European Journal of Cardio-Thoracic Surgery 55 (2019) i31–i37
doi:10.1093/ejcts/ezy444

REVIEW

Cite this article as: Schramm R, Morshuis M, Schoenbrodt M, Boergermann J, Hakim-Meibodi K, Hata M *et al*. Current perspectives on mechanical circulatory support. Eur J Cardiothorac Surg 2019;55:i31–i37.

Current perspectives on mechanical circulatory support

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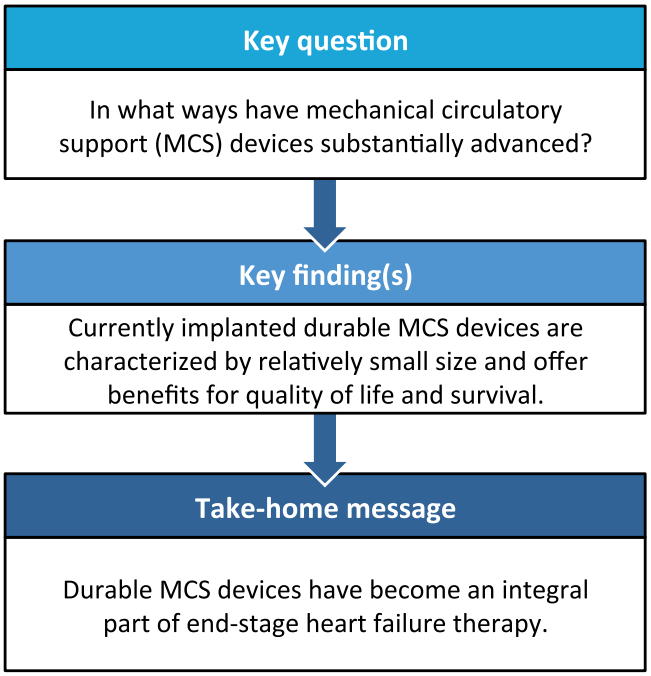
Received 20 August 2018; received in revised form 7 November 2018; accepted 8 November 2018

Summary

Mechanical circulatory support gained a significant value in the armamentarium of heart failure therapy because of the increased awareness of the prevalence of heart failure and the tremendous advances in the field of mechanical circulatory support during the last decades. Current device technologies already complement a heart transplant as the gold standard of treatment for patients with end-stage heart failure refractory to conservative medical therapy. This article reviews important aspects of mechanical circulatory support therapy and focuses on currently debated issues.

Keywords: Mechanical circulatory report • Left ventricular assist device • Total artificial heart • Biventricular assist device



INTRODUCTION

Heart failure (HF) remains a significant cause of morbidity and mortality. A heart transplant (HTx) remains the ultimate gold standard of treatment for selected patients with end-stage HF that is refractory to optimal medical treatment. The registry of the International Society for Heart and Lung Transplantation reports the excellent short- and long-term outcomes of an HTx with 1- and 10-year survival rates of approximately 85% and 50%, respectively [1]. The shortage of donor organs enforces the establishment of waiting lists and allocation algorithms. This shortage encouraged the search for therapeutic alternatives, allowing for both adequate circulatory homeostasis and prompt availability when needed.

Improvements in device technology have made mechanical circulatory support (MCS) an attractive alternative for the treatment of end-stage HF. More durable MCS systems have permitted bridge to transplant (BTT) therapy, saving patients with impending secondary organ dysfunction awaiting a transplant [2]. The use of MCS for this group of patients is a class IIa C recommendation [3]. Growing numbers of patients with end-stage HF who are ineligible for a transplant can be implanted with MCS as destination therapy (DT) in order to improve survival and quality of life (class IIa B recommendation) [3].

This article is a review of the aspects of MCS therapy that are important for end-stage HF and focuses on current concepts and contemporarily debated issues.

