Send Orders for Reprints to reprints@benthamscience.net

Current Cardiology Reviews, 2021, *17*, e160721192831

REVIEW ARTICLE

Surgical Management of Heart Failure

Stephanie L. Wayne[1,*] and Adam D. Zimmet[1]

[1]*CJOB Department of Cardiothoracic Surgery, Alfred Health, Melbourne, Victoria, Australia*

ARTICLE HISTORY

Received: May 25, 2020
Revised: October 12, 2020
Accepted: October 12, 2020

DOI:
10.2174/1573403X17666210414094452

Abstract: Optimal management of heart failure is collaborative, with the involvement of specialist heart failure physicians, nurses, interventionalists, and surgeons. In addition to medical optimisation and cardiac resynchronisation therapy, surgery plays a valuable role in many patients. We herein study the evidence and the role of surgical intervention in functional mitral regurgitation, coronary revascularisation in ischaemic cardiomyopathy, and surgical ventricular reconstruction. Additionally, we describe techniques of temporary and durable mechanical circulatory support, with their relative advantages and disadvantages, and applications. Finally, we describe the history and nomenclature around heart transplants, their indications, techniques, present-day outcomes, complications, and new developments in the field.

Keywords: Surgical management, heart failure, mechanical circulatory support, mitral regurgitation, ischaemic cardiomyopathy, heart transplant.

1. INTRODUCTION

There is a wide spectrum of cardiac surgery for heart failure, from traditional Coronary Artery Bypass Grafting (CABG) to heart transplantation and Total Artificial Heart (TAH) implantation. The indication for each depends on the aetiology of the heart failure, individual patient risk profile, and severity of the disease. The shift towards less invasive options in cardiac surgery will allow for intervention at different timelines for patients. The decision to perform surgery and the operation that is to be performed-should be evidence-based and discussed in by a heart team, including a cardiac surgeon, an interventional/structural cardiologist, and a cardiologist specialising in heart failure. We review the procedures most commonly performed to treat this challenging patient cohort.

2. SURGERY IN FUNCTIONAL MITRAL REGURGITATION

Understanding mitral valve anatomy is fundamental to functional (secondary) Mitral Regurgitation (MR) surgery. The mitral apparatus comprises the annulus, leaflets, chordae tendineae, and papillary muscles, as well as the Left Ventricle (LV). Unlike primary MR, secondary MR is predominantly due to ventricular pathology rather than leaflet pathology. A distorted LV alters the complex mitral apparatus geometry. LV dilatation and remodelling causes papillary muscle displacement, consequent tethering of the leaflets causing reduced coaptation, and enlargement and flattening of the usually saddle-shaped annulus [1]. Ventricular pathology may be focal, from ischaemia or infarction, or global, in non-ischaemic dilated cardiomyopathy [1]. Ischaemic cardiomyopathy may produce asymmetric leaflet tethering with eccentric MR from a regional wall motion abnormality, becoming more symmetric with increasing global systolic dysfunction, producing more central MR [1]. Dilated cardiomyopathy is typically symmetric [1, 2]. Increased LV sphericity causes annular dilatation and central MR [1]. Long-standing changes in flow dynamics can create leaflet pathology, often lengthened as an adaptive response to increase coaptation, 1,3 apart from any primary leaflet pathology in these patients [3].

Functional MR carries a poor prognosis [4]. It is unclear if this is independent of the associated LV dysfunction [5]. There is no clear evidence that surgical reduction of functional MR improves survival [5], whether isolated or with concomitant CABG. Recent European 'Guidelines for the management of valvular heart disease' (2017) caution a "lower level of evidence for treatment recommendations" and "highlight the importance of decision making by the Heart Team" [5]. The only Class I recommendation (Level C evidence) is an intervention for severe MR with concomitant CABG in patients with LV ejection fraction (LVEF) >30%.5 With LVEF <30%, surgery should only be considered for symptomatic patients with a revascularisation option with viability demonstrated (Class IIa, Level C) [5]. For isolated MR without revascularisation, surgery should only be considered in symptomatic patients with LVEF >30% despite optimal medical therapy (including cardiac resynchronisation therapy) where surgical risk is low (Class IIb, Level C) [5].

The selection of repair *vs.* replacement is also debatable. Unlike primary MR, where repair is the gold standard [5, 6], evidence varies for functional MR. A Cardiothoracic Surgical Trials Network randomised trial of 251 patients with severe ischaemic MR demonstrated insignificantly different 1-year mortality for repair *versus* replacement (14.3% cf

* Address correspondence to this author at the CJOB Department of Cardiothoracic Surgery, Alfred Health, 55 Commercial Rd. Melbourne, Victoria 3004, Australia; E-mail: stephaniewayne@alfred.org.au

17.6% respectively) [7]. Both groups' high mortality rates highlighted the poor prognosis in these patients. There was a higher rate of moderate or severe MR recurrence with repair (32.6% *vs*. 2.3%), though no differences in major adverse cardiac or cerebrovascular events, functional status, or quality of life were found [7]. The relatively good performance of replacement may relate to the preservation of the chordal and entire subvalvular apparatus [7].

Conversely, although annuloplasty rings were used in all repairs to stabilise and "cinch in" the annulus, there was no detail regarding important adjuncts such as addressing leaflet tethering and papillary elongation [8]. A meta-analysis of repair *versus* replacement for ischemic MR identified reduced peri-operative and late mortality following repair *versus* replacement, more pronounced with longer follow-up beyond 3 years [9]. However, patients within the replacement cohorts had more comorbidities than those with the repair. Although propensity matching was performed, this is inferior to randomisation [9].

