantages in terms of training robustness and efficiency at the prediction time. Decision trees predict the outcome by recursively splitting the training sample into disjoint sets, generating a "tree" whose "leaf" nodes are homogeneous groups that can be summarized to generate a prediction, for example by taking the average within the "leaf". Decision trees allow for automatic interaction discovery but are prone to overfitting. Finally, random forests are ensembles of decision trees that have been regularized by random sampling of training rows (bootstrapping) and random subsampling of columns (feature sampling). They have been found to negate some of the overfitting encountered by plain decision trees, and often perform well without the need for extensive hyperparameter tuning.

The output of the built model consists of a confusion matrix out of which the sensitivity and specificity, the positive and the negative predictive values are shown. Furthermore, a receiver operating characteristic (ROC)-curve is used with the corresponding area under the curve (AUC) to assess performance of the model.

Evaluation

In the evaluation process all results are evaluated and next steps are determined. As evaluation processes are not all technically related and are partly dependent on the context of project, Auto-Crisp supports this to only a very limited degree. Users can upload a new cohort on which the model can be applied and evaluated.

Deployment

Deployment relates to the tasks of implementation, planning, monitoring and maintenance. This phase is also highly dependent on the context. Ultimately, well developed scoring models are implemented in healthcare systems but obviously this depends on the type of systems used. In an apart tab of Auto-Crisp, users can upload a patient file and can get a prediction for the likelihood that some event will occur in the selected coming days.

Figure 1. Appendix: Feature extraction: 'summary' method

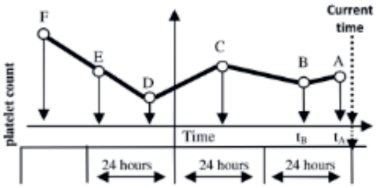


Figure 2. Appendix: Frequent sequential pattern mining

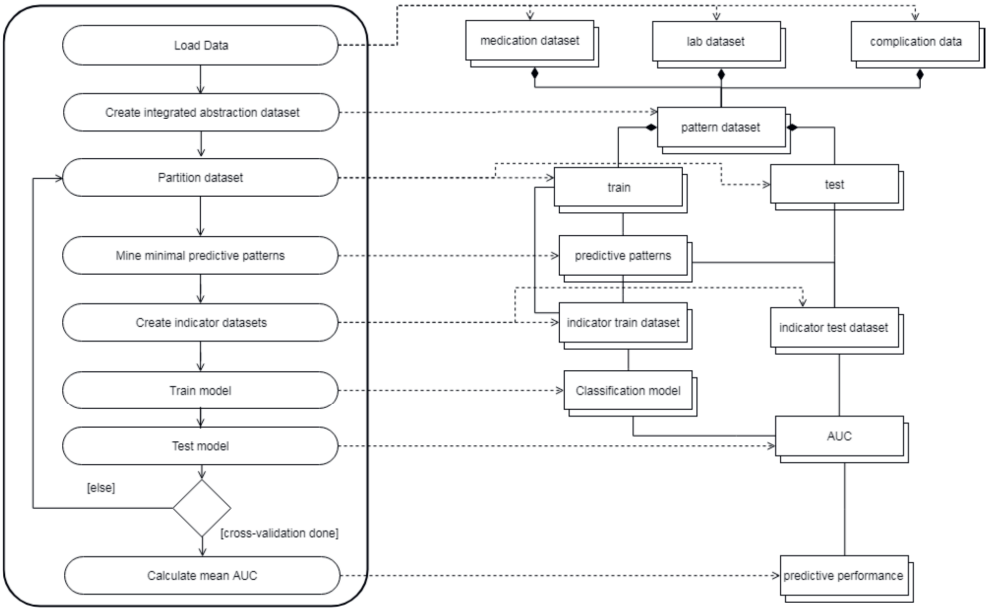
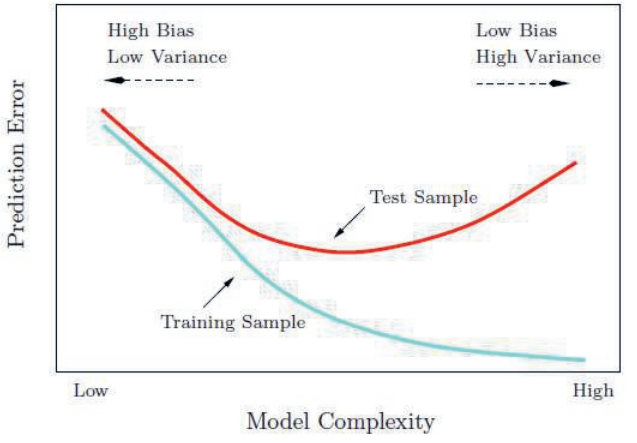


Figure 3. Appendix: The Bias-Variance tradeoff

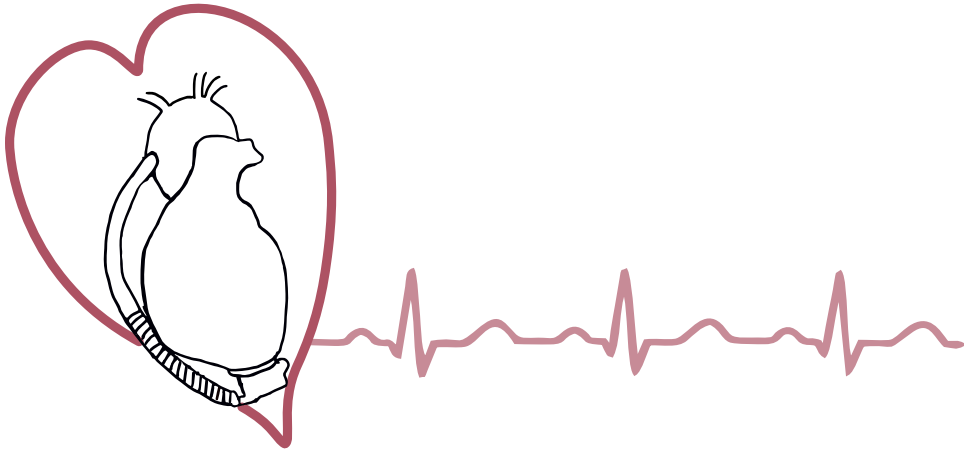


CHAPTER 6

6

Late right heart failure in chronic mechanical circulatory support: incidence and risk factors

Submitted



Abstract

*Objectives***:** We aimed to identify risk factors in all patients developing late right heart failure (LRHF) in long-term mechanical circulatory support (MCS).

Background: LRHF is an important complication related to long-term MCS and limiting prognosis. Only scarce data are available on this medical problem.

Methods: All patients treated in our center by MCS between 2006-2019 and surviving the perioperative period were included for analysis (n=262). Univariate stratified Cox proportional hazards models were used to assess the association between each of the demographic, pre- and peri-operative covariates and LRHF. Subsequently, the univariate variables with $p<0.10$ entered the multivariable Cox model. For patients with available echocardiographic and/or right catheterization variables an extension of the model was assessed.

Results: In total, 19% patients suffered from LRHF, of which 67% required hospitalization. The multivariable model showed a history of atrial fibrillation (AF), cardiogenic shock (INTERMACS 1) at implantation, higher pre-operative body mass index (BMI) and longer intensive care unit (ICU) duration to be independent predictors of LHRF. Preoperative echocardiographic and/or hemodynamic variables assessed by right heart catheterization did not independently predict LRHF in addition to clinical factors. Patients with LRHF demonstrated a lower maximal work load and peak VO2 during exercise test at 6 months postoperatively.

Conclusion: LRHF is an important problem, affecting 19% of the patients on MCS. Pre-operative echocardiographic assessment and hemodynamic data do not predict LRHF adequately. The clinical factors INTERMACS 1, a history of AF, higher pre-operative BMI and longer ICU stay may aid in the identification of patients at (high) risk for LRHF.

Introduction

Mechanical circulatory support (MCS) has been established as a valuable treatment option for patients with advanced heart failure (HF). [1] The number of patients on left ventricular assist device (LVAD) support continues to increase due to the shortage of donor hearts and the use as destination therapy.

Durable LVAD therapy is characterized by a good survival (81% at 1 year and 63-72% at 3 years) [2,3] improved quality of life [4] and exercise capacity. [5,6] Despite this favourable outcome, adverse events in patients on LVAD support, including infection, bleeding, thrombosis, arrhythmias and right heart failure (RHF), may occur in up to 40% of patients. [4,7]

As a result of the increased use of MCS and the longer duration of support per patient, more information on adverse events and long term management is obtained. Right heart failure after LVAD implantation is a major clinical problem, that may occur early after implantation, but also later in the course. Early perioperative RHF is encountered in approximately 10% of the patients and is associated with impaired survival. [4] Several risk scores were developed for the prediction of early RHF, including the EUROMACS-RHF score, which is based on data derived from the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) database. [8-10] Despite these risk scores, early RHF remains difficult to predict in daily clinical practice. [4,8,10]

Late RHF after MCS however, has hardly been studied. Apart from the need for hospitalization, late RHF has been associated with a decreased functional capacity (6-minute walk distance) and a reduced quality of life. [11] In addition, the occurrence of late RHF might increase the need for urgent heart transplantation. Furthermore, the definition of late RHF used in current literature is not uniform.

Recently, the MCS academic research consortium updated the definition of all adverse events related to MCS. [12] Late RHF was defined as the need for implantation of an RVAD >30 days following LVAD implantation or the need for hospitalization >30days post-implant with the requirement of intravenous diuretics or inotropes for at least 72 hours in association with clinical signs of right sided congestion or hemodynamic compromise (e.g. renal failure, elevated

lactate). [12] Two studies on this subject defined late RHF as the need for hospitalization after indexed LVAD implant hospitalization and either the need for inotropes or the need for intensified diuretic therapy, inotropic support and right ventricular assist device (RVAD) implantation. [11,13]

The above definitions only include patients who need to be admitted to the hospital, but in clinical practice also many outpatients on MCS do show signs of progressive right sided heart failure requiring increasing dosages of diuretics without the direct need for hospitalization. This specific group also needs to be considered as patients suffering from LRHF. We therefore aimed to identify risk factors for the development of late RHF in patients on MCS, including patients without hospitalization.

Methods

Study sample and data collection

Between 2006 and 2019, 262 out of 296 patients were successfully discharged after LVAD implantation with the HeartMate II (HM-II, Abbott, St. Paul, MN, USA), the HeartMate 3 (HM 3, Abbott, St. Paul, MN, USA) or the HeartWare (HVAD, Medtronic, Framingham, MA, USA) at the University Medical Centre of Utrecht, all initially implanted as a bridge to transplantation or bridge to decision (BTT or BTD). Cardiopulmonary exercise test (CPET) was prospectively planned at 6 months postoperatively together with laboratory test including haemoglobin and B-type natriuretic peptide (BNP).

Baseline data, including pre-implant demographics, medical history and clinical status were collected in a central database, with complete data for all patients, and is further addressed as "baseline dataset". This dataset was further enhanced with the data obtained from the post-operative CPET results and adverse events defined according to the Inter-agency Registry for Mechanically Assisted Circulatory Support (INTERMACS) criteria. 4 Pre-operative right ventricular function was assessed by echocardiogram and hemodynamic measurements including the right ventricular stroke work index (RVSWI), maximally 90 days before LVAD implantation were

registered by an independent cardiologist. Echocardiographic parameters included the tricuspid annular plane systolic excursion (TAPSE, in mm), peak systolic velocity on tissue Doppler imaging (TDI-RV, in cm/s), severity of tricuspid regurgitation (TR, categorized as no/mild or moderate/severe TR) and overall right ventricular function (categorized as poor, intermediate and good). TAPSE and TDI-RV were scored if correctly measured. Invasively measured hemodynamic parameters included central venous pressure (CVP, in mmHg), mean pulmonary artery pressure (mPAP, in mmHg), cardiac index (CI, in l/min/m^2) and RVSWI (in mL x mmHg/m^2).

Retrospectively, the occurrence of late RHF during MCS, in outpatients as well hospitalized patients was extracted from the electronic health records. Follow-up was completed for all patients until death, heart transplantation or the end of the study (March 2019). This study was approved by our institutional ethical board.

Definitions of RHF and end points

Late RHF was defined as the occurrence of right ventricular dysfunction associated with symptoms of right heart failure, including jugular venous distension, hepatic congestion and peripheral edema, if diagnosed after the index hospitalization for cf-LVAD implantation.

Early (perioperative) RHF was defined as right ventricular dysfunction, requiring right ventricular assist device (RVAD)-implantation, inhaled nitric oxide or inotropic therapy for more than 1 week during the index hospitalization for cf-LVAD implantation.

The primary end point of this study was the diagnosis of late RHF in combination with the need for intensification of diuretics (either with or without hospitalization) and/or the need for inotropes and/or RVAD. Secondary outcomes include the requirement for hospitalization due to late RHF and functional capacity, examined by CPET at 6 months postoperatively.

Statistical analysis

Categorical variables are reported in percentages. Comparison of dichotomous variables between patients with and without late RHF were performed with chi-square test or Fisher's exact test.

Continuous variables are reported as mean ± standard deviation or median (interquartile range). Differences in continuous variables between patients with and without late RHF were analyzed with an independent t-test or non-parametric test. Cumulative incidence of late RHF was assessed using competing risk analysis, with death and heart transplantation (HTX) as competing risk and was evaluated up to 5 years after implantation.

Univariate stratified Cox proportional hazards models were used to assess the association between each of the demographic, pre- and peri-operative covariates and the occurrence of late RHF. We stratified by device type, since the hazards were not proportional for the different devices. Subsequently, univariate variables with $p<0.10$ entered the multivariable Cox model. In addition, we separately assessed an extension of this multivariate Cox model in a subset of patients who had a complete assessment of right ventricular function by echocardiography and/or right catheterization prior to the cf-LVAD implantation. All covariates with $p<0.05$ were defined significant in the multivariable analysis.

Results

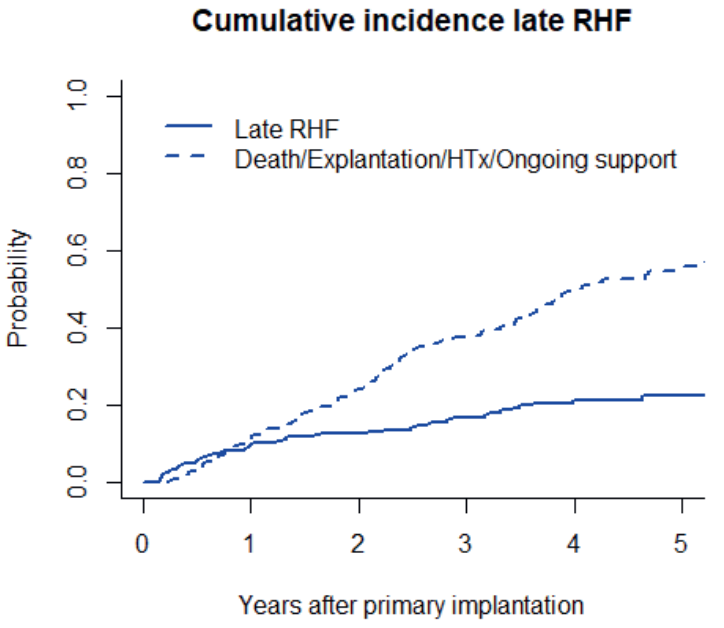
Between 2006 and 2019, 296 cf-LVAD implants with a HM-II, HVAD or HM3 were performed at our center. Thirty-four (11%) patients died during the index hospitalization, so 262 patients (66% male, mean age 51±13 years at implantation) were included in this study. Duration of MCS was 901±643 days, resulting in 647 patient-years MCS experience.

During follow-up, 49 (19%) patients developed late RHF, resulting in a cumulative incidence of 22% at 5 years after implantation (Figure 1).

Figure 1. Cumulative risk analysis

Patients at risk

262	187	130	81	39	20



In all patients medical therapy was intensified, 2/3 (n=33, 67%) required hospitalization but none of them required RVAD implantation. Late RHF occurred after a median of 363 (interquartile range: 131-1001) days after cf-LVAD implantation. Nineteen patients who suffered from late RHF died after a median of 120 (2-674) days after diagnosis and 12 were transplanted after a median of 200 (23-717) days after the first diagnosis of late RHF.

