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The State of Current and Future Therapies for Congestive Heart Failure: A Review

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Abstract

Heart failure is a significant cause of morbidity and mortality globally. An estimated 38 million patients suffer from heart failure worldwide, and its prevalence is expected to increase. In Canada, 1% of the population suffers from heart failure and the number of admissions for this disease is expected to increase 300% from 1996 to 2050. In the United States, the number of patients with heart failure is estimated to increase 25% by 2030 with an estimated cost of $69.8 billion. Despite advances in modern medical care, heart transplantation remains the definitive treatment. Heart transplantation has had progressive, improved success in survival due to improvements in immuno-suppression. However, the availability of donor organs remains limited. Mechanical circulatory support has been an increasingly utilized option for patients with end-stage heart failure as bridge-to-transplantation, or for permanent destination therapy, but multiple complications can occur. As an alternative, stem cell therapy has emerged as a promising new field for the treatment for heart failure. It brings the possibility of regenerating new functional myocardium from donated or autologous cells. However, this field is still in its early stages and clinical success has been modest, to date. This field may gain assistance by developments in nanotechnology and tissue engineering where patches, grafts, and even whole replacement organs may shape the future of heart failure therapy. We review the current and future states of these advancing technologies.

Keywords Heart failure; Heart transplantation; Regenerative medicine; Stem cell

Abbreviations

BiVAD: Biventricular Assist Device; BMD: Bone Marrow-Derived; BTT: Bridge to Transplant; CDC: Cardiosphere Derived Cell; CSC: Cardiac Stem Cell; CyA: Cyclosporin-A; DT: Destination Therapy; EPC: Endothelial Progenitor Cell; FN: Fibronectin; HSC: Hematopoietic Stem Cell; iPSC: Induced Pluripotent Stem Cell; LVAD: Left Ventricular Assist Device; MCS: Mechanical Circulatory Support; MI: Myocardial Infarction; MMF: Mycophenolatemofetil; MNC: Mononuclear Cell; MSC: Mesenchymal Stem Cell; PCL: Polycaprolactone; PEG: Polyethylene Glycol; PG: Poly(ε-Caprolactone)/Gelatin; PSI: Proliferation Signal Inhibitor; SKM: Skeletal Myoblast; RVAD: Right Ventricular Assist Device; TAH: Total Artificial Heart; VAD: Ventricular Assist Device

Introduction

Cardiovascular disease was the cause of less than 10 % of deaths worldwide at the turn of the twentieth century and now has become the number one non-communicable cause of death worldwide. More recently, the WHO estimated 17.3 million deaths from cardiovascular diseases in 2008, representing 30% of all global deaths. The WHO also estimates that the number of deaths from cardiovascular disease will increase to 23.3 million by the year 2030, with cardiovascular disease remaining the leading cause of death. Of note, over 80% of these deaths took place in low and middle-income countries [1].

Heart failure accounts for a significant portion of the cardiovascular disease burden. An estimated 38 million patients suffer from heart failure worldwide, and this number is also expected to increase with aging of the population. In high income nations, it is the most common diagnosis for admission to the hospital for patients age 65 and over [2].

In Canada, 1% of the population suffers from congestive heart failure [3] and the number of admissions for heart failure is expected to increase 300% from 1996 to 2050. In the U.S in 2008, one out of every nine deaths mentioned heart failure on the death certificate [4], and according to the American Heart Association, an estimated 6.6 million Americans suffered from heart failure in 2010 [5]. This number is expected to increase by approximately 3 million by the year 2030, representing a 25% increase in prevalence [6]. Also, the cost of heart failure in the U.S. in 2008 was $30.7 billion, which is expected to increase over 100% to $69.8 billion by 2030 [5,6].

In Europe, the incidence of heart failure was estimated to have increased from 296 per 100,000 person-years in 2000 to 390 per 100,000 person-years in 2007 [7]. This also carried a risk-adjusted mortality from heart failure of 12.1% at 30 days, 28.8% at 1 year, and 61.4% at 4 years. Thus, heart failure is a significant cause of mortality worldwide, with a progressive increase in mortality risk over the course of the disease.

Despite modern advances in medicine, heart failure still progresses to end-stage failure with little impediment. The limited supply of donor replacement organs to supply the enlarging need for heart failure treatment has prompted the search for alternative treatments beyond management with medication. This review discusses the current state and potential future for treatment options delivered by surgical methods or invasive procedures, including transplantation, mechanical circulatory support devices, and surgical or catheter-delivered cell-based therapies.

Heart Transplantation

The Current State

Approximately 4,000 heart transplants are performed each year worldwide, according to the International Society for Heart and Lung Transplantation (ISHLT) (Figure 1) [8]. The number of heart transplants has not changed appreciably since the 1980's despite a 20% increase in the number of adults on the heart transplant waiting list [9]. Also, achieving transplant wait-list status is difficult, with stringent criteria and priority reserved for patients with end stage heart failure. Only 6,679 patients were placed on the transplant list in the US in 2012, and of these, only 36% received a donor heart. Also, due to limited donor organ availability, only 2% of patients with a rejected or failed graft received a new transplant. This means that of the estimated 6.6 million Americans with heart failure, only 2,378, or approximately 0.04%, will received definitive, long-term treatment.

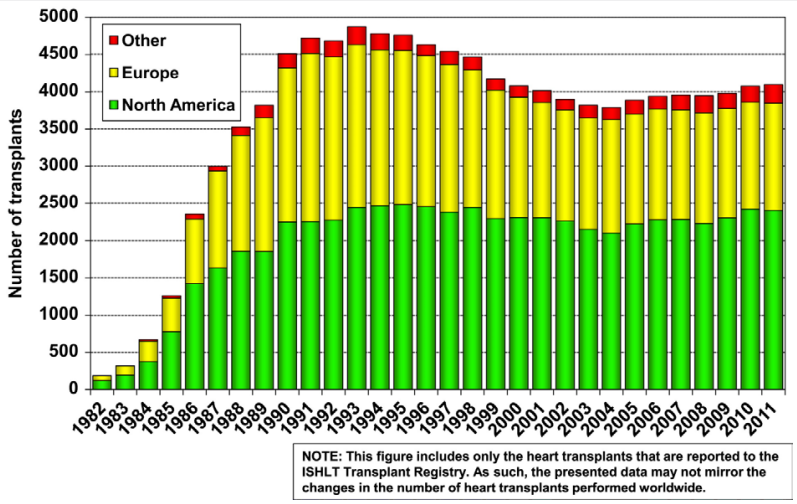

Figure 1: Number of heart transplants (all recipient ages) by year (1982–2011) and geographic region.
• ISHLT= International Society for Heart and Lung Transplantation.
• Reprinted with permission from Lund et al. [9]

Medical comorbidities among donors and recipients have also increased [12]. Recent donors have had more diagnoses of diabetes and hypertension while recipients have had higher percentages of malignancy (7%), diabetes (25%), allosensitization (33%), hypertension (45%), and priorsternotomy (46%) [13]. The demographics of transplant recipients have also changed with 30% of recipients being over the age of 60 [12].

The Future State

Over the last few decades, five year survival after heart transplant has been approximately 70%, median survival has been approximately 11 years, and the mortality rate per year has been approximately 3-4% [9]. Although a donor heart may be available, there are still problems of post-transplant morbidity and mortality. Hypertension, diabetes, and renal disease can cause morbidity as a result of chronic immunosuppression. Malignancies can also arise due to decreased immune surveillance. Cardiac allograft vasculopathy (CAV) can lead to coronary stenosis, myocardial ischemia, and increased mortality, and despite immunosuppression, graft rejection can occur, causing 44% of deaths during the first five years [10,14]. For this reason, graft rejection is the primary cause of death in the first few years after transplantation (Figure 2).