GENERAL ASPECTS

The clinical use of MCS devices underlies distinct considerations with respect to urgency as well as individual patient prognosis long term. In the short term, MCS may be established by percutaneous implantation of an intra-aortic balloon pump, an Impella® (ABIOMED, Danvers, MA, USA) device or venoarterial extracorporeal membrane oxygenation. In the venoarterial setting for acute circulatory decompensation, extracorporeal membrane oxygenation is frequently termed extracorporeal life support (ECLS) and is basically closed-circuit cardiopulmonary bypass [4]. When established via the groin vessels, it requires an additional distal leg perfusion cannula to avoid hypoxia/ischaemia of the lower extremity. The peripheral ECLS cannulation may carry the risk of the development of the so-called harlequin syndrome, i.e. concomitant pulmonary insufficiency in parallel with incomplete cardiopulmonary bypass via the ECLS system may cause hypoxia in the upper half of the body. Markedly increased afterload may cause complete cessation of left ventricular volume ejection under peripheral ECLS, triggering pulmonary oedema and congestion. Problem solving is variable and may include central cannulation techniques, escalation into a venoarterial-venous setting or various combinations of MCS devices, e.g. insertion of the Impella device for ventricular unloading in parallel with peripheral ECLS [5].

Acute MCS is never a cure but rather a therapeutic bridge. It may be a bridge to recovery for decision-making or, rarely, to a transplant. Acute MCS may be instituted as well to allow for otherwise risky or impossible therapeutic interventions, for example lung or even multiorgan transplants [6]. Finally, it can precede the implantation of durable MCS devices, again demanding adjustment of the patient-specific therapeutic long-term goals [7].

The rationale for implantation of durable MCS devices follows basically the same thought pattern as that used for short-term MCS devices; however, one is planning for the long term. Ventricular assist devices (VADs) are implanted as a bridge to wait listing (candidacy) and to a transplant but may just as well be explanted in the rare case of cardiac recovery. Patients who are not and will not be eligible for an HTx may qualify for DT, i.e. a VAD is implanted for permanent, life-long support (Table 1) [8].

Table 1: Strategies in durable MCS therapy

Bridge to recovery	Durable MCS is implanted to allow the patient to recover from the underlying cardiac disease; device explantation may be performed
Bridge to transplantation	Durable MCS is implanted into patients who are eligible for a heart transplant with a high risk of waitlist mortality
Bridge to candidacy	Durable MCS is implanted into patients who are not yet transplant candidates but might become eligible for transplant
Bridge to decision	Durable MCS is implanted into patients at subacute high risk and in whom perspective decision-making needs to be postponed
Destination therapy	Durable MCS is implanted into patients for permanent, life-long support when a heart transplant is not a therapeutic option

MCS: mechanical circulatory support.

PATIENT SELECTION

Durable MCS therapy in patients with end-stage HF is challenging and demands a multidisciplinary approach in experienced high-volume centres, preferably with a transplant background. The continuous involvement of various disciplines expands beyond the perioperative setting into ambulatory care. There is a constant 24/7 need, not only for MCS-dedicated cardiologists and surgeons but also for a team of specifically trained technicians and physiotherapists. The psychological burden must not be neglected, and specialized psychologists frequently cover the entire social environment of the patient with MCS, including the long-term issues [9].

Previous experience has shown that patient selection for and the timing of the implantation of left ventricular assist devices (LVADs) are crucial for optimal outcomes [10]. Selecting the ideal patients from the extremely heterogeneous cohort of patients with end-stage HF is an extremely challenging task. LVAD-specific risk-predicting scoring models have been introduced, including the HeartMate II Risk Score, the Destination Therapy Risk Score and the non-LVAD specific Seattle Heart Failure Model [11–13]. So far, none of these risk assessment scores accurately predicts the postimplant clinical course. Thus, an improved model for risk stratification is clearly needed.

The leading indication for LVAD therapy is no longer BTT but DT in patients who are ineligible for an HTx [10, 14]. Deciding on one or the other strategy requires a balance of the predicted natural course of the patient with HF versus the chances of the patient surviving the complications of and the quality of life with LVAD therapy. This challenge is hardly feasible in clinical practice. Clinicians often default to a 'no clear intent' strategy of 'bridge to candidacy'. Eligibility for a transplant is dynamic and must be continuously re-evaluated [15]. The initial strategic decision is changed in more than 40% of patients after 2 years. It is therefore currently under debate whether a definition of the strategic intent is useful.