In comparison to patients without late RHF (n=213), patients with late RHF had a significantly higher pre-operative body mass index (BMI), were more frequently classified as INTERMACS 1 and less frequently INTERMACS 3 at the time of cf-LVAD implantation. In addition, the duration of index hospitalization (including stay on the intensive care unit (ICU)) was longer, as shown in

Table 1. Baseline laboratory results representing renal and liver function did not differ between patients with or without late RHF.

Table 1. Baseline data in patients with and without late RHF

Patient characteristics	**No RHF (n=213)**	**RHF (n=49)**	**p-value**
Gender – male	70 (32.9)	18 (36.7)	0.605
Age at implant	50.5 ± 13	51.5 ± 12.3	0.718
Body mass index (kg/m2)	24.1 ± 4.3	26.1 ± 5.1	0.008
Etiology – ischemic cardiomyopathy	60 (28.2)	13 (26.5)	0.818
INTERMACS 1	36 (16.9)	19 (38.8)	0.001
INTERMACS 2	87 (40.8)	19 (38.8)	0.790
INTERMACS 3	70 (32.9)	8 (16.3)	0.022
INTERMACS 4-6	20 (9.4)	3 (6.1)	0.585
Previous history			
Hypertension	22 (10.3)	3 (6.1)	0.589
Diabetes mellitus	23 (10.8)	9 (18.4)	0.145
COPD	9 (4.2)	3 (6.1)	0.759
TIA/CVA	19 (8.9)	2 (4.1)	0.384
Atrial fibrillation	47 (22.1)	17 (34.7)	0.064
Pre-operative laboratory results			
Blood urea nitrogen, mg/dL	33 ± 18	36 ± 21	0.354
Kreatinin, mg/dL	1.34 ± 0.52	1.34 ± 0.64	0.784
eGFR < 60ml/min/m2	89 (42)	25 (51)	0.250
Bilirubin total, mg/dL	1.5 ± 0.9	1.5 ± 0.9	0.768
AST, U/L	105 ± 210	73 ± 133	0.872
ALT, U/L	150 ± 286	84 ± 111	0.371
Right heart function – echo (n=159)			
TAPSE, mm	15 ± 4	14 ± 4	0.747
TDI-RV, cm/s	8.5 ± 2.7	8.9 ± 2.9	0.450
No/mild tricuspid regurgitation	64/127 (50)	7/26 (27)	0.029

Moderate/severe tricuspid regurgitation	63/127 (50)	19/26 (73)	0.029
Overall poor RV function	13/131 (10)	7/28 (25)	0.053
Overall intermediate RV function	102/131 (78)	19/28 (68)	0.260
Overall good RV function	16/131 (12)	2/28 (7)	0.742
Right heart catheterization (n= 165)			
Central venous pressure, mmHg	9 ± 6	13 ± 7	0.014
Mean pulmonary artery pressure, mmHg	32 ± 10	31 ± 11	0.775
Cardiac index, l/min/m^2	1.83 ± 0.64	1.84 ± 0.55	0.920
Right ventricular stroke work index, mL x mmHg/m^2	450 ± 252	364 ± 180	0.074
Details cf-LVAD implantation			
Pre-op temporary support	31 (14.6)	17 (34.7)	0.001
AoV concomittant	4 (1.9)	1 (2)	1.000
TV/MV concomittant	31 (14.6)	8 (16.3)	0.753
Other concomittant	26 (12.2)	8 (16.3)	0.439
CPB time, min	120 ± 39	123 ± 35	0.278
Hospitalization			
ICU stay, days	8.7 ± 8.9	14.8 ± 16.2	0.006
Total duration hospitalization, days	47.3 ± 24.7	58.3 ± 32.2	0.033
Adverse events post-operative			
Early right heart failure	49 (23)	16 (32.7)	0.159
Dialysis	21 (10)	7 (14)	0.366
Hypertension	11 (5.2)	1 (2)	0.703
Atrial fibrillation	64 (30)	27 (55)	0.001

Normally distributed variables: mean +/- SD, not normally distributed: median (25^{th} -75^{th} percentile)

In the postoperative course, significantly more patients with late RHF had also atrial fibrillation (AF, p=0.001). A history of AF prior to MCS implantation was more prevalent in patients developing late RHF (35%) in comparison to patients without late RHF (22%), though was not statistically significant (p=0.064).

There was no relation between the occurrence of early RHF and late RHF (p=0.159), although one third of the patients who developed late RHF, did also suffer from early RHF and a quarter of patients showing early RHF later-on developed late RHF.

Cox proportional hazard analysis

Univariate factors significantly associated with late RHF were cardiogenic shock (i.e. INTERMACS profile 1) at implantation (hazard ratio (HR) 2.69; 95% confidence interval (95% CI) 1.25 to 5.77) with INTERMACS 3-6 as reference. Furthermore, a history of AF prior to the operation (HR 1.91; 95% CI 1.05 to 3.48), a higher BMI (in kg/m2, HR 1.06; 95% CI 1.01 to 1.12), a longer duration (in days) on the ICU (HR 1.03; 95% CI 1.01 to 1.05) after implantation were significantly associated with late RHF, as shown in Table 2. Renal and liver function before MCS implantation did not associate to the occurrence of late RHF.

Table 2. Univariate and significant multivariable demographic and perioperative risk factors for late RHF ("baseline dataset", n= 262)

	Univariate risk factors		**Significant multivariable risk factors**	
Parameters	p-value	HR (95% CI)	p-value	HR (95% CI)
Gender - male	0.850	1.06 (0.59-1.90)		
Age at implantation (years)	0.802	1.00 (0.97-1.02)		
Etiology – ischemic heart disease	0.483	0.80 (0.42-1.51)		
Body mass index (kg/m^2)	0.028	1.06 (1.01-1.12)	0.035	1.06 (1.00-1.12)
History of atrial fibrillation	0.034	1.91 (1.05-3.48)	0.021	2.14 (1.12-4.10)

History of hypertension	0.864	0.90 (0.28-2.92)		
History of COPD	0.401	2.26 (0.69-7.40)		
History of TIA/CVA	0.519	0.63 (0.15-2.60)		
Diabetes mellitus	0.213	1.59 (0.77-3.28)		
INTERMACS profile (ref. 3 to 6)	0.040			
Profile 1	0.011	2.69 (1.25-5.77)	0.035	2.48 (1.07-5.78)
Profile 2	0.105	1.86 (0.88-3.92)		
Blood urea nitrogen (mg/dL)	0.382	1.01 (0.99-1.02)		
Kreatinin (mg/dL)	0.295	1.31 (0.79-2.16)		
Bilirubin (mg/dL)	0.930	1.02 (0.73-1.41)		
Aspartate aminotransferase (U/L)	0.326	1.00 (0.996-1.00)		
Alanine transaminase (U/L)	0.162	1.00 (0.996-1.00)		
Duration of hospitalization (days)	0.081	1.01 (1.00-1.02)		
Duration on ICU (days)	0.006	1.03 (1.01-1.05)	0.040	1.03 (1.01-1.06)

Multivariable stratified Cox proportional hazard analysis showed a history of AF (HR 2.14; 95% CI 1.12 to 4.10, p=0.021), cardiogenic shock at implantation (HR 2.48; 95% CI 1.07 to 5.78, p=0.035), a higher pre-operative BMI (in kg/m^2, HR 1.06; 95% CI 1.00 to 1.12, p=0.035) and longer duration on the ICU (in days, HR 1.03; 95% CI 1.00 to 1.06, p=0.028) to be independent predictors of late RHF.

Additional pre-operative diagnostic results to predict late right heart failure

Complete echocardiographic data, including TAPSE, TDI-RV, severity of tricuspid regurgitation and overall right ventricular function, were available in 159 (61%) patients. In 93 patients TDI-RV and/or TAPSE were missing from the echocardiographic examination and therefore not included in this analysis. Right heart catheterization before LVAD implantation was available in 165 (63%) patients. Complete echocardiographic and right heart catheterization together were available in 109 (42%) patients. The incidence of late RHF in this subgroup with complete echocardiographic data and hemodynamic data (109 patients) was similar to the incidence in the whole group in the "baseline dataset" (262 patients). Baseline characteristics did not differ either, apart from the percentage of patients in INTERMACS profile 1. In the "baseline dataset", more patients were in INTERMACS 1 in comparison to the datasets of patients who had an echocardiogram and echocardiogram + right heart catheterization prior to MCS.

On univariate analysis, a moderate/severe TR associated significantly to late RHF (HR 2.43; 95% CI 1.00 to 5.89 (p=0.049). This also applied to a higher CVP ((HR 1.08; 95% CI 1.02 to 1.14, p=0.009) assessed by right heart catheterization. There was a trend towards a lower RVSWI in association with late RHF (HR 1.00; 95% CI 0.997 to 1.00, p=0.067).

To analyze the contribution of echocardiography and/or right heart catheterization at baseline to the prediction of late RHF, these parameters were included in the multivariable Cox regression model in subsets of patients with complete echocardiographic and/or invasive hemodynamic assessment of right ventricular function. Hazard ratio's for pre-operative BMI and ICU duration remained unchanged. The hazard ratio for a history of AF decreased from 2.5 to 1.5 and for INTERMACS 1 from 2.5 to 2.3. None of the echocardiographic or right heart catheterization variables were independent predictors on multivariable Cox regression analysis (Supplementary table 1-3).

Supplementary table 1. Multivariable Cox regression analysis including significant clinical factors and echocardiographic right ventricular parameters (n=159)

Parameters	**Multivariable risk factors**	
	p-value	**Hazard ratio (HR, 95% CI)**
Pre-operative body mass index (kg/m^2)	0.082	1.07 (0.99-1.15)
History of atrial fibrillation	0.371	1.55 (0.59-4.09)
INTERMACS profile (ref. 3 to 6)	0.198	
Profile 1		2.23 (0.57-8.62)
Profile 2		2.63 (0.92-7.57)
Duration on ICU (days)	0.082	1.03 (0.997-1.06)
Moderate to severe tricuspid regurgitation	0.157	2.00 (0.77-5.22)

Supplementary table 2. Multivariable Cox regression analysis including significant clinical factors and right heart catheterization parameters (n=165)

Parameters	**Multivariable risk factors**	
	p-value	**Hazard ratio (HR, 95% CI)**
Pre-operative body mass index (kg/m^2)	0.172	1.06 (0.98-1.15)
History of atrial fibrillation	0.415	1.42 (0.61-3.30)
INTERMACS profile (ref. 3 to 6)	0.333	
Profile 1		2.45 (0.75-8.06)
Profile 2		1.54 (0.55-4.26)
Duration on ICU (days)	0.016	1.04 (1.01-1.07)
Right ventricular stroke work index	0.157	2.00 (0.77-5.22)
Central venous pressure (mmHg)	0.082	1.06 (0.99-1.13)

Supplementary table 3. Multivariable Cox regression analysis including significant clinical factors, echocardiographic and right heart catheterization parameters (n=109)

Parameters	**Multivariable risk factors**	
	p-value	**Hazard ratio (HR, 95% CI)**
Pre-operative body mass index (kg/m^2)	0.573	1.03 (0.93-1.13)
History of atrial fibrillation	0.585	1.38 (0.44-4.37)
INTERMACS profile (ref. 3 to 6)	0.279	
Profile 1		3.60 (0.75-17.36)
Profile 2		1.90 (0.55-6.59)
Duration on ICU (days)	0.097	1.03 (1.00-1.06)
Central venous pressure (mmHg)	0.324	1.04 (0.96-1.14)
TDI right ventricle (peak cm/s)	0.194	1.12 (0.94-1.33)

Functional capacity

Since it is known that patients with late RHF have an impaired exercise tolerance, we analyzed the results of routinely planned CPET at 6 months after implantation. Results of the CPET were compared between patients who developed late RHF (after a median of approximately 1 year after implantation) and patients who did not develop late RHF. CPET data at 6 months after cf-LVAD implantation were available in 146 patients. Those patients who developed late RHF (n=23) demonstrated already a significant lower maximal work load and peak VO2 (both $p<0.001$) 6 months after LVAD implantation in comparison to patients without late RHF (n=123), while respiratory quotient did not differ significantly (p=0.185) (Table 3). So, in both groups, anaerobic metabolism and/or effort did not differ. In addition, patients with late RHF had a significantly lower peak heart rate during the test (p=0.011).

Table 3. Results of cardiopulmonary exercise test at 6 months postoperatively in patients with and without late RHF (n=146)

Parameter	No late RHF (n=123)	Late RHF (n=23)	p-value
Gender - male (no, %)	89 (72%)	13 (57%)	0.129
Age (years, mean ± SD)	49.4 ± 12.8	50.6 ± 11.4	0.910
Body mass index (kg/m^2)	24.4 ± 3.4	23.7 ± 3.6	0.277
Max load (Watt, mean ± SD)	106 ± 33	76 ± 18	< 0.001
VO2 (L/min, mean ± SD)	1.28 ± 0.40	0.96 ± 0.24	< 0.001
VO2 % predicted (mean ± SD)	53 ± 12	42 ± 9	< 0.001
VO2/kg (mean ± SD)	16.7 ± 4.8	13.2 ± 3.5	< 0.001
VO2/kg % predicted (mean ± SD)	52 ± 12	43 ± 12	0.001
Anaerobic threshold (mean ± SD)	11.1 ± 3.0	9.1 ± 2.6	0.004
Respiratory exchange ratio (mean ± SD)	1.21 ± 0.11	1.21 ± 0.12	0.737
EqCO2 (mean ± SD)	36.4 ± 6.5	38.2 ± 5.5	0.185
Max heart rate (bpm, mean ± SD)	140 ± 28	122 ± 30	0.011
Hemoglobin (g/dL, mean ± SD)	12.9 ± 1.5	12.6 ± 1.4	0.474
B-type natriuretic peptide (pg/ml, mean ± SD)	180 ± 146	312 ± 330	0.060

Discussion

To our knowledge, this is the first study on the prevalence and risk factors for late right heart failure in a large patient group on long-term MCS, not only including patients requiring hospitalization, but also patients presented at the outpatient clinic. In a cohort of 262 patients, successfully discharged after cf-LVAD implantation, 19% of patients suffered from late RHF, indicated by the need for intensification of diuretics with/without inotropes, of which two third required hospitalization. The incidence of late RHF is higher in comparison to previous studies [11,13], which is probably related to the definition we used, which also included patients treated in the outpatient clinic in contrast to the definition used by INTERMACS and others. [11-13] Using the stricter criteria, 1/3 of the cases in our study (16 patients) would have been missed. We think this

is very important as early recognition and treatment of late RHF might even prevent rehospitalization. Re-admission for late RHF was necessary in 33 patients (13% of the total population), which is in line with current literature (8-17%). [11,13,14]

One third of the patients who suffered from late RHF also had early RHF, though only a quarter of the patients with early RHF developed late RHF. So the occurrence of late RHF seemed not to be associated with the occurrence of early RHF. Probably late RHF is caused by other mechanisms than RHF in the early postoperative phase. The latter can be caused by acute volume overload and septal shift of the RV at the start of left ventricular unloading by the pump (LVAD) in combination with a rise in pulmonary vascular resistance due to excessive blood loss. [15,16]

Late RHF in our study was associated with a worse clinical condition (INTERMACS profile 1) at the time of implantation. Furthermore, duration on the ICU was independently associated with the occurrence of late RHF, also likely related to the severity of disease in the perioperative phase. The relation between these parameters and the occurrence of late RHF could be explained by different mechanisms. First, in the severely hemodynamic compromised patients, volume overload of the right ventricle might result in increased cardiomyocyte apoptosis, compromising the remaining cardiomyocytes in the RV with dire consequences in the long run. [17] Furthermore, progression of the underlying disease, such as dilating cardiomyopathy, might enhance further deterioration of right ventricular function. [18-21] In addition, pump speed of the LVAD is important to the pre- and afterload of the right ventricle, also affecting the position of the interventricular septum. In chronic 'over-support' by the LVAD, the interventricular septum shift leftward together with an increased preload to the right ventricle as result of the increased flow, may result in RV overload. [22] Initially this volume overload is well tolerated by the RV but in the end it will result in RV failure. [16] This could well explain the timing of clinical appearance of right heart failure in MCS patients. Therefore, echocardiographic follow-up is very important to identify alterations in right ventricular dimensions, function and the position of the interventricular septum.