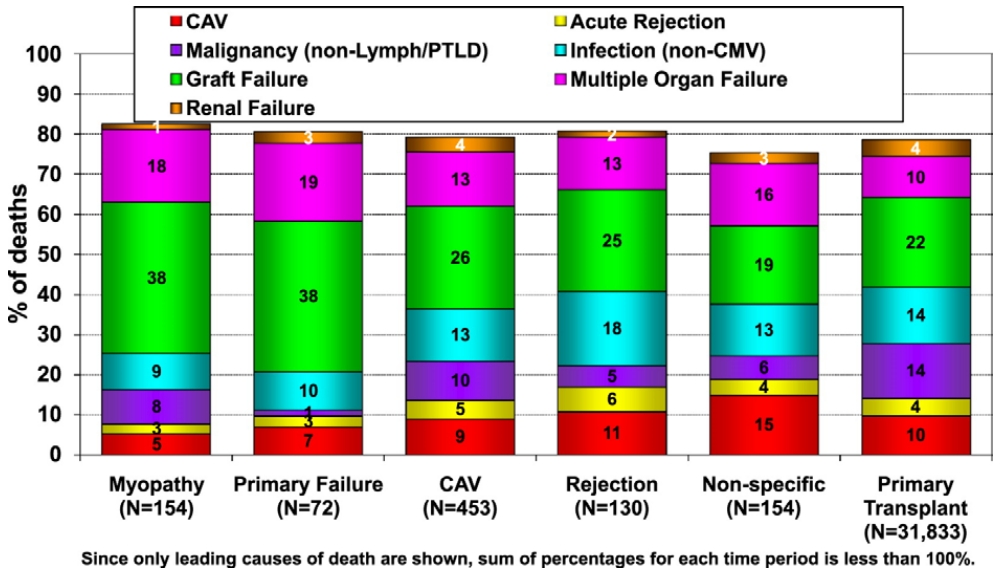

Figure 2: Causes of death (1994-June 2013) by primary vs different indications for retransplantation in adult heart primary transplants and retransplants.

- CAV= cardiac allograft vasculopathy; CMV= cytomegalovirus; PTLD= post-transplant lympho-proliferative disorder.
- Reprinted with permission from Lund et al. [86]

Efforts to improve the current state of heart transplant morbidity and mortality have focused on improving immunosuppression and prevention of graft rejection due to this early mortality. Though, surgical technique for heart transplantation has changed little since the first transplant operations, significant improvements have been made in intraoperative and postoperative immunosuppression since the first procedures in the 1960's. These advances have transformed transplantation into its current state as an acceptable treatment for heart failure today.

A key to this success was the selective suppression of immune elements. Corticosteroids were effective immunosuppressants, but they are non-selective, and there was significant morbidity and mortality from post-transplant infections. Glucocorticoids inhibit expression of inflammatory cytokines as well as T-cell proliferation and B-cell receptor expression. When a postoperative infection emerged, this non-selective immunosuppression was reduced, leaving the graft vulnerable to rejection until the infection cleared.

This changed with the introduction of Cyclosporin-A (CyA) (trade name Neoral or Sandimmune). Sandoz laboratories (now Novartis) first produced Cyclosporinin 1970 from the fungus *Tolypocladium inflatum* isolated from Norwegian soil samples [15]. It was used in experimental transplantation in 1978 and was introduced into clinical practice in 1983 as the first lymphocyte-specific immunosuppressant [16]. While glucocorticoids affect multiple arms of the immune system, Cyclosporin specifically inhibits calcineurin which is integral to T-cell activation signal transduction and IL-2 transcription. This allowed suppression of graft rejection while freeing other immune elements to combat infection and it changed the success of transplantation as a field. In the late 1960's and the early 1970's, the 1 year survival rate after heart transplantation was approximately 30%, while with the use of Cyclosporin, 1 year survival improved to almost 90% in the 2000's [16,17].

Further improving on the success of CyA, a newer calcineurin inhibitor, Tacrolimus (trade name Prograf or Advagraf), has become a mainstay of immune suppression (Figure 3). Today, over 80% of heart transplant recipients are undergoing maintenance immunosuppression with Tacrolimus, while less than 20% are maintained with Cyclosporine. These are nearly opposite percentages from maintenance therapy in the year 2000 [10,14].

Though it has similar action to Cyclosporin, Tacrolimus has a greater effect with fewer episodes of rejection and improved survival [15]. A Cochrane Review of 16 randomized trials found liver transplant patients treated with Tacrolimus had decreased 1-year acute rejection (RR 0.81, 95% CI 0.75 to 0.88), steroid-resistant rejection (RR 0.54, 95% CI 0.47 to 0.74), graft loss (RR 0.73, 95% CI 0.61 to 0.86), and mortality (RR 0.85, 95% CI 0.73 to 0.99). Also, when taking Tacrolimus plus MycophenolateMofetil (MMF), cardiac transplant patients in a randomized trial had fewer Grade 2R or higher infections and fewer treated episodes of graft rejection than patients taking Cyclosporine plus MMF [18].

Mycophenolate Mofetil (MMF) (trade name Cell Cept) or Mycophenolate Sodium (trade name Myfortic) is an anti-proliferative agent or proliferation signal inhibitor (PSI) and has become another mainstay of modern immunosuppression. Derived from the fungus *P. echinulatum,* it reversibly inhibits the guanosine monophosphate pathway of purine synthesis involved in expansion of B and T-cells. Together with a corticosteroid and a calcineurin inhibitor, the addition of a PSI forms the standard three-compound regimen for immunosuppression.

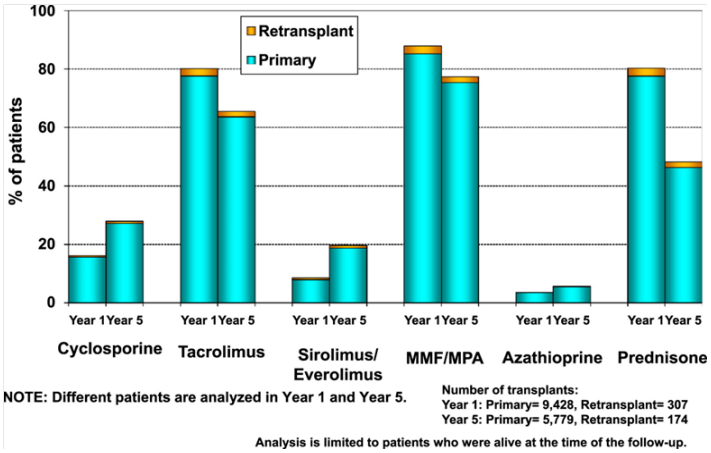

Figure 3: Maintenance immunosuppression at 1-year and 5-year follow-up by location and type of transplant for adult heart primary transplants and retransplants (2008-June 2013)

• MMF= mycophenolatemofetil, MPA= mycophenolic acid.

• Reprinted with permission from Lund et al. [86]

Meanwhile, to further target other specific pathways in the immune response, newer immunosuppressants are being developed and tested. Bortezomib, for example, is an inhibitor of the 26S proteasome shown to be effective in CD30+ lymphocytes and may be responsible for increasing cell death by increasing the presence of apoptotic factors in a cell [19]. According to small studies, this drug could be useful for refractory antibody-mediated rejection, or if given preoperatively, for reducing the possibility of rejection in highly sensitized patients [20].

Another newer agent is Belatacept, a selective blocker of T-cell activation. It is a fusion protein of an immunoglobulin G1 (IgG1) Fc segment and part of a cytotoxic lymphocyte associated-4 (CTLA-4) marker which blocks co-stimulation of T-lymphocytes. In a small study of renal transplant patients, when compared to Cyclosporin, delivering Belatacept resulted in similar percentages of graft rejection with improved glomerular filtration rate [21,22].

To target another pathway, To facitinib is an inhibitor of the Janus-kinase signal transducer and activator of transcription (JAK-STAT) signaling system. Inhibition of this pathway prevents the production of inflammatory mediators and activation of some T-cells and natural killer cells. In a study of renal transplant patients, it was found to be as effective as Tacrolimus [23]. However, when used in combination with MMF, its use was associated with a higher incidence of viral infections.

