Heart transplantation: focus on donor recovery strategies, left ventricular assist devices, and novel therapies

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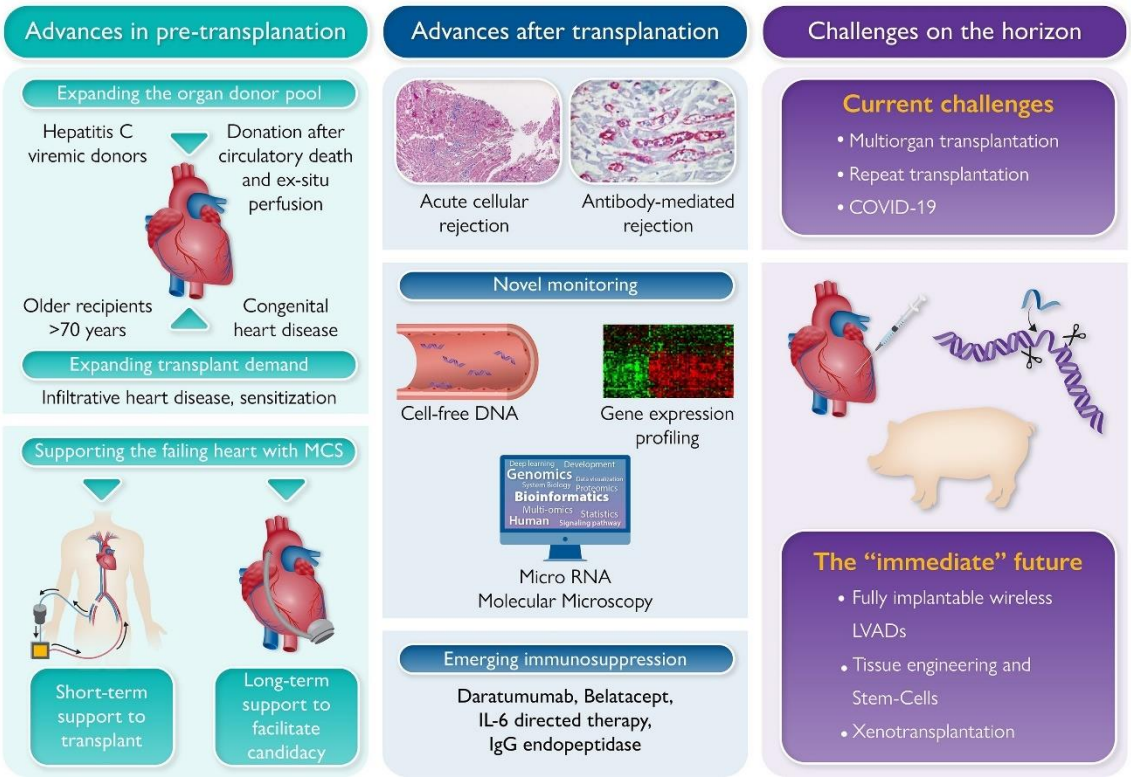
Abstract

Heart transplantation is advocated in selected patients with advanced heart failure in the absence of contraindications. Principal challenges in heart transplantation centre around an insufficient and underutilized donor organ pool, the need to individualize titration of immunosuppressive therapy, and to minimize late complications such as cardiac allograft vasculopathy, malignancy, and renal dysfunction. Advances have served to increase the organ donor pool by advocating the use of donors with underlying hepatitis C virus infection and by expanding the donor source to use hearts donated after circulatory death. New techniques to preserve the donor heart over prolonged ischaemic times, and enabling longer transport times in a safe manner, have been introduced. Mechanical circulatory support as a bridge to transplantation has allowed patients with advanced heart failure to avoid progressive deterioration in hepato-renal function while awaiting an optimal donor organ match. The management of the heart transplantation recipient

remains a challenge despite advances in immunosuppression, which provide early gains in rejection avoidance but are associated with infections and late-outcome challenges. In this article, we review contemporary advances and challenges in this field to focus on donor recovery strategies, left ventricular assist devices, and immunosuppressive monitoring therapies with the potential to enhance outcomes. We also describe opportunities for future discovery to include a renewed focus on long-term survival, which continues to be an area that is under-studied and poorly characterized, non-human sources of organs for transplantation including xenotransplantation as well as chimeric transplantation, and technology competitive to human heart transplantation, such as tissue engineering.

Graphical abstract



This figure describes five advances in heart transplantation including (i) the expanding donor pool and increased donor demand, (ii) short- and long-term mechanical circulatory support (MCS) of the failing heart, (iii) enhanced monitoring for acute cellular rejection and antibody-medicated rejection, (iv) emerging immunosuppressive agents, and (v) challenges and opportunities for the future (including tissue engineering, xenotransplantation, and stem cell therapy). IL-6, interleukin-6; LVAD, left ventricular assist device.

Keywords: Heart transplantation, Donors, Rejection, Immunosuppression

Introduction

Heart transplantation (HT) is the treatment of choice for patients with advanced heart failure in the absence of contraindications[1] with an overall median survival of 12.5 years and conditional survival of 14.8 years for those who survive the first year.[2] Heart transplantation improves the quality of life, allows an active lifestyle including employment. Principal challenges centre around an insufficient and underutilized donor organ pool,[3] need to individualize titration of immunosuppressive therapy, and to minimize late complications such as cardiac allograft vasculopathy, malignancy, and renal dysfunction.

Advances in several arenas have served to increase the organ donor pool by the use of donors with underlying hepatitis C virus (HCV) infection or by expanding the donor source to use hearts donated after circulatory death. New techniques to preserve the donor heart over prolonged ischaemic times and enabling safe transport have been introduced. Mechanical circulatory support (MCS) as a bridge to transplantation has allowed patients with advanced heart failure to avoid progressive clinical deterioration while awaiting a suitable donor. Advances in immunosuppression are associated with early gains in reduction of rejection but plagued by infection-related complications and late-outcome challenges. In this article, we bring together a practical review of selected contemporary advances and challenges in this field (*Graphical Abstract*).