The landscape is, however, changing. Two recent randomised trials - the French MITRA-FR and the United States' COAPT - examined edge-to-edge percutaneous mitral repair using the MitraClip (Abbott) device in patients with symptomatic heart failure and severe (MITRA-FR) or moderate-to-severe and severe (COAPT) functional MR [4]. MITRA-FR randomised 304 patients to either optimal medical therapy (OMT) plus MitraClip or OMT alone; COAPT randomised 614 patients similarly. In MITRA-FR, the MitraClip reduced MR to Grade 2+ or less in 92% of patients by hospital discharge but with no impact on all-cause mortality or heart failure rehospitalisation [4]. In COAPT, the MitraClip similarly reduced MR periprocedurally to Grade 2+ or less in 95% of patients. In contrast, however, MitraClip implantation showed a substantial reduction in the 2-year all-cause mortality (29.1% *vs*. 46.1%) and the composite of death and heart failure rehospitalization (45.7% *vs*. 67.9) [4]. Further information awaits the eventual publication of the RESHAPE-HF-2 and MATTERHORN trials [4]. Not all mitral valves are anatomically amenable to edge-to-edge percutaneous repair. Ascertaining who will derive the most benefit is challenging [10]. Percutaneous Transcatheter Mitral Valve Replacement (TMVR) techniques are at the preclinical and clinical trial stage, showing "promising results." However, "further development, testing, and trials need to be conducted before TMVR can become a sensible MR treatment" [11].

3. SURGICAL REVASCULARISATION IN ISCHAEMIC CARDIOMYOPATHY

Revascularisation in unstable coronary artery disease and management of the stable symptomatic coronary disease is well-established. However, prior to the publication of the 'Surgical Treatment for Ischemic Heart Failure' ('STICH') trial in 2011, there was limited evidence regarding surgical revascularisation in ischaemic cardiomyopathy. The STICH trial's first hypothesis was that CABG plus OMT would improve long-term survival compared to OMT alone [12].

STICH evaluated adults with LVEF ≤ 35% with coronary disease suitable for surgical revascularisation, excluding those requiring surgical aortic valve replacement, recent myocardial infarction, significant left main disease, or mechanical support [12]. 1,212 patients were randomised to either CABG plus OMT or OMT alone [13]. 52% in each group only had Canadian Cardiovascular Society (CCS) angina class O or I angina [13]. The median LVEF was 28% [14]. 30-day operative mortality was 5.1% [13]. At first publication in 2011 (median follow-up 56 months), there was no difference in death from any cause or from cardiovascular causes. CABG did, however, confer an advantage for death from any cause plus either hospitalisation for heart failure, hospitalisation for cardiovascular causes, hospitalisation for any cause, or need for revascularisation [13]. The 'STICH Extended Study' (STICHES)-published in 2016 extended median follow-up to 9.8 years [14]. At this time, CABG conferred advantage across all endpoints evaluated - death from any cause (mortality rate 58.9% for CABG patients *vs*. 66.1% for OMT alone), death from cardiovascular causes, hospitalisation for any cause, cardiovascular causes or heart failure, need for subsequent revascularisation, nonfatal myocardial infarction and nonfatal stroke [14]. STICH and STICHES provided high-quality evidence for revascularisation in ischaemic cardiomyopathy, even without angina.

STICH also evaluated myocardial viability. Of the 1,212 patients, 601 underwent viability testing using Single-Photon Emission Computed Tomography (SPECT), dobutamine Transthoracic Echocardiogram (TTE), or both [15]. 487 (81.0%) demonstrated viability; 114 (19.0%) demonstrated non-viability; these were almost evenly distributed between the CABG and the OMT alone groups. The presence or absence of myocardial viability did not affect the benefit of CABG over OMT alone [15]. This subset study was probably underpowered to detect the impact of viability on outcomes. However, the subset of patients amenable to surgical ventricular reconstruction (SVR), *i.e*., those with anterior wall akinesis/dyskinesis, implying full-thickness infarction in the left anterior descending artery (LAD) territory, particularly benefited from CABG [14]. This counters the traditional impression that the prognostic advantage of CABG mainly relates to grafting LAD territory with the left internal thoracic artery, suggesting that LAD territory viability may be inconsequential.

4. SURGICAL VENTRICULAR RECONSTRUCTION

With modern techniques for acute revascularisation in ST-elevation myocardial infarction, including PCI and thrombolysis, ventricular aneurysms have become uncommon [16]. SVR is, therefore, rarely performed in most centres. 90% of aneurysms are anterior (LAD territory); 10% arise posteriorly or laterally [17]. Unlike scar or infarct, an aneurysm has a more delineated area of a thinned fibrous scar-with few muscle fibres [16]. Often, aneurysm diagnosis can only be definitively made during surgery [16]. The akinetic/dyskinetic area of the LV directly wastes systolic work; with increasing size, there is also remote LV remod-

elling from increased wall tension, as per LaPlace's law [17]. Additionally, the right ventricular function can be impacted by higher left atrial pressures, septal involvement in the aneurysm, and increased LV size within a constrained pericardial cavity [16]. Mural thrombi may form, and ventricular arrhythmias may occur [16].

SVR aims to reduce LV size and excise or exclude this area of the fibrous scar; "plastic" as opposed to "linear" techniques also aim to reapproximate normal geometry [18]. Linear repair, described by Cooley and colleagues (1958), entails longitudinal incision of the aneurysm, parallel and lateral to the LAD, with excision of most of the aneurysm [16, 17]. The defect is then sutured closed, taking these through the septum medially, excluding as much scar as possible [16, 17]. Incorporating the LAD into the suture line eliminates the possibility of LAD grafting [17]. "Plastic" techniques described by Dor and McCarthy [17] entail opening the aneurysm adjacent to the LAD. Mural thrombus is excised. A purse-string endoventricular suture from the junction of the aneurysm and healthy myocardium is drawn tight and tied, reducing the "orifice" area of the aneurysm [16, 17]. A patch (*e.g.*, polyester lined by autologous pericardium) can be sutured in place, closing the residual defect (Dor) [16, 17] or further purse-strings to tighten the orifice and eliminate the defect (McCarthy) [17]. The residual rim of scar tissue is then closed over this repair [17]. A preshaped balloon (*e.g.*, 50-60ml) can be utilised to size the ventricular cavity [16]. The LAD is preserved for revascularisation [17]. Randomised trials are likely needed to compare the techniques [17].

