

Heart Transplantation: What are the Alternatives?

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Undeniably, heart transplant is an effective treatment option for patients with end stage heart failure. The ten-year survival after receiving a heart in adults is over 60% [1]. However, heart transplantation suffers from the lack of available donors and patients must wait long periods to receive a heart, often dying before a heart is made available. For this reason, appropriate management of patients on the waiting list is a difficult and complex clinical issue. Currently, there are no curative therapies for patients with heart failure except heart transplantation.

Cell-based therapies including cell transplantation and myocardial grafting are new and emerging alternatives to heart transplantation currently under development [2]. Individual cells that are force generating or can be induced to generate force can be delivered to injured hearts. These cells can also be engineered into sheets with biomaterial support to graft to defect myocardium. To achieve therapeutic effects, a large supply of cardiac lineage-committed cells is essential since up to millions of cardiomyocytes may be damaged during myocardial infarction. The majority of mammalian cardiomyocytes undergo terminal differentiation and rapidly lose their proliferative ability during the early postnatal period [3-6]. The inability to proliferate is a fundamental roadblock to cardiac repair after injury [7]. Recent identification of cardiac stem cells has offered new hope of developing novel approaches to stimulate cardiac regeneration. Nevertheless, mammalian hearts have limited regenerative potential after cardiac injuries although fish, amphibians, and birds have remarkable regenerative capability and can regenerate amputated ventricle without any scar [3,8,9]. It is not completely understood why a mammalian heart cannot repair itself with the addition of new cardiomyocytes from the stem cell pool. The scarcity and stress-induced senescence of cardiac stem cells may contribute to the low renewal ability of the heart.

To aid and accelerate cardiac repair, different stem/precursor/progenitor cells that can replicate and differentiate to functional cardiomyocytes are have been supplied to injured myocardium [2]. Due to their plasticity and broad differentiation capacity, pluripotent embryonic or induced stem cells have greatest therapeutic potential. However, attempts to promote cardiac regeneration by stem cell therapy have been hampered by the difficulty in inducing them to differentiate into fully functional cardiomyocytes [10-12]. In addition, current methods to derive, propagate, and differentiate stem cells with biologic materials raise serious health concerns of intruding foreign pathogens. However, Parsons et al. have developed methods to derive human ES cells and induce them to differentiate into cardiomyocytes in a defined medium without the use of foreign biologic materials [13]. They found that ES cell pluripotency in the epiblast could be sustained by the activin-A-SMAD signaling from primitive endoderm-like cells under the defined culture conditions. With this system, a large quantity of clinically-suitable human myocardial cells can be produced using small molecule induction. Further investigations to define the minimal essential components necessary and sufficient for maintaining the pluripotency and differentiation potential of ES cells and generate effective differentiation protocol for maximal cardiac induction in

biologics-free system will be essential for clinical applications of stem cell-based therapy.

Donation after circulatory death (DCD) organ donation has been routinely used in other solid organ rather than heart transplantation despite that fact that the initial heart transplant was performed using an organ removed after death of a donor [14]. Together with the brain, the heart is the most vulnerable organ to ischemic injury. Circulatory arrest can result in unreparable and sustained ischemic myocardial injury and thus affects short- and long-term donor heart viability. New and improved heart harvesting and preserving techniques can help to expand heart donor pools to DCD. Human DCD hearts have been successfully resuscitated in-vivo through prompt extracorporeal perfusion. During a retrospective analysis of DCD organ donors procured for liver and kidney transplantation between May 1st 2003 and March 1st 2007, Ali et al. determined what proportion of donors might have been suitable for cardiac donation based on their past medical history and pre-terminal cardiovascular status [15]. Among the 67 DCD donors who consented for liver and kidney donation, they found 80% (53/67) of donors had normal cardiac function and no history of cardiac disease. Thus, they could potentially donate their hearts for transplantation. It has not determined, however, what percentage of these donor hearts can be successfully resuscitated and what maximal time interval after circulatory arrest is still suitable for donation. Therefore, more research is required to determine what kind of DCD hearts can be resuscitated and how to resuscitate them. Another important and unanswered question is how well DCD hearts will function in recipients. Hemodynamic challenge of resuscitated DCD hearts in a Langendorff apparatus will help refine selection criteria and predicate how a DCD heart will function in a recipient. In summary, several issues such as donor selection criteria, minimal time after circulatory arrest, resuscitation method, and long-term functionality, have to be resolved before we consider using DCD hearts. Nevertheless, the use of DCD hearts can potentially allow for a significant expansion of the donor pool.