Donor organ selection, preservation, and techniques

Organ selection

Liberal donor acceptance practices have been implemented in the context of advances in allograft preservation, innovations in perioperative care, and in post-transplant management (*Figure 1*). When a donor is identified, cardiac function is evaluated with echocardiography (to also evaluate valvular pathology), and in older donors (>40 years)

evaluating for pre-existing coronary artery via invasive or non-invasive angiography disease is recommended but not always feasible. Once cardiac function is assessed as satisfactory, donor–recipient size and sex match, best approximated by the calculated donor–recipient predicted heart mass ratio is evaluated, since discrepancy in size between the recipient and the donor (a predicted heart mass ratio of <0.86) leads to increased adverse events.[4] Using predicted heart mass may increase the acceptable pool by a third. Although increased donor age is associated with higher recipient mortality risk, favourable survival has been shown with organs from donors >50 or even >60 years old, a practice primarily in Europe.[5] Donor comorbidities such as diabetes mellitus and hypertension affect post-transplant outcomes, and such hearts are used after excluding irreversible structural cardiac abnormality. The impact of donor risk factors is augmented by longer allograft ischaemic time and distance from the transplant centre.[6,7] Risk scores have been developed to assist clinicians in these complex decisions.[8,9]

The rise in drug abuse resulted in an increase in organ donors who die of drug overdose. Post-transplant survival in such recipients of such organs seems favourable and the use of these organs is increasing, especially in the US.[10] Curative therapies for HCV infection have allowed re-exploration for the use of HCV-positive donors for organ transplantation, previously shunned.[11] Two principal strategies are used with donor organs from an HCV-infected donor—either a pan-genotypic drug regimen, initiated perioperatively consisting of 4 weeks of sofosbuvir/velpatasvir[12] or 8 weeks of glecaprevir/pibrentasvir, or second, therapy initiated after establishment of HCV infection, typically sofosbuvir/velpatasvir (12 weeks) or glecaprevir/pibrentasvir (8–12 weeks).[11] An early prophylaxis strategy only permits low levels of viral transmission and avoids the establishment of a recipient infection with a shorter duration of therapy which reduces cost, however, payor coverage remains challenging. In the 1-year time frame, outcomes from HCV-positive donors are similar to HCV-negative donors, although longer-term outcomes as they pertain to immunological activation, allograft rejection, and cardiac allograft vasculopathy remain uncertain.

Immunological considerations

An increasing number of heart transplant candidates have circulating anti-HLA antibodies as a result of exposures that result in allosensitization such as multi-parous women, those with MCS due to associated use of blood products or those operated with congenital heart disease. The ideal outcome in allosensitized patients after transplant is the absence of donor-specific antibody (DSA). This is achieved by selecting a donor without HLA antigens to which the prospective recipient is sensitized. Accurate identification of the antibody specificity pre-transplant allows for determination of immune compatibility without a prospective direct crossmatch through an approach called virtual crossmatch.[13] Alternatives include desensitization therapies before the transplant or altered immunosuppression directed at removal, reduced production, and/or neutralization of circulating antibodies after transplant in patients with DSA.[14]

Organ allocation policies

Organ allocation policy determines the sequence in which heart transplant candidates on the waiting list are offered an available donor organ, designed to minimize the risk of death on the waiting list and maximize post-transplant survival, while assuring equitable access to transplantation.[15] Establishing an allocation score that accurately reflects risk of death on the heart transplant waiting list has proven difficult.[16] This is due to the heterogeneity of phenotypes of patients on the waiting list, evolving treatment options for heart failure, and non-transplant treatment modalities such as MCS that can alter the predicted mortality in patients with heart failure.

Organ allocation policies are established by national regulatory agencies or multi-national collectives. An allocation algorithm incorporates clinical characteristics such as disease aetiology and haemodynamic stability, the treatment modalities being used, and duration on the waiting list but is challenged by changing treatment paradigms. Modifications aimed to maintain fairness of the allocation algorithm have been implemented frequently.[15–19] Some changes include expanded regional sharing of donor organs, lower priority for stable patients with durable left ventricular assist devices (LVADs), stratification of patients with types of temporary MCS (t-MCS), or higher priority status in patients not suitable for MCS such as those with congenital or infiltrative heart disease.

Despite challenges, the implementation of current allocation algorithms balances waitlist death risk with favourable post-transplant survival.

Organ preservation techniques and distant procurement

Successful cardiac transplantation is still largely dependent on the viability and condition of the donor myocardium at the time of implantation. Following organ procurement, ischaemia is the main cause of tissue injury.[20] Therefore, cardiac preservation is a key component for distant procurement and successful outcomes. After cardioplegia, the heart is excised, placed in preservation solution, and stored on ice, in commercially available cooling boxes, at a temperature range of 4–8°C.[19,21] Three general principles guide the formulation of cardioplegic and preservation solutions: (i) rapid reduction of tissue metabolic rate by profound hypothermia and electro-mechanical arrest of the heart, (ii) provision of a biochemical medium that maintains tissue viability and structural integrity, and (iii) prevention of reperfusion injury.[22] There are a number of preservation solutions available; however, there is no consensus regarding the optimal composition of the preservation solution, with widespread variability among transplant centres worldwide.[23] Currently, heart preservation via cold static preservation is limited to 4–6 h. Longer periods of ischaemia adversely affect patient survival.[24] Moreover, current preservation strategies of marginal donor hearts (such as those with older age or structural cardiac disease) have been associated with higher mortality, especially when coupled with longer ischaemic times.[7] Over 70% of potential donor hearts worldwide are discarded for transplantation, partly due to limitations of current preservation techniques.[25] Little progress has been made in extending myocardial preservation and storage times following procurement. Temperature-controlled transportation devices have shown stable temperatures during preservation with a promise to lower rates of primary graft dysfunction and shorter post-operative intensive care unit stay.[26,27] Alternatively, normothermic machine perfusion (NMP) systems have been tested to improve outcomes and reduce ischaemic times during preservation. Warm oxygenated machine perfusion has played a key role in enabling the usage of donation after circulatory death hearts and allowing longer intervals between procurement and implantation over the last years.[28,29] The Portable Organ Care System Heart for Preserving and Assessing Expanded Criteria Donor Hearts for Transplantation study demonstrated that the use of *ex situ* perfusion for

expanded-criteria hearts may be a viable method for increasing the use of donor hearts.[29] Another system, where the donor heart is continuously perfused with a cold (8°C) oxygenated cardioplegic nutrition–hormone solution containing erythrocytes has been tested successfully in clinical transplantation.[30] These technologies have the potential to increase the donor pool and to expand the feasible travel distance of procurement teams.