Evidence varies regarding the utility of SVR. Hypothesis 2 of the STICH trial was that SVR plus CABG (n=499) compared to CABG alone (n=501), in patients with an anterior LV aneurysm, would improve survival free of cardiac hospitalisations [12]. The results published in 2009 with a median follow-up of 48 months demonstrated that although SVR improved LV geometry, this did not translate to any significant clinical difference in symptoms, death, or hospitalisation [19]. However, there have been-criticisms of the handling of Hypothesis 2 in this paper. Dor and colleagues described SVR results in 117 operated patients who would have been excluded from the STICH trial for reasons including unsuitable vessels for CABG, recent myocardial infarction, and pre-operative inotropy [20]. The 1-year mortality rate was 5.1%. LVEF and LV geometry improved markedly in the 101 patients assessed with magnetic resonance imaging (MRI) preoperatively and at 1 year [20]. Without a control or matched group, no survival benefit could be demonstrated. It is purported that advocates and regular performers of SVR did not participate in STICH, being unwilling to subject patients with anterior aneurysms to randomisation not to undergo SVR.

With minimal evidence and infrequent occurrence, SVR features minimally in heart failure management guidelines. American guidelines have a Class IIb recommendation for SVR in "carefully selected patients" for specific indications, including intractable heart failure and ventricular arrhythmias" [21]. European guidelines state that SVR "seems of no benefit," however, it may be considered in patients with large aneurysms and intractable heart failure or recurrent ventricular arrhythmias" [22].

5. MECHANICAL CIRCULATORY SUPPORT

Mechanical Circulatory Support (MCS) can be broadly divided into temporary and durable categories. These differ in both technology and application.

5.1. Temporary

Temporary MCS devices provide temporary for right, left or biventricular failure. This includes prophylaxis in high-risk PCI, cardiogenic shock and arrest, and acute decompensated heart failure, including post-cardiotomy [23]. In decompensated heart failure and cardiogenic shock, temporary MCS-can stabilise critically ill patients for organ recovery, allowing time for decision-making regarding durable MCS insertion - a "bridge to a bridge" [24, 25]. Generally, temporary devices are used for hours up to 30 days. There are five main device categories: Intraaortic Balloon Pump (IABP); TandemLife (LivaNova) percutaneous pumps (for left or right heart support); Extracorporeal Membrane Oxygenation (ECMO) in central or peripheral venoarterial configurations for heart-lung support; Impella (Abiomed) percutaneous devices (for right or left heart support); and temporary LVADs (utilising the Thoratec CentriMag [Abbott] pump) [23, 24].

The IABP comprises a balloon catheter positioned in the proximal descending thoracic aorta, inflated cyclically with helium, and a console, set to inflate/deflate the balloon according to either arterial pressure or ECG signal. Inflating in diastole and deflating in systole, the IABP increases diastolic pressure, reducing systolic afterload. This increases diastolic coronary perfusion and Mean Arterial Pressure (MAP) and reduces ventricular load and myocardial oxygen consumption [23]. IABP is a percutaneous device, most commonly transfemoral. IABP has recently been downgraded in international guidelines after the publication of the IABP-SHOCK II trial and recent 6-year outcome update [26]. This multicentre trial randomised 600 patients with cardiogenic shock complicating acute myocardial infarction, undergoing early revascularisation, to IABP *vs.* control. IABP had no impact on all-cause mortality at 30 days, 1 year, or 6 years [26]. Consequently, IABP is "not routinely recommended in cardiogenic shock" (Class III recommendation, Level of evidence B) [25].

TandemLife (Livanova) provides percutaneous left atrial-to-femoral artery (TandemHeart) and right atrium- to-pulmonary artery (Protek Duo) circulatory support pumps for left and right heart bypass, respectively [27]. The former entails a transseptal puncture, with drainage cannula in the left atrium and return cannula in the femoral artery. The latter utilises a single cannula either *via* the internal jugular or femoral vein, with drainage holes in the right atrium and return into the pulmonary artery [27]. Although indicated for temporary left or right heart bypass for only 6 hours [27], the TandemHeart has been used for several days [28], pro-

viding circulatory support up to 5 L /min, without any oxygenation capacity [27].

Impella (Abiomed) "intravascular microaxial" devices 21 are percutaneous and peripheral cut-down devices for either left heart (Impella 2.5, Impella CP, Impella 5.5, Impella 5.0) or right heart (Impella RP) support; insertion percutaneously or cut-down depends on device size and consequent flow rate capacity [29]. For left-heart support, the catheter is placed across the aortic valve into the left ventricle, pulling in blood from the ventricle and expelling it into the aorta. For right-heart support, a cannula is placed transvenously through the Inferior Vena Cava (IVC) and right heart into the pulmonary artery, pulling in blood from the IVC and expelling it in the pulmonary artery [29]. Two retrospective studies, however, failed to show benefit for the Impella devices [30, 31]. One study matched 237 patients treated with left ventricular Impella devices to 237 patients from the IABP-SHOCK II trial, treated with either medical or IABP therapy. This found no difference in 30-day all-cause mortality (48.5% *versus* 46.4%); however, severe or life-threatening bleeding (8.5% *versus* 3.0%) and peripheral vascular complications (9.8% *versus* 3.8%) occurred more often in the Impella group [30]. The second study involved 28,304 patients who underwent PCI for myocardial infarction complicated by cardiogenic shock. An Impella device was used in 6.2% of patients and IABP in 29.9%. Among 1680 propensity-matched pairs, there was a-higher risk of in-hospital death associated with Impella (45.0%) *versus* IABP (34.1%) and a higher risk of in-hospital major bleeding (Impella 31.3% *vs*. IABP 16.0%) [31].

Utilising a pump such as the CentriMag (Abbott), a temporary surgical left ventricular (LVAD) or right ventricular assist device (RVAD) circuit can be created. Temporary LVAD entails direct surgical cannulation of the left ventricle for drainage, passage extracorporeally through the pump (without gas exchange or oxygenation), and passage back through a side-graft sutured onto the ascending aorta. Temporary RVAD or biVAD configurations can also be created [32]. In one metaanalysis of CentriMag as temporary VAD support, average survival varied from 61% in post-transplant graft rejection or failure to 83% for temporary RVAD after durable LVAD insertion [32]. Surgical placement (sternotomy or thoracotomy) is required [32].