Also recently studied, Sotrastaurin is a protein C kinase inhibitor which targets T-lymphocytes [24]. This inhibition of protein C kinase showed improved graft survival in heart transplanted rats, and also prolonged graft survival in humans after renal transplants [25].

Another important pathway for suppression is the compliment pathway since compliment activation causes significant deterioration of allografts. Eculizamab is a monoclonal antibody of compliment protein C5 that prevents inflammation and assembly of the complement membrane attack complex. In renal transplant patients, it has been reported to prevent antibody-mediated rejection [26]. It could also have potential for improved graft survival after heart transplantation.

Mechanical Circulatory Support Devices

The Current State

With the limited availability of donor organs, some patients with end-stage heart failure have been supported with mechanical devices. These blood pumps augment or replace one or both ventricles, serving as temporary or long-term circulatory support. Depending on the degree of support needed, a patient can receive a left ventricular assist device (LVAD), right ventricular assist device (RVAD), both LVAD and RVAD (BiVAD), or total artificial heart (TAH). A ventricular assist device (VAD) assists the heart in situ (Figure 4) while a TAH requires removal of the native heart. Currently, the use of VADs outnumbers the use of total artificial hearts TAHs. LVADs have provided effective support with patients showing significant functional gains in the first year such as improvements in distance walked and peak oxygen consumption [27].

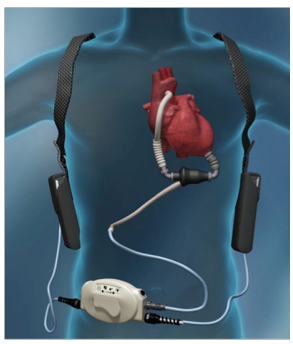

Figure 4: External view of the HeartMate II LVAD

• Reprinted with permission from John R. [87]

In 2007, 337 mechanical assist devices were implanted and this increased to 2,671 devices in 2013 [28]. Most often used as bridge-to-transplant (BTT) therapy, over 40% of adult heart transplant recipients were bridged to transplant with devices in 2012, more than double the percentage bridged in 2000 [29]. Also, as a result of the success with adult transplant recipients, pediatric patients have also been increasingly supported with mechanical devices (Figure 5).

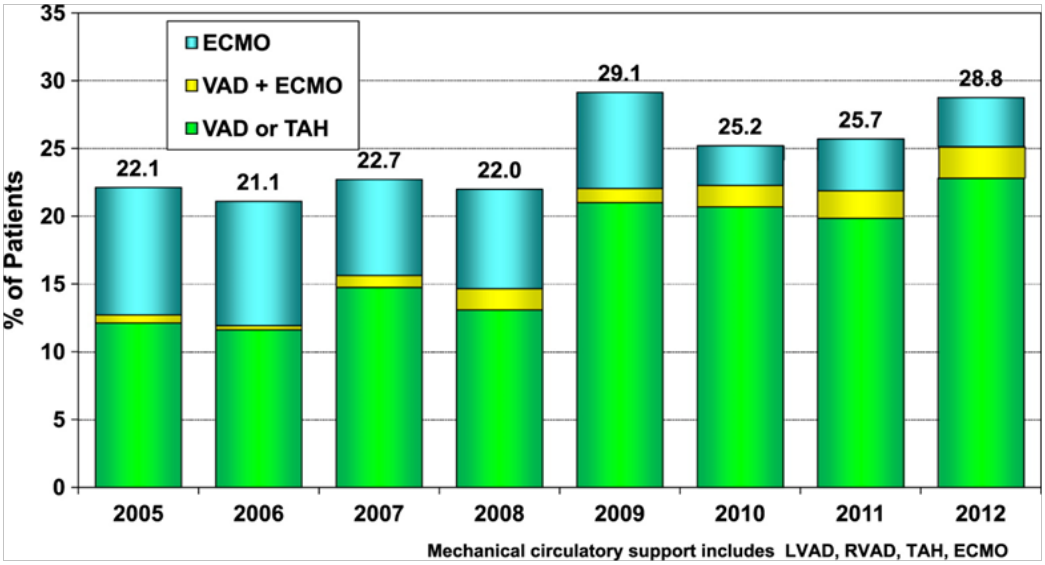

Figure 5: Percentage of patients bridged with mechanical circulatory support by year (transplants: January 2005-December 2012).

• ECMO= extracorporeal membrane oxygenation; LVAD= left ventricular assist device; RVAD= right ventricular assist device; TAH= total artificial heart; VAD= ventricular assist device.

• Reprinted with permission from Benden et al. [88]

While VADs have been effective means of support as BTT, they have also become increasingly effective as destination therapy (DT), or permanent implantation without a plan for transplantation. VAD implantations for DT comprised 14% of devices placed in 2007, and this increased to 42% in 2013 [15].

TAHs have also been implanted for BTT or DT, though experience with these devices is more limited. In 2007, the Syncardia Cardio West TAH, the only US FDA fully approved TAH, was implanted in 22 patients. This increased to 73 patients in 2013, accounting for 3% of implanted devices that year. The longest implantation time with a Cardio West TAH before successful transplant was 1,373 days [29].

The Future State

Mechanical support devices, however, have had several complications. Frequently, they have arisen in the form of infection, hemorrhage, thromboembolism, and mechanical failure [30]. Device-related, and non-device-related, infections cause significant morbidity and mortality from pneumonia, wound infections, sepsis, driveline infections, and hematogenous seeding of artificial surfaces. Among patients with VADs, infection occurs in up to 42% of patients by day 60 and upto 94% of patients at 1 year [29,31].

Hemorrhage, including gastrointestinal and intracranial hemorrhage, has been another source of morbidity and mortality due to anticoagulation to prevent thromboembolism.Gastrointestinal bleeding is common among patients with VADs, occurring in 10–40% [31-34]. Most commonly involve the small bowel.

Another set of complications has been from local thrombi and distant emboli, including stroke, transient ischemic attack, and infarction of other organs. Thromboemboli formed on artificial surfaces and in turbulent blood flow due to shear forces caused by mechanical devices. Though not all strokes are from thromboembolism, recent reports have found approximately 15% of patients with devices present with stroke and 12% present with transient ischemic attack (TIA) [35-37]. Arterial and venous thrombosis and thromboembolism also occur in 7-9% of patients with devices after 1 year [35,38].

Mechanical devices have also had unexpected device malfunctions or structural failures as well as difficulty with device durability after long implantations. In the past three years, the mortality rate from device failure has been approximately 3% [35,39].

The future success of these devices depends on prevention of these major causes of morbidity and mortality. To reduce device-related infections, drivelines could be reduced or eliminated. Hemorrhage could be reduced by decreased need for anticoagulation through improved pump-blood contact surfaces with less thrombogenicity. Thromboembolism could be reduced with improved flow characteristics that cause less blood stasis or shear forces within the pump. Finally, improved designs with less friction or wear on moving parts could lead to less mechanical device failure.

Cellular Therapy

The Current State

In recent years, attempts have been made to improve failing hearts by introduction of stem cells to revive or regenerate myocardial tissue. Stem cells can be harvested from embryonic sources to be used as allografts, or from adult donors to be used as allografts or autografts. Common adult sources have been skeletal muscle, bone marrow, peripheral blood, and cardiac tissue. Cells are harvested from other donors or patients, then stimulated to expand and differentiate into cardiac tissue. Once expanded, the cells are introduced or reintroduced to the patient by intravenous, intracoronary, or intramyocardial routes (Figure 6). Allogenic sources may have the advantages of being more readily available or available well in advance of treatment, but autologous sources may causeless immunogenicity. Also, embryonic stem cells have been studied less extensively than adult donor or autologous sources due to issues of scarcity, ethical or political difficulties. The following are several categories of stem cells that have been tested with potential for cardiac regeneration in humans, and (Table 1) shows recent clinical trials using these cell populations.