Heart transplantation from donation after circulatory death donors

After the first report of successful distant retrieval and transplantation of three adult donation after circulatory death (DCD) hearts in 2014,[31] DCD heart transplant programmes commenced in the UK, Europe, and North America. While the upper age limit for acceptance of DCD donors for HT varies between centres, it is lower than for brain death donors (typically <50 years). This is due to the limited ability to screen the DCD donor for pre-existing heart disease and the concern regarding susceptibility of the heart from older donors to the obligatory period of warm ischaemia intrinsic to the DCD pathway. An echocardiogram demonstrating normal biventricular and valve function before withdrawal of life-support therapy (WLST) is the major requirement.

Assessing functional warm ischaemia during withdrawal of life support

In trials, functional warm ischaemic time (FWIT) is defined as the total time from when mean systolic blood pressure (SBP) decreases below 50 mmHg or peripheral arterial oxygen saturation drops to <70% to the initiation of aortic cross-clamp and administration of cardioplegia in the donor. Preclinical studies suggest that provided the FWIT is <30 min, the DCD heart is recoverable and transplantable.[32,33] However, whereas progression to circulatory death in these preclinical models is rapid and predictable, the time course of progression to circulatory arrest in human DCD donors is variable.[34] Although there is agreement that a sustained fall in SBP below normal marks, the onset of FWIT there is ongoing debate as to what precise level of SBP should be used in such a definition.[33] These criteria are likely to be refined as data on histological ischaemia emerge which will allow for potential expansion of the population.

Retrieval protocols for donation after circulatory death hearts

Jurisdictional variations regarding the diagnosis of circulatory death and interventions permitted before and after death have influenced the development of retrieval protocols (*Table 1*). Ante-mortem interventions including administration of heparin and placement of perfusion catheters before WLST reduce the risk of post-mortem thrombosis and shorten the FWIT, respectively, but are disallowed in some jurisdictions. The mandated 'stand-off' time between the declaration of death and commencement of retrieval surgery varies from 2 to 20 min and has a major impact on FWIT. There is variation regarding what post-mortem interventions are permitted. Specifically, re-establishment of the circulation *in situ* is prohibited in some jurisdictions. In jurisdictions that do not permit re-establishment of the circulation after death, direct procurement of the DCD heart followed by NMP (DP-NMP) has allowed successful transplantation of DCD hearts.[30,35] In jurisdictions that permit re-establishment of the circulation after death, thoraco-abdominal normothermic regional perfusion (TA-NRP) after isolation of the cerebral circulation has allowed resuscitation and functional assessment of the DCD heart *in situ* before retrieval and transplantation (*Figure 2*).[36] Whether one technique is better than the other remains to be adequately studied. If *in situ* reanimation followed by static cold storage is non-inferior to direct procurement with *ex situ* normothermic perfusion, it may be preferred due to the ability to evaluate the reanimated heart *in situ* and may lower overall cost since the transport machine will not be required; however, this technique requires more clinician resources which balance cost savings. Current published DCD retrieval protocols for retrieval of the adult DCD highlighting variability between centres due to regional differences in legislation are shown in *Table 1*.[34–39]

Outcomes of heart transplants from donation after circulatory death donors

Two large programmes reported that 4- and 5-year survival of DCD heart transplant recipients is comparable with those DBD donors.[35,40] A multicentre US study of DP-NMP completed recruitment of 180 subjects and reported top-line results.[41] Heart transplant candidates were randomized 3:1 to either DCD Heart Possible (DCD) or DBD cold-stored transplant (Control). The DCD arm met the non-inferiority endpoint of patient survival at 6 months, with an organ utilization rate of 89%. In addition, several US centres reported

successful heart transplants from DCD donors following TA-NRP. Currently, DCD heart transplants account for 30–40% of heart transplant activity in centres with established DCD organ use. Globally, DCD has the potential to increase heart transplant activity by up to 2000 cases annually.

Mechanical circulatory support as bridge to transplantation

Many patients with advanced heart failure present late or in cardiogenic shock and may not be expected to survive waiting for a donor heart even when placed in high urgency status. Some patients may have temporary contraindications to transplantation such as fixed elevated pulmonary vascular resistance or recent neoplasia. These patients must be bridged to transplantation by MCS to allow for sufficient end-organ recovery and physical rehabilitation before transplantation. In the period from 2010 to 2018, 45% of cardiac allograft recipients in the ISHLT registry had MCS at the time of transplant, mainly LVADs.[2] MCS can be temporary, using extracorporeal pumps, or durable, with intracorporeally placed devices. Mechanical circulatory support enables restoration of end-organ function, nutritional status, and rehabilitation before transplant surgery. There are risks associated with MCS when transplantation is performed, which include coagulopathy, infection, stroke, bleeding, and the need for re-sternotomy (in durable LVAD recipients). This raises questions of balancing immediate recipient survival vs. optimal use of donor organs as the outcome risk increases.

Temporary mechanical circulatory support

Temporary MCS includes intra-aortic balloon pumps, percutaneous LVADs such as the Impella, Centrimag, or the TandemHeart and veno-arterial extra-corporeal membrane oxygenation (VA-ECMO) with femoral access. Temporary LVADs and right ventricular assist devices may also be placed surgically, typically by sternotomy and usually in the setting of post-cardiotomy shock. Veno-arterial extra-corporeal membrane oxygenation can be placed centrally if biventricular support is needed, or oxygenation is insufficient due to concomitant lung failure. Right ventricular support can be achieved percutaneously by the Impella RP or the Protek Duo dual-lumen device in combination with percutaneous or durable LVADs. The use of VA-ECMO has escalated significantly in recent years.