We showed for the first time that a history of AF doubles the risk of developing late RHF. Others also did notify the association between late RHF and atrial fibrillation. [13] In general, atrial fibrillation is known to affect prognosis in heart failure patients in a negative way, both in heart failure with a reduced ejection fraction and heart failure with a preserved ejection fraction. [23,24] Furthermore, a recent study identified an association between atrial fibrillation and the development of right ventricular dysfunction in patients with a preserved left ventricular systolic function during 4 year follow-up. [25] This is an interesting observation and seems analogous to the situation in long-term MCS.

In this study we noticed that the hazards for the significant clinical parameters on multivariable Cox regression analysis did not differ importantly between analyses of the baseline dataset and the datasets of patients with complete data of echocardiographic and/or right heart catheterization. The consistent effect on the risk of late RHF in different datasets proves the robustness of the results. In contrast to previous studies, we could not demonstrate an association between pre-operative renal function and late RHF. [11,13] Generally, BUN levels in these two studies were higher in comparison to our study, probably reflecting an older population with a higher prevalence of ischemic heart disease. In addition, Takeda et al. also analyzed renal function during the first year after implantation and noted significantly higher BUN levels in patients with late RHF suggesting that BUN levels are more likely to be a correlate rather than a predictor of late RHF in that study.

The current study showed that TR severity and CVP were univariate significantly associated with late RHF. When added to the multivariate Cox model, these variables, however, did not substantially contribute to the prediction of late RHF. Although echocardiography and right catheterization provide valuable information on right ventricular function prior to LVAD implantation, these findings do not seem to contribute to the prediction of late RHF. Echocardiography still remains important however for the follow-up of right ventricular function after LVAD implantation.

An important finding in our study is that physical impairment in patients developing late RHF is already apparent at an exercise test 6 months postoperatively, long before the RHF is clinically

discernable. The reduced exercise capacity probably results from subclinical right heart failure, as the right ventricular ejection fraction is related to pVO2 in patients with advanced heart failure.[26] Thus, a reduced exercise capacity during follow-up might indicate the need for closer monitoring and early treatment of late RHF in these patients.

Limitations

There are some inherent limitations to this study. First, this study was conducted in patients initially implanted as a BTT or BTD but supported for a longer time as a result of the shortage of donor hearts. Results might not be extrapolated directly to patients with MCS as destination therapy which generally is an older population. Since the data were not complete for all patients, we performed the multivariate stratified Cox model with the addition of echocardiography and right heart catheterization parameters in a subpopulation, which may not account for the whole population.

Conclusion

Late RHF warranting increased medical therapy with or without admission to hospital is a dreaded complication of chronic MCS and affects 19% of the patients. Baseline echocardiographic and invasive hemodynamics did not predict late RHF, but we demonstrate that late RHF can be predicted by cardiogenic shock before implant (INTERMACS 1), a history of atrial fibrillation, a higher pre-operative BMI and longer duration on the ICU after the implantation. Furthermore, a reduced exercise capacity at 6 months after implantation is an important early sign of late RHF.

Therefore, it remains very important to closely follow patients with the above mentioned risk factors, together with an exercise test 6 months after LVAD implantation, to diagnose late RHF as early as possible allowing optimization of treatment in the hope that admission to the hospital can be averted.

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CHAPTER 7

7

One year improvement of exercise capacity in patients with mechanical circulatory support as bridge to transplantation

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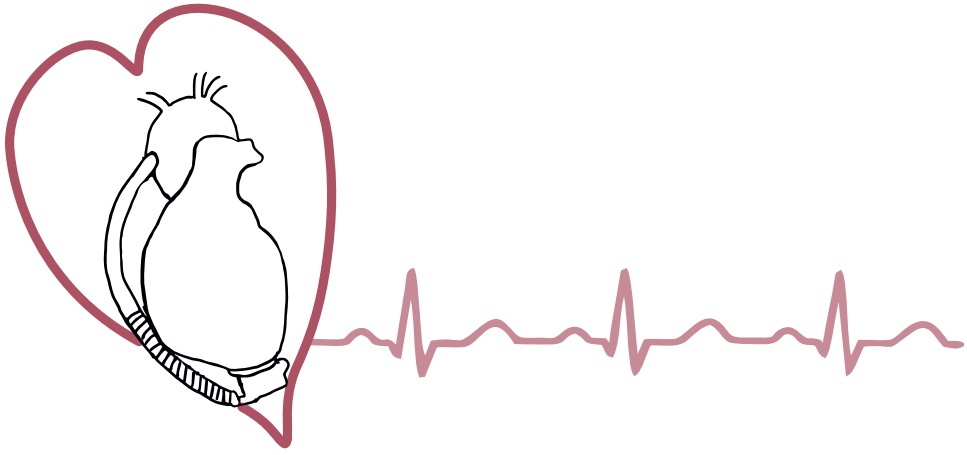


Abstract

Aims: Mechanical circulatory support (MCS) results in substantial improvement of prognosis and functional capacity. Currently, duration of MCS as a bridge to transplantation (BTT) is often prolonged due to shortage of donor hearts. Because long-term results of exercise capacity after MCS are largely unknown, we studied serial cardiopulmonary exercise tests (CPETs) during the first year after MCS implantation.

Methods and results: CPETs at 6 and 12 months after MCS implantation in BTT patients were retrospectively analyzed, including clinical factors related to exercise capacity. 105 MCS patients (67% male, 50±12 years) underwent serial CPET at 6 and 12 months after implantation. Power (105±35 to 114±40 W; p=< 0.001) and peak VO2 per kilogram (pVO2/kg) improved significantly (16.5±5.0 to 17.2±5.5 ml/kg/min (p=0.008)). Improvement in pVO2 between 6 and 12 months after LVAD implantation was not related to heart failure etiology or hemodynamic severity prior to MCS. We identified maximal heart rate at exercise as an important factor for pVO2. Younger age and lower BMI were related to further improvement. At 12 months, 25 (24%) patients had a normal exercise capacity (Weber classification A, pVO2 > 20ml/kg/min).

Conclusion: Exercise capacity (power and pVO2) increased significantly between 6 and 12 months after MCS independent of Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile or heart failure etiology. Heart rate at exercise importantly relates to exercise capacity. This long-term improvement in exercise capacity is important information for the growing group of long-term MCS patients as this is critical for the quality of life of patients.

Introduction

Mechanical circulatory support (MCS) by a continuous-flow left ventricular assist device (cf-LVAD) has shown to improve survival and quality of life in selected patients with end-stage heart failure. [1-4] The present generation of cf-LVADs consists of axial or centrifugal flow pumps operating at a fixed pump speed (RPM), thereby creating a totally different physiology than the native heart. Because of the shortage of donor hearts, resulting in longer waiting time and the use of LVAD's as destination therapy, long-term MCS has increased substantially. In this respect, functional capacity after implantation is getting more and more important for a better quality of life and the opportunity to reintegrate into society.

Previous small studies reported improved exercise capacity after MCS compared to the situation prior to implantation, as assessed by cardiopulmonary exercise test (CPET). [5-9] However, information about long-term exercise capacity in MCS patients is currently sparse. Previously, lower age, aerobic training and LVAD settings, such as pump speed, pump flow and power have been associated with improved exercise capacity after MCS. [8-11] Etiology of the cardiomyopathy was not associated with CPET results.[8] Markers for cardiac function, such as left ventricular ejection fraction (LVEF), peak heart rate, right ventricular function and aortic valve opening, have not consistently been associated with better CPET results. [8-10]

At our center, MCS patients perform a CPET, together with an echocardiogram at rest, laboratory test and full examination on a routine basis at 6 and 12 months after implantation. As a result, many data were collected over the years.

The aim of this study was to investigate whether exercise capacity during the first year of MCS treatment showed a long-term improvement, measured by CPET at 6 and 12 months after implantation, in a large cohort of MCS patients. Also, factors associated with exercise capacity were analyzed, including etiology of heart failure, echocardiographic parameters, markers for left ventricular unloading, heart failure medication, chronotropic (in)competence and pre-operative Inter-agency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification. [12]

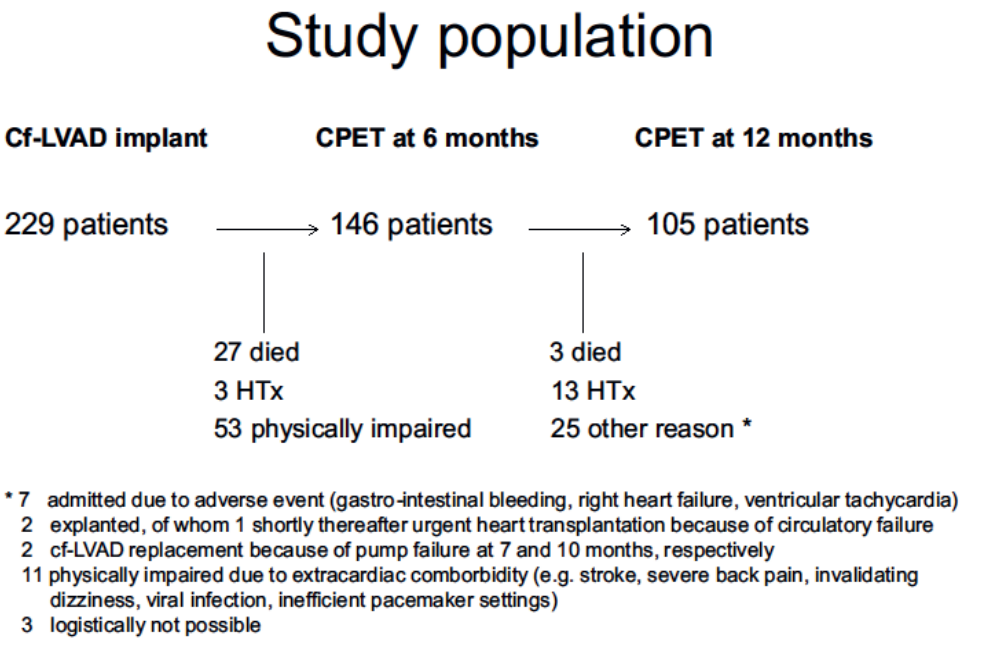
Methods

Study population

Between 2006 and 2017, 229 adult patients received MCS (HeartMate-II (HM-II, Abbott), HVAD (Heartware, Medtronic) or HeartMate3 (HM3, Abbott)) at the University Medical Center Utrecht, the Netherlands, all implanted as a bridge-to-transplantation (BTT). After MCS, patients underwent cardiac rehabilitation two times a week for 1 hour per session under supervision of a second-line physiotherapist. Outpatient rehabilitation started after discharge for a total duration of 6 weeks up to 3 months, conforming individual needs. During the training patients improved their exercise tolerance on a treadmill/hometrainer and trained the large muscles for strength and endurance. Afterwards patients are supported to improve or at least maintain the exercise performance achieved at the end of the rehabilitation program. This study was approved by our institutional ethics committee.

Eighty-three patients did not perform a CPET at all in the first year following MCS implantation, because of physical impairment in 53 patients (23%), early heart transplantation in 3 patients (1%) and death in 27 patients (12%). At 6 months, 146 patients performed a CPET. Thereafter, 13 patients underwent a heart transplantation, 3 patients died and 25 were physically unable to perform a CPET at 12 months, mainly due to extra-cardiac morbidity (Figure 1). Thus, 105 patients underwent sequential CPET both at 6 and 12 months after MCS implantation.

Figure 1. Study population



Routine CPET, echocardiography and laboratory testing

CPET was planned prospectively at 6 and 12 months after MCS, together with an echocardiogram at rest, blood test and full examination. CPET was performed on a bicycle ergometer using a symptom-limited ramp protocol with an increase of workload by 10 Watt every minute. Respiratory gas analysis was analyzed continuously (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany).

Peak VO2 (pVO2), peak VO2 per kilogram (pVO2/kg), percentage of predicted peak VO2 (per kilogram) levels according to Jones [13], the anaerobic threshold (AT), the respiratory exchange ratio (RER), EqCO2, maximal heart rate and maximal workload were reported. The anaerobic threshold was defined as the oxygen uptake before the increase in the ventilatory equivalent for oxygen (VE/VO2), without an increase in the ventilatory equivalent for carbon dioxide

(VE/VCO2), and using the V-slope method. The ventilatory response to exercise was defined as VE/VCO2 (EqCO2) at peak exercise.
Delta pVO2 and delta pVO2/kg were defined as the absolute difference between pVO2(/kg) at 6 and 12 months. Results of CPET were reported by an independent cardiologist.
Echocardiography at rest was used to measure 2D left ventricular dimensions. Furthermore, assessment of the right ventricular function by the tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler imaging (TDI-RV), and (intermittent) opening of the aortic valve was performed.
Laboratory tests included hemoglobin (g/dL), bilirubin (mg/dL), B-type natriuretic peptide (BNP) (pg/mL) and the kidney function, where the latter was divided into normal (estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73m^2) and moderately impaired (eGFR 30-60 ml/min/1.73m^2).

Statistical analysis
For this retrospective analysis, the results of the CPET were collected in a central database, together with baseline characteristics, results of echocardiogram at rest, laboratory results and medication at 6 and 12 months. Data were extracted to IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) for statistical analysis.
Comparison of continuous variables between two groups was performed by a T-test or non-parametric test if not normally distributed. Dichotomous variables were compared by Chi-square or Fisher's exact test in unrelated variables, and by McNemar in related variables. Correlation between continuous variables was tested using a Pearson or Spearman rank test. Analysis of factors related to differences between the two test moments were analyzed by univariable and multivariable linear regression.

Results

Patient characteristics
A total of 105 patients (67% male, mean age 50 ± 12 years at MCS implantation) performed serial CPET in the first year following MCS implantation after a mean of 5.4 (±1.4) months and 12

(±1) months. Prior to MCS implantation 45% of patients were in INTERMACS profile 2 ("sliding on inotropes") and 29% were stable on inotropes (INTERMACS 3). Because of severe cardiogenic shock (INTERMACS 1), temporary mechanical support (Centrimag, intra-aortic balloon pump or extracorporeal membrane oxygenator) as bridge to implantation was necessary in 19% of the patients. Most patients (n=75; 71%) received a HM-II, followed by HVAD in 22 patients (21%) and HM3 in 8 patients (8%). The underlying etiology of heart failure was a dilated cardiomyopathy (DCM) in 55 (52%) patients, 35 (33%) patients suffered from ischemic heart disease (IHD). Other etiologies included myocarditis and toxic (chemotherapy-induced) cardiomyopathy (Table 1).