Unlike the above MCS, ECMO in veno-arterial configuration (VA-ECMO) does not just augment native cardiac activity (IABP and Impella) nor create single-ventricle bypass/replacement (TandemLife devices and temporary LVAD) but rather biventricular circulatory bypass plus gas exchange, thereby supporting both the heart and lungs [33]. VA-ECMO is "an effective technique to support refractory cardiogenic shock while ensuring continuous organ perfusion to wait for cardiac function recovery, transplantation, or left ventricular assist device" [33, 34]. No randomised controlled studies have been conducted, likely due to logistical and ethical issues involved in patients with severe cardiogenic shock or arrest [35]. However, improved survival and neurological outcomes have been observed in some groups, particularly in in-hospital cardiac arrest [35]. Most common indications include cardiogenic shock due to fulminant myocarditis, acute myocardial infarction, post-heart transplantation, or post-cardiotomy [34]. Utilising pumps such as the CentriMag, ECMO can provide support for up to 30 days [24]. Cannulae can be centrally placed surgically, with cannulation of the right atrium for venous drainage and aorta for arterial antegrade return, or percutaneously or *via* cut-down of peripheral vessels, commonly the femoral artery and vein, providing retrograde arterial flow. For the latter, an additional "backflow" cannula is required for antegrade femoral arterial flow, preventing ischaemia of the cannulated leg. Aside from bleeding and peripheral vascular complications, the 'Achilles heel' of VA ECMO is the lack of direct ventricular drainage and offloading, particularly in a compromised left ventricle. This can increase afterload, causing the closure of the aortic valve [24]. Strategies to unload the left ventricle include inotropy, systemic vasodilation, IABP, balloon atrial septostomy, surgical left ventricular vents, and percutaneous ventricular support such as the Impella devices ('ECPELLA') [24, 35]. Decision-making for VA-ECMO is complex and multidisciplinary, involving intensive care specialists, cardiac surgeons, and cardiologists. Tools such as the SAVE score may predict patients with the highest likelihood of survival with VA-ECMO [34].

5.2. Durable

Durable MCS may provide long-term myocardial support for patients with advanced heart failure despite optimal medical management, from patients with advanced New York Heart Association (NYHA) III symptoms to those deteriorating despite temporary MCS (INTERMACS® patient profiles 1 to 7) [36]. Although internationally durable MCS has been approved and utilised as 'Destination therapy,' *i.e*., permanent support where heart transplant is not an option in Australia, use is confined to 'Bridging therapy' - an interim measure to either heart transplant, recovery, or transplant candidacy in those not yet eligible [37]. Driving its development is the increasing number of patients in the developed world with advanced heart failure, where a limited organ donor pool stimulates the need for alternative or bridging therapies to heart transplantation [38]. The current options are Ventricular Assist Devices (VADs) to augment native ventricular activity, implantable in left (LVAD), right (RVAD), or biventricular (biVAD) conformations, and TAH, replacing the ventricles in an orthotopic location.

The landmark trial supporting LVAD in advanced heart failure was the 'REMATCH' study (2001), utilising a first-generation pulsatile-flow device, which randomised 129 patients ineligible for heart transplant with NYHA IV symptoms to either optimal medical therapy or LVAD. LVAD conferred a "clinically meaningful survival benefit and an improved quality of life," including 48% reduction in risk of all-cause death at 2 years [39]. Subsequently, VAD technology has rapidly advanced. VADs are-described as 'pulsatile flow' volume-displacement devices or 'continuous flow' rotary devices. The latter can be subdivided into centrifugal and axial pumps [40]. Of all primary LVAD implants

(n=20,469) in the Intermacs registry between June 2006 and December 2017, most (n=19,206) were continuous flow [41]. Pulsatile flow devices incorporate inflow and outflow unidirectional valves with a chamber between which volume changes between ejections. Continuous flow devices utilise rotating impellers driving forward flow continuously [40]. Continuous flow device output is determined by inflow pressure (preload), outflow pressure (systemic vascular resistance/afterload), the pressure gradient across these, and the rotation speed of the impeller (set by the clinician) [40].

Three devices approved by the Therapeutic Goods Administration (TGA) are the third-generation HeartWare HVAD (Medtronic) and the HeartMate 2 and 3 (second- and third-generation) (Abbott). The HeartWare HVAD and the HeartMate 2 were compared as destination therapy in the randomised 'ENDURANCE' trial (2017) of 446 patients. At two years, the HVAD group demonstrated more strokes (29.7% *vs*. 12.1%), the Heartmate II exhibited greater device malfunction or failure requiring replacement (16.2% *vs*. 8.8%); however, there was no difference in overall survival (55.4% for HVAD *vs*. 59.1% for HeartMate 2) [42]. The Heartmate 3 Fig. (**1**) and 2 were recently compared in the 'MOMENTUM 3' study (2019), in which 1,028 patients were randomly assigned to receive one or the other device as bridging or destination therapy. The primary end-point was survival at 2 years free of disabling stroke or reoperation to replace or remove a malfunctioning device. The magnetically-levitated centrifugal HeartMate 3 pump was superior to the axial flow HeartMate 2 pump, with 76.9% in the former as compared to 64.8% in the latter for the primary end-point at two years. Additionally, the incidence of any stroke, major bleeding, and gastrointestinal bleeding was lower-with HeartMate 3 [43]. Extrapolating the ENDURANCE and MOMENTUM 3 trial results suggests the overall superiority of the HeartMate 3 over the HVAD device.