Owing to the 2018 revision of the donor heart allocation rules, a marked increase in the use of bridge t-MCS devices has been observed in the US.[42] This is also seen in some European countries but varies as a function of differences in organ allocation systems. In a study from Spain, post-transplant survival was inferior in patients with VA-ECMO or temporary Bi-VAD, but no different in patients with temporary LVAD.[43] A study from the ISHLT registry showed an increased post-transplant mortality in patients supported with VA-ECMO and with percutaneous, temporary LVADs.[44] Taken together, the available evidence suggests that post-transplant outcome in patients supported to urgent transplantation with t-MCS may be inferior, although as experience ensues, this is likely to improve with time. A recent UNOS study shows better clinical outcomes in patients listed for HT supported with VA-ECMO, with lower mortality on the list and less time on the waiting list.[45] Some patients may benefit from transitioning t-MCS to a durable LVAD after initial stabilization and subsequently deciding on patient candidacy (*Figure 3*).

Durable mechanical circulatory support

Patients implanted with durable MCS may be supported for years until transplantation is possible. Patients with increased pulmonary vascular resistance almost invariably show lowering to levels acceptable for transplantation.[46,47] Support duration for patients waiting for transplantation may be extensive. In the European ELEVATE registry of patients implanted with a Heartmate 3 pump <10% of patients were transplanted at 2 years even though 2/3rd were so intended.[48] Outcomes are equivalent compared with unsupported patients.[49–52] The Heartmate 3 LVAD has so far been associated with the lowest risk of adverse events such as pump thrombosis, bleeding, and stroke.[47–49,53]

Immunosuppression tailored to immune monitoring and graft damage

Great strides in molecular diagnostics in the field of HT occurred over the past decade in non-invasive monitoring of acute rejection, to enhance biopsy-based diagnosis, and to individualize immunosuppression. The field of HT is largely protocol-driven in the administration of immunosuppressive therapies, even though patients vary greatly in their

immune responses.[54,55] Thus, there has been increasing interest in the use of molecular assays to achieve the goal of personalization in HT.

The AlloMap® assay (CareDx, Inc.) is a gene expression profiling test comprised of 11-genes differentially expressed in the setting of acute cellular rejection (ACR).[56] The clinical utility of the AlloMap assay was demonstrated in the Invasive Monitoring Attenuation through Gene Expression trial,[54] which showed that clinical outcomes (rejection with haemodynamic compromise, graft dysfunction, death, and re-transplantation) were non-inferior using AlloMap for non-invasive rejection surveillance rather than a traditional biopsy-based approach, although concerns were raised that the study may not have been conclusive.[57] Subsequently, variability in AlloMap scores over time was shown to be associated with future clinical events, and low variability associated with better clinical outcomes. This assay may guide maintenance immunosuppression due to its high negative predictive value but has not been validated in antibody-mediated rejection (ABMR).

Donor-derived cell-free DNA (ddcfDNA), another non-invasive diagnostic test for acute rejection monitoring, is a sensitive marker of graft injury.[58,59] Elevated ddcfDNA levels are found in the setting of both ACR and ABMR, and levels often start to rise weeks to months before biopsy-based rejection diagnosis. This early and sensitive marker of graft injury could potentially be used to tailor immunosuppression—rising levels may prompt augmentation of maintenance immunosuppression to prevent impending rejection, while low levels could allow immunosuppressive weaning. These non-invasive tests can be performed more frequently than biopsies, and can therefore be used to assess allograft health in response to changes in immunosuppression, but cost-effectiveness has not been adequately demonstrated.[60]

Anelloviruses (torque teno viruses) are benign commensal viruses that are present in the majority of warm-blooded animals and are not known to cause clinical disease in humans. Prior cell-free DNA sequencing studies showed that anelloviruses replicate rapidly in the setting of immune system suppression, and the abundance of anellovirus in the blood is inversely associated with the strength of the immune response.[61] Subsequent clinical studies in solid organ transplantation have shown that high anellovirus levels are associated with the development of opportunistic infections and malignancy post-transplant, while low levels with development of acute rejection.[62,63] There is now interest

in developing clinically available anellovirus assays for monitoring the strength of the alloimmune response in organ transplant recipients.

The molecular microscope (MMDx-Heart) assay can be used to refine the biopsy-based diagnosis of acute rejection. This assay measures intra-graft gene expression using microarrays, and provides molecular scores of the probability of ACR, ABMR, and mixed rejection.[64] Given the poor concordance among pathologists in biopsy grading, such tools may diagnose acute rejection more accurately.[65] While such novel tools allow us to assay the status of the alloimmune response and to titrate immunosuppressive therapy prospective clinical trials are needed to develop and refine usefulness of such approaches (*Figure 4*).

Advances in post-transplantation immunosuppression and immunomodulation

Currently available immunosuppressive drugs

Traditional immunosuppression using calcineurin inhibitors (tacrolimus and cyclosporine) in concert with corticosteroids and adjunctive agents (mycophenolate mofetil or mTOR inhibitors such as sirolimus or everolimus) has reduced the clinical impact of ACR but management of ABMR remains an unmet need. Antibody-mediated rejection is the result of endothelial injury caused by circulating antibodies directed against graft antigens, mainly represented by Class I or II HLA antigens. It is relevant to differentiate pre-formed antibodies, detectable before transplant from those arising post-transplantation.[66] Available therapies may be directed towards antibody removal or neutralization, inhibition of antibody synthesis, or complement deactivation. Such strategies include repurposing of drugs developed in other diseases.[67]

Intravenous immunoglobulins (IVIG) can be used to reduce the impact of pre-formed antibodies, as well as to treat ABMR. Intravenous immunoglobulins inhibit complement-mediated inflammation, neutralization of anti-HLA antibodies, cytokines, and inhibition of macrophages and antigen-presenting cell maturation.[68] In sensitized patients, IVIG alone or in combination with plasma exchange may increase the chance of being transplanted,[69–72] while combination with other agents, such as rituximab and bortezomib, additionally reduces ABMR incidence.[73] Rituximab is an anti-CD20 chimeric murine-

human monoclonal antibody, selectively depleting B-cells via antibody-mediated cytotoxicity. Rituximab has been used as desensitization therapy,[74] as well as treatment for ABMR with conflicting results.[75–77] In association with IVIG and plasma exchange, it is effective in reducing circulating antibodies before transplant, but not to improve long-term survival. A randomized study in heart transplant patients showed increase in the development of cardiac allograft vasculopathy in patients treated with rituximab as induction therapy early after transplantation.[78]