Table 1. Baseline characteristics of patients who performed serial CPET at 6 and 12 months (n=105)

Baseline characteristics	
Gender - male (%)	70 (67%)
Age at MCS implantation (years, mean ± SD) ll	50 ± 12
Device type	
HM-II (%) *	75 (71.4%)
HVAD (%) ‡	22 (21%)
HM3 (%) †	8 (7.6%)
Etiology	
Dilated	55 (52%)
Ischemic	35 (33%)
Myocarditis	1 (1%)
Hypertrophic	1 (1%)

Peripartum	1 (1%)
Congenital	1 (1%)
Toxic	5 (5%)
Other	6 (6%)
INTERMACS profile §	
1 with temporary support	20 (19 %)
1 without temporary support	1 (1%)
2	47 (45%)
3	30 (29%)
4	6 (6%)
6	1 (1%)
Hospital duration - days (mean ± SD)	48 ± 22

** HM-II = HeartMate-II; † HM3 = HeartMate 3; ‡ HVAD = HeartWare; § INTERMACS = Inter-agency Registry for Mechanically Assisted Circulatory Support; ll MCS = mechanical circulatory support*

Cardiopulmonary exercise test

Patients achieved a maximal workload of 105 ± 35 Watt at 6 months, which increased to 114 ± 40 Watt (p=<0.001) at 12 months. The pVO2 and pVO2/kg at 6 months postoperatively were 1.26 ± 0.42 L/min (53 ± 12 % of predicted) and 16.5 ± 5.0 ml/kg/min (52 ± 12 % of predicted). Peak VO2 further improved at 12 months after MCS both uncorrected (1.35 ± 0.46 L/min; p =<0.001) and corrected for body weight (17.2 ± 5.5 ml/kg/min; p=0.008), corresponding to an absolute increase in pVO2 of 7% (L/min). The percentage of the predicted pVO2 increased to 57 ± 12 % (p=<0.001) and to 55 ± 13 % (p=<0.001) for pVO2/kg. The AT increased from 10.8 ± 3.1 to 12.1 ± 3.7 ml/kg/min (p=<0.001). Both maximal heart rate (141 ± 26 bpm vs. 144 ± 26 bpm; p

=0.178) and EqCO2 (36.1 ± 6.0 vs. 36.7 ± 5.8; p=0.162) did not change between 6 and 12 months. Interestingly, RER was significantly lower during the CPET at 12 months (1.21 ± 0.11 resp. 1.18 ± 0.11; p=0.021), indicating lower anaerobic metabolism and/or effort (Table 2). [14] At 12 months, 25 (24%) patients had a normal exercise capacity, according to the Weber classification (pVO2 > 20ml/kg/min, Weber A).[15] This subgroup of patients (mean age 40 ± 13 years, 80% male) had a maximal work load of 158 ± 41 Watt, a pVO2/kg of 24.6 ± 5.6 ml/kg/min, a RER of 1.18 ± 0.1 and a peak heart rate of 164 ± 19 bpm (91±8% of maximal predicted heart rate).

Factors related to exercise capacity

Hemoglobin levels at 6 and 12 months after implantation were included in the analysis as anemia is associated with worse CPET results due to lower oxygen-carrying capacity. [14] Mean hemoglobin level at the first CPET was 12.9 ± 1.5 g/dL and increased to 13.4 ± 1.6 g/dL at the second CPET (p=<0.001), but no correlation was found between the increase in hemoglobin levels and the increase (delta) in pVO2/kg (*r*=0.183, p=0.068). BNP levels (151 ± 113 pg/mL versus 190 ± 143 pg/mL; p=0.398) and left ventricular end-diastolic diameter did not change between 6 and 12 months after MCS suggesting a similar amount of LV unloading over time (Table 2). Right ventricular function, assessed by TAPSE and TDI-RV, did not change between 6 and 12 months after MCS. Furthermore, kidney function as a marker of organ perfusion, bilirubin level as a marker for right ventricular failure, heart failure medication affecting the afterload (i.e. ACE-inhibitors) and heart rate (beta blocker) were analyzed as these factors might influence the CPET results. However, no difference in kidney function, bilirubin level and heart failure medication was noted (Table 2).

Table 2. Diagnostic results at serial follow-up after MCS implantation (n=105)

	6 months after implant	**12 months after implant**	**p-value**
BMI (kg/m^2, mean ± SD) *	24.5 ± 3.5	25.7 ± 5.0	<0.001
CPET results †			
Max workload (Watt, mean ± SD)	105 ± 35	114 ± 40	<0.001
VO2 (L/min, mean ± SD)	1.26 ± 0.42	1.35 ± 0.46	<0.001
VO2 % predicted (mean ± SD)	53 ± 12	57 ± 12	<0.001
VO2/kg (ml/kg/min, mean ± SD)	16.5 ± 5.0	17.2 ± 5.5	0.008
VO2/kg % predicted (mean ± SD)	52 ± 12	55 ± 13	<0.001
Anaerobic threshold (mean ± SD)	10.8 ± 3.1	12.1 ± 3.7	<0.001
Respiratory exchange ratio (mean ± SD)	1.21 ± 0.11	1.18 ± 0.11	0.021
EqCO2 (mean ± SD)	36.0 ± 6.0	36.7 ± 5.8	0.162
Max heart rate (bpm, mean ± SD)	141 ± 26	144 ± 26	0.094
Percentage of max predicted heart rate (mean ± SD)	83 ± 14	85 ± 14	0.055
Echocardiography ‡			
LVEDD (mean ± SD)	59 ± 12	58 ± 12	0.073
TAPSE (mean ± SD)	12 ± 3	13 ± 3	0.637
TDI-RV (mean ± SD)	6.1 ± 1.6	6.4 ± 2.1	0.640
Aortic valve opening (%)	18/68 (17%)	20/60 (19%)	0.302
Laboratory results §			
Hemoglobin level (g/dL, mean ± SD)	12.9 ± 1.5	13.4 ± 1.6	<0.001
Bilirubin (mg/dL, mean ± SD)	0.78 ± 0.35	0.88 ± 0.35	0.165
BNP-level (pg/ml, mean ± SD)	151 ± 113	190 ± 143	0.398
Kidney function – eGFR > 60 ml/min/1.73m^2 (%)	85/104 (81%)	80/104 (76%)	0.227
Kidney function - eGFR 30-60 ml/min/1.73m^2 (%)	19/104 (18%)	24/104 (23%)	0.344

Heart failure medication ll			
ACE inhibitor/ARB (%)	54/97 (56%)	56/94 (60%)	0.289
Beta blocker (%)	11/97 (11%)	17/94 (18%)	0.063
Antihypertensive (%)	6/97 (6%)	7/94 (7%)	1.000
Anti-arrhythmica (%)	44/97 (45%)	47/94 (50%)	0.727
Sildenafil (%)	24/97 (25%)	23/94 (24%)	1.000
Diuretic (%)	59/96 (62%)	52/93 (56%)	0.092

** BMI = body mass index*

† CPET = cardiopulmonary exercise test; VO2(/kg) % predicted = Percentage of predicted value according to Jones (ml/kg/min)'; EqCO2 = ventilatory equivalent for carbon dioxide; Percentage of max predicted heart rate: predicted maximal heart rate = 220-age

‡ LVEDD = 2D left ventricular end-diastolic diameter, measured in parasternal long axis (mm); TAPSE = tricuspid annular plane systolic excursion (mm); TDI-RV = peak systolic tissue Doppler value of the right ventricle (cm/s)

§ BNP= B-type natriuretic peptide; eGFR = estimated glomerular filtration rate

ll ACE inhibitor = angiontensin converting enzyme inhibitor; ARB = angiotensin receptor blocker

Subgroup analyses

Dilated cardiomyopathy versus ischemic heart disease

Previous studies did not show differences in exercise capacity between patients with IHD and a non-ischemic cardiomyopathy, probably related to small sample sizes. [16,17] In our analysis, patients with a DCM (n=55) had significant better CPET results both at 6 and 12 months after implantation compared to patients with IHD (n=35). At 6 months, pVO2 was 1.35 ± 0.46 L/min in DCM patients and 1.11 ± 0.26 L/min in patients with IHD (p=0.011). This increased to 1.46 ± 0.45 L/min (DCM) versus 1.18 ± 0.36 L/min (IHD) at 12 months (p=0.003). Maximal workload was also substantially higher in DCM compared to IHD patients both at 6 months (110 ± 36 Watt vs. 90 ± 25 Watt; p=0.014) and 12 months (120 ± 39 Watt vs. 99 ± 33 Watt; p=0.015) after implantation. Importantly, the improvement in pVO2 (delta pVO2) and pVO2/kg (delta pVO2/kg) from 6 to 12 months was similar in both groups (p=0.27 and p=0.23), as shown in Table 3. Age, gender, heart failure medication, BNP and hemoglobin levels did not differ between DCM and IHD patients.

Table 3. Diagnostic results in dilated and ischemic cardiomyopathy (n=90)

	Dilated cardiomyopathy	Ischemic cardioyopathy	p-value
Baseline			
Number of patients (%)	55 (61%)	35 (39%)	
Age at implant	48.2 ± 14	53.1 ± 8.1	0.181
Male (%)	38 (69%)	23 (66%)	0.738
INTERMACS 1 with temporary support ¶	7 (13%)	12 (34%)	0.015
INTERMACS 1 without temporary support	0 (0%)	1 (3%)	0.389
INTERMACS 2	25 (46%)	15 (43%)	0.809
INTERMACS 3	18 (33%)	5 (14%)	0.051
INTERMACS 4	4 (7%)	2 (6%)	1.000
INTERMACS 6	1 (2%)	0 (0%)	1.000
HM-II ‡	42 (76.4%)	22 (63%)	0.168
HVAD II	10 (18.2%)	10 (26%)	0.248
HM3 §	3 (5.5%)	3 (9%)	0.674
Diagnostics - 6 months			
Body mass index (kg/m^2, mean ± SD)	24.4 ± 3.7	24.7 ± 3.1	0.524
Max load (Watt, mean ± SD)	110 ± 36	90 ± 25	0.014
VO2 (L/min, mean ± SD)	1.35 ± 0.46	1.11 ± 0.27	0.011
VO2/kg (ml/kg/min, mean ± SD)	17.4 ± 5.5	15.1 ± 3.7	0.057
Anaerobic threshold (mean ± SD)	11.3 ± 3.4	10.3 ± 2.6	0.250
Respiratory exchange ratio (mean ± SD)	1.20 ± 0.11	1.22 ± 0.10	0.312
Max heart rate (bpm, mean ± SD)	142 ± 26	133 ± 26	0.127
EqCO2 (mean ± SD) †	35.3 ± 6.2	38.1 ± 4.6	0.021
Hemoglobin (g/dL, mean ± SD)	13 ± 1.7	12.6 ± 1.3	0.444
BNP (pg/ml, mean ± SD) *	186 ± 162	211 ± 100	0.061
Bilirubin (mg/dL, mean ± SD)	0.86 ± 0.44	0.71 ± 0.22	0.242
Use of beta blocker (%)	5/50 (10%)	4/33 (12%)	1.000
Use of ACE-inhibitor/ARB (%)	30/50 (60%)	16/33 (49%)	0.302
Use of antihypertensive (%)	5/50 (10%)	1/33 (3%)	0.395

Diagnostics - 12 months			
Body mass index (kg/m^2, mean ± SD)	25.3 ± 3.8	26.5 ± 6.5	0.413
Max load (Watt, mean ± SD)	120 ± 39	99 ± 33	0.015
VO2 (L/min, mean ± SD)	1.46 ± 0.45	1.18 ± 0.36	0.003
VO2/kg (ml/kg/min, mean ± SD)	18.3 ± 5.3	15.3 ± 4.5	0.002
Anaerobic threshold (mean ± SD)	12.2 ± 3.6	11.5 ± 3.3	0.477
Respiratory exchange ratio (mean ± SD)	1.18 ± 0.09	1.17 ± 0.11	0.659
Max heart rate (bpm, mean ± SD)	147 ± 26	137 ± 26	0.166
EqCO2 (mean ± SD) †	35.6 ± 5.0	38.9 ± 5.8	0.008
Hemoglobin (g/dL, mean ± SD)	13.6 ± 1.7	13 ± 1.6	0.137
BNP (pg/ml, mean ± SD) *	115 ± 88	190 ± 126	0.390
Bilirubin (mg/dL, mean ± SD)	0.88 ± 0.4	0.8 ± 0.3	0.092
Use of beta blocker (%)	6/51 (11%)	6/30 (17%)	0.345
Use of ACE-inhibitor/ARB (%)	32/51 (63%)	16/30 (53%)	0.405
Use of antihypertensive (%)	5/51 (9%)	2/30 (6%)	1.000
Delta VO2 (L/min, mean ± SD)	0.1 ± 2.3	0.1 ± 3.5	0.27
Delta VO2/kg (ml/kg/min, mean ± SD)	0.9 ± 2.8	0.2 ± 2.2	0.23

** BNP = B-type natriuretic peptide; † EqCO2 = ventilatory equivalent for carbon dioxide ǂ HM-II = HeartMate-II; § HM3 = HeartMate 3; ll HVAD = HeartWare; ¶ INTERMACS = Inter-agency Registry for Mechanically Assisted Circulatory Support; Delta VO2(/kg) corresponds to the difference between the CPET results at 6 and 12 months postoperatively.*

INTERMACS profile

As patients with INTERMACS profile 1 at time of implantation are in a considerably worse condition, we compared the CPET results of these patients to the results of patients in INTERMACS profile 2 and 3. At both test moments, CPET results were comparable between INTERMACS 1 (n=21) and INTERMACS 2+3 (n=77), both uncorrected and corrected for body weight. At 6 months, pVO2 was 1.31 ± 0.52 and 1.25 ± 0.40 L/min (p=0.806) and pVO2/kg 17.4 ± 6.1 and 16.2 ± 4.8 ml/kg/min (p=0.556) for INTERMACS 1 and INTERMACS 2+3, respectively. At 12 months, pVO2 was 1.35 ± 0.56 and 1.37 ± 0.44 (p=0.792) and pVO2/kg 17.4 ± 7.1 and

17.2 ± 5.2 ml/kg/min (p=0.710), respectively. Delta pVO2 (p=0.216) and pVO2/kg (p=0.188) were also similar between INTERMACS 1 and 2+3.

Chronotropic (in)competence

Previous studies evaluating the chronotropic response after MCS showed a significantly lower maximal heart rate during CPET compared to healthy individuals. [18,19] Therefore, we compared exercise capacity in patients with chronotropic incompetence (CI) versus patients without CI, defined as a peak heart rate <80% of the predicted maximal heart rate for age (220-age). At 6 months 67 patients (46%) met the criteria for CI, 79 (54%) patients reached a maximal heart rate above 80% of predicted (not CI). Compared to patients without CI, patients with CI had a significantly lower pVO2 (1.07 ± 0.24 L/min versus 1.37 ± 0.45 L/min; p<0.001) and pVO2/kg (14.1 ± 2.8 ml/kg/min versus 18.0 ± 5.4 ml/kg/min; p<0.001). Importantly, RER did not differ between the groups (1.21 ± 0.11, p=0.972). The importance of heart rate was further illustrated by the presence of a significant correlation between the percentage of predicted maximal heart rate and pVO2/kg at both 6 months (r =0.299; p=0.002) and 12 months (r=0.310; p=0.001) after implantation as a continuous variable.

Predictors for pVO2/kg over time

Using linear regression analysis, factors contributing to the difference between pVO2/kg at 6 and 12 months (delta pVO2/kg, Appendix 1) were identified. Multivariable linear regression analysis including CPET results at 6 months, age and gender, resulted in a significant model; F(7,89)=4.879, p<0.001, explaining 22% of the variance in delta VO2/kg (adjusted R^2=0.22). Significant predictors for a higher delta pVO2/kg were a younger age, a lower body mass index, lower maximal work load and anaerobic threshold during the CPET at 6 months.
An improvement of peak oxygen uptake > 6% on repeated CPET, which is defined clinically important in heart failure patients, was observed in 46 (44%) of the patients. [20]

Patients with one CPET (6 months only)

Selection bias may be introduced as 53 patients were physically not able to perform any CPET in the first year after MCS implantation and 41 only performed one CPET at 6 months (physically impaired, died or received heart transplantation). To gain more insight into the reasons for physical impairment, the 1-year incidence of adverse events was registered. In patients who were not able to perform any CPET, the incidence of stroke (hemorrhagic or ischemic), VAD-related infection, sepsis and major bleeding were higher compared to patients who performed a CPET at 6 and 12 months (0.23, 0.25, 0.54 and 0.90 events per patient year, versus 0.12, 0.13, 0.16 and 0.62).

Importantly, no differences were observed in patient characteristics including age, gender, etiology, INTERMACS profile and duration of hospitalization in patients who performed no or only 1 CPET compared to patients who performed a CPET at both 6 and 12 months. Furthermore, pVO2(/kg), echocardiographic and laboratory results did not differ between patients who performed 1 CPET and patients who performed 2 CPETs during the first year after implantation.

Discussion

This single center study is the first study to examine exercise capacity in a large cohort of MCS patients during one-year of follow-up. It demonstrated an increase of maximal workload by 9% and pVO2 by 7% between 6 and 12 months postoperatively. Although this increase seems only modest, a recent position paper on the role of CPET in heart failure patients showed that an increase of >6% in maximal exercise capacity is considered clinically relevant and related to improved prognosis.[20] This was observed in almost half of the patients. Furthermore, approximately a quarter of patients had a normal maximal exercise capacity after one year, defined as a pVO2/kg >20 ml/kg/min according to Weber. [15]

The improvement in exercise capacity could not be explained by increasing effort or motivation, as the respiratory exchange ratio was lower at 12 months while pVO2 values increased. Although a considerable amount of patients were not able to perform sequential exercise testing at 6 and 12 months, selection bias seems unlikely. No differences were observed in pVO2 at 6 months

between patients who were physically able to perform 2 CPETs and those who performed a CPET at 6 months only. Patient characteristics, echocardiographic and laboratory results were also similar and the most important reason for drop-out was extra-cardiac morbidity.