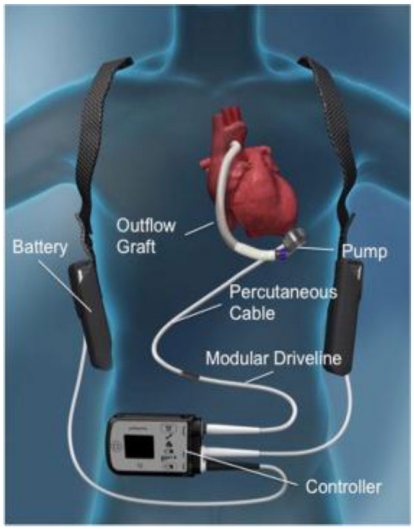

Fig. (1). Artistic representation of the Abbott HeartMate 3 LVADTM [55] (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Although the proportion of biVAD implants to LVAD implants is low (1,013 *vs*. 19,116 over approximately 11 years in the USA as described in the Intermacs annual report [41]), and isolated RVAD implantation is rare, the decision to implant an RVAD when implanting an LVAD is complex. Right ventricular failure may coexist or be consequent to left ventricular failure. A continuous LVAD requires sufficient inflow generated by the right ventricle to sustain forward flow. After LVAD implantation, the right ventricle may benefit from unloading of left-sided pressures. However, the leftwards shift of the interventricular septum with tricuspid annular distortion and the higher systemic venous return may cause progressive right ventricular failure. This can cause difficulty weaning from cardiopulmonary bypass, increased perioperative morbidity, and mortality [44]. Early utilisation of right ventricular MCS (temporary or durable) may improve outcomes compared to delayed biVAD support in right ventricular failure after LVAD insertion [45]. However, patients requiring biVAD demonstrate lower survival than those requiring only LVAD [41]. Temporary right ventricular MCS is favoured if there is uncertainty, bridging to recovery or durable RVAD [37]. Prediction scores *e.g*., the CRITT score (CVP >15mmHg, severe right ventricular failure, pre-operative intubation, severe tricuspid regurgitation, and tachycardia >100) are of modest use in determining the need for biVAD support [46]. The HeartMate 3 and HVAD have both been used for biVAD support as off-label usage [37].

An alternative to biVAD is TAH, a form of 'cardiac replacement therapy' [38]. Internationally, fewer than 20 centres report the use of the most common device, the Syncardia TAH (Syncardia Systems) [38]. In the Intermacs report where 20,469 patients had primary durable MCS implanted for left ventricular support between 2006 and 2017, 19,116 underwent LVAD implantation, 1,013 had biVAD, and only 339 had TAH [41]. The first Australian device was implanted at St. Vincent's Hospital in Sydney in 2010 [47]. The devices are sutured to the native atria, the native ventricles excised, thereby replacing the ventricles and outflow valves. These can only be utilised as a bridge to transplant (or destination therapy) with no capacity for recovery. Other than the indications for biVAD implantation, a rare indication for TAH is isolated cardiac neoplasia with no reconstructive options [38].

6. HEART TRANSPLANT

Heart transplant was first described in 1905 by Carrel and Guthrie in dogs [48]. The first human heart transplant - utilising a chimpanzee "xenograft" heart was unsuccessfully performed in 1964 by Hardy [48]. The first successful human heart transplant using a human heart was performed by Barnaard in South Africa in late 1967. 102 patients underwent heart transplants internationally by the end of 1968 [48]. Understanding the immune response through parallel research in other organ transplants (including skin and kidney) facilitated this. A critical milestone was the introduction of cyclosporine in 1981 [48], which "accelerated the evolution of cardiac transplantation from the experimental

phase to a clinically useful treatment modality for patients with advanced heart failure" [48].

The four broad indications for cardiac transplantation are: 1) advanced heart failure despite optimal medical therapy, cardiac resynchronisation therapy and surgery as indicated; 2) refractory angina despite optimal medical therapy with no further PCI or surgical revascularisation options; 3) recurrent life-threatening ventricular arrhythmias refractory to medical and implantable defibrillator therapy; and rarely, 4) non-resectable cardiac tumour with very low metastatic probability [48]. Advanced heart failure may be from ischaemic or non-ischaemic dilated cardiomyopathy, hypertrophic or restrictive cardiomyopathy, or end-stage congenital heart disease (although severe pulmonary hypertension may warrant heart-lung en bloc transplant). Advanced heart failure may be described using INTERMACS Profiles [36] or the American or European Guidelines [21, 25], utilising symptomatic criteria (such as advanced NYHA III onwards) [36], functional physiological criteria (*e.g*., VO2 max of less than 12-14 ml/kg/min) [21], as well as the potential need for inotropy or circulatory support in critical stages [36]. To warrant the risks of transplant, this must then be coupled with sufficiently low expected survival, such as predicted by the Heart Failure Survival Score (HFSS), to warrant transplant risks [49], maximal predicted benefit [48, 49] as well as sufficient psychosocial support and robustness [48]. Contraindications broadly include age (above approximately 65 years), irreversible non-cardiac organ dysfunction, recent malignancy, and inadequate psychosocial support or robustness [48].

Multiple terminologies are utilised in heart transplant. "Orthotopic": replacement of the recipient heart with the donor heart in the "same place"; "heterotopic": placement of a donor heart in different location, *i.e*: as a parallel circuit. Of 2,974 heart transplants performed in Australia and New Zealand from 1984-2018, only 31 were heterotopic; the remainder orthotopic [50]. "Allograft": a heart of the same species (*i.e*., human); "xenograft": a transplanted organ of another species (still experimental) [48]. Another distinction regards 'Donation after Brain Death' (DBD) *versus* "Donation after Circulatory Death' (DCD). Most heart transplants are from DBD donors, but to increase the donor pool, Australia pioneered the use of DCD hearts, publishing their first series in 2015 [51]. They were followed by four centres in the UK [51], and in the past few months by the first DCD heart transplant in the USA [52]. Whereas in DBD donors, procurement proceeds during intact (supported) ventilatory and circulatory function, DCD donation entails certifying futility, withdrawal of ventilatory and circulatory support, and natural progression of circulatory death with the loss of cardiac output. If this occurs within a pre-specified time frame (usually 30 minutes for cardiac donation, minimising 'warm ischaemic time' whilst the heart is warm though malperfused) [52], the donor is rapidly wheeled to the operating theatre for procurement. Remote DCD procurement generally necessitates perfusion, minimising ischaemic time for transport [51, 52]. Excellent results demonstrate survival and rejection episodes matching the DBD cohort [51].

Another developing area to increase the donor pool is 'Extended Criteria Cardiac Transplant' (ECCT). This involves matching donors and recipients excluded from transplant due to age or comorbidity [53]. Duke University detailed their 10-year experience with ECCT. Recipients were included despite traditional exclusion criteria, *e.g*., age over 65 and comorbidities such as significant renal insufficiency and poorly controlled diabetes. Similarly, donor organs used would traditionally have been regarded as having unfavourable or high-risk characteristics, *e.g*., older donors, single-vessel coronary artery disease, left ventricular dysfunction, and high-dose inotropic support [53]. In their 454 patients, of whom 84 were on the ECCT pathway, standard criteria patient survival was higher than ECCT at 1 (89% *vs*. 86%) and 5 (77% *vs*. 66%) years. However, these outcomes still demonstrated an "acceptable alternative" for treatment of advanced heart failure in these patients [53].