Bortezomib is a proteasome inhibitor developed to treat multiple myeloma and reduces the synthesis of immunoglobulins by mature plasma cells. It can be used in association with IVIG in desensitization protocols,[79] but without convincing efficacy and significant rate of adverse events.[80,81] Single case reports showed effectiveness in treatment of ABMR, not confirmed, however, in controlled studies.[82]

Eculizumab is a humanized monoclonal antibody, which inhibits cleavage of C5 to C5a, limiting the formation of membrane attack complex and terminal complement-mediated injury.[83] Recently, in randomized studies and in one single-arm heart transplant study, eculizumab was noted to prevent ABMR and graft loss when used as prophylactic induction in highly sensitized recipients.[84–86]

Alemtuzumab is a humanized monoclonal antibody against CD52 and causes depletion of T and B lymphocytes, monocytes, and NK cells. It is used in induction and anti-rejection therapy while sparing steroids. With most evidence coming from kidney transplant setting, alemtuzumab induction is similar to anti-thymocyte globulin in preventing rejection.[87,88] In HT, alemtuzumab induction is effective in preventing cellular rejection, but not ABMR,[89,90] and has been reported effective in refractory rejection.[89,91]

Daratumumab is a monoclonal antibody directed against CD38, expressed on some lymphocyte subsets and plasma cells. It has been used to treat ABMR in isolated cases and is a candidate for further study.[92]

Extracorporeal immunosuppressive therapies in heart transplantation

Plasmapheresis involves extracorporeal removal, return, or exchange of blood plasma or components by either centrifugation or filtration using semipermeable membranes. Plasmapheresis rapidly reduces anti-HLA or isoagglutinin antibodies and has predictable kinetics but requires central vascular access and is expensive. Alone or in combination

with IVIG therapy and/or rituximab, plasmapheresis can be used preoperatively in highly sensitized heart transplant candidates or for the treatment of ABMR due to either pre-existing or *de novo* DSA.[93] The ISHLT Guidelines state that desensitization therapies, including plasmapheresis, should be considered when sensitization is high enough to significantly decrease the likelihood for a compatible donor match or to decrease the risk of rejection when unavoidable mismatches occur.[93] Immunoadsorption removes the IgG 1, 2, and 4 subclasses but *not* the complement-binding IgG 3. Although the indications are similar to those of plasmapheresis, immunoadsorption has higher costs and risk of infection and lesser effectiveness when used alone.[93]

Extracorporeal photopheresis involves the collection and treatment of white blood cells contained in the buffy coat with a photoactive 8-methoxy psoralen compound with subsequent irradiation with ultraviolet-A light. This process is thought to cause DNA and RNA crosslinking, ultimately leading to immune cell destruction. The true mechanism of therapeutic action remains unknown[94] (see Supplementary material online, *Table S1*).

Emerging immunosuppressive drug therapy

Belatacept

Belatacept is a high-affinity CTLA4Ig indicated for rejection prophylaxis in adult renal transplant recipients in combination with mycophenolic acid and corticosteroids, to primarily stabilize renal function, but is contraindicated in those without immunity to Ebstein-Barr virus due to risk of central nervous system lymphoproliferative disease. In a retrospective observational study of 40 heart transplant recipients, belatacept was noted to improve glomerular filtration rate (GFR), particularly if used within 3 months. However, when started in the late phase post-transplant, rejection rates were higher and suggest that the experience is insufficient to permit inferences on safety and effectiveness.[95]

Interleukin-6-directed therapy

Interleukin (IL)-6 is a pro-inflammatory cytokine implicated in allograft injury through acute inflammation, adaptive cellular/humoral responses, innate immunity, and fibrosis. Interleukin-6 promotes acute phase reactions, induces B cell maturation/antibody

formation, directs cytotoxic T-cell differentiation, and inhibits regulatory T-cell development. Blockade of the IL-6/IL-6R signalling pathway in animal models ameliorates allograft rejection.[96] Agents for IL-6 signalling inhibition include monoclonal antibodies against IL-6 or IL-6R and Janus kinase inhibitors. In a human arterial allograft model, IL-6 signalling inhibition attenuated vasculopathy.[97] Ongoing clinical studies are examining the use anti-IL-6 mAb clazakizumab and IL-6 signalling blockade with tocilizumab early after HT.

IdeS

The protease IdeS from Streptococcus pyogenes is an immunomodulating enzyme that cleaves IgG in the lower hinge region. After hydrolysis, IgG loses its effector functions, such as binding to leucocytes and complement activation, and targets highly HLA-sensitized patients before transplantation. This has been tested in kidney transplants that allowed transplantation across highly sensitized systems albeit with an increased risk of treatable ABMR but remains to be investigated in HT.[98]

Multiorgan transplantation

Hepatic and renal dysfunction is frequent in advanced heart failure and combined transplantation may be an option for some of these patients. Some cardiac conditions may require heart–liver transplantation (HLI) in forms of amyloidosis, or heart–lung (HL) transplantation in those with advanced congenital heart disease. The number of multiorgan transplants has been gradually increasing to 2–4% of all heart transplants, the majority of them, HL or heart–kidney (HK) and less frequently, HLI.[99] Combined HK transplantation seems to be favoured in retransplantation, likely due to chronic renal dysfunction related to calcineurin inhibitor toxicity. Multiorgan transplants comprised 12.8% of retransplants compared with 2.4% of *de novo* heart transplants.[99] When considering simultaneous vs. sequential HK transplantation, the use of dialysis of a GFR < 30 mL/min suggests that the former is a better strategy while a GFR of 30–45 mL/min shows equivalent outcomes to either strategy.[100]

Multiorgan transplantation increases the risk of early mortality but has been shown to offer immunoprotection for the cardiac allograft in combined HL,[101,102] HK,[102] and HLI

transplantation.[103] In highly sensitized patients, a heart-after-liver transplantation protocol enabled near-elimination of DSA and prevented adverse immunological outcomes when combined HLI transplantation was indicated.[104] One and 5-year survival after HL transplantation is worse than isolated HT at 70 and 30%, respectively.[105] Other combined transplants have similar survival compared with isolated cardiac transplantation.[99]