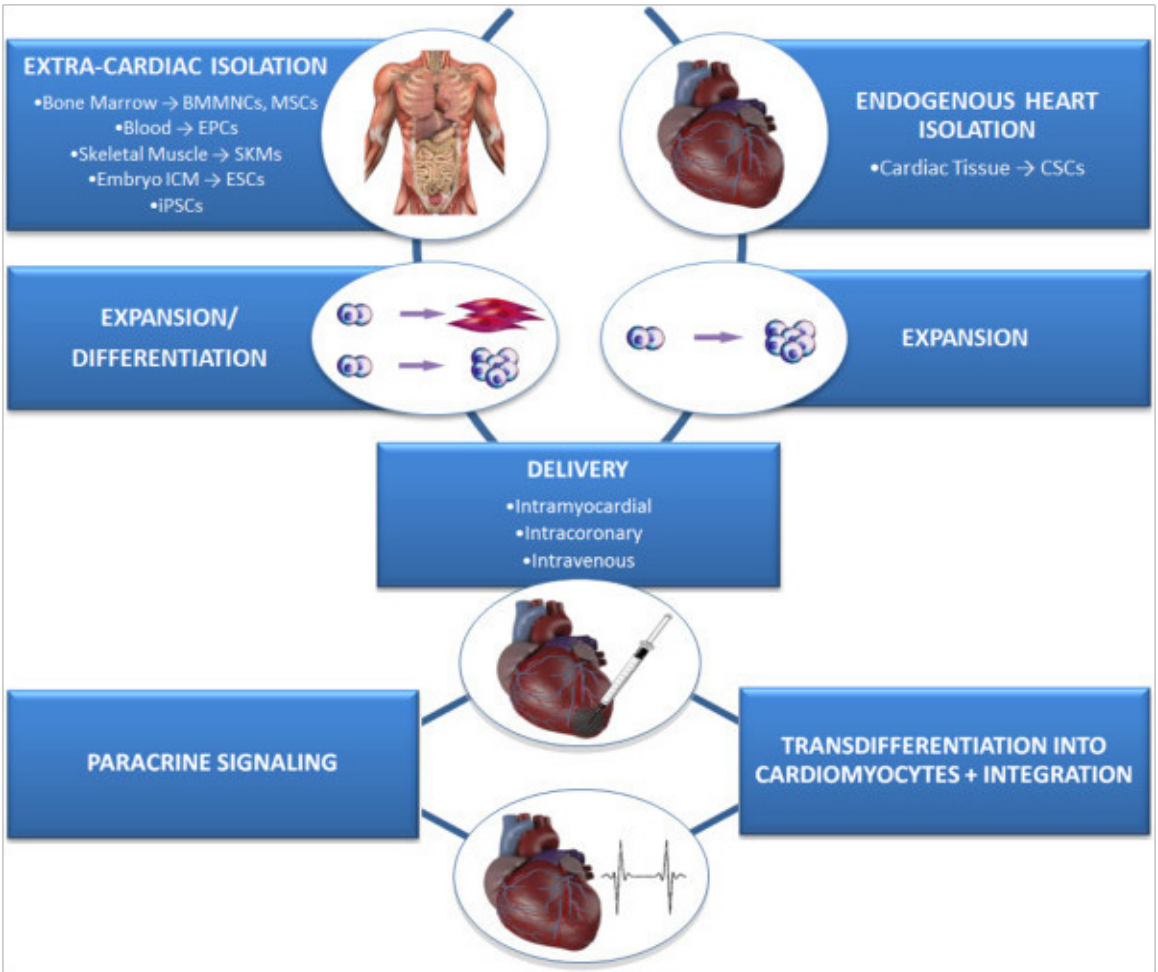

Figure 6: Schematic representation of the potential sequence of events involved in successful regenerative stem cell treatment of cardiac tissue in an infarcted heart.

• BMMNC= Bone Marrow Mononuclear Cell, CSC= Cardiac Stem Cell, EPC= Endothelial Progenitor Cell, ESC= Embryonic Stem Cell, iPSC= Induced Pluripotent Stem Cell, MSC= Mesenchymal Stem Cell, SKM= Skeletal Myoblast.

• Reprinted with permission from Matar and Chong [89]

Cell Type	Source	Study	Heart Failure	Patients	Delivery Route	Follow up (months)	LVEF Increase	NCT Identifier
BMD	Autologous	REPAIR-AMI [77]	Ischemic	204	IC	12	+2.5% (p=0.01)	NCT00279175
BMD	Autologous	TOPCARE-CHD [78]	Ischemic	121	IC	12	+1.8% (p<0.001)	NCT00962364
BMD	Autologous	BOOST [79]	Ischemic	60	IC	6	+6.7% (p=0.003)	NCT00224536
BMD	Autologous	STAR-heart [80]	Ischemic	391	IC	60	+6.2% (p<0.017)	N/A
BMD	Autologous	Bocchi et al. [81]	Non-Ischemic	22	IC	15	+8.8% (p=0.016)	N/A
BMD	Autologous	Seth et al. [82]	Non-Ischemic	85	IC	36	+5.9% (p<0.05)	N/A
MNC	Autologous	ASTAMI [83]	Ischemic	100	IC	6	No change	NCT00199823
MNC	Autologous	FocusHF [84]	Ischemic	30	IM	6	No change	NCT00824005
MSC	Autologous	PROMETHEUS [53]	Ischemic	45	IM	18	+9.4 (p=0.002)	NCT00587990
MSC	Autologous	TAC-HFT [54]	Ischemic	67	IM	12	No change	NCT00768066
CSC	Autologous	SICIPIO [60]	Ischemic	14	IC	4	+8.2% (p=0.001)	NCT00474461
CDC	Autologous	CADUCEUS [62]	Ischemic	25	IC	6	No change	NCT00893360
CDC	Allogenic	ALLSTAR	Ischemic	Enrolling	IC	Pending	Pending	NCT01458405
EPC	Autologous	Cardio133 [85]	Ischemic	60	IM	6	No change	NCT00462774

Table 1: Recent Stem Cell Trials
BMD= Bone marrow-derived stem cells without specific lineage, these could include hematopoietic, mononuclear, mesenchymal, or other stem cells, CSC= Cardiac stem cell, EPC= Endothelial progenitor cell, IC= Intracoronary, IM= Intramedullary, MNC= Mononuclear cells, MSC= Mesenchymal stem cell

Skeletal Myoblasts

Skeletal myoblasts (SKMs), the precursor cells to mature skeletal myocytes, have been tested as potential stem cell therapy for heart failure but the results have been discouraging. In one randomized trial, SKMs were injected epicardially into hearts with left ventricular (LV) dysfunction during coronary artery bypass grafting (CABG) [29]. However, there was no improvement in LV function at six months follow-up. Also, ventricular arrhythmias were prevalent and attributed to islands of skeletal muscle cells which were unable to propagate cell signaling between cardiomyocytes adequately. This led to the realization that connexin-43 is an important factor for arrhythmia prevention during stem cell therapy since it provided channels for cardiomyocyte intercellular coupling and depolarization during signal transduction [40].

Bone Marrow Derived Mononuclear Cells

Within bone marrow derived mononuclear cells (MNCs) harvested, there is a small percentage (less than 0.1%) consisted of hematopoietic stem cells [41]. Favorable effects were first observed in mice injected with these bone marrow derived cells [43], and since then, multiple trials in humans have taken place. Recent conclusions from these experiments have shown that bone marrow derived cells do not differentiate well into cardiomyocytes, but more likely have a positive, regenerative effect through paracrine effects that stimulate resident cardiomyocytes, cardiac progenitor cells, or epithelial progenitor cells to promote cardiomyocyte growth and angiogenesis [42]. The FOCUS trial by the Cardiovascular Cell Therapy Research Network (CCTRN) did not find a significant change in left ventricular end-systolic volume but a few meta-analyses have found minor clinical improvements after implantation of MNCs [44,45]. Currently, a large, multi-center Phase 3 randomized trial (The Effect of Intracoronary Reinfusion of Bone Marrow-derived Mononuclear Cells on All Cause Mortality in Acute Myocardial Infarction: BAMI) is being performed in Europe to investigate the effectiveness of intracoronary delivery of MNCs on mortality after MI. With an estimated enrollment of 3000 patients, it should be completed in 2018 (NCT01569178).