The explanation for the further improvement of exercise performance over the first year after LVAD implantation is probably multifactorial. [21-23] As a consequence of the continuous flow, hemodynamics change dramatically with MCS. Device output is mainly determined by the pump speed and the pre- and afterload of the left ventricle. During exercise total output might be further enhanced by residual left ventricular output through the aortic valve. As mentioned above, in cf-LVADs the pump speed (RPM) presently is fixed, independent of the physical activity of the patient. [23] In our study, LVAD settings during the exercise test were not changed. Earlier studies evaluating the effect of increasing pump speed also showed an increase in pVO2. [17,24] Although performed in a small number of patients, this might advocate the need for an algorithm to adapt speed settings during exercise in cf-LVADs.

Previous reports did not show a clear correlation between right ventricular function and exercise capacity in MCS recipients. [10,16,17] More recently, no correlation was found between right ventricular ejection fraction (measured by 4D cardiac computed tomography) and pVO2. [25] In line with these data, our study observed an identical right ventricular function (TAPSE and TDI-RV) at 6 and 12 months after MCS, while maximal exercise performance increased, further negating the importance of RV function for exercise capacity in MCS patients.

On the other hand, maximal heart rate seems to play an important role in exercise capacity after MCS. [26,27] Approximately half of the MCS recipients in our study, were chronotropic incompetent, as was also observed in previous studies. [18,19,26]

Furthermore we demonstrated a significant correlation between maximal heart rate and pVO2/kg, and patients who achieved a normal exercise capacity had a peak heart rate >90% of predicted during exercise. Therefore, an impaired chronotropic response might largely explain the relatively limited maximal exercise performance in the majority of MCS patients.

Nevertheless, the improvement of maximal exercise capacity between 6 and 12 months in our study did not go hand in hand with a significant additional increase in maximal heart rate. So,

other factors must also contribute to the improvement of pVO2 beyond 6 months postoperatively.
Despite the significantly higher hemoglobin levels at 12 months, it is not obvious that this is an important factor because the (small) increase in hemoglobin did not correlate with delta pVO2/kg. Unfortunately, we were not informed about the iron status (and possible iron deficiency) in these patients, as it is known that iron deficiency is associated with reduced exercise capacity in heart failure patients, improving by intravenous iron suppletion. [28] Additionally increased muscle strength may also contribute to improved exercise capacity over time, which is probably enhanced by the cardiac rehabilitation program after MCS. [29]

We identified that the magnitude of improvement of exercise capacity was more pronounced in younger patients and in those with a lower BMI. The fact that a relatively lower maximal workload and AT at 6 months were predictive of further improvement at 12 months illustrates that cf-LVAD patients might benefit from prolonged cardiac rehabilitation, extending even beyond 6 months after implantation. Cardiac rehabilitation has already demonstrated to affect maximal exercise capacity in MCS patients positively, together with an increased muscle strength. [29] However, the effect of long-term cardiac rehabilitation on maximal exercise capacity in chronic MCS has not been studied yet.

Subgroups

In this study, patients with a DCM showed a better exercise capacity than patients with IHD at both test moments, which could not be explained by differences in age and/or gender. Hypothetically, a lower maximal exercise performance in IHD might relate to the presence of generalized atherosclerosis and a subsequent decrease in organ and muscle perfusion compared to DCM patients, in which primarily the heart is affected.
Another important finding was that maximal exercise capacity in INTERMACS 1 patients was identical to that of INTERMACS 2+3 patients. Although survival differs substantially, improvement in exercise capacity in patients surviving the first year is similar between

INTERMACS 1 and 2+3. These findings illustrate that functional 'recovery' after receiving MCS is substantial, even for hemodynamically severely compromised patients.
This does not correspond to the findings of a recent study by Gustafsson et al. which identified an INTERMACS profile 1 or 2 before HM 3 implantation to be predictive of a lower exercise capacity (i.e. 6 minute walk distance below 300m) at 6 months postoperatively. However, because of the relatively low number of INTERMACS 1 and 2 patients included in that study, the results may be less reliable and cannot be fully compared to our group of LVAD patients, consisting 20% INTERMACS 1and 45% INTERMACS 2. [30]
The detrimental effect of an impaired chronotropic response on maximal exercise capacity in MCS patients advocates the need for studies evaluating the mechanisms of chronotropic incompetence in these patients, and analysis of interventions to increase maximal heart rate, for example a more aggressive rate response in patients with pacing devices. [26]

Limitations

The study sample consisted of patients with MCS implanted as a bridge to transplantation. Results of CPET might not be extrapolated to implantations as destination therapy, as these patients generally are older and have a worse outcome than patients who received MCS as a bridge to transplantation. Although echocardiograms during the actual CPET were not made, resting echocardiograms showed no difference in aortic valve opening at 6 and 12 months, suggesting comparable intrinsic contractile contribution. The effect of adaptive pump speed changes during exercise were not investigated in the current study, but may lead to further improvement in exercise capacity based on the study by Jung et al. [17] This may also account for optimization of pacemaker settings, for example rate response, as a substantial number of patients on MCS has a cardiac resynchronization device and/or implantable cardioverter defibrillator in situ. [31] The improvement between 6 and 12 months was more pronounced in pVO2 (7%) than pVO2/kg (4%). This is likely related to the increase in body weight over time.

Conclusion

This study demonstrates a significant increase in exercise capacity between six and twelve months after MCS in end-stage heart failure patients. Maximal heart rate at exercise plays an important role in this improved exercise capacity. RV function seems to be less important. DCM patients generally have a better exercise capacity after MCS than patients with IHD, irrespective of age, but improvement over time was equal in both groups. Another important finding was that patients in INTERMACS 1 at the time of LVAD implantation, meaning severe cardiogenic shock, are able to achieve the same exercise capacity after MCS as less sick patients (INTERMACS 2 and 3). The improvement of exercise capacity over time after MCS correlates with younger age and lower BMI at the time of LVAD implantation and highlights the importance of prolonged cardiac rehabilitation.

Our results are important information for the growing group of patients on long-term MCS, as improvement in exercise capacity is critical for the quality of life of patients.

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CHAPTER 8

The role of long-term mechanical circulatory support in patients with advanced heart failure

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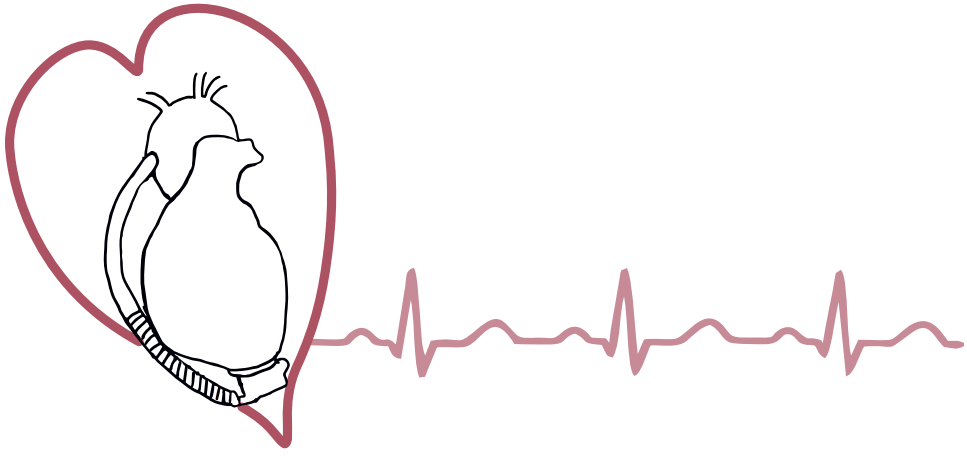


Abstract

In patients with end-stage heart failure, advanced therapies such as heart transplantation and long-term mechanical circulatory support (MCS) with a left ventricular assist device (LVAD) have to be considered. LVADs can be implanted as a bridge to transplantation or as an alternative to heart transplantation: destination therapy. In the Netherlands, long-term LVAD therapy is gaining importance as a result of increased prevalence of heart failure together with a low number of heart transplantations due to shortage of donor hearts. As a result, the difference between bridge to transplantation and destination therapy is becoming more artificial since, at present, most patients initially implanted as bridge to transplantation end up receiving extended LVAD therapy. Following LVAD implantation, survival after 1, 2 and 3 years is 83%, 76% and 70%, respectively. Quality of life improves substantially despite important adverse events such as device-related infection, stroke, major bleeding and right heart failure. Early referral of potential candidates for long-term MCS is of utmost importance and positively influences outcome. In this review, an overview of the indications, contraindications, patient selection, clinical outcome and optimal time of referral for long-term MCS is given.

Dutch contribution to the field

- Since the introduction of continuous-flow LVAD's in the Netherlands in 2006, the number of implantations has increased substantially, outnumbering heart transplantation as treatment for advanced heart failure
- The results after LVAD implantation justify the use as an alternative to heart transplantation
- Presently, the four implanting centers (UMCU, EMC, UMCG and LUMC) have sufficient capacity for the LVAD implantations needed
- Early referral to a LVAD-implanting center is mandatory for optimal timing and outcome of LVAD implantation

Introduction

Patients suffering from advanced heart failure despite individualised optimal medical treatment, with or without cardiac resynchronisation therapy, should be considered for heart transplantation or long-term mechanical circulatory support (MCS).[1] Currently, heart transplantation is still considered to be the gold standard, showing a relatively good median survival of 15 years.[2-5] Meanwhile, long-term MCS is becoming more and more important due to the growing number of heart failure patients together with the decline in the number of donor hearts. First generation left ventricular assist devices (LVADs) were big pulsatile devices with limited durability. Already in 1993, LVADs were used as bridge to transplantation in the University Medical Center Utrecht.[6] From 2006, smaller and more reliable continuous flow devices became available. The short-term outcome was very promising with a 2-year survival of 76%.[7] Since that time, MCS has become an important part of therapy in advanced heart failure and the number of centers in the Netherlands implanting LVADs has increased to four. Outcome parameters are registered per center and reported yearly to a central European database (EUROpean registry for patients with Mechanical Assisted Circulatory Support, EUROMACS). LVADs can be used as bridge to transplantation, or as an alternative to heart transplantation, which is known as destination therapy and in some patients as a bridge to decision in case of

temporary contraindications. The present situation in the Netherlands is that most patients with an LVAD as bridge to transplantation will have to wait several years before a donor heart becomes available and many patients will never be transplanted at all. In that way the difference between bridge to transplantation and destination therapy is becoming more and more artificial. Currently, the HeartWare Ventricular Assist Device (HVAD) (Medtronic, Framingham, MA, USA) and the Heartmate 3 (HM3, Abbott, St. Paul, MN, USA) are the most frequently used devices for long-term MCS (Fig. 1).

Figure 1. Left ventricular assist device (LVAD)

The HM3 replaced the Heartmate II (HM-II, Abbott, St. Paul, MN, USA) some years ago, resulting in less need for pump replacements and improved survival free of disabling stroke or reoperation for malfunction than its predecessor.[8] Both HVAD and HM3 are small centrifugal pumps implanted in the pericardial cavity showing very low rates of haemolysis, but necessitating intensive anticoagulation. The percutaneous abdominal driveline is still one of the shortcomings in the design, potentially leading to recurrent or persistent infections.

Indications for long-term MCS

Indications for long-term MCS generally follow those of heart transplantation. In case of contraindications for heart transplantation, MCS may be considered as an alternative to transplantation in selected patients for which all the below-mentioned criteria also apply:

- Advanced heart failure with a low left ventricular ejection fraction <30% despite optimal therapy consisting of maximally tolerable medication with or without resynchronisation therapy and other interventions to optimise the cardiac condition, as indicated by the current heart failure guideline;[2]
- Exercise tolerance, assessed by cardiopulmonary exercise testing, reveals a peak VO2 <12 ml/min/kg (<14 ml/kg/min if intolerant to beta blocker) or <50% of the predicted value for age and sex in ambulatory patients;
- Strong intrinsic motivation;
- Inter-agency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile 2-6 (Table 1).[12]

Table 1. INTERMACS classification

NYHA class	INTERMACS profile	Popular term	BTT/DT	Prognosis
IV	1. Critical cardiogenic shock	'crash and burn'	NO *	Hours to weeks
IV	2. Progressive decline	'sliding fast'	YES	
IV	3. Stable but inotrope dependent	'stable dependent'	YES	Weeks to months
IV	4. Recurrent advanced heart failure	'frequent flyer'	YES	
IIIb-IV	5. Exertion intolerant	'housebound'	To be considered	Months to years
IIIb	6. Exertion limited	'walking wounded'	To be considered	

III	7. Advanced NYHA III	NYHA class III	In the long term	

Legend: NYHA=New York Heart Association

Contraindications for long-term MCS

Patients in cardiogenic shock (INTERMACS profile 1) despite an intra-aortic balloon pump, temporary MCS and/or inotropic support are not eligible for long-term MCS. In addition, a life expectancy of less than 2 years, based on extracardiac disease, is a contraindication for long-term MCS. Furthermore, severe comorbidities may be temporary or persistent contraindications (Table 2).

Table 2. Contra-indications for long-term LVAD therapy

1	INTERMACS 1 (Cardiogenic shock) despite IABP, temporary MCS and/or inotropics
2	Life expectancy < 2 years due to extra-cardiac disease
3	Severe comorbidity/end organ failure o Severe renal failure (estimated GFR < 30 mL/min/1.73m^2), unlikely to improve after LVAD-implantation o Severe liver failure/cirrhosis or portal hypertension, unlikely to improve after LVAD-implantation o Severe pulmonary disease (with a FEV1 < 1liter), or pulmonary disease resulting in an important component of symptomatology that could result in de absence of improvement of symptoms after LVAD implantation o Severe central/peripheral artery disease and/or abdominal aorta >5cm (untreated) o Symptomatic cerebral pathology in the recent 6 months and/or severe disability after neurologic event and/or carotid artery stenosis >80% that cannot be treated o Severe neuromuscular pathology, limiting exercise capacity and/or ventilation postoperatively

	o Increased bleeding risk (which will not improve after LVAD implantation) - Persisting thrombocytopenia (< 50.000 x 10^9/L) - Active bleeding - Severe coagulopathy otherwise o Cognitive or psychosocial factors - (Beginning) dementia - Depression, unlikely to improve after LVAD implantation
4	Severe right heart failure, with a high risk for the need for right ventricular assist device (despite in BTT, implanting a biventricular assist device may be considered)
5	Phenotype of heart failure, in which implantation of a LVAD is impossible/complex: o Hypertrophic cardiomyopathy (unless, in dilating phase) o Restrictive cardiomyopathy/endomyocardial fibrosis o Complex uncorrected congenital heart disease/valvular disease
6	Difficulties in ventilation in intubated patients
7	Severe cachexia (BMI < 18.5 kg/m^2), unlikely to be corrected
8	Morbid obesity (BMI > 35 kg/m^2), uncorrected
9	(Increased risk for) systemic infection
10	Severely calcified ascending aorta (where outflow cannula is inserted, to be considered to insert the outflow cannula at another location)
11	Intolerance to coumarin derivates and/or thrombocyte aggregation inhibitors
12	Non-compliance, substance abuse (drugs/alcohol/nicotin)
13	Absence of social network, severe language barrier

Patient selection

Patient selection is of utmost importance for outcome after LVAD implantation and is performed by a specialised, multidisciplinary team in LVAD-implanting centers, who take the above-mentioned indications and contraindications into consideration.[9]