Retransplantation

Re-transplantation (Re-HT) is a successful treatment strategy in those patients who develop graft failure due to primary graft failure, acute rejection, cardiac allograft vasculopathy, or chronic non-specific cardiac dysfunction, that is, refractory to conventional treatment. Cardiac re-transplantation remains a rare indication and requires careful patient selection to optimize outcomes.[2,106,107]

Clinical outcomes of Re-HT compared with a first transplant are worse, especially within 1-year.[106,108] A systematic review and meta-analysis that included 7791 patients with a first HT and 345 with a Re-HT (mean of 5 years after the first HT), observed worse survival after Re-HT vs. those after the first HT at 1 and 10 years, respectively.[109]. However, when the indication is cardiac allograft vasculopathy and the time after the first HT is more than 5 years, the results are similar to a *de novo* transplant.[106]

SARS-CoV-2 infection, COVID-19, and heart transplantation

The COVID-19 pandemic created a need to protect immunocompromised patients and significantly altered the management of transplant candidates and recipients. Organ donation and transplantation have been retained during the pandemic with models proposed to accommodate clinical practice despite the high level of COVID-19 hospitalizations and control on waitlist mortality.[110–113] Transplantation was performed using protocols to minimize the risk of transmission of SARS-CoV-2 infection from donor to recipient, and of transplanting potentially infected candidates.[114,115] Although transmission of SARS-CoV-2 infection has been reported in lung transplantation from a donor with a PCR negative nasopharyngeal swab, but positive bronchoalveolar lavage,[116] a heart and liver were successfully transplanted from a donor with persistent viral

shedding from the upper respiratory tract, with no transmission of the infection to the recipients.[117]

It has been noted that SARS-CoV-2 death rate in solid organ transplant recipients ranges between 15 and 25%, up to 10-fold higher than in the general population. The use of antimetabolites and age >60 years have been identified as strong risk factors for mortality.[118,119]

SARS-CoV-2 vaccination in immunosuppressed transplant recipients results in a significantly lower immune response than in healthy subjects.[120] A 'booster' dose of the vaccine is used to improve the efficacy of vaccination in transplant recipients.[121] Two studies reported >80% reduction in the risk of symptomatic COVID-19 in vaccinated transplant recipients and about 40% reduction in the risk of death, in the context of high effectiveness in reducing asymptomatic infection.[122,123] When compared with the general population, however, vaccinated transplant recipients are estimated to have higher risks of breakthrough infection with associated hospitalization and death.[124] Many centres mandate vaccination in transplant candidates while on the waitlist since their immunological responses may be adequate to offer protection, at least in the early post-transplant period when the immunocompromised status is greatest.

The future of heart transplantation

We envision three important directions to consider in the future therapeutic role of HT.[125] These include (i) a renewed focus on long-term survival, which continues to be an area that is under-studied and poorly characterized, (ii) non-human sources of organs for transplantation including xenotransplantation as well as chimeric transplantation, and (iii) technology competitive to human HT, such as tissue engineering[126] and fully implantable mechanical assist systems. While early outcomes are dependent on addressing immunological risk, long-term outcomes may benefit from a focus on non-immunological pathways in the realm of cardio-metabolic perturbations (such as hyperlipidaemia, hyperglycaemia, and inflammation) that coalesce together to propagate the development of cardiac allograft vasculopathy and consequent allograft failure.[127] Abrogating cardio-metabolic risk in long-term survivors of HT may be facilitated by use of novel molecules such as small interfering RNA based drugs to tackle hyperlipidaemia (e.g. inclisiran).[125] The impact of the microbiome community on innate or adaptive immune systems is

increasingly appreciated, knowledge of which might aid in helping to alter alloimmune responses and promote allograft tolerance.[128]

On January 7th 2022, a successful genetically edited porcine to human heart transplant was performed with 60 day patient survival.[129] Xenotransplantation has required scientific advances to overcome challenges of evolutionary distance between species, transmission of zoonosis into the human pool, immunological barriers that cause hyperacute rejection, allograft failure due to thrombotic microangiopathy, and raises ethical concerns of distributive justice.[129] Competing technologies to HT, such as tissue engineering, including organ reconditioning and regeneration during *ex situ* machine perfusion of organs (such have been shown in lungs and livers), and fully implantable mechanical assist total heart systems, will undoubtedly provide new options for our patients in the future.[125,130]

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: All individuals listed as authors qualify for authorship and have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Authors included in the manuscript meet all of the following conditions: (i) substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (ii) drafting the article or revising it critically for important intellectual content; and (iii) final approval of the version to be published. Individuals COI disclosure forms are attached.

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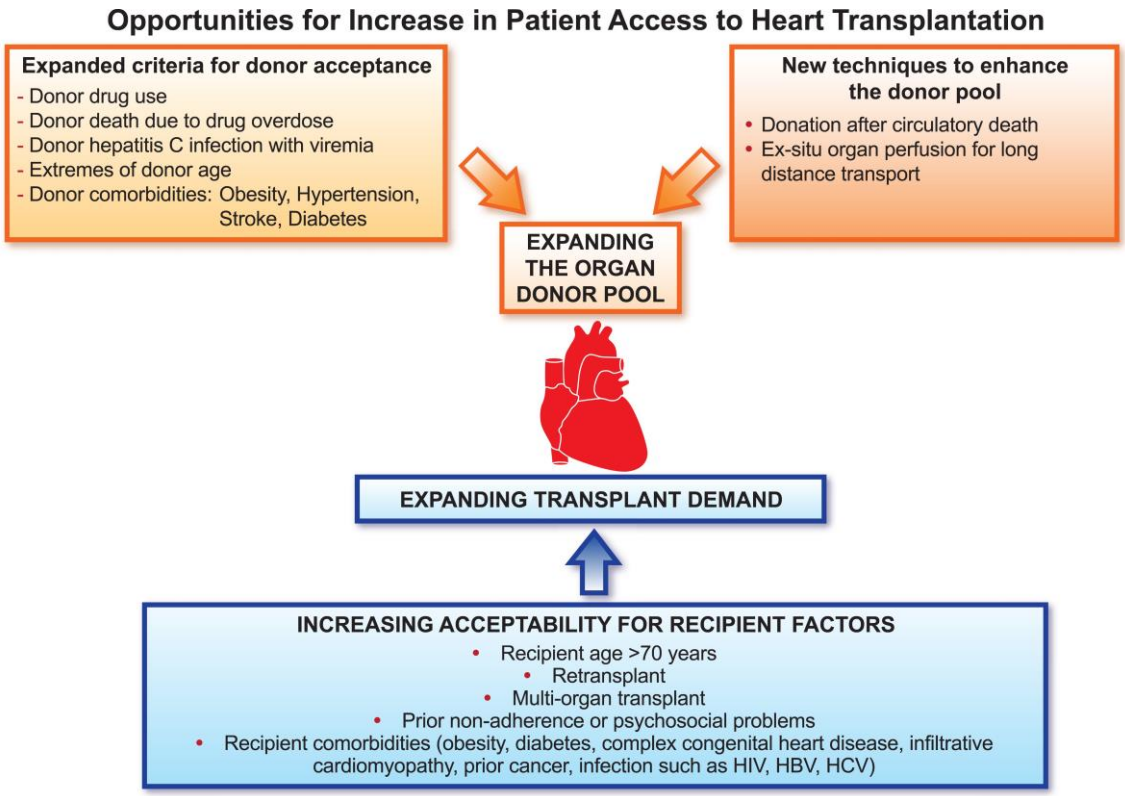