Bone Marrow Derived Mesenchymal Cells

Mesenchymal stem cells (MSCs) can be found in bone marrow and adipose tissue. Also known as colony-forming unit fibroblasts, they can differentiate into mature cardiomyocytes if co-cultured with other adult cardiomyocytes [46-48]. In animal studies, treatment with MSCs showed improved cardiac function after induced myocardial infarction [49,50]. A recent randomized trial (Prospective Randomized Study of MSC Therapy in Patients Undergoing Cardiac Surgery: PROMETHEUS) also found improvement in left ventricular ejection fraction (LVEF) (+9.4 ± 1.7%, p=0.002) and decreased infarction scar mass (-47.5 ± 8.1%, p<0.0001) after 18 months in patients with ischemic cardiomyopathy treated with intramyocardial injections of MSCs [51,52]. In another study (Transendocardial Autologous Cells in Ischemic Heart Failure Trial: TAC-HFT), percutaneous intramyocardial injections of MSCs improved ventricular function (peak Eulerian circumferential strain -4.9%, p=0.03) and reduced infarct size (-18.9%, p=0.004) [53].

Endothelial Progenitor Cells

Some bone marrow-derived stem cells expressing the CD34 or CD133 markers have been found to differentiate into vascular endothelium. These endothelial progenitor cells (EPCs) could promote neovascularization in ischemic myocardium by direct differentiation into endothelial cells, as they do in wound healing, or by paracrine mechanisms with release of endothelial growth factors. Currently, a Phase 3 clinical trial to investigate the potential of EPCs has begun recruiting patients (Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells for Improving Exercise Capacity in Subjects with Refractory Angina: RENEW, NCT01508910).

Induced Pluripotent Stem Cells

Some adult somatic cells have been found to be able to become induced into pluripotent stem cells (iPSCs) [54]. Since these autologous cells could have significant potential for cardiac regeneration, there is much interest in their development. Human dermal fibroblasts were recently converted to iPSCs with a retrovirus containing Oct3/4, Sox2, Klf4, and c-Myc transcription factors. These cells were differentiated into cardiomyocytes with approximately 90% yield and implanted into pigs with surgically-created ischemic cardiomyopathy. There was a significant improvement in LVEF (+25% at 4 and 8 weeks, $p<0.01$). However, the human cells did not have long-term survival in the porcine model [55]. Large trials for treatment of heart failure with iPSCs have not been attempted to date.

Cardiac Stem Cells

The adult heart has been found to contain small numbers of stem cells that are capable of regenerating myocardium. This challenged the theory that the heart is a terminally differentiated organ, and since then, these cardiac progenitor cells have been harvested from both animals and humans [56]. One population, known as c-kit, or CD 117, positive cells have had success in animal testing and have recently been studied in a human clinical trial. In rats, c-kit+ cardiac stem cells (CSCs) injected after myocardial infarction improved cardiac function, causing angiogenesis and forming new cardiomyocytes [57-59]. In humans, during the Stem Cell Infusion in Patients with Ischemic Cardiomyopathy (SCIPIO) trial, patients receiving intracoronary infusion of c-kit+ CSCs after coronary artery bypass grafting (CABG) for myocardial infarction had increased LVEF (+8.2%, $p=0.001$) and decreased infarction scar size (-30% at 1 year, $p=0.04$) [58].

Also, groups of cardiac stem cells, known as "cardiospheres", retrieved from cardiac biopsies have been tested for therapeutic potential. These collections contain c-kit+ CSCs as well as other surrounding cells, including CD105+ stromal cells [60]. In mice, these cardiosphere-derived cells (CDCs) differentiated into functional endothelial cells and cardiomyocytes. Left ventricular function was also better preserved in mice treated with CDCs with greater fractional shortening of infarcted anterior walls (36.9% vs 17.9%, $p=0.05$). In a recent study in humans (Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular Function, CADUCEUS), CDCs from endocardial biopsies from patients with MI were re-introduced by intracoronary injection [61]. Patients treated with CDCs showed reduced infarction scar mass ($p=0.001$), increased viable heart mass ($p=0.01$), and increased regional ventricular wall contractility ($p=0.02$) at 6 months by MRI. A new randomized trial is also currently also underway to test the effectiveness of CDCs for treatment of ischemic heart failure (Allogenic Heart Stem Cells to Achieve Myocardial Regeneration, ALLSTAR, NCT1458405). Similar to the CADUCEUS trial, it will deliver CDCs by intracoronary injection after myocardial infarction. However, the source of the cells will be allogenic, not autologous.

The Future State

New advances in nanotechnology and tissue engineering are enhancing the field of stem cell therapy. By creating new scaffolds for cell culturing and cell delivery, nanotechnology may improve the quality of stem cell products and facilitate their incorporation into patients to provide improved myocardial function. Tissue engineering could also establish a new paradigm with the creation of whole organ replacements from stem cells combined with nanofiber or biological cardiac scaffolds.

Nanofiber cell culturing environments have already shown improvements over conventional stem cell culturing methods. To best prepare stem cells for replacement of native tissue, it is best to mimic the structural, chemical, and physical environment in which cardiomyocytes are produced. Native myocardium undergoes changes during development that is guided in part by external cues and stresses. Growth hormones and physical stresses such as cell-cell tension and electrical stimulation are important for developing elongated, interconnected, and dynamic cardiomyocytes [62].

For these reasons, research has shown that cells grown on patterned surfaces, such as those with nanoscale ridges, have shown greater tissue organization, contractile strength, and electrochemical conduction than those grown on non-patterned surfaces. In a rat model of myocardial infarction, the use of a polyethylene glycol (PEG) culturing scaffold with patterned ridges improved stem cell retention, growth, and integration over non-ridged surfaces [63]. In another study, cells grown on a surface with pillars of PEG had significantly greater cell adhesion, three-dimensional growth, signal conduction, and contractility [64]. Carbon nanofiber scaffolds which improve electrical signal conduction during development have also been shown to improve growth of functional cardiomyocytes [65].

To improve delivery of stem cells for heart failure therapy, researchers have developed nanofiber patches (Figure 7). In one study, poly (ε-caprolactone)/gelatin (PG) nanofiber patches were seeded with rat bone marrow-derived MSCs, then placed in areas of infarction on the rat left ventricular walls. The MSCs within the patches migrated toward the infarction scars and promoted angiogenesis [66]. After addition of the patches, there was reduced overall infarction scar size ($p<0.01$) and improved LVEF ($p<0.01$) over control group.

In another study, umbilical cord blood-derived MSCs were seeded onto fibronectin (FN)-immobilized polycaprolactone (PCL) nanofibers [67]. The nanofibers improved cell elongation and adhesion, and there was upregulation of genes for mesenchymal differentiation and angiogenesis. After induction of MI in rats, the nanofiber with MSC patches were implanted

into infarction zones. Results at 4 weeks showed decreased infarction size and fibrosis ($p<0.05$) and increased LVEF ($p<0.05$) compared to controls.