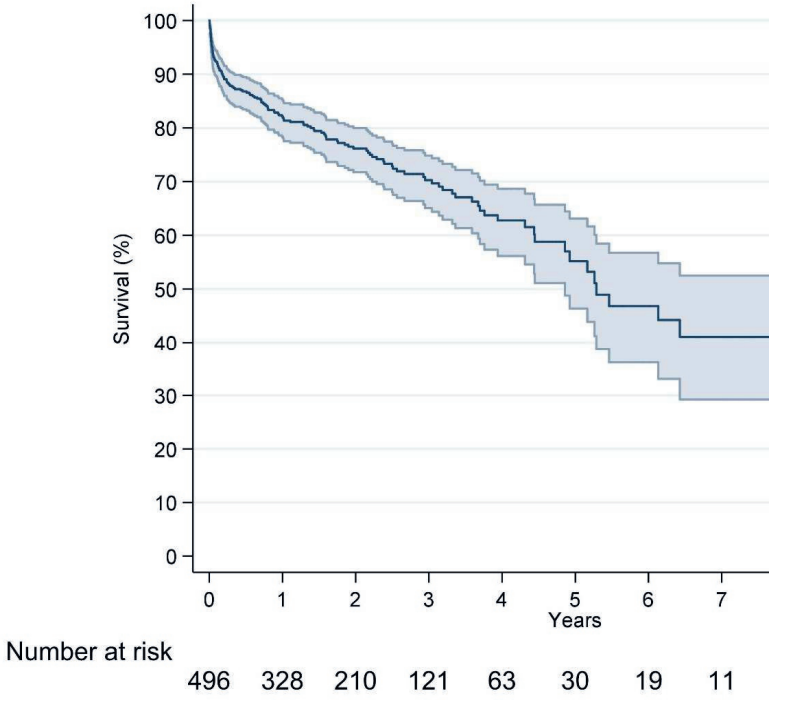
As mentioned previously, patients in INTERMACS profile 1 (refractory cardiogenic shock) are generally not candidates for long-term MCS directly, but require stabilisation on temporary MCS first, to see if organ function recovers. Primary LVAD implantation in these patients has a proven

worse outcome in comparison with patients in INTERMACS profile 2-4.[10,11]
Besides INTERMACS classification, the evaluation of right ventricular function is very important as there are no reliable options for long-term right ventricular support and right heart failure (RHF) is one of the main complications after LVAD implantation. It is thought to occur in 20-30% of patients, especially early postoperatively after LVAD implantation and is the primary cause of death in 10%.[8,10,11] Many criteria are formulated to try to predict perioperative RHF after LVAD implantation. No single criterion suffices, but recently a risk score based on the EUROMACS data was developed, in which invasive pressure measurements, echocardiographic and clinical parameters were combined.[12] Based on this score, a reasonable prediction of early postoperative RHF can be made (C-index of 0.70).
The final decision on LVAD implantation is made by the MCS team (consisting of at least a cardiologist, cardiothoracic surgeon and specialised nurses and technicians) weighing indication, contraindications, right ventricular function, age, previous operations and the ability and willingness of the patient to comply to a complex medical regime against a prospect of potential improvement after LVAD implantation.
With respect to contraindications, potential reversibility has to be analysed, especially with regard to renal insufficiency and hepatic failure.[13-15] Age has to be judged as a biological component in the decision to implant an LVAD. Although there is no absolute upper limit, given the poorer results in elderly people, it is generally not advisable to proceed in patients older than 75 years.[1]

Survival

EUROMACS data, including 2113 patients, demonstrated a survival of 69% (CI 66-71%), 55% (CI 52-58%) and 44% (CI 40-47%) at 1, 2 and 3 years after continuous-flow LVAD implantation, respectively.[16] In the Netherlands, 496 patients (72% male, median age 55 (range 16-74) years) received MCS between 2006 and 2019. Current survival of the four LVAD centers combined is 83%, 76% and 70% after 1, 2 and 3 years, respectively (Fig. 2), with heart transplantation (26%), death (28%), explantation of LVAD (2%) and alive on LVAD on 31 December 2018 (44%) as the endpoint.

Figure 2. Kaplan-Meier survival curve of patients with an LVAD in the Netherlands, implanted between 2006 and 2019



These data are quite promising given the poor prognosis of the patients before LVAD implantation.[17] Following LVAD implantation, not only survival, but also quality of life and exercise capacity improves impressively, allowing a return to a normal life, including sports activities and even resumption of work.[18-20] Despite this promising survival, morbidity after LVAD implantation remains substantial, as was confirmed in a recent publication showing major bleeding and ventricular tachycardia as the most commonly encountered adverse events.[21]

Adverse events

Infection

Device-related infections might be limited to the exit site of the driveline but may also extend to other parts of the system. Incidence rates are highest in the first 3 months postoperatively, namely 0.25 events per patient-year. Thereafter, incidence is 0.17 events per patient-year.[10] Patients often require longstanding antibiotic and/or surgical treatment. A recent study identified that the risk for LVAD-associated infections is increased in HM-II when compared with HVAD and in patients who need post-LVAD ICD-related procedures.[22] In the MOMENTUM 3 trial, comparing outcome in HM3 versus HM-II, device-related infections occurred equally in HM3 and HM-II.[8]

Right heart failure

RHF is defined by INTERMACS as increased central venous pressure (>15 mmHg) with echocardiographic (right heart dysfunction, dilatation and/or significant tricuspid regurgitation) and clinical signs of venous congestion.[11] This may require an increased dose of diuretics and/or inotropics and/or nitric oxide ventilation and/or temporary mechanical support. RHF can occur in the early postoperative phase, but may also develop later in the course of the disease. Patients with late RHF have a worse prognosis in terms of survival and functional capacity, and are more frequently readmitted in comparison with patients without late RHF.[23]

Device malfunction

Device malfunction, including pump thrombosis and driveline-related problems, were most often seen in the HM-II resulting in the need for LVAD replacement. Technical improvement led to almost elimination of pump thrombosis in HM3, as shown in the MOMENTUM 3 trial.[8] However, in HVAD patients, pump thrombosis is still an important problem.[24] In HM3, rare cases of outflow graft twisting have been reported, resulting in decreased pump flow and the need for reparative treatment.[25]

Bleeding

Major bleeding is defined as a suspected internal or external bleeding, resulting in death, rethoracotomy, hospitalisation and/or transfusion of red blood cells (within the first 7 days after the implantation requiring transfusion ≥4 units of packed red blood cells, or any transfusion beyond 7 days postoperatively).[11]

Bleeding is related to the use of anticoagulation and antiplatelet therapy in combination with acquired Von Willebrand syndrome after LVAD implantation as a result of decreased pulsatility.[26-28] This may result in recurrent episodes of gastrointestinal bleeding and nose bleeds.

Stroke

Patients on MCS may suffer from ischaemic and/or haemorrhagic stroke. In the MOMENTUM 3 trial strokes occurred equally (0.10 and 0.26 events per patient-year, p=0.09, respectively) in both devices during short-term follow-up (31-180 days postoperatively), but beyond this period strokes were 3.3 times less frequently seen with HM3.[28] Stroke is not only an important cause of morbidity, but also a predictor of mortality.[29,30] In case of ischaemic or haemorrhagic stroke, the anticoagulation regimen often needs to be revised, thereby increasing the risk for either a haemorrhagic transformation of the ischaemic stroke or pump thrombosis, respectively. This delicate balance between thrombosis and bleeding, known as haemocompatibility, remains one of the major challenges in MCS management.

Arrhythmias

Ventricular arrhythmias are highly prevalent during MCS (30%), both in the early postoperative phase and later in the course of the disease.[31] Ventricular arrhythmias might be tolerated relatively well (i.e. no loss of consciousness) because output is preserved by the LVAD. However, clinically patients may present with RHF. Most often, the underlying cardiomyopathy leads to ventricular arrhythmias, especially in those patients who already had ventricular arrhythmias prior to the LVAD implantation.[31] There is no consensus about ICD tachytherapy in MCS patients, where a shock in conscious patients is unfortunate, while on the other hand ventricular arrhythmias are detected early to prevent RHF and hypoperfusion. Most often, ICD settings are adapted to only treat very fast ventricular arrhythmias including ventricular fibrillation. Apart from ventricular arrhythmias, atrial fibrillation is also common in MCS, and depending on the clinical effect, might require rhythm control.[2]

Referral

Given the fact that the optimal timing of LVAD implantation is crucial and that the outcome after LVAD implantation in patients with rapidly progressive heart failure (INTERMACS I) is far inferior to outcome in patients with less severe heart failure, early referral to a transplant and MCS center is mandatory. Several characteristics suggesting referral are:

- Severely symptomatic: NYHA III+ to IV despite optimal heart failure treatment;
- Relatively young patients with symptomatic heart failure;
- Genetic cardiomyopathies with a likelihood of rapid progression of disease (e.g. PLN mutation);
- Recurrent admissions for heart failure;
- Inotrope dependency;
- Difficulties in titration of heart failure medication (as a result of hypotension, renal failure, intolerance);
- The need for high-dose diuretics (arbitrary >4 mg bumetanide/ >160 mg furosemide).

The mnemonic 'I Need Help', is a helpful tool for timely referral (Table 3).[32]

Table 3. Patient selection for referral to advanced heart failure center using I NEED HELP

I	Inotropics	Previous or current need for inotropics
N	NYHA III-IV/Natriuretic peptides	Persisting NYHA III-IV or increased (NT-pro)BNP
E	End organ failure	Deteriorating kidney and/or liver function
E	Ejection fraction	Severely depressed left ventricular function (ejection fraction <20%)
D	Defibrillator shocks	Repeated ICD shocks
H	Hospitalizations	More than 1 admission for heart failure in the last 12 months
E	Edema or escalating diuretics	Persisting congestion or increasing diuretic dose
L	Low blood pressure	Consistent low systolic blood pressure (<90-100 mmHg)
P	Prognostic medication	Inability to titrate evidence based medication (ACE-inhibitor/ARB/beta blocker/MRA or ARNI)

Legend: NYHA=New York Heart Association; (NT-pro)BNP=(N-terminal-pro) B-type natriuretic peptide; ICD= implantable cardioverter defibrillator ACE-inhibitor=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; MRA=mineralocorticoid receptor antagonist; ARNI=angiontensin receptor neprilysin inhibitor

Conclusions and future directions

All patients with advanced heart failure that proves refractory to optimal conventional therapy have to be considered for heart transplantation and/or long-term MCS. Early consultation and referral to a tertiary center for evaluation of treatment options and the correct timing of advanced therapies is mandatory. In this analysis, many factors have to be weighed, including prognosis without heart transplantation /MCS, outcome after heart transplantation /MCS with regard to mortality and morbidity as well as an idea on potential improvement after heart transplantation /MCS implantation.

Currently, survival after LVAD therapy in the Netherlands approximates 83%, 76% and 70% after 1, 2 and 3 years, respectively. However, this therapy is still associated with substantial morbidity. The intensive management of LVAD patients is reserved to implanting centers, but in case of adverse events, these patients may present to other hospitals. Therefore, all cardiologists need to be aware of the management of adverse events in MCS patients.[33] Outcome after LVAD therapy can be improved by technical adjustments in the design; infectious complications surely will be diminished if there is no longer a need for a driveline to deliver energy to the pump.[34] Personalised anticoagulation may decrease bleeding problems as well as thrombosis. In this way outcome after LVAD implantation will improve even more. Therefore, it has to be expected that long-term MCS will become more and more important as a generally accepted, frequently applied therapy in advanced heart failure.

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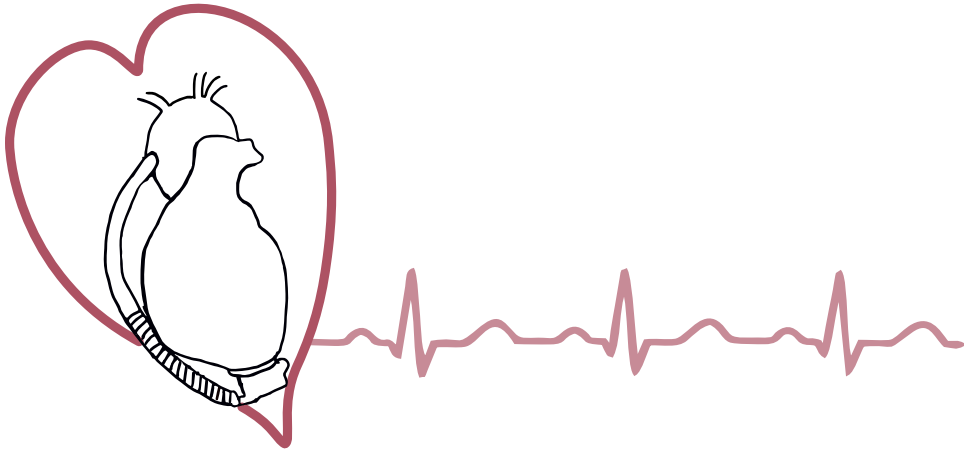
CHAPTER 9

9

General discussion



Introduction

For advanced heart failure patients, refractory to medical therapy with or without cardiac resynchronization therapy, a heart transplantation has been the gold standard for years. [1,2] However, as a result of the shortage of donor hearts, only a few patients may benefit from this therapy. As the number of donor hearts is unlikely to increase substantially, while the prevalence of heart failure certainly increases, alternative treatments have been developed. In the past decades, mechanical circulatory support (MCS) by left ventricular assist devices (LVADs) has demonstrated improved life expectancy and quality of life in these patients. [3-6] However, the use of long-term MCS is still associated with different categories of adverse events, including infection, bleeding, stroke and right-sided heart failure. [7]

In this chapter, we focus on the interpretation of our findings on the long-term outcome of patients treated with MCS, placed in a broad clinical and future perspective. The main question is whether and how MCS could become an alternative to heart transplantation in the near future.

Challenges in the treatment with MCS

In the total trajectory of MCS therapy, the medical management of patients is associated with challenges, starting with patient selection and optimal timing of implantation. In addition, the long-term care after MCS implantation is accompanied by difficulties that have to be addressed by a multidisciplinary team consisting of MCS-dedicated cardiologists, cardiothoracic surgeons, specialised nurses, technicians and paramedics.
In the paragraphs below, different elements of long-term MCS are described, including current practice and future perspectives.

Indication and timing

Advanced heart failure is defined if patients meet all of the following criteria: [8]

1. Severe and persistent symptoms of heart failure (New York Heart Association (NYHA) class III or IV)
2. Severe cardiac dysfunction defined by a reduced left ventricular ejection fraction (LVEF ≤30%), isolated right ventricular failure or non-operable severe valve abnormalities or congenital abnormalities or persistent high B-type natriuretic peptide (BNP) or N-terminal-proBNP brain natriuretic peptide values and data of severe diastolic dysfunction or left ventricular structural abnormalities according to the ESC definition of heart failure with preserved ejection fraction and mid-range ejection fraction.
3. Episodes of pulmonary or systemic congestion requiring high doses of diuretics or episodes of low output requiring inotropes or vasoactive drugs, or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months
4. Severe impairment of exercise capacity, estimated to be of cardiac origin

In patients with advanced heart failure, long-term mechanical circulatory support may be considered. Careful selection and timing of implantation is assigned to dedicated centers who are able to provide the entire spectrum of care for MCS patients. For referring cardiologists, it is very important to identify patients with advanced heart failure who might benefit from additional therapies, at an early stage.

As described in **Chapter 2 & 8,** early referral of a patient with advanced heart failure is important for the outcome, because patients in critical cardiogenic shock (Inter-agency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile 1) have worse outcome than patients with a better clinical situation (INTERMACS profile 2-4). [7,9] A combination of clinical, laboratory, imaging and risk score data may be used to trigger referral, but for daily clinical practice the mnemonic "I NEED HELP" is helpful. [2, 10] It is important to realize that the selection

of patients in MCS centers includes different diagnostic tests to evaluate the presence of contra-indications for long-term MCS. Here, also the psychosocial aspect is taken into account. [11]

When MCS is indicated by the multidisciplinary advanced heart failure team of an expertise center, the timing of LVAD implantation needs to be determined. Several studies have evaluated the optimal timing of different clinical categories according to the INTERMACS profiles. [2, 12] For patients in cardiogenic shock (INTERMACS 1), the hemodynamic situation first requires stabilization on temporary MCS.
Patients in INTERMACS 2, who have a declining function despite inotropes, require an LVAD within a few days, while patients in INTERMACS 3 (stable, but inotrope dependent) could be implanted elective over a period of weeks. [13] In our experience, especially young patients in INTERMACS 2-3 might deteriorate quickly despite an apparently stable situation. Close monitoring, including invasive hemodynamics using a Swan-Ganz catheter is helpful in these situations. For INTERMACS 4, implantation of a LVAD has shown to be associated with better survival, functional capacity and improved quality of life when treated in comparison to optimal medical treatment, but could be implanted elective within weeks to a few months. [13,14] The clinical classification according to INTERMACS is therefore helpful with regard to timing of LVAD implantation.

