



Advanced strategies for end-stage heart failure: combining regenerative approaches with LVAD, a new horizon?

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Despite the improved treatment of cardiovascular diseases, the population with end-stage heart failure (HF) is progressively growing. The scarcity of the gold standard therapy, heart transplantation, demands novel therapeutic approaches. For patients awaiting transplantation, ventricular-assist devices have been of great benefit on survival. To allow explantation of the assist device and obviate heart transplantation, sufficient and durable myocardial recovery is necessary. However, explant rates so far are low. Combining mechanical circulatory support with regenerative therapies such as cell (-based) therapy and biomaterials might give rise to improved long-term results. Although synergistic effects are suggested with mechanical support and stem cell therapy, evidence in both preclinical and clinical setting is lacking. This review focuses on advanced and innovative strategies for the treatment of end-stage HF and furthermore appraises clinical experience with combined strategies.

Keywords: heart failure, ventricular-assist device, mechanical circulatory support, regenerative therapies, cell therapy, cardiac recovery

INTRODUCTION

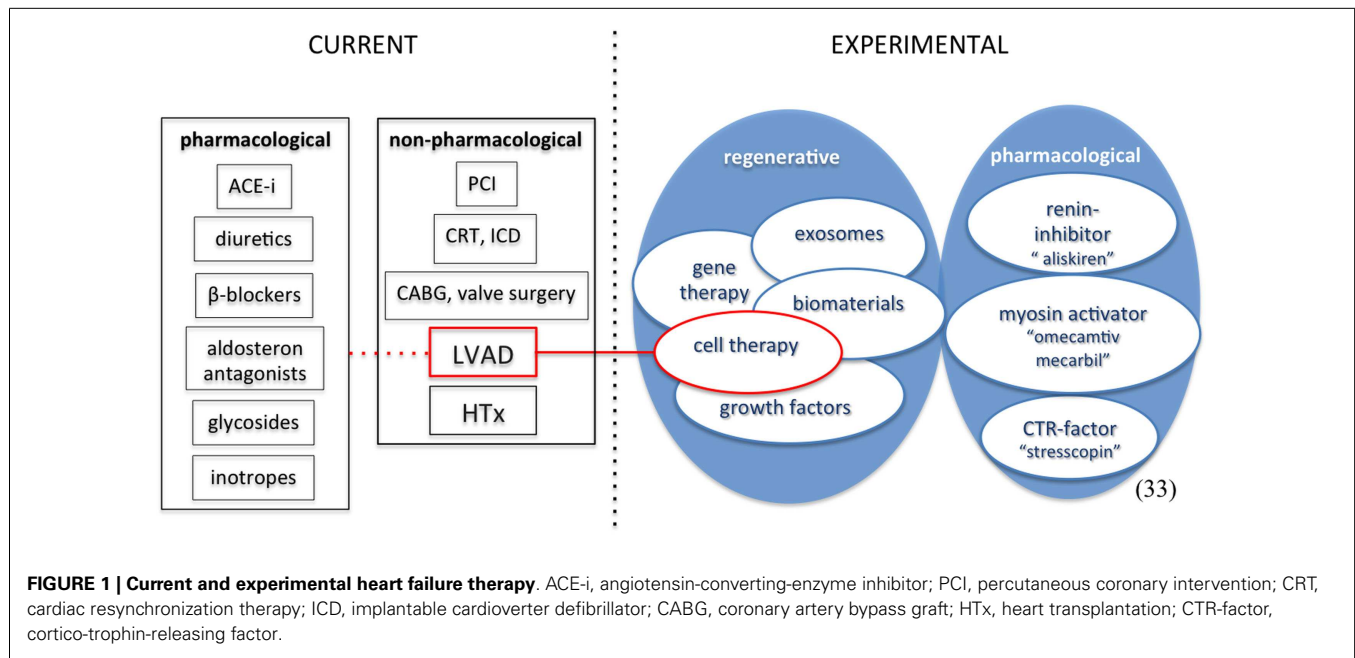
Heart failure (HF) is a progressive disease with an important economic burden on today's healthcare. After initial injury, progressive worsening maladaptive (cellular and structural) changes result in a process called ventricular remodeling, eventually leading to diminished cardiac function (1, 2). According to the Framingham study, the incidence of HF has remained stable since the 1970s (3). Despite this unchanged incidence, the population of HF patients is growing, affecting up to around 23 million patients worldwide, due to various aspects. Improvement in the acute therapy of myocardial infarction (MI) has played a major role in survival rates. Other non-pharmacological treatment options such as ICD therapy have further decreased mortality. In addition, the widespread use of ACE-inhibitors, ATII-blockers, beta-blockers, and aldosterone-antagonists, but also cardiac resynchronization therapy further enhanced survival among HF patients. These developments in combination with an aging population translate into an increase in the prevalence of chronic "end-stage HF" (4, 5). Although not clearly defined, according to the guidelines for heart transplantation, heart transplantation should be considered in patients with severe symptoms of HF, intractable angina, or rhythm disturbances, without any alternative form of treatment

available and with a poor prognosis (6). Concerning the guidelines for HF, there are different types of management approaches, which can be broadly subdivided in three groups, (1) general/non-pharmacological measures, (2) pharmacological therapy, and (3) devices and surgery (7, 8). The only current available therapy for end-stage HF is heart transplantation. Opposed to an increasing demand for donor hearts, the number of heart transplantations in Europe has diminished in recent years. In the Netherlands especially, decreasing mortality after traffic accidents, older donors, and shift from heart-beating donation to non-heart-beating procedures gave rise to a further decreasing amount of donors (6). To compensate for the shortcoming of donors, novel therapeutic strategies are inevitable. Experimental regenerative therapies, intended to restore functional cardiac cells and myocardial function are of great interest (9, 10). An overview of heart failure treatment is depicted in **Figure 1**. For some patients, mechanical circulatory support (MCS) with a ventricular-assist device (VAD) is an option. This review will focus on current and novel, advanced therapeutic strategies for end-stage HF.

CURRENT THERAPIES FOR END-STAGE HEART FAILURE HEART TRANSPLANTATION

In European countries that are represented by the European Society of Cardiology (ESC), there are estimated to be over 10 million patients with HF (7). For the Netherlands, this number