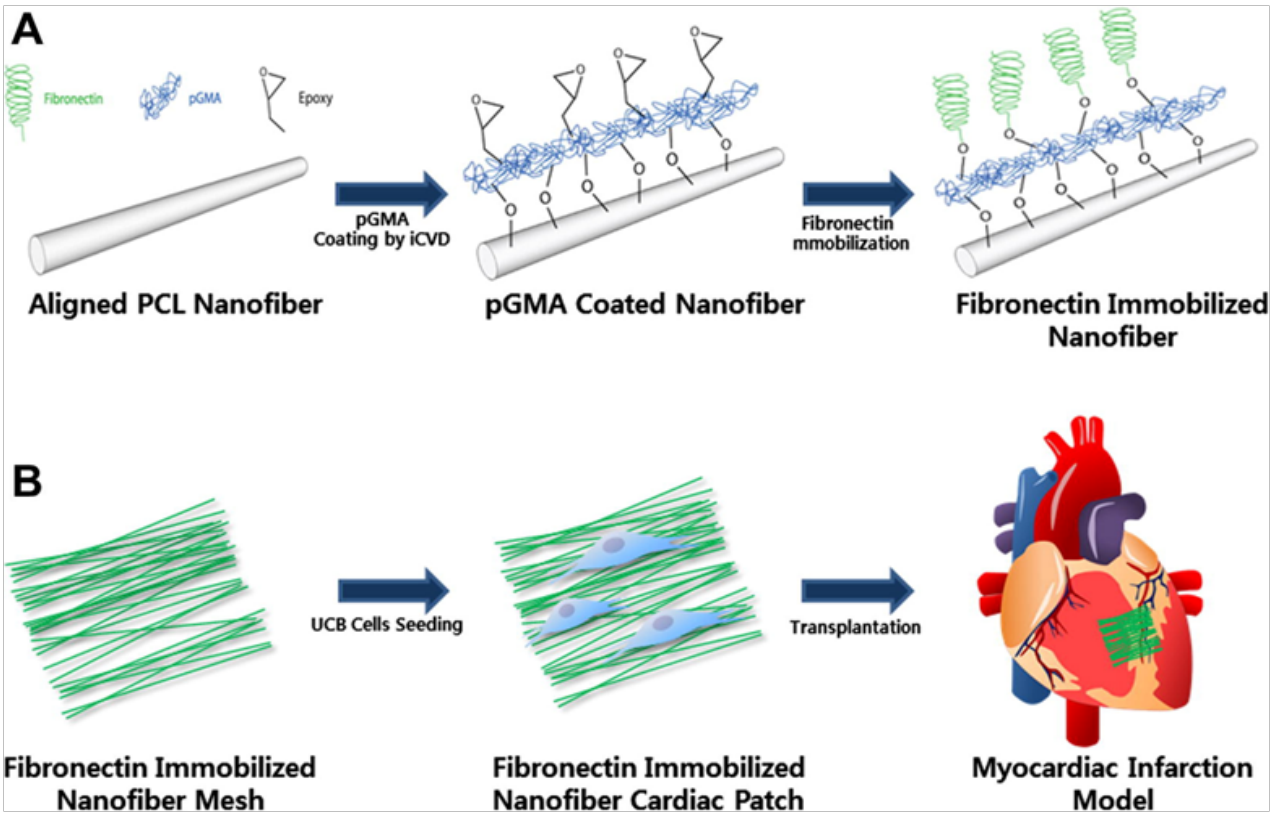

Figure 7: Schematic illustration of fabrication of functionalized nanofibers for myocardial infarction

• A: Polycaprolactone (PCL) nanofibers were prepared and coated with poly (glycidylmethacrylate) (pGMA) by initiated chemical vapor deposition. Fibronectins (FN) were immobilized onto the pGMA-PCL nanofibers

• B: Umbilical cord blood (UCB)-derived mesenchymal stem cells were seeded onto the FN-immobilized PCL nanofibers and transplanted onto a myocardial infarction model rat

• Reprinted with permission from Kang et al. [68]

Meanwhile, beyond creating stem-cell seeded patches, researchers have begun engineering tissues to create whole new organs [68]. Their goal has been to create heart scaffolds populated with progenitor cells that differentiate into cardiomyocytes, stromal cells, and blood vessels. Using large animal or human cadaveric hearts, these organs have been decellularized by detergent washing and left bare of native cellular material, leaving only fibrous tissue. The decellularized skeletons then become the culturing scaffold for multiple stem cells with the hope of creating a functional, beating heart. Artificial nano- and micro-fibrous scaffolds also have potential, but at this time, biological scaffolds are superior to synthetic matrices since the complexity of a native biologic structure is difficult to reproduce.

In 2008, the first hearts from dellecularized organ matrix were bioengineered by repopulation with stem cells [69]. Intact collagen cardiac skeletons were created from rat hearts dissolved of cellular components in detergent solution. After injection of cardiac and vascular progenitor cells, the seeded scaffolds were supported in an organic reactor that simulated the preload and afterload of native cardiac physiology. The results after 8 days were the detection of macroscopic cardiac contractions and an overall pump strength equivalent to 2% of an adult heart, or 25% of a functional 16-week fetal heart [70]. For larger models, porcine hearts have been decellularized for potential re-injection with cells [71-73] and a human heart has been decellularized as a scaffold for potential repopulation with human mesenchymal cells and murine cardiomyocytes.

Conclusion

Heart failure is a prevalent disease worldwide and its burden is estimated to increase. Despite improvements in modern medications, restorative medical treatment for heart failure remains elusive. Heart transplantation still remains the only definitive therapy to date.

Major advances in the field of transplantation have been made due to improved understanding and manipulation of the immune response to donor

grafts. However, despite these advances and improved recipient survival, there are only a limited number of donor organs available each year and therefore, only a small percentage of patients on transplant waiting lists receive a heart.

For these reasons, recent and future research will continue to focus on mechanical circulatory support, stem cell therapies, nanotechnology, and tissue engineering to mend or replace the failing hearts. VADs and TAHs will likely support greater numbers of patients with ventricular failure without hope for myocardial recovery until transplantation or as permanent support without transplantation. Stem cell therapies are still in the early stages of testing, but could one day provide routine cell injections or off-the-shelf replacement patches for patients with cardiomyopathy or to replace tissue loss after myocardial infarction. Tissue engineering may even be able to provide whole hearts in the future for an alternative to transplantation. These may even be derived from a patient's own cell lines without the need for or complications of immunosuppression.

Important hurdles still exist, including the difficulty of large-scale production of cardiomyocytes from stem cells and potential complications from pluripotent cells such as unwanted differentiation, including teratoma formation from iPSCs, in particular [74]. Also, though tissue engineering avoids problems with synthetic materials or mechanical devices for heart failure which are subject to foreign-body reactions and hardware or software malfunction, it is still difficult to reproduce the exact cell lineages in proper concentration and alignment, under the proper stimulating conditions, to engineer a coordinated, beating heart with the strength to work against adult physiologic afterload. For now, heart failure remains a pervasive disease with limited treatment options, but if the challenges mentioned are overcome, then there is a bright future for one or several of these technologies [75,76].