The final decision on LVAD implantation is made by the multidisciplinary MCS team weighing the indication, (temporary) contraindications, right ventricular function, age, previous operations and the ability and willingness of the patient to comply to a complex medical regime against a prospect of potential improvement after LVAD implantation.
LVADs can be implanted as a bridge to heart transplantation (BTT), bridge to candidacy or, as an alternative to heart transplantation, as destination therapy (DT). In The Netherlands, the difference between BTT and DT has become more artificial. This is related to the shortage of donor hearts, where most patients initially implanted as BTT end up receiving extended MCS. In addition, eligibility for a heart transplantation might change over time and should be constantly re-evaluated. [15] As a result, in >40% of patients, the initial strategic intention of implantation has changed after 2 years. [16]

Survival

As presented in **Chapter 3**, not only short-term outcome, but also 5-year survival after LVAD implantation demonstrated that MCS is a promising therapy for patients with advanced heart failure. Currently, in the first years after implantation, survival on MCS approximate survival after heart transplantation, though MCS survival rates beyond 5 years postoperatively are not available yet. Technological developments (e.g. HeartMate 3, HM 3) could provide long-term survival, as the HM 3 was superior to the HM II with respect to survival free of disabling stroke or reoperation or remove a malfunctioning device in the landmark trial MOMENTUM 3. [17] Apart from stroke and malfunction of the devices, other adverse events should also be reduced to provide long-term MCS.

Management of adverse events

Following LVAD implantation, patients may suffer from different adverse events, for example bleeding, thrombosis and right heart failure, as discussed in **Chapter 4 to 6**. Prediction remains difficult for all adverse events. This is probably related to the multifactorial etiology together with a dynamic risk of a specific adverse events over time. [18]

Hemocompatibility related adverse events, e.g. pump thrombosis, stroke and bleeding, occur less frequently in HM 3 devices in comparison to HM II devices. [6,9] However, bleedings still had an incidence of 0.61 events per patient year (EPPY). [17] It is well-known that the increased risk of bleeding in MCS patients is multifactorial, though importantly determined by the combination of both a vitamin K antagonist and a platelet inhibitor. The decreased incidence of thrombotic events in HM 3 has led to the investigation of a lower intensity anticoagulation regimen. For example, the Magentum study (including 15 patients), analyzed the freedom of thrombotic adverse events using a lower target INR (1.5-1.9 instead of 2-3) for the vitamin K antagonists. This study showed no thrombo-embolic events over 6 months after HM 3 implantation. [19] However, it was a small study, so this alternative anticoagulation regimen has not led to clinical implications (yet). Furthermore, a lower dose of Aspirin (81mg) instead of the usual dose (325mg) prescribed in the USA revealed similar rates of bleeding and thrombotic events during

2-year follow-up. [20] In the Netherlands, patients are already treated with a lower dose antiplatelet therapy (Carbasalaatcalcium 100 or 200mg) in comparison to the dose prescribed in the USA. Future studies are necessary to determine whether Aspirin is required at all in HM 3 patients, or the target INR range could be decreased. Hopefully, the randomized trial The Antiplatelet Removal and Hemocompatibility EventS With the HeartMate 3 Pump IDE Study trial (NCT04069156), will provide sufficient evidence to the need for platelet inhibition. [21] Probably, removal of antiplatelet therapy is most promising to lower the intensity of anticoagulation regimen in the newer devices.

In addition, early detection of hemocompatibility related adverse events could help prevent major events. Actual pump data, including power, flow and speed are visualized on the screen of the controller, but long-term data are now collected by the manufacturer. Temporal changes might detect pump thrombosis at an early stage and could be visualized by an app for example. [22] Ultimately, pump data together with clinical data collected in the electronic health record, could result in a risk model to identify a patient at risk for an adverse event. This may result in closer monitoring of patients at risk and/or interventions to limit or even prevent the adverse event.

To reduce stroke rates after LVAD implantation, it is proposed to regulate the anticoagulation regimen and blood pressure regulation (MAP < 90mmHg) optimally, together with statin therapy in patients with cardiovascular risk factors. [23,24]

The above-mentioned adverse events are less prevalent since the advent of the HM 3. However, other adverse events unfortunately still occur unchanged with the third generation devices. For example infections, who are sub classified into device-specific (pump and/or cannula, pocket, driveline), device-related (bloodstream infections, mediastinitis), and non-device infections (respiratory, urinary tract, other). [25] The development of an internalized system, without the need for a driveline that exits the body through the abdominal wall, has the potential to substantially reduce the risk of infection. [26,27]

In addition, right heart failure remains a major challenge in MCS, both early after implantation but also during long-term support. The identification of patients at risk and early intervention

might prevent further clinical deterioration and rehospitalization. Currently, we are only at the verge of acquiring accurate risk stratification for late RHF. To gain insight into risk factors for all patients suffering from late RHF, we also included patients who were treated for late RHF at the outpatient clinic. Pre-operative clinical parameters and longer ICU stay increased the risk of late RHF, as described in **Chapter 6**. In our analysis, echocardiographic and hemodynamic data before implantation did not independently predict late RHF in addition to baseline clinical parameters. Based on these findings, it is now only possible to monitor patients during follow-up, both clinically and echocardiographically, to identify early signs of right heart failure.
In patients refractory to medical therapy for severe RHF, some centers have implanted durable devices, most HVAD and a few HM 3, for chronic mechanical right ventricular support. [28,29] In these small case series, a few patients were supported > 12 months. [28,29] The potential for long-term biventricular support should be analyzed in future studies. [30]

Functional outcome

Improvement of functional capacity is increasingly important in patients on long-term MCS to improve quality of life and the opportunity to reintegrate into the society. In **Chapter 7**, the results of serial cardiopulmonary exercise tests in the first year after LVAD implantation were presented. An improvement of exercise capacity from six to twelve months after implantation is an important finding for patients with MCS as extended bridge to heart transplantation and those with MCS as destination therapy.

At our center, all patients receive a cardiac rehabilitation program after implantation, under supervision of a second-line physiotherapist. Additional evidence on the main determinants of exercise capacity in MCS patients may optimize cardiac rehabilitation and thereby further improve the functional capacity of our patients. Unfortunately, there are currently no guidelines on the specific exercise training, modality and duration for MCS patients. The main evidence is summarized in a position paper on exercise training in LVAD patients, published by the committee on exercise physiology and training and the committee of advanced heart failure of the heart failure association of the European society of cardiology (2019), accompanied by

practical advice. [31] Based on the available evidence, both dynamic and resistance exercise is indicated.

The diagnostic value of exercise testing also relates to the identification of patients who are more vulnerable for late RHF, as described in **Chapter 6**. Patients developing late RHF had significantly worse exercise capacity at 6 months after implantation.

Based on these results, poor exercise capacity on cardiopulmonary exercise test could trigger either closer monitoring for the detection of (early) signs of right ventricular failure and/or select patients who may benefit from prolonged cardiac rehabilitation to improve respiratory status and muscle strength. The association between limb muscle strength, inspiratory muscle strength and pVO2 in this patient category should be further analyzed to provide an optimal rehabilitation program per patient.

The role of long-term MCS in advanced heart failure – future perspectives

Currently, in the Netherlands, long-term MCS is associated with survival of 83%, 76% and 70% after 1, 2 and 3 years, respectively, as described in **Chapter 8**. The specialized MCS care is reserved to the four implanting centers, but patients may present with adverse events to other hospitals as well. Therefore, all cardiologist should be aware of the most prevalent adverse events related to this therapy, especially with regard to the future where long-term MCS will likely become a more frequently applied therapy in advanced heart failure.

Technological improvements of the devices have already translated into improved clinical outcome for advanced heart failure patients treated with durable MCS. [17] It is to be expected that further technological developments will result in a lower risk of device-specific infections, by the introduction of an internalized LVAD without driveline. However, other adverse events like right heart failure are unlikely to resolve with technical improvements of LVAD devices. At present, especially in biventricular failure, a heart transplantation is the best durable therapy. Although associated with adverse events, median survival of heart transplant recipients reaches approximately 15 years. [32,33] An improved long-term survival on MCS allows postponement of a

heart transplantation. Consequently, overall survival will improve significantly, as the period of MCS is added to the survival period after heart transplantation.

Furthermore, because of a persistent shortage of donor hearts, heart transplantations may become reserved for an even more select group of patients, in which MCS is not sufficient. Examples include congenital heart disease, biventricular failure and patients with therapy-refractory adverse events on MCS. For these patients, total artificial hearts might become an alternative therapy as well. [34] In addition, the shortage of donor hearts may be somewhat reduced by the potential of heart transplantation with donors after circulatory determination of death (DCD), which might increase the donor pool by 20-30%. [35]

As a consequence of these developments, the treatment perspective for patients with advanced heart failure will change in the coming years. MCS will likely enhance its function as mainstay in the treatment of advanced heart failure, resulting in a further improvement of prognosis and quality of life of patients. This is supported by the findings of this thesis, including survival rates approaching those of the first years after heart transplantation and the ability to achieve a normal functional capacity in a substantial number of patients.

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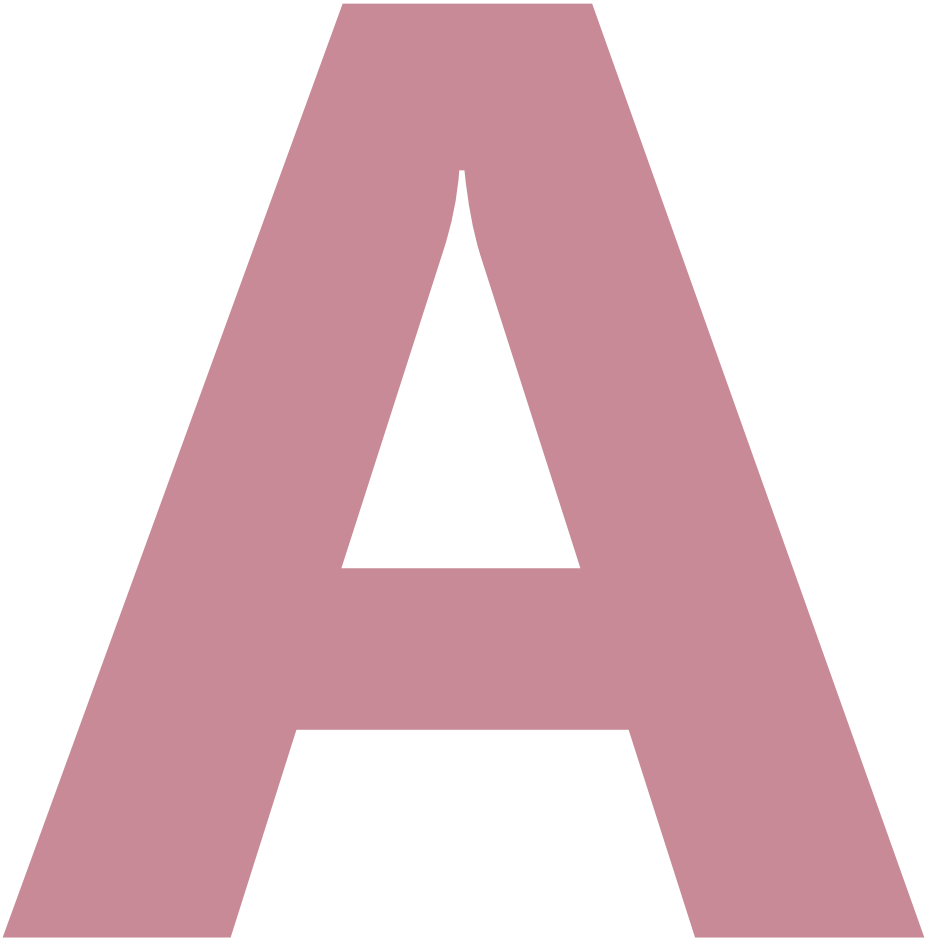
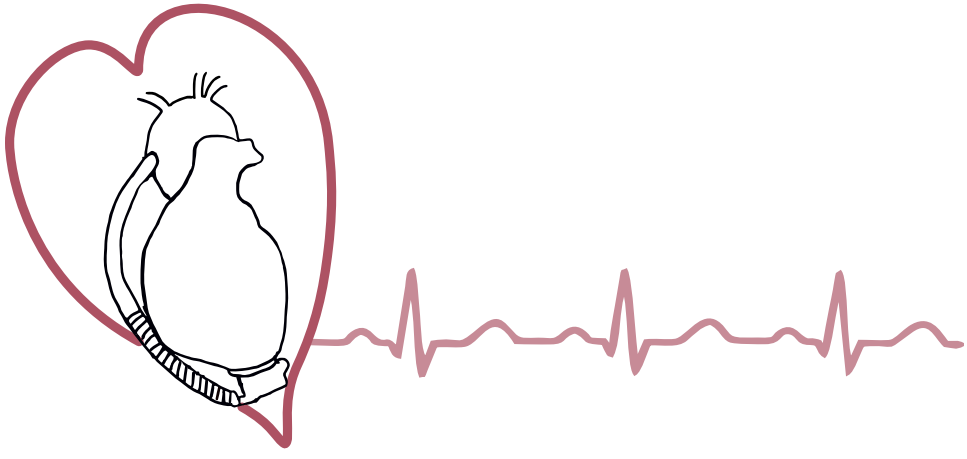


Appendix



Summary

In patients with advanced systolic heart failure (defined as New York Heart Association class IIIb or IV), advanced therapies such as heart transplantation or durable mechanical circulatory support (MCS) may be considered. Heart transplantation is an excellent treatment for many patients, however the number of suitable donor hearts is extremely limited.
In the last decades, the use of MCS has increased substantially. Initially, MCS was only implanted as a bridge to heart transplantation. As a result of improved technology, especially the use of durable continuous flow left ventricular assist devices (cf-LVADs), together with the shortage of donor hearts, MCS is used for extended periods of time or even permanent support ('destination therapy').
MCS has proven to increase life expectancy and improve quality of life importantly. However, the use of MCS is associated with potential adverse events, for example infection, bleeding, stroke and right-sided heart failure.

Since cf-LVADs were first implanted in 2006 at the University Medical Center Utrecht, a lot of experience has been gained in the complex management of these patients, including patient selection, timing of implantation and the management of adverse events during follow-up. In this thesis, we aimed to analyze different outcome parameters in patients treated with MCS in our center. Due to misbalance between the number of patients with advanced heart failure and the limited number of suitable donor hearts, duration of MCS in general is longer at our center. As a result, we could study the outcome in long-term MCS. We present the current situation and elaborate on future perspectives of this therapy in the general discussion.

Mechanical circulatory support in heart failure with reduced ejection fraction
Many etiologies may result in a reduced systolic heart function, defined as heart failure with reduced ejection fraction (HFrEF). Patients with resistant symptoms despite optimal medical therapy, and cardiac resynchronization when indicated, may be treated by MCS.

MCS by cf-LVADs results in substantial hemodynamics changes. As a result of the continuous flow, pulsatility is reduced in comparison to the physiologic situation. Consequently, arterial pulsations are most often not or hardly palpable on physical examination and blood pressure is hard to measure. If a patient presents with a ventricular arrhythmia, which can be deceptively well tolerated in MCS patients, an electrocardiogram is therefore required for the diagnosis. In addition, unloading of the left ventricle leads to diminished or abolished aortic valve opening with possible subsequent aortic valve fusion and/or regurgitation. These, and other effects of cf LVADs are described in **Chapter 2**, together with adverse events associated with this therapy, and are illustrated by cases.