With operating, there are two main techniques for recipients with normal anatomy - bicaval and biatrial implantation. Recipient cardiectomy entails aorto-bicaval cardiopulmonary bypass, aortic cross clamping, transection of the ascending aorta, pulmonary trunk, and then either transection of the cavae (for the bicaval technique) with a left atrial cuff around the pulmonary veins remaining intact, or else cuffs kept of both the right atrium (with cavae intact) and left atrium (for the biatrial technique) [48]. For the bicaval technique, donor heart implantation usually proceeds with the left atrial anastomosis, followed by inferior vena cava, then the pulmonary trunk, then aortic (with de-airing maneouvres followed by the release of aortic cross-clamp), then superior vena cava, and finally pulmonary trunk anastomosis. The biatrial technique usually starts with left atrial anastomosis, then right atrial, aortic, and finally the pulmonary trunk [48]. Post-operative care is similar to other cardiac surgical patients. The donor heart is entirely denervated, which may cause temporary bradycardia, requiring chronotropy [48]. The right ventricular function may be impaired by its greater susceptibility to graft ischaemia, or by pulmonary hypertension (pre-existing, related to cardiopulmonary bypass or protamine reaction) [48]. Finally, graft ischaemia may reduce ventricular diastolic compliance, requiring higher filling pressure to maintain output [48]. The mainstay of post-operative care is infection prophylaxis and immunosuppressant use.

Of the centres captured by the International Society of Heart and Lung Transplant (ISHLT), the annual number of heart transplants exceeds 5000 [54, 55], with 100-150/year in Australia and New Zealand in recent years. 50 Global median survival is 12.5 years (for patients transplanted between 2002-2009); median conditional survival 14.8 years (*i.e*., for those surviving at 1 year post-transplant) [54]. As of the late 2000s, globally, the approximate survival rates are: 1-year- 90%, 5-year- 70%, and 20-year- 20% [49]. More recent Australian/New Zealand data revealed 87.4% 1-year survival, 78.9% at 5 years, 64.7% at 10 years, 50.0% at 15 years and 36.6% survival at 20 years [50]. Whereas shorter-term survival is mostly eroded by early graft failure, rejection, and infection, mortality after 1 year is increasingly due to coronary

disease in the transplanted heart - 'cardiac allograft vasculopathy' (CAV) - and malignancy [48].

CONCLUSION

Alongside many medical developments, cardiac surgery has multiple options in its armamentarium for heart failure management. Surgical revascularisation of ischaemic myocardium increases survival, irrespective of myocardial viability. Coupling this with SVR, whilst predominantly a historical procedure, is of uncertain benefit. Surgical correction of functional MR, whether with repair or replacement, may improve symptoms. However, it displays no survival benefit. The management of secondary MR may be changing, with some evidence suggesting survival and morbidity benefit of percutaneous edge-to-edge repair. For patients with refractory heart failure, surgically-implanted durable VAD therapy offers improved survival over OMT and offers a bridge to potential transplantation. Temporary MCS can be offered to facilitate stabilisation or bridging to durable therapy, albeit limited data supports this, and observational data only supports the use of VA-ECMO. Heart transplantation is now accompanied by excellent outcomes, with approximately 50% of recipients still alive at 15 years. Patient complexity and the evolving therapeutic landscape necessitate multidisciplinary team management of heart failure, of which the surgeon must therefore play an integral part, with careful patient selection and tailoring of procedures accordingly.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol 2015; 65(12): 1231-48. http://dx.doi.org/10.1016/j.jacc.2015.02.009 PMID: 25814231

[2] Carpentier A, Adams DH, Filsoufi F. Dilated Cardiomyopathy. In: Carpentier's reconstructive valve surgery. (1st Ed.). Saunders, PA, United States 2010; pp. 297-9.

[3] Carpentier A, Adams DH, Filsoufi F. Ischemic Valvular Disease. In: Carpentier's reconstructive valve surgery. (1st Ed.). Saunders, PA, United States 2010; pp. 291-6.

[4] Praz F, Grasso C, Taramasso M, *et al.* Mitral regurgitation in heart failure: time for a rethink. Eur Heart J 2019; 40(27): 2189-93. http://dx.doi.org/10.1093/eurheartj/ehz222 PMID: 31005977

[5] Falk V, Baumgartner H, Bax JJ, *et al.* ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur J Cardiothorac Surg 2017; 52(4): 616-64. http://dx.doi.org/10.1093/ejcts/ezx324 PMID: 29156023

[6] Nishimura RA, Otto CM, Bonow RO, *et al.* American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63(22): 2438-88. http://dx.doi.org/10.1016/j.jacc.2014.02.537 PMID: 24603192

[7] Acker MA, Parides MK, Perrault LP, *et al.* CTSN. Mitral-valve repair *versus* replacement for severe ischemic mitral regurgitation. N Engl J Med 2014; 370(1): 23-32. http://dx.doi.org/10.1056/NEJMoa1312808 PMID: 24245543

[8] Rankin J, Alkhouli M, Wei L, *et al.* Mitral valve repair *vs*. replacement for ischemic MR: an ongoing debate. Available from: https://www.acc.org/latest-in-cardiology/articles/2016/09/06/07/12/mitral-valve-repair-vs-replacement-for-ischemic-mr

[9] Virk SA, Sriravindrarajah A, Dunn D, *et al.* A meta-analysis of mitral valve repair *versus* replacement for ischemic mitral regurgitation. Ann Cardiothorac Surg 2015; 4(5): 400-10. PMID: 26539343

[10] Thaden J, Malouf J, Nkomo V, *et al.* Mitral valve anatomic predictors of hemodynamic success with transcatheter mitral valve repair. J Am Heart Assoc 2018; 7: e007315. http://dx.doi.org/10.1161/JAHA.117.007315