REGISTRIES AND DATABASES

The Interagency Registry for Mechanically Assisted Circulatory Support (Intermacs) was founded in 2005 at the University of Alabama at Birmingham, United States, and is a North American database summarizing the clinical outcome profiles of patients with HF who receive a Food and Drug Administration (FDA)-approved MCS device [16]. Since January 2018, it has become an integral part of the audited Society of Thoracic Surgeons (STS) database with more than 25000 patients currently enrolled at 157 active sites [10]. Pedimacs is a part of the Intermacs registry designated for the special issues inherent in paediatric HF. Euromacs is the European equivalent of Intermacs and has become a committee of the European Association of Cardio-Thoracic Surgeons. It was founded in Berlin, Germany, in 2009 and went 'live' in 2012 [17]. The last Euromacs report, published in 2017, had 52 participating hospitals in the registry with close to 3000 implants [18]. The goal of these registries is to provide information facilitating optimal device–patient matching and objective evaluation of MCS pumps.

Table 2: Currently used durable mechanical circulatory support devices

	Manufacturer	Remarks
Intracorporeal ventricular assist devices		
Incor®	BerlinHeart®	First implant 2002, CE mark 2003
HVAD®	Medtronic®	CE mark 2008, FDA approval BTT 2012, FDA approval lateral implantation 2015
HeartMate II®	Abbott®	First implant 2003, FDA approval BTT 2008, DT 2010
HeartMate III®	Abbott®	First implant 2014, CE mark 2015
EVAHEART® 2	Evaheart Inc.®	First implants 2005 in Japan, Investigational Device Exemption (IDE) approval by FDA, BTT trial ongoing
Jarvik2000®	JarvikHeart®	First implant 2000, CE mark 2005, FDA approval BTT 2005, DT trial ongoing
Heart Assist 5	Reliant Heart Inc.®	First implant 1998, CE mark 2001, BTT trial ongoing
Paracorporeal ventricular assist devices		
Excor®	BerlinHeart®	First implant 1990, CE mark 1996, FDA approval paediatric 2011
Total artificial heart		
SynCardia TAH®	SynCardia®	First implant 1986, FDA approval BTT 2004
Carmat TAH®	Carmat SA®	First implant 2013, investigational device

BTT: bridge to transplant; CE: Conformité Européene (European conformity); DT: destination therapy; FDA: Federal Food and Drug Administration.

THE EVOLUTION OF DURABLE MECHANICAL CIRCULATORY SUPPORT DEVICES

Technological progress has improved durable MCS devices substantially over the last decades. The heart team's choice of the device depends on the implantation strategy, e.g. BTT or DT, and on patient-specific factors, e.g. anatomical conditions or a distinct pathophysiological aetiology of the HF (restrictive vs eccentric).

Durable MCS gained public awareness when the Jarvic-7 total artificial heart (TAH) was successfully implanted in a patient in December 1982 [8]. In the 1990s, increasing numbers of patients were bridged to transplant with LVADs [2]. The landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) was published in 2001 and opened the era of DT in patients with end-stage HF not eligible for an HTx [19]. The implantation of pulsatile-flow LVADs resulted in a clinically meaningful survival benefit and improved quality of life, superior to that obtained with optimal medical treatment. However, even if the device was successfully implanted, a multitude of adverse events was observed in the device group. The first-generation VADs mimicked the natural circulation because they produced pulsatile flow (PF). The setup of the pneumatic chamber, driveline, controller and power source was relatively big and noisy [8]. The lack of improvement of patient survival in the post-REMATCH era was mainly due to the durability of and technical issues associated with these early MCS systems.

Engineering second- and third-generation pumps targeted size, biocompatibility, durability, effectiveness and infection issues. Miniaturization and improved efficiency were the main drivers of further developments [20]. The novel devices were more reliable with a reduced failure rate [8]. Currently used durable MCS devices are summarized in Table 2. The most important second generation VAD, the redesigned HeartMate II (Abbott, St. Paul, MN, USA) proved successful as a BTT device in a prospective multicentre study published in 2007 [2]. Patients with end-stage HF profited greatly after implantation of this device in terms of functional status and quality of life [2]. The HeartMate II was approved by the FDA as a BTT in 2008 and a DT in 2010. Surgical implantation may require substantial abdominal dissection and creation of an LVAD pocket in anatomically small patients. Clinical results after implantation of the HeartMate II improved steadily to 85% 1-year survival in the postapproval period [14, 21]. Patients with this continuous flow (CF) device demonstrated dramatically improved survival compared with patients on first-generation PF devices [22].