Reference

1. World Health Organization. Global status report on noncommunicable diseases 2010. Geneva 2011.
2. Braunwald E (2015) The war against heart failure: the Lancet lecture. Lancet 385: 812-824.
3. Chow CM, Donovan L, Manuel D, Johansen H, Tu JV, et al. (2005) Regional variation in self-reported heart disease prevalence in Canada. Can J Cardiol 21: 1265-1271.
4. Johansen H, Strauss B, Arnold JM, Moe G, Liu P (2003) On the rise: The current and projected future burden of congestive heart failure hospitalization in Canada. Can J Cardiol 19: 430-435.
5. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, et al. (2012) Heart disease and stroke statistics-2012 update: a report from the American Heart Association. Circulation 125: e2-e220.
6. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, et al. (2011) Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation 123: 933-944.
7. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, et al. (2013) Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 6: 606-619.
8. Gomez-Soto FM, Andrey JL, Garcia-Egido AA, Escobar MA, Romero SP, et al. (2011) Incidence and mortality of heart failure: a community-based study. Int J Cardiol 151: 40-45.
9. Lund LH, Edwards LB, Kucheryavaya AY, Dipchand AI, Benden C, et al. (2013) The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report-2013; focus theme: age. J Heart Lung Transplant 32: 951-964.
10. Colvin-Adams M, Smith JM, Heubner BM, Skeans MA, Edwards LB, et al. (2013) OPTN/SRTR 2011 Annual Data Report: heart. Am J Transplant 1: 119-148.
11. Silver D, Macinko J, Bae JY, Jimenez G, Paul M (2013) Variation in U.S. traffic safety policy environments and motor vehicle fatalities 1980-2010. Public Health 127: 1117-1125.
12. Stehlik J, Stevenson LW, Edwards LB, Crespo-Leiro MG, Delgado JF, et al. (2014) Organ allocation around the world: insights from the ISHLT International Registry for Heart and Lung Transplantation. J Heart Lung Transplant 33: 975-984.
13. Nativi JN, Brown RN, Taylor DO, Kfoury AG, Kirklin JK, et al. (2010) Temporal trends in heart transplantation from high-risk donors: are there lessons to be learned? A multi-institutional analysis. J Heart Lung Transplant 29: 847-852.
14. Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, et al. (2012) The Registry of the International Society for Heart and Lung Transplantation: 29th official adult heart transplant report-2012. J Heart Lung Transplant 31: 1052-1064.
15. http://www.ishlt.org/registries
16. Borel JF (1976) Comparative study of in vitro and in vivo drug effects on cell-mediated cytotoxicity. Immunology 31: 631-641.
17. Oyer P, Stinson E, Jamieson S (1983) Cyclosporin-A in cardiac allografting: a preliminary experience. Transplantation Proceedings 15: 1247-1252.
18. Haddad EM, McAlister VC, Renouf E, Malthaner R, Kjaer MS, et al. (2006) Cyclosporin versus tacrolimus for liver transplanted patients. Cochrane Database Syst Rev 18: CD005161.
19. Kobashigawa JA, Miller LW, Russell SD, Ewald GA, Zucker MJ, et al. (2006) Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. Am J Transplant 6: 1377-1386.
20. Bonvini P, Zorzi E, Basso G, Rosolen A (2007) Bortezomib-mediated 26S proteasome inhibition causes cell-cycle arrest and induces apoptosis in CD-30+ anaplastic large cell lymphoma. Leukemia 21: 838-842.
21. Morrow WR, Frazier EA, Mahle WT, Harville TO, Pye SE, et al. (2012) Rapid reduction in donor-specific anti-human leukocyte antigen antibodies and reversal of antibody-mediated rejection with bortezomib in pediatric heart transplant patients. Transplantation 93: 319-324.

22. Patel J, Everly M, Chang D, Kittleson M, Reed E, et al. (2011) Reduction of alloantibodies via proteasome inhibition in cardiac transplantation. J Heart Lung Transplant 30: 1320-1326.
23. Vincenti F, Larsen C, Durrbach A, Wekerle T, Nashan B, et al. (2005) Costimulation blockade with belatacept in renal transplantation. N Engl J Med 353: 770-781.
24. Busque S, Leventhal J, Brennan DC, Steinberg S, Klintmalm G, et al. (2009) Calcineurin-inhibitor-free immunosuppression based on the JAK inhibitor CP-690,550: a pilot study in de novo kidney allograft recipients. Am J Transplant 9: 1936-1945.
25. Fang YH, Joo DJ, Lim BJ, Kim JY, Kim MS, et al. (2010) AEB-071 versus tacrolimus monotherapy to prevent acute cardiac allograft rejection in the rat: a preliminary report. Transplant Proc 42: 976-97.
26. Russ GR, Tedesco-Silva H, Kuypers DR, Cohney S, Langer RM, et al. (2013) Efficacy of sotrastaurin plus tacrolimus after de novo kidney transplantation: randomized, phase II trial results. Am J Transplant 13: 1746-1756.
27. Locke JE, Magro CM, Singer AL, Segev DL, Haas M, et al. (2009) The use of antibody to complement protein C5 for salvage treatment of severe antibody-mediated rejection. Am J Transplant 9: 231-235.
28. Abshire M, Dennison Himmelfarb CR, Russell SD (2014) Functional status in left ventricular assist device-supported patients: a literature review. J Card Fail 20: 973-983.
29. http://www.uab.edu/medicine/intermacs/images/Federal_Quarterly_Report/Statistical_Summaries/Federal_Partners_Report_2014_Q3.pdf
30. Gerosa G, Scuri S, Iop L, Torregrossa G (2014) Present and future perspectives on total artificial hearts. Ann Cardiothorac Surg 3: 595-602.
31. Allen SJ, Sidebotham D (2012) Postoperative care and complications after ventricular assist device implantation. Best Pract Res Clin Anaesthesiol 26: 231-246.
32. Topkara VK, Kondareddy S, Malik F, Wang IW, Mann DL, et al. (2010) Infectious complications in patients with left ventricular assist device: etiology and outcomes in the continuous-flow era. Ann Thorac Surg 90: 1270-1277.
33. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, et al. (2001) Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 345: 1435-1443.
34. Zierer A, Melby SJ, Voeller RK, Guthrie TJ, Ewald GA, et al. (2007) Late-onset driveline infections: the Achilles' heel of prolonged left ventricular assist device support. Ann Thorac Surg 84: 515-520.
35. Genovese EA, Dew MA, Teuteberg JJ, Simon MA, Kay J, et al. (2009) Incidence and patterns of adverse event onset during the first 60 days after ventricular assist device implantation. Ann Thorac Surg 88: 1162-1170.
36. Stern DR, Kazam J, Edwards P, Maybaum S, Bello RA, et al. (2010) Increased incidence of gastrointestinal bleeding following implantation of the HeartMate II LVAD. J Card Surg 25: 352-356.
37. Wang I, Guthrie T, Ewald G, Geltman E, Joseph S, et al. (2010) Gastrointestinal bleeding complications in continuous flow LVAD patients - is it device specific? J Heart Lung Transplant 29: 8.
38. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, et al. (2009) Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 361: 2241-2251.
39. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, et al. (2007) Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 357: 885-896.
40. Menasche P, Hagege AA, Vilquin JT, Desnos M, Abergel E, et al. (2003) Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. J Am Coll Cardiol 41: 1078-1083.
41. Roell W, Lewalter T, Sasse P, Tallini YN, Choi BR, et al. (2007) Engraftment of connexin 43-expressing cells prevents post-infarct arrhythmia. Nature 450: 819-824.
42. Challen GA, Boles NC, Chambers SM, Goodell MA (2010) Distinct hematopoietic stem cell subtypes are differentially regulated by TGF-beta1. Cell Stem Cell 6: 265-278.
43. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, et al. (2001) Bone marrow cells regenerate infarcted myocardium. Nature 410: 701-705.
44. Laflamme MA, Murry CE (2011) Heart regeneration. Nature 473: 326-335.
45. Ruger BM, Breuss J, Hollemann D, Yanagida G, Fischer MB, et al. (2008) Vascular morphogenesis by adult bone marrow progenitor cells in three-dimensional fibrin matrices. Differentiation 76: 772-783.
46. Abdel-Latif A, Bolli R, Tleyjeh IM, Montori VM, Perin EC, et al. (2007) Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. Arch Intern Med 167: 989-997.
47. Clifford DM, Fisher SA, Brunskill SJ, Doree C, Mathur A, et al. (2012) Long-term effects of autologous bone marrow stem cell treatment in acute myocardial infarction: factors that may influence outcomes. PLoS One 7: e37373.
48. Martin-Rendon E, Brunskill SJ, Hyde CJ, Stanworth SJ, Mathur A, et al. (2008) Autologous bone marrow stem cells to treat acute myocardial infarction: a systematic review. Eur Heart J 29: 1807-1818.
49. Li X, Yu X, Lin Q, Deng C, Shan Z, et al. (2007) Bone marrow mesenchymal stem cells differentiate into functional cardiac phenotypes by cardiac microenvironment. J Mol Cell Cardiol 42: 295-303.
50. Rangappa S, Entwistle JW, Wechsler AS, Kresh JY (2003) Cardiomyocyte-mediated contact programs human mesenchymal stem cells to express cardiogenic phenotype. J Thorac Cardiovasc Surg 126: 124-132.
51. Schuleri KH, Feigenbaum GS, Centola M, Weiss ES, Zimmet JM, et al. (2009) Autologous mesenchymal stem cells produce reverse remodelling in chronic ischaemic cardiomyopathy. Eur Heart J 30: 2722-2732.
52. Shake JG, Gruber PJ, Baumgartner WA, Senechal G, Meyers J, et al. (2002) Mesenchymal stem cell implantation in a swine myocardial infarct model: engraftment and functional effects. Ann Thorac Surg 73: 1919-1925.