Fig. 1. Simultaneous expansion of the donor pool and recipient phenotypes in heart transplantation.

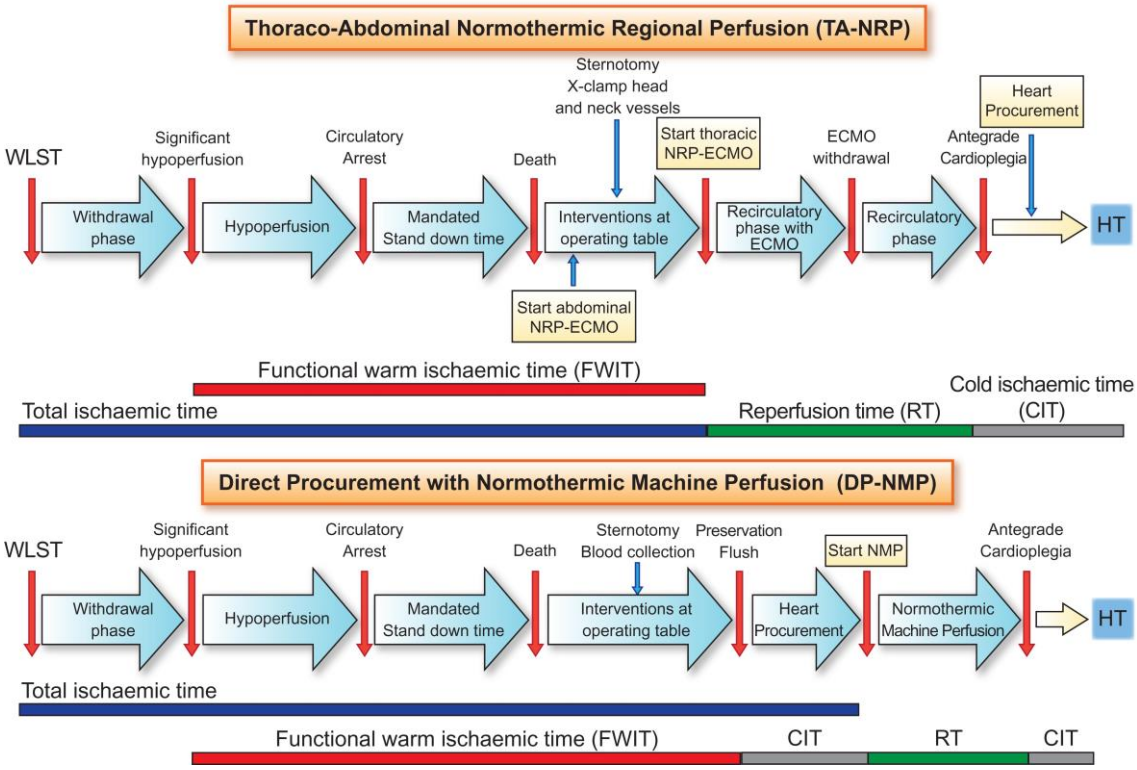

Fig. 2. The two major pathways and key time-points for retrieval of the heart from DCD donors: thoraco-abdominal normothemic regional perfusion and direct procurement. Provided the functional warm ischaemic time < 30 min, completed recovery of the DCD heart can be expected.

Table 1 Current published DCD retrieval protocols for retrieval of the adult DCD heart highlighting variability between centres due to regional differences in legislation (adapted from Scheuer et al.[34])

	St Vincent's (Aus)[35]	Papworth (UK)[36,37]	Liege (Belgium)[38]	Vanderbilt[39]
Donor age group	Adult < 55 years	Adult < 55 years	Adult and paediatric	Adult < 35 years
Location of WLS	ICU or Anaesthetic bay	ICU or Anaesthetic bay	Operating room	Not stated
Ante-mortem interventions	Nil	Nil	Heparin Perfusion cannulas TOE + Swan-Ganz	Heparin
Sedation (comfort care)	Variable	Variable	Sevoflurane	Variable
Death	Circulatory arrest + 2–5 min	Circulatory arrest + 5 min	Arterial BP < 30 mmHg + 5 min	Circulatory arrest + 2–5min
fWIT	<30 min after SBP < 90 mmHg	<30 min after SBP < 50 mmHg	Not stated[a]	<35 min after SBP < 50 mmHg
Post-mortem interventions	Cold flush (direct procurement)	Normothermic regional perfusion OR Cold flush	Normothermic regional perfusion	Normothermic regional perfusion
Graft retrieval	DP-NMP	DP-NMP, NRP-NMP for distant retrieval NRP-SCS (co-location)	NRP-SCS (co-located, or interhospital transfer)	NRP-SCS for distant retrieval

DP-NMP, direct procurement followed by normothermic machine perfusion; fWIT, functional warm ischaemic time; ICU, intensive care unit; NRP-NMP, normothermic regional perfusion followed by normothermic machine perfusion; NRP-SCS, normothermic regional perfusion followed by static cold storage; SBP, systolic blood pressure; TOE, transoesophageal echocardiogram; WLS, withdrawal of life support.