Third-generation LVADs generate continuous blood flow through a centrifugal pump design. The first relevant third-generation LVAD is the HeartWare ventricular assist device (HVAD®) (Medtronic, Minneapolis, MN, USA), which allows intrapericardial and less invasive implantation [23, 24]. An international clinical trial evaluated the safety and effectiveness of the HVAD as BTT, which led to CE Mark approval in 2008. The ADVANCE (HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure) trial reported 86% 1-year survival after HVAD implantation with significant improvement in functional capacity and quality of life [25]. Based on this BTT evaluation, the HVAD received FDA approval in 2012. The company-funded ENDURANCE trial compared the HVAD with the HeartMate II for DT in patients ineligible for an HTx and showed non-inferiority with respect to survival free from disabling stroke or the need for device replacement [26]. Of note, the use of the study device was associated with a higher risk of stroke, right HF and sepsis, whereas the use of the control device was associated with a higher risk of device malfunction and failure requiring surgical intervention.

The HeartMate III is the latest third-generation LVAD, a centrifugal CF LVAD with a fully magnetically levitated impeller. The MOMENTUM 3 (Multicentre Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3) study compared the HeartMate III with the axial flow pump HeartMate II; the follow-up data are promising. The important finding was that none of the patients with the HeartMate III experienced a pump thrombosis [27]. This complication is probably restrained by the design of the pump, which is characterized by the relatively large housing of the impeller and the intermittent creation of at least some 'pulsatility' by the automated rotational speed variation. The 2-year data are promising, showing superiority with respect to survival free of disabling stroke or exchange reoperation [27]. The CE Mark was warranted in 2015. Advanced surgical techniques for a less invasive process for implanting the HeartMate III have been suggested [28]. Of note, the pump and its outflow socket are somewhat larger