DCD is not only technically challenging as a source of heart donation, but also poses ethically difficult questions regarding to donor selection, family consent, and timing of organ procurement. Ali et al. discussed the ethicality of heart transplantation from DCD [16]. Patients with irreversible loss of brain-stem function can be certified as dead due to brain-stem death, and their beating hearts can be harvested

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for cadaveric donation. Many patients with severe neurological injury may not show irreversible loss of brain-stem function during neurologic testing before making the decision to withdraw therapy. In this situation, the lack of heart beat and blood flow (cardiac death) is a major clinical requirement for certification of death. If the heart is resuscitated from a patient declared as cardiac death, the recovery of heart beat and blood flow would potentially negate the diagnosis of cardiac death. Therefore, certification of death needs new definitions in the DCD donor.

The long-term survival of the graft is adversely affected by chronic rejection with advancements in treating acute rejection [1]. Coronary artery vasculopathy (CAV) is a major cause of graft failure and diminishes long-term survival [17]. In pediatric heart recipients, epicardial fibrosis also contributes to diastolic dysfunction of end-stage cardiac allografts [18]. We found that canonical Wnt signalling which regulates epithelial-mesenchymal transformation during development was activated in fibroblasts of fibrotic epicardial tissue. The nuclear accumulation of β -catenin, a hallmark of canonical Wnt signalling activation, was identified fibroblasts in epicardial fibrosis [19]. Among four T-cell factor/lymphoid enhancer factor (TCF/LEF) family members, only TCF7L2 (TCF4), was detected in epicardial fibroblasts [19]. Although β -catenin has no DNA binding domain, it is a strong transcriptional activator. With Wnt signalling, β -catenin is stabilized and enters the nucleus to form a complex with TCF/LEF family transcriptional factors, activating transcription of target genes such as c-myc and cyclin D1. These findings suggest that canonical Wnt/ β -catenin signalling can be potentially targeted to prevent epicardial fibrosis.

The improvement of long-term survival and the immunosuppressive status make heart transplant recipients susceptible to the development of malignancy. Chiu and Sergi conducted a systematic review of the incidence of and risk factors for malignancy after heart transplantation [20]. Compared with other solid organ transplant recipients, heart transplant patients had a higher risk of cancer. Based on 20 publications analyzed, the incidence of malignancy in transplant recipients ranges from 4.1% to 16.3%, representing a 2 to 4-fold overall increased risk of cancer over the general population.

The molecular and cellular mechanisms that underline and contribute to heart failure remain poorly defined. It is also unclear why heart failure patients resist conventional therapies. Fibroblast growth factor-23 (FGF23), a bone derived hormone, is elevated in patients with heart failure. In fact, Richter et al. found that cardiomyocytes express and secrete FGF23 [21]. In failing hearts, inflammatory cells such as macrophage produce oncostatin M (OSM) which stimulates cardiomyocytes to produce more FGF23. Therefore, inhibition of cardiac inflammation and targeting the OSM-FGF23 axis can be explored as novel therapies for heart failure.

Angiotensin II has been implicated in the pathogenesis of cardiac fibrosis, hypertrophy, and heart failure. Interestingly, the angiotensin-converting enzyme homologue ACE2 and the peptide angiotensin 1-7 (Ang 1-7) have antifibrotic effects. Battl et al. examined the expression levels of Ang 1-7 Mas receptor and ACE2 in failing and non-failing human hearts [22]. They found the expression of components of the ACE2 pathway were higher in patients with detectable MMP3 expression than in ones with non-detectable MMP3. However, it is unclear whether the ACE2 pathway has a protective or deleterious role in cardiac remodeling.

Arrhythmia is often difficult to manage in patients with heart

diseases. Atrial fibrillation (AF) is the most common arrhythmia. Patients with AF before surgical procedures such as coronary artery bypass surgery (CABG) have higher in-hospital and long-term mortality rates than patients without AF. On the other hand, patients who undergo CABG can develop AF afterwards. Earlier reports revealed patients with AF after CABG had an increased in-hospital and long-term mortality rate than patients without AF, but this has been refuted by more recent investigations. Chen-Scarabelli et al reexamined this issue by performing a retrospective review of patients with CABG at a large university medical center [23]. They found AF after CABG was associated with a higher EuroSCORE, but it was neither associated with, nor predictive of increased hospital mortality. However, whether AF after CABG adversely affects long-term survival after hospital discharge was not studied.

Heart transplantation remains the best treatment options for patients with heart failure. Better medical therapies can help manage patients in the waiting list and delay their need for donor hearts. Stem cell based regenerative medicine has opened exciting and promising revenue for patients with heart failure. However, this approach may not help patients with large transmural infarction, and is best suitable for patients with dilated cardiomyopathy and multifocal small infarction. In the future, we need to define criteria to stratify patients for different treatment options.

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