Survival and adverse events in MCS

Improved survival in advanced heart failure patients treated with MCS, translates not only for the first year, but up to five years after implantation. In **Chapter 3**, survival rates of MCS patients implanted at the University Medical Center Utrecht, are described. At 1, 3 and 5 years, survival was 83%, 72% and 57%, respectively. These results support its use as extended bridge to heart transplantation, as necessitated by the shortage of donor hearts. Survival in the period 2006-2012 did not differ from that in 2013-2017. In addition, we report on the adverse events associated with MCS. Besides localised infections, not specifically related to the MCS, such as urinary tract infections and pneumonias, the three most commonly encountered adverse events were major bleeding, ventricular tachycardia and minor haemolysis with corresponding event rates of 0.51, 0.35 and 0.26 per patient year, respectively.

Chapter 4 elaborates on the prediction of major bleeding and thrombosis in MCS patients, as the delicate balance between bleeding and thrombosis is one of the difficulties in these patients. This is related to either an increased risk of thrombosis provoked by the interaction of the pump and blood and, on the other hand, the increased risk of bleeding, related to the use of anticoagulation and the acquired von Willebrand syndrome. In this study, we observed that the interruption of the vitamin K antagonist with heparin bridging identified patients at high risk of bleeding. A history of atrial fibrillation doubled the risk of thrombotic adverse events (TIA,

ischemic stroke or pump thrombosis). Furthermore, older age showed to be an important factor in the prediction, frequency and timing of hemorrhagic events in MCS.

As the risk of bleeding changes over time, we aimed to analyze the risk of a bleeding event in MCS patients at any moment during follow-up, as discussed in **Chapter 5**. The initial postoperative phase (30 days) was excluded, as the prevalence and etiology is different from the period thereafter. In this study, not only baseline data, but all data out of the electronic health records were included. These data were entered into a data mining-based approach according the cross-industry standard process for data mining (CRISP-DM), named Auto-Crisp. Using Auto-Crisp, different models were created to predict a major bleeding within 3, 7 and 30 days from any moment during MCS. The performance of these models was acceptable, represented by an area under the curve (AUC) of 0.792, 0.788, and 0.776 for bleedings in the next 3, 7, and 30 days, respectively.

Chapter 6 focuses on the prediction of another important complication related to long-term MCS: late right heart failure (LRHF). LRHF is defined as the occurrence of right ventricular dysfunction associated with symptoms of right heart failure, including jugular venous distension, hepatic congestion and peripheral edema, if diagnosed after the index hospitalization for cf-LVAD implantation. LRHF is associated with worse outcome, including the need for readmission in 8-17% of patients. However, in daily practice, also outpatient MCS patients show signs of progressive right-sided heart failure necessitating increased doses of diuretics, without the direct need for hospitalization. We think this has also to be taken into account as LRHF, and therefore used this definition to identify risk factors in all patients with LRHF, in contrast to the definition used by INTERMACS. In our study, LRHF occurred in 19% of patients. Baseline echocardiographic and invasive hemodynamics did not predict LRHF, but we demonstrated that LRHF can be predicted by cardiogenic shock before implant, a history of atrial fibrillation, a higher pre-operative body mass index and longer duration on the intensive care unit.

Apart from survival rates and the occurrence of different adverse events in patients treated with MCS, we were also interested in the functional outcome in terms of exercise capacity. Especially in long-term support, functional capacity after implantation is getting more and more important for a better quality of life and the opportunity to reintegrate into the society. In **Chapter 7**, we

analyzed the exercise capacity in the first year after MCS, assessed by a routinely planned cardiopulmonary exercise tests (CPETs). Between 6 and 12 months, power and peak oxygen uptake (pVO2) increased significantly. Almost half of patients (44%) showed an increase of >6% in maximal exercise capacity, which is defined as clinically relevant in heart failure patients. This is important information for the growing group of patients on long-term MCS, as improvement of exercise capacity is critical for quality of life in these patients.

Chapter 8 summarizes the role of MCS in the Netherlands. We presented survival rates of the four implanting centers together and revealed an overview of the indications, contraindications, patient selection, clinical outcome and optimal time of referral for long-term MCS.

In the last chapter of this thesis, **Chapter 9**, we further explored our findings on the long-term outcome of patients treated with MCS. We discussed the challenges related to this treatment and elaborate on future perspectives. Further technological optimization might include the development of totally internalized devices, reducing the risk of infection. In addition, in the newer devices, the intensity of anticoagulation might be lowered without leading to an increase of thrombotic events. As prospect for the future, patients with advanced heart failure could be treated with durable MCS for longer periods, thereby further increasing life expectancy and quality of life.

Nederlandse samenvatting

Bij patiënten met vergevorderd hartfalen met een verminderde systolische linker ventrikel functie (gedefinieerd als New York Heart Association klasse IIIb of IV), kunnen geavanceerde behandelingen zoals een harttransplantatie of chronische mechanische circulatoire ondersteuning worden overwogen.
Harttransplantatie is een uitermate goede behandeling voor veel patiënten, echter het aantal geschikte donorharten is erg beperkt.
In de laatste decennia is de toepassing van chronische mechanische ondersteuning (vanaf hier genoemd mechanical circulatory support, MCS) behoorlijk toegenomen. Initieel werd MCS alleen toegepast ter overbrugging van een harttransplantatie. De verbeterde technologie, met name de toepassing van duurzame continue flow left ventricular assist devices (cf-LVADs), tezamen met het tekort aan donorharten, heeft ertoe geleid dat MCS voor langere periodes of zelfs permanente ondersteuning ('destinatie therapie') wordt gebruikt.
MCS heeft bewezen de levensverwachting en kwaliteit van leven van patiënten met vergevorderd hartfalen in belangrijke mate te verbeteren. Echter, de toepassing van MCS kan gepaard gaan met complicaties, zoals infectie, bloeding, cerebrovasculair accident en rechtszijdig hartfalen.

In 2006 werd in het Universitair Medisch Centrum Utrecht de eerste cf-LVAD geïmplanteeerd. Sindsdien is er veel ervaring opgedaan met de complexe begeleiding van deze patiënten, waaronder de selectie van patiënten, de timing van implantatie en de identificatie en behandeling van complicaties tijdens follow-up.
In dit manuscript hebben we diverse uitkomstmaten geanalyseerd van patiënten behandeld met MCS in ons centrum. Door de onbalans tussen het aantal patiënten met vergevorderd hartfalen en het beperkte aantal geschikte donorharten is de gemiddelde duur van MCS in ons centrum in het algemeen langer. Als gevolg hiervan konden we de uitkomsten van langdurige MCS

bestuderen. We presenteren de huidige situatie en gaan in de algemene discussie dieper in op de toekomstperspectieven van deze therapie.

MCS voor hartfalen met een verminderde systolische linker ventrikel functie.
Hartfalen met een verminderde systolische hartfunctie (ejectiefractie) kan veroorzaakt worden door diverse ziektebeelden. Indien patiënten symptomatisch blijven ondanks optimale medicamenteuze therapie, eventueel gecombineerd met cardiale resynchronisatietherapie op indicatie, kunnen ze worden behandeld met MCS.
MCS met cf-LVADs restulteert in substantiële hemodynamische veranderingen. De continue flow leidt ertoe dat de pulsatiliteit is afgenomen ten opzichte van de fysiologische situatie. Daardoor zijn de arteriële pulsaties meestal niet of nauwelijks palpabel bij lichamelijk onderzoek, en is de bloeddruk lastig te meten. Wanneer een patiënt zich presenteert met een kamerritmestoornis, welke door MCS patiënten goed verdragen kan worden, is daarom een elektrocardiogram nodig voor het stellen van de diagnose.
Daarnaast leidt het unloaden van de linker ventrikel tot een verminderde of afwezige opening van de aortaklep, wat kan resulteren in fusie van de aortaklepbladen en/of aortaklepinsufficiëntie. Deze, en andere effecten van cf-LVADs worden beschreven in **Hoofdstuk 2**, evenals de potentiële complicaties die verband houden met deze therapie. Dit wordt geïllustreerd met enkele casus.

Overleving en complicaties van MCS
De verbeterde overleving van patiënten met vergevorderd hartfalen die worden behandeld met MCS wordt niet alleen in het eerste jaar gezien, maar tot vijf jaar na implantatie. In **Hoofdstuk 3** worden de overlevingscijfers van MCS patiënten van het Universitair Medisch Centrum Utrecht beschreven. Na 1, 3 en 5 jaar bedroeg de overleving respectievelijk 83%, 72% en 57%. Deze resultaten ondersteunen de mogelijkheid om MCS voor een langere periode toe te passen ter overbrugging van een harttransplantatie, wat noodzakelijk is door het tekort aan donorharten. De overlevingscijfers tussen 2006-2012 waren niet anders dan die tussen 2013-2017. Daarnaast beschrijven we de complicaties van MCS. Naast gelokaliseerde infecties, niet specifiek

gerelateerd aan MCS, zoals urineweginfecties en pneumonieën, waren de 3 meest voorkomende complicaties majeure bloeding, ventrikeltachycardie en milde hemolyse, met een incidentie van respectievelijk 0.51, 0.35 en 0.26 events per patiëntjaar.

In **Hoofdstuk 4** gaan we in op de voorspelling van majeure bloeding en trombose bij MCS patiënten, aangezien de delicate balans tussen bloeding en trombose één van de moeilijkheden is bij deze patiëntengroep. Dit komt door enerzijds een verhoogde kans op trombose door de interacte van bloed en de pomp, en anderzijds een verhoogde kans op bloeding door het gebruik van bloedverdunners en het verworven von Willenbrand syndroom. In deze studie toonden we aan dat met het gebruik van heparine, ter overbrugging van de onderbreking van de vitamine K antagonist, patiënten worden geïdentificeerd die een verhoogd risico hebben op bloeding. Verder verhoogde een voorgeschiedenis van atriumfibrilleren het risico op trombotische events (TIA, ischemisch herseninfarct of pomptrombose). Daarnaast namen we waar dat een hogere leeftijd een belangrijke factor is in de voorspelling, frequentie en timing van bloedingen gedurende MCS.

Aangezien het risico op bloedingen gedurende de periode van MCS verandert, hebben we een studie verricht om een bloeding op ieder moment tijdens follow-up te voorspellen. Deze studie wordt beschreven in **Hoofdstuk 5**. Hierbij werd de eerste postoperatieve fase (30 dagen) uitgesloten, omdat de prevalentie en etiologie verschillen van de periode daarna.
In deze studie werden niet alleen de baseline gegevens, maar ook alle gegevens uit de elektronische patiënten dossiers meegenomen. Deze gegevens werden ingevoerd in een op data mining gebaseerde toepassing volgens het 'cross-industry standaard proces voor data mining (CRISP-DM)', genaamd Auto-Crisp. Met behulp van Auto-Crisp werden diverse modellen ontwikkeld om een majeure bloeding te voorspellen binnen 3, 7 en 30 dagen vanaf ieder moment gedurende MCS. Deze modellen hadden een acceptabele accuraatheid, weergegeven door een area under the curve (AUC) van respectievelijk 0.792, 0.788, en 0.776 voor bloedingen binnen 3, 7, en 30 dagen.

Hoofdstuk 6 focust op de voorspelling van een van de andere belangrijke complicaties gerelateerd aan langdurige MCS: laat rechter kamer falen (LRKF). LRKF wordt gedefinieerd als het optreden van rechter ventrikel dysfunctie in combinatie met symptomen passend bij rechter kamer falen, waaronder gestuwde halsvenen, leverstuwing en perifere oedemen, indien gediagnosticeerd na de index opname voor cf LVAD implantatie.
LRKF is geassocieerd met slechtere uitkomsten, waaronder de noodzaak tot heropname in het ziekehuis in 8-17% van de patiënten. Echter, in de dagelijkse klinische praktijk, kunnen MCS patiënten zich ook op de polikliniek presenteren met tekenen van progressief rechtszijdig hartfalen, waarvoor behandeling met hogere dosering diuretica nodig is zonder directe ziekenhuisopname. Wij zijn van mening dat dit ook gerekend moet worden als LRKF.
Daarom hebben we deze definitie gebruikt om risicofactoren bij alle patiënten met LRKF te identificeren, in tegenstelling tot de definitie die door INTERMACS wordt gebruikt. In onze studie trad LRKF op bij 19% van de patiënten. Echocardiogafische metingen voor de rechter ventrikel functie en invasieve hemodynamische parameters waren naast de klinische factoren bij implantatie niet voorspellend voor LRKF. In onze studie waren een cardiogene shock voor implantatie, een voorgeschiedenis van atriumfibrilleren, een hogere pre-operative body mass Index en een langere duur op de intensive care voorspellend voor LRKF.

Naast overleving en het optreden van verschillende complicaties bij patiënten behandeld met MCS, waren we ook geïnteresseerd in de functionele uitkomsten, met name de inspanningcapaciteit. Zeker in geval van langdurige MCS wordt functionele capaciteit meer van belang voor een betere kwaliteit van leven alsook de mogelijkheid om opnieuw te functioneren in de maatschappij.
In **Hoofdstuk 7** hebben we de inspanningscapaciteit gedurende het eerste jaar na MCS geanalyseerd, gemeten met routinematig geplande cardiopulmonale inspanningstest (VO2 max test). De maximale zuurstofopname (piek VO2) steeg significant tussen de test op 6 maanden en de test op 12 maanden na implantatie. Bij ongeveer de helft (44%) van de patiënten bedroeg de toename van maximale inspanningscapaciteit meer dan 6%, wat wordt beschouwd als een klinisch significante toename bij hartfalen patiënten. Dit is belangrijke informatie voor het

toenemende aantal patiënten met langdurige MCS, aangezien een verbetering van de inspanningcapaciteit een voorwaarde is voor een goede kwaliteit van leven.

Hoofdstuk 8 vat de huidige rol van MCS in Nederland samen. We presenteren de overlevingscijfers van de vier implanterende centra samen en geven een overzicht van de indicaties, contra-indicaties, patiënt selectie, klinische uitkomst en optimale moment voor verwijzing naar een LVAD implanterend centrum voor langdurige MCS.

In het laatste hoofdstuk van dit manuscript, **Hoofdstuk 9**, evalueren we onze bevindingen ten aanzien van de lange termijn uitkomsten van patiënten die met MCS zijn behandeld. We beschrijven de uitdagingen die gerelateerd zijn aan deze therapie en gaan in op de toekomstperspectieven. Verdere technologische optimalisatie kan inhouden dat er devices worden ontwikkeld die geen driveline hebben die de buikwand penetreert, waarmee het risico op infecties afneemt. Daarnaast zou de intensiteit van antistolling verlaagd kunnen worden in de nieuwere type devices, zonder het risico op trombose te verhogen.
Als vooruitzicht voor de toekomst kunnen patiënten met vergevorderd hartfalen voor langere tijd met duurzame MCS worden behandeld, waardoor de levensverwachting en kwaliteit van leven verder toenemen.

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Curriculum vitae

Susanne Elisabeth Agnes was born on July 25th 1985 in Boxtel, the Netherlands. After attending the Jacob Roelandslyceum (Boxtel) where she obtained her gymnasium diploma in 2003, she studied medicine at the University of Maastricht. Even before she got her propaedeutic, she wanted to become a cardiologist. During the last year of the study, she had a scientific internship at the cardiology department under supervision of prof. Heymans. She studied on idiopathic dilated cardiomyopathy. Her clinical internship was at the Maxima Medical Center in Veldhoven.

After graduation from medical school, she started working as a resident (ANIOS) at the cardiology deparment of the Jeroen Bosch hospital from August 2009 untill the beginning of 2010. Then, she started at the UMC Utrecht, first as ANIOS at the cardiology department and from September 2010 – September 2011, she assisted in the cardiology courses of the UMC Utrecht medical school.

From 2011 to 2018, she had the cardiology training at the UMC Utrecht under supervision of dr. J.H. Kirkels. In the last year of the training, she combined clinical work with this PhD on the outcome of long-term mechanical circulatory support. After completing the cardiology training, she subsequently started a fellowship on cardiovascular imaging in combination with the PhD until October 2020. Since then, she works as Chef the Clinique imager at the Catharina Hospital, Eindhoven.

Susanne is married to Giel van Giersbergen and together they have 3 children: Koen (2014), Lisa (2016) and Daan (2019).

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