53. Karantalis V, DiFede DL, Gerstenblith G, Pham S, Symes J, et al. (2014) Autologous mesenchymal stem cells produce concordant improvements in regional function, tissue perfusion, and fibrotic burden when administered to patients undergoing coronary artery bypass grafting: The Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) trial. Circ Res 114: 1302-1310.

54. Heldman AW, DiFede DL, Fishman JE, Zambrano JP, Trachtenberg BH, et al. (2014) Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: the TAC-HFT randomized trial. JAMA 311: 62-73.

55. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, et al. (2007) Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131: 861-872.

56. Kawamura M, Miyagawa S, Miki K, Saito A, Fukushima S, et al. (2012) Feasibility, safety, and therapeutic efficacy of human induced pluripotent stem cell-derived cardiomyocyte sheets in a porcine ischemic cardiomyopathy model. Circulation 126: S29-37.

57. Bearzi C, Rota M, Hosoda T, Tillmanns J, Nascimbene A, et al. (2007) Human cardiac stem cells. Proc Natl Acad Sci U S A 104: 14068-14073.

58. Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, et al. (2003) Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell 114: 763-776.

59. Linke A, Muller P, Nurzynska D, Casarsa C, Torella D, et al. (2005) Stem cells in the dog heart are self-renewing, clonogenic, and multipotent and regenerate infarcted myocardium, improving cardiac function. Proc Natl Acad Sci U S A 102: 8966-8971.

60. Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, et al. (2011) Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet 378: 1847-1857.

61. Messina E, De Angelis L, Frati G, Morrone S, Chimenti S, et al. (2004) Isolation and expansion of adult cardiac stem cells from human and murine heart. Circ Res 95: 911-921.

62. Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LE, et al. (2012) Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. Lancet 379: 895-904.

63. Adams JC (2001) Cell-matrix contact structures. Cell Mol Life Sci 58: 371-392.

64. Kim DH, Kshitiz, Smith RR, Kim P, Ahn EH, et al. (2012) Nanopatterned cardiac cell patches promote stem cell niche formation and myocardial regeneration. Integr Biol (Camb) 4: 1019-1033.

65. Kim DH, Kim P, Song I, Cha JM, Lee SH, et al. (2006) Guided three-dimensional growth of functional cardiomyocytes on polyethylene glycol nanostructures. Langmuir 22: 5419-5426.

66. Stout DA, Basu B, Webster TJ (2011) Poly(lactic-co-glycolic acid): carbon nanofiber composites for myocardial tissue engineering applications. Acta Biomater 7: 3101-3112.

67. Kai D, Wang QL, Wang HJ, Prabhakaran MP, Zhang Y, et al. (2014) Stem cell-loaded nanofibrous patch promotes the regeneration of infarcted myocardium with functional improvement in rat model. Acta Biomater 10: 2727-2738.

68. Kang BJ, Kim H, Lee SK, Kim J, Shen Y, et al. (2014) Umbilical-cord-blood-derived mesenchymal stem cells seeded onto fibronectin-immobilized polycaprolactone nanofiber improve cardiac function. Acta Biomater 10: 3007-3017.

69. Badylak SF, Taylor D, Uygun K (2011) Whole-organ tissue engineering: decellularization and recellularization of three-dimensional matrix scaffolds. Annu Rev Biomed Eng 13: 27-53.

70. Ott HC, Matthiesen TS, Goh SK, Black LD, Kren SM, et al. (2008) Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart. Nat Med 14: 213-221.

71. Wainwright JM, Czajka CA, Patel UB, Freytes DO, Tobita K, et al. (2010) Preparation of cardiac extracellular matrix from an intact porcine heart. Tissue Eng Part C Methods 16: 525-532.

72. Singelyn JM, DeQuach JA, Seif-Naraghi SB, Littlefield RB, Schup-Magoffin PJ, et al. (2009) Naturally derived myocardial matrix as an injectable scaffold for cardiac tissue engineering. Biomaterials 30: 5409-5416.

73. Weymann A, Loganathan S, Takahashi H, Schies C, Claus B, et al. (2011) Development and evaluation of a perfusion decellularization porcine heart model-generation of 3-dimensional myocardial neoscaffolds. Circ J 75: 852-860.

74. Sanchez-Fernandez P, Costanza S, Rodrıguez-Abella H, Garrido G (2011) Decelularizacio n de corazones humanos para el desarrollo de matrices cardiacas que sirvan como soporte a la bioingenierıa de tejidos cardiacos funcionales. Rev Esp Cardiol 64: 4.

75. Yamashita JK (2010) ES and iPS cell research for cardiovascular regeneration. Exp Cell Res 316: 2555-2559.

76. Yoshida Y, Yamanaka S (2011) iPS cells: a source of cardiac regeneration. J Mol Cell Cardiol 50: 327-332.

77. Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, et al. (2006) Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. N Engl J Med 355: 1210-1221.

78. Assmus B, Fischer-Rasokat U, Honold J, Seeger FH, Fichtlscherer S, et al. (2007) Transcoronary transplantation of functionally competent BMCs is associated with a decrease in natriuretic peptide serum levels and improved survival of patients with chronic postinfarction heart failure: results of the TOPCARE-CHD Registry. Circ Res 100: 1234-1241.

79. Meyer GP, Wollert KC, Lotz J, Pirr J, Rager U, et al. (2009) Intracoronary bone marrow cell transfer after myocardial infarction: 5-year follow-up from the randomized-controlled BOOST trial. Eur Heart J 30: 2978-2984.

80. Strauer BE, Yousef M, Schannwell CM (2010) The acute and long-term effects of intracoronary Stem cell Transplantation in 191 patients with chronic heARt failure: the STAR-heart study. Eur J Heart Fail 12: 721-729.

81. Bocchi EA, Bacal F, Guimaraes G, Mendroni A, Mocelin A, et al. (2010) Granulocyte-colony stimulating factor or granulocyte-colony stimulating factor associated to stem cell intracoronary infusion effects in non ischemic refractory heart failure. Int J Cardiol 138: 94-97.
82. Seth S, Bhargava B, Narang R, Ray R, Mohanty S, et al. (2010) The ABCD (Autologous Bone Marrow Cells in Dilated Cardiomyopathy) trial a long-term follow-up study. J Am Coll Cardiol 55: 1643-1644.
83. Lunde K, Solheim S, Aakhus S, Arnesen H, Abdelnoor M, et al. (2006) Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med 355: 1199-1209.
84. Perin EC, Silva GV, Henry TD, Cabreira-Hansen MG, Moore WH, et al. (2011) A randomized study of transendocardial injection of autologous bone marrow mononuclear cells and cell function analysis in ischemic heart failure (FOCUS-HF). Am Heart J 161: 1078-1087.
85. Nasseri BA, Ebell W, Dandel M, Kukucka M, Gebker R, et al. (2014) Autologous CD133+ bone marrow cells and bypass grafting for regeneration of ischaemic myocardium: the Cardio133 trial. Eur Heart J 35: 1263-1274.
86. Lund LH, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, et al. (2014) The registry of the International Society for Heart and Lung Transplantation: thirty-first official adult heart transplant report-2014; focus theme: retransplantation. J Heart Lung Transplant 33: 996-1008.
87. John R (2008) Current axial-flow devices-the HeartMate II and Jarvik 2000 left ventricular assist devices. Semin Thorac Cardiovasc Surg 20: 264-272.
88. Benden C, Goldfarb SB, Edwards LB, Kucheryavaya AY, Christie JD, et al. (2014) The registry of the International Society for Heart and Lung Transplantation: seventeenth official pediatric lung and heart-lung transplantation report-2014; focus theme: retransplantation. J Heart Lung Transplant 33: 1025-1033.
89. Mattar AA, Chong JJ (2014) Stem cell therapy for cardiac dysfunction. Springerplus 3: 400.

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