[a] Expected fWIT < 30 min.

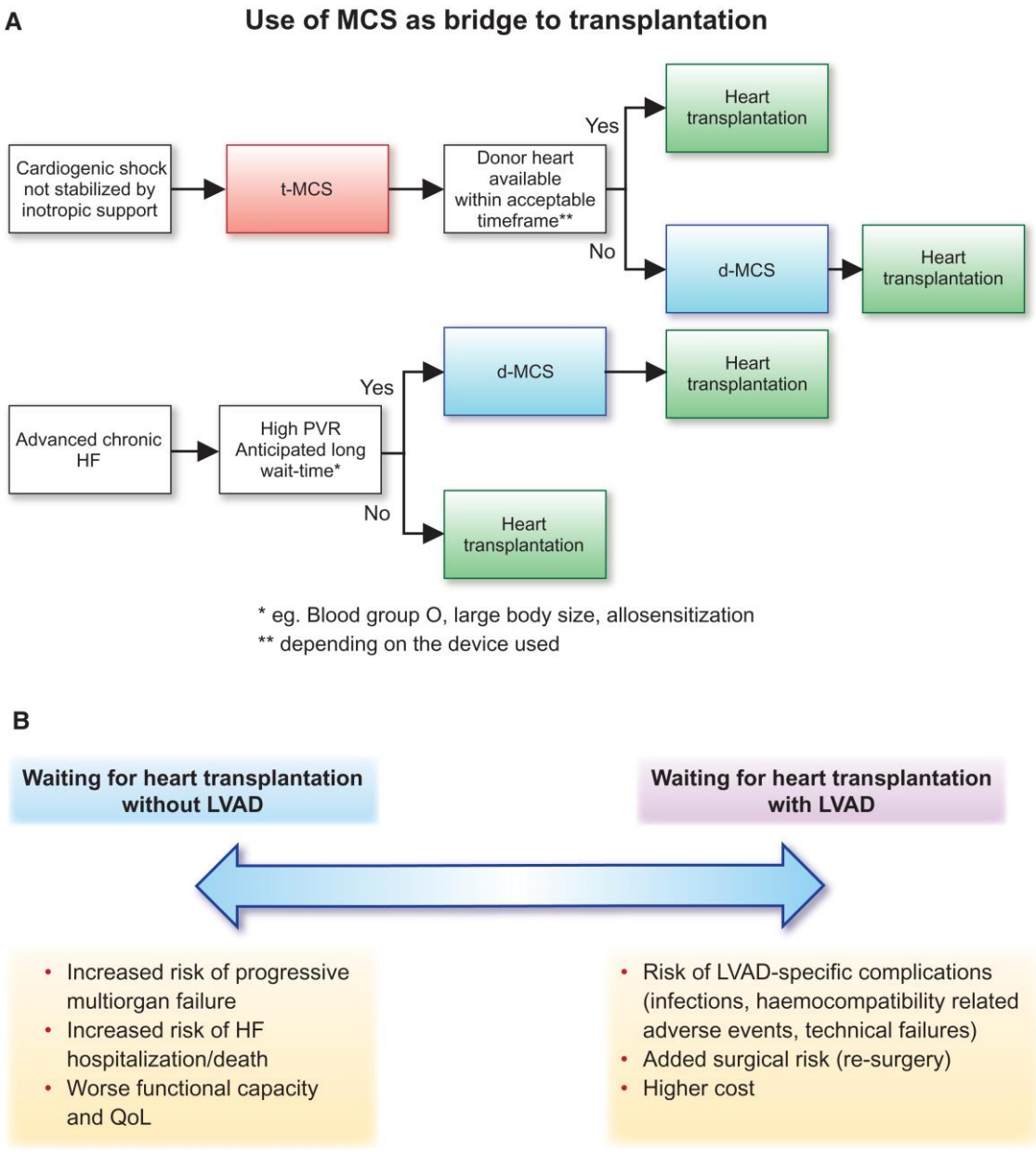

Fig. 3. Mechanical circulatory support as a bridge to transplantation. Decision tree (A), benefits, and limitations (B).

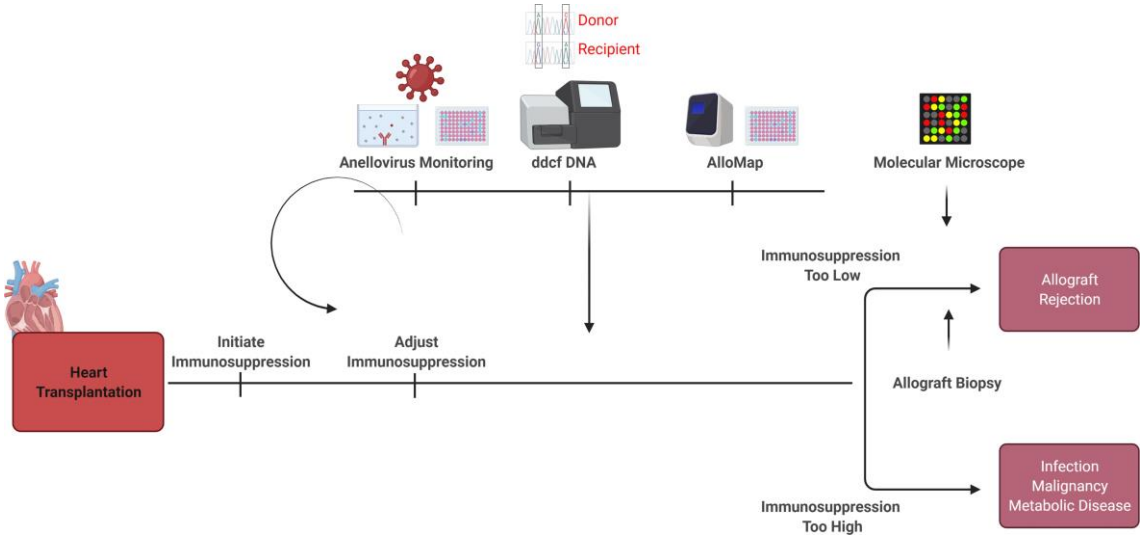

Fig. 4. Novel techniques in cardiac allograft rejection monitoring and immunosuppression titration.