[11] Goode D, Dhaliwal R, Mohammadi H. Transcatheter mitral valve replacement: state of the art. Cardiovasc Eng Technol 2020; 11(3): 229-53. http://dx.doi.org/10.1007/s13239-020-00460-4 PMID: 32130653

[12] Velazquez EJ, Lee KL, O'Connor CM, *et al.* STICH Investigators. The rationale and design of the Surgical Treatment for Ischemic Heart Failure (STICH) trial. J Thorac Cardiovasc Surg 2007; 134(6): 1540-7. http://dx.doi.org/10.1016/j.jtcvs.2007.05.069 PMID: 18023680

[13] Velazquez EJ, Lee KL, Deja MA, *et al.* STICH Investigators. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med 2011; 364(17): 1607-16. http://dx.doi.org/10.1056/NEJMoa1100356 PMID: 21463150

[14] Velazquez E, Lee K, Jones R, *et al.* Coronary artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med 2016; 379(16): 1511-20. http://dx.doi.org/10.1056/NEJMoa1602001

[15] Panza JA, Ellis AM, Al-Khalidi HR, *et al.* Myocardial viability and long-term outcomes in ischemic cardiomyopathy. N Engl J Med 2019; 381(8): 739-48. http://dx.doi.org/10.1056/NEJMoa1807365 PMID: 31433921

[16] Left Ventricular Aneurysm. In: Nicholas T, Kouchoukos MD, Eugene H, *et al*. Kirklin/Barratt-Boyes cardiac surgery. 4th Ed. Elsevier 2013.

[17] Ruzza A, Czer LSC, Arabia F, *et al.* Left ventricular reconstruction for postinfarction left ventricular aneurysm: review of surgical techniques. Tex Heart Inst J 2017; 44(5): 326-35. http://dx.doi.org/10.14503/THIJ-16-6068 PMID: 29259502

[18] Shapira OM, Davidoff R, Hilkert RJ, Aldea GS, Fitzgerald CA, Shemin RJ. Repair of left ventricular aneurysm: long-term results of linear repair *versus* endoaneurysmorrhaphy. Ann Thorac Surg 1997; 63(3): 701-5. http://dx.doi.org/10.1016/S0003-4975(96)01112-5 PMID: 9066387

[19] Jones RH, Velazquez EJ, Michler RE, *et al.* STICH Hypothesis 2 Investigators. Coronary bypass surgery with or without surgical ventricular reconstruction. N Engl J Med 2009; 360(17): 1705-17. http://dx.doi.org/10.1056/NEJMoa0900559 PMID: 19329820

[20] Dor V, Civaia F, Alexandrescu C, Sabatier M, Montiglio F. Favorable effects of left ventricular reconstruction in patients excluded from the Surgical Treatments for Ischemic Heart Failure (STICH) trial. J Thorac Cardiovasc Surg 2011; 141(4) 905-916, 916.e1-4. http://dx.doi.org/10.1016/j.jtcvs.2010.10.026 PMID: 21419901

[21] Yancy CW, Jessup M, Bozkurt B, *et al.* Writing Committee Members; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation

2013; 128(16): e240-327.
http://dx.doi.org/10.1161/CIR.0b013e31829e8776 PMID: 23741058

[22] Ibanez B, James S, Agewall S, *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation – Web Addenda. Eur Heart J 2017; 00: 1-8.

[23] Rihal CS, Naidu SS, Givertz MM, *et al.* Society for Cardiovascular Angiography and Interventions (SCAI); Heart Failure Society of America (HFSA); Society of Thoracic Surgeons (STS); American Heart Association (AHA), and American College of Cardiology (ACC). SCAI/ACC/HFSA/STS Clinical Expert Consensus Statement on the Use of percutaneous mechanical circulatory support devices in cardiovascular care: Endorsed by the American Heart Assocation, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencion; Affirmation of value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie d'intervention. J Am Coll Cardiol 2015; 65(19): e7-e26.
http://dx.doi.org/10.1016/j.jacc.2015.03.036 PMID: 25861963

[24] Jeevanandam V, Eisen H, Pinto D. Short-term mechanical circulatory assist devices. Available from: https://www.uptodate.com/contents/short-term-mechanical-circulatory-assist-devices#H384154364

[25] Ponikowski P, Voors AA, Anker SD, *et al.* ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37(27): 2129-200.
http://dx.doi.org/10.1093/eurheartj/ehw128 PMID: 27206819

[26] Thiele H, Zeymar U, Thelemann N, *et al.* Intraaortic balloon pump in cardiogenic shock complicating acute myocardial infarction; Long-term 6-year outcome of the randomised IABP-SHOCK II trial. Circulation 2019; 139: 395-403.
http://dx.doi.org/10.1161/CIRCULATIONAHA.118.038201

[27] LivaNova: Health innovation that matters. Tandemlife. Available from: http://www.tandemlife.com/

[28] Thiele H, Lauer B, Hambrecht R, Boudriot E, Cohen HA, Schuler G. Reversal of cardiogenic shock by percutaneous left atrial-to-femoral arterial bypass assistance. Circulation 2001; 104(24): 2917-22.
http://dx.doi.org/10.1161/hc4901.100361 PMID: 11739306

[29] Abiomed: Heart recovery. Available from: http://www.abiomed.com/impella

[30] Schrage B, Ibrahim K, Loehn T, *et al.* Impella support for acute myocardial infarction complicated by cardiogenic shock. Circulation 2019; 139(10): 1249-58.
http://dx.doi.org/10.1161/CIRCULATIONAHA.118.036614 PMID: 30586755

[31] Dhruva SS, Ross JS, Mortazavi BJ, *et al.* Association of use of an intravascular microaxial left ventricular assist device *vs*. intra-aortic balloon pump with in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock. JAMA 2020; 323(8): 734-45.
http://dx.doi.org/10.1001/jama.2020.0254 PMID: 32040163

[32] Borisenko O, Wylie G, Payne J, *et al.* Thoratec CentriMag for temporary treatment of refractory cardiogenic shock or severe cardiopulmonary insufficiency: a systematic literature review and meta-analysis of observational studies. ASAIO J 2014; 60(5): 487-97.
http://dx.doi.org/10.1097/MAT.0000000000000117 PMID: 25010916