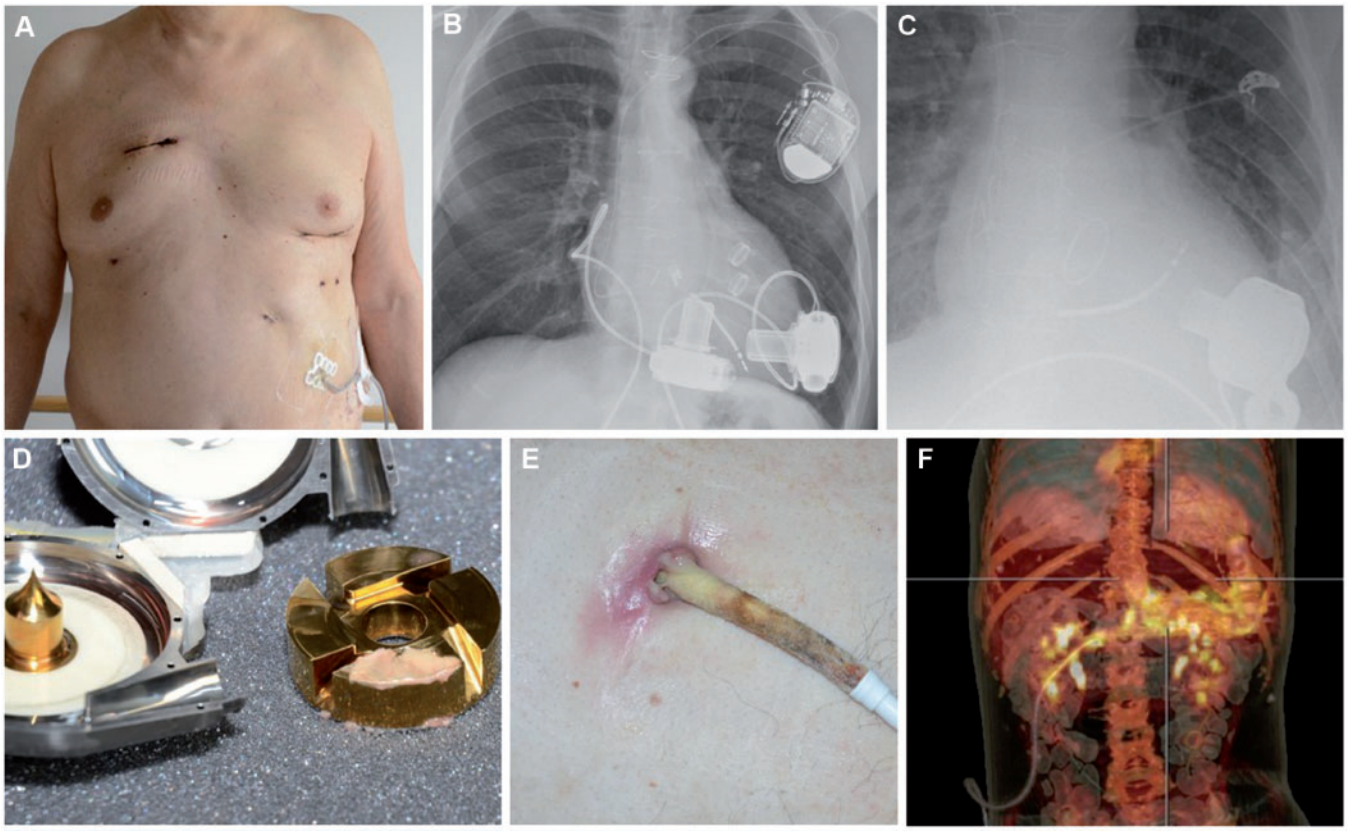


Figure 1: (**A**) Less invasive left ventricular assist device (LVAD) implantation techniques may preserve pericardial integrity and facilitate later median sternotomy in bridge to transplant patients. (**B**) Chest radiograph showing 2 centrifugal continuous flow pumps (HeartWare HVAD®, Medtronic, Minneapolis, MN, USA) for biventricular support. (**C**) A perfectly aligned inflow cannula of the Heartmate 3® within the inflow of the left ventricle and away from the septum may prevent low flow and pump thrombosis. (**D**) Pump thrombosis is a major complication in LVAD therapy. The image shows the impeller of an explanted HeartWare ventricular assist device with fibrin coating. (**E**) Peripheral driveline infections may be treated by antibiotic and local surgical means. (**F**) Positron emission tomography-computed tomography scans may uncover ascending infection of the LVAD, here a Heartmate II.

compared to those of the HVAD, which can turn the less invasive implantation of the HeartMate III into a real challenge, particularly in small patients (Fig. 1A).

The less invasive implantation techniques for the third-generation centrifugal CF pumps preserve the pericardial integrity. Whether this advance will help prevent short-term periprocedural and long-term right HF remains to be seen.

BIVENTRICULAR SUPPORT

The survival data on durable biventricular MCS are sobering [14], which is in opposition to the principle of biventricular support with prompt and complete unloading of the heart in parallel with high-flow organ perfusion. These patients may simply be further down the road of HF and have more severe end-organ dysfunction [29]. In fact, the Intermacs data revealed that those LVAD patients with preoperatively impaired secondary organ functions have a higher risk of death [14]. Which candidates for MCS would profit from a direct, durable biventricular MCS remains an open question, although several parameters have been suggested to be indicative [30, 31]. Right HF complicates up to 40% of CF LVAD implants [32]. Further debate addresses the timing of additional right ventricular (RV) support implanted contemporaneously as durable or temporary. Current clinical practice most frequently favours primary LVAD implantation and, if the right ventricle fails, additional temporary right heart assistance. With the bridge to adaptation or recovery of the failing right heart, patients have the chance to leave the hospital solely on LVAD support. Whether these patients really profit long term and reach both improved survival times and quality of life as do patients with HF after straightforward LVAD implantation remains to be seen. Regardless, if this bridging approach fails, staged implantation of a durable right VAD, a TAH or an urgent HTx is the final option.

A slowly growing number of patients are receiving 2 CF pumps for biventricular support. Primarily the HVAD, but also the HeartMate III and even the Jarvik 2000, have been used clinically [33–35]. Yet, these devices are not approved for right heart assistance. There are no conclusive data on CF pumps for biventricular support available at present, but promising data would definitely challenge the future use of TAH technologies. A company-sponsored, retrospective analysis of the HVAD is about to be published, summarizing the preliminary international experience (Fig. 1B).

William De Vries implanted the first durable biventricular MCS in 1982, i.e. the Jarvik-7 TAH. This device consisted of 2 intracorporeal, pneumatic replacement pumps with transcutaneous air power tubes connected to a computer-assisted driving unit. Despite the tremendous reduction in the weight and size of the

extracorporeal components, the basic principle has been modified only slightly, and this TAH is still in use today. The company rights were transferred to CardioWest Technologies and finally to SynCardia (Tucson, AZ, USA). The Syncardia TAH is still in use, approaching 2000 implants worldwide [36].