[33] Abrams D, Combes A, Brodie D. Extracorporeal membrane oxygenation in cardiopulmonary disease in adults. J Am Coll Cardiol 2014; 63(25 Pt A): 2769-78.
http://dx.doi.org/10.1016/j.jacc.2014.03.046 PMID: 24814488

[34] Schmidt M, Burrell A, Roberts L, *et al.* Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. Eur Heart J 2015; 36(33): 2246-56.
http://dx.doi.org/10.1093/eurheartj/ehv194 PMID: 26033984

[35] Rao P, Khalpey Z, Smith R, Burkhoff D, Kociol RD. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest. Circ Heart Fail 2018; 11(9): e004905.
http://dx.doi.org/10.1161/CIRCHEARTFAILURE.118.004905 PMID: 30354364

[36] Appendix O: INTERMACS Profiles of Advanced Heart Failure accessed at https://www.uab.edu/medicine/intermacs/intermacs-documents

[37] Schramm R, Morshuis M, Schoenbrodt M, *et al.* Current perspectives on mechanical circulatory support. Eur J Cardiothorac Surg 2019; 55 (Suppl. 1): i31-7.
http://dx.doi.org/10.1093/ejcts/ezy444 PMID: 30608535

[38] Noly PE, Ben Ali W, Lamarche Y, Carrier M. Status, indications, and use of cardiac replacement therapy in the era of multimodal mechanical approaches to circulatory support: a scoping review. Can J Cardiol 2020; 36(2): 261-9.
http://dx.doi.org/10.1016/j.cjca.2019.11.027 PMID: 32036867

[39] Rose EA, Gelijns AC, Moskowitz AJ, *et al.* Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001; 345(20): 1435-43.
http://dx.doi.org/10.1056/NEJMoa012175 PMID: 11794191

[40] Kouchoukos N, Blackstone E, Hanley F, *et al.* Mechanical Circulatory Support. Kirklin/Barratt-Boyes Cardiac Surgery. (4th Ed.), London, United Kingdom: Elsevier Health Sciences 2012.

[41] Kormos RL, Cowger J, Pagani FD, *et al.* The Society of Thoracic Surgeons Intermacs database annual report: Evolving indications, outcomes, and scientific partnerships. J Heart Lung Transplant 2019; 38(2): 114-26.
http://dx.doi.org/10.1016/j.healun.2018.11.013 PMID: 30691593

[42] Rogers JG, Pagani FD, Tatooles AJ, *et al.* Intrapericardial left ventricular assist device for advanced heart failure. N Engl J Med 2017; 376(5): 451-60.
http://dx.doi.org/10.1056/NEJMoa1602954 PMID: 28146651

[43] Mehra MR, Uriel N, Naka Y, *et al.* MOMENTUM 3 Investigators. A fully magnetically levitated left ventricular assist device - final report. N Engl J Med 2019; 380(17): 1618-27.
http://dx.doi.org/10.1056/NEJMoa1900486 PMID: 30883052

[44] Argiriou M, Kolokotron SM, Sakellaridis T, *et al.* Right heart failure post left ventricular assist device implantation. J Thorac Dis 2014; 6 (Suppl. 1): S52-9.
PMID: 24672699

[45] Fitzpatrick JR III, Frederick JR, Hiesinger W, *et al.* Early planned institution of biventricular mechanical circulatory support results in improved outcomes compared with delayed conversion of a left ventricular assist device to a biventricular assist device. J Thorac Cardiovasc Surg 2009; 137(4): 971-7.
http://dx.doi.org/10.1016/j.jtcvs.2008.09.021 PMID: 19327526

[46] Kalogeropoulos AP, Kelkar A, Weinberger JF, *et al.* Validation of clinical scores for right ventricular failure prediction after implantation of continuous-flow left ventricular assist devices. J Heart Lung Transplant 2015; 34(12): 1595-603.
http://dx.doi.org/10.1016/j.healun.2015.05.005 PMID: 26123950

[47] Australia and New Zealand Organ Transplant Registry. Available from: http://www.anzcotr.org.au/

[48] Nicholas T, Kouchoukos MD, Eugene H, *et al.* Cardiac transplantation. Kirklin/Barratt-Boyes cardiac surgery. (4th Ed.), Elsevier 2013.

[49] Alraies M, Eckman P. Adult heart transplant: indications and outcomes. J Thorac Dis 2014; 6(8): 1120-8.

[50] Australia and New Zealand Cardiothoracic Organ Transplant Registry (ANZCOTR) 2018. Available from: http://www.anzcotr.org.au/pub/e0cc941a/PDFS/ANZCOTR2018_text.pdf

[51] Chew HC, Iyer A, Connellan M, *et al.* Outcomes of donation after circulatory death heart transplantation in Australia. J Am Coll Cardiol 2019; 73(12): 1447-59.
http://dx.doi.org/10.1016/j.jacc.2018.12.067 PMID: 30922476

[52] Abbasi J. "Donation After Circulatory Death" heart transplant is a US first. JAMA 2020; 323(2): 111.
http://dx.doi.org/10.1001/jama.2019.21073 PMID: 31935007

[53] Samsky MD, Patel CB, Owen A, *et al.* Ten-year experience with extended criteria cardiac transplantation. Circ Heart Fail 2013;

6(6): 1230-8.
http://dx.doi.org/10.1161/CIRCHEARTFAILURE.113.000296 PMID: 24088293

[54] Khush KK, Cherikh WS, Chambers DC, *et al.* International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report - 2019; focus theme: Donor and recipient size match. J Heart Lung Transplant 2019; 38(10): 1056-66.
http://dx.doi.org/10.1016/j.healun.2019.08.004 PMID: 31548031

[55] Heatley G, Sood P, Goldstein D, *et al.* MOMENTUM 3 Investigators. Clinical trial design and rationale of the Multicenter Study of MagLev Technology in patients undergoing mechanical circulatory support therapy with HeartMate 3 (MOMENTUM 3) investigational device exemption clinical study protocol. J Heart Lung Transplant 2016; 35(4): 528-36.
http://dx.doi.org/10.1016/j.healun.2016.01.021 PMID: 27044532