Carpentier *et al.* founded the biomedical company Carmat (Vélizy-Villacoublay, France) in order to develop a TAH that would be autoregulative and bioprosthetic. Carmat let the public know that the first implant took place in Paris, France, in December 2013. The 76-year-old patient died 74 days after the operation. The Carmat TAH is bioprosthetic with respect to the pericardial tissue membrane facing the blood phase. Autoregulation is mimicked by an assembly of sensors for the detection and processing of varying filling pressures [37]. Because it weights nearly 900 g, it requires certain anatomical conditions. Recently, Carmat announced the first successful HTx following 8 months of Carmat TAH support in Astana, Kazakhstan. Safety and performance remain to be confirmed in a clinical trial. Nevertheless, the Carmat TAH reflects the rationale of the ongoing development of TAH technologies. Yet, a completely implantable, biotechnologically engineered device mimicking the physiological modulation of right and left ventricular output with transcutaneous energy transfer is still out of reach.

The most important clinically used biventricular assist device systems are the Thoratec (Pierce-Donachy) VAD® (Pleasanton, CA, USA) and the Berlin Heart Excor®. Both are extracorporeal replacement pumps with transcutaneous guided cannulas for blood drainage and supply. Both are approved for left, right and biventricular support [29, 37]. Both have been frequently used for biventricular BTT therapy and also allow the heart to recover and the subsequent explantation of the device. As of 2016, the Thoratec VAD was no longer available for the company's main interest focussing on CF devices. The Berlin Heart Excor is the only device available for durable MCS in small paediatric patients and newborns [38].

COMPLICATIONS

RV failure represents a major contributing factor to the mortality rate among patients with an LVAD, particularly in patients who are at Intermacs levels 1 and 2 at the time of the implant. The time point of RV failure is variable and the risk of death after LVAD implantation due to RV failure is highest in the early postoperative period [14]. Late onset RV failure contributes to morbidity and mortality after initially successful LVAD implantation [10]. In such cases, potential candidacy for a HTx, escalation of medical and/or MCS options and, importantly, palliative therapy constructs, particularly in DT patients, have to be re-evaluated.

Pump thrombosis is a severe complication requiring either surgical pump exchange or systemic thrombolysis. Although each of these options is technically feasible, each results in a major reduction in the subsequent 1-year survival rate compared to that with a primary implant [14]. This complex issue has been extensively studied in patients with the HeartMate II. Similar rates have been reported by the ADVANCE trial investigators in patients with the HVAD [39]. The obvious increase in LVAD thrombosis [8, 40] may be explained by significantly longer support duration with CF devices. The PREVENTion of HeartMate II pump Thrombosis Through Clinical Management (PREVENT) trial uncovered the fact that adherence to standard recommendations can result in at least a reduction in the risk of pump thrombosis [41], e.g. by adherence to individualized anticoagulation regimens or by central positioning of the device inflow well within the inflow portion of the LV, but away from the septum in order to avoid filling-dependent low flow phases (Fig. 1C and D). Interestingly, MOMENTUM 3 trial shows a lack of pump thrombosis in patients with the HeartMate III, but it should be noted that stroke rates were still comparable in the early analysis [27].

Bleeding complications, mainly gastrointestinal, are a major risk of death after VAD implantation [14]. The occurrence of major bleeds may approximate 23% with a recurrence of nearly 10% [42]. It seems that bleeding rates decrease in the more recent era of LVAD therapy [8, 14]. It remains an open question if and how the long-term lack of physiological pulsatility triggers the development of arteriovenous malformations and bleeding events, because CF devices carry a somewhat higher risk for bleeding complications compared to PF devices. Previous studies have further suggested a link between CF devices and the development of von Willebrand syndrome [43]. It seems unlikely that an artificial pulse mode may help to reduce bleeding rates, e.g. with the HeartMate III. At least the available MOMENTUM 3 data do not allow for such a conclusion [27].

Device-related infections remain a common cause of morbidity and mortality in patients with VADs. Transcutaneous drivelines obviously facilitate ascending staphylococci-dominated infections [44]. The incidence of device infections varies between 13% and even 80%, depending on the definition, but the accumulating experience appears to support the decreased numbers of patients with VADs with infected devices and related complications in the more recent eras of durable MCS [10, 14, 27]. Infection of the non-biological materials can affect the peripheral driveline exit site in most cases but may ascend up to the intrathoracic pump and outflow prosthesis (Fig. 1E and F). Additionally, germs may settle on the pump material via the bloodstream, which creates a device endocarditis. The diagnosis of a device infection is difficult, because blood cultures that are positive for a particular organism are not a reliable proof, echocardiography may be inconclusive because of device-related artefacts and positron emission tomography-computed tomography scans are associated with a remarkable rate of false-positive results. If antimicrobial therapy is not effective, device exchange or a high-urgency HTx may be considered. Persistent peripheral driveline infections may be treated surgically by local revision or dislocation in rare, individual cases. The indications for an HTx must be critically and repeatedly reviewed, with particular attention paid to the prognostic net benefit of the transplanted organ. The prognostic value of an HTx in patients with a VAD, particularly in the presence of severe device-related infection or sepsis, must be carefully considered, because it has been suggested that the short-term mortality rate is increased [10, 44]. Country-specific differences in allocation algorithms and policies of organ donation may confound the reported outcome data.

Neurological complications represent the most devastating risk of death mid to long term after LVAD implantation [14]. This risk stays constant throughout the first 4 years after LVAD implantation. The clinical presentation may vary from transient ischaemic attacks with complete resolution to a severe life-threatening stroke. A history of cerebrovascular accident, hyponatremia, low albumin levels, elevated right atrial pressure, enlarged RV end-diastolic dimensions, atrial fibrillation, postoperative infection and supratherapeutic anticoagulation levels correlate with the

incidence of stroke [45]. The Intermacs level at the time of VAD implantation did not correlate well with the postoperative incidence of neurological complications [14, 46].

About 50% of patients with a durable MCS experience device malfunctions other than pump thrombosis within 1 year postoperatively [47]. The durability and functionality of LVADs are influenced by numerous factors including implantation technique; anatomical constraints; and complications such as infection and bleeding, anticoagulation, pump settings and device design. Although CF devices have demonstrated improved durability compared with PF devices in studies with up to 24 months of follow-up, several causative factors have been identified that contribute to maintained rates of device failure [48]. Device malfunctions, other than thrombosis, account for a small number of deaths, considering that the 1-year survival after LVAD implantation currently approaches 90% [49]. Malfunctions, particularly of the extracorporeal components, can be managed in most cases, but in rare instances, exchange of the entire MCS system is unavoidable. Obviously, surgical exchange of a VAD carries a certain procedural risk, and the 1-year survival rate after VAD exchange is inferior to that after the primary implant [10, 14].

PERSPECTIVES

The original vision of a fully implantable device that offers patients complete autonomy remains elusive. The LionHeart LVS 2000 was the only fully implantable device with a transcutaneous energy transfer, but the relatively high stroke rate did not permit continuation of use in a clinical environment [50]. The development of an effective transcutaneous energy transfer system and advances in biocompatibility will probably be game changers in HF therapy in broader terms. Such advances will contribute greatly to increase patients' quality of life and to reduce driveline and extracorporeal component-associated MCS devices as well as anticoagulation-associated bleeding complications.

SUMMARY

The technological advances of the current CF devices have resulted in a marked improvement in the survival of patients on durable MCS. Complication rates related to durable MCS devices have markedly decreased, but still, neurological and bleeding complications as well as infections represent major obstacles. Careful patient selection by a dedicated multidisciplinary team with sustained postoperative patient care is key for a good outcome. The HVAD and the HeartMate III are currently the most frequently implanted CF LVADs for BTT and DT worldwide. PF VADs play a role in biventricular MCS therapy, but the need for biventricular support is still accompanied with unsatisfactory results. Reduction of MCS device-associated complications and solutions for an effective energy supply and improved biocompatibility will challenge the HTx as the current gold-standard treatment in end-stage HF.

Funding

This paper was published as part of a supplement supported by an educational grant from Medtronic.

Conflict of interest: M.M. proctors for Abbott, HeartWare and Syncardia. M.M. and J.F.G. are advisory board members for Medtronic. J.F.G. is advisory board member for Berlin Heart. R.S. and J.F.G. received travel funding by Abbott. The authors M.S., M.H., J.B. and K.H.-M. have no conflicts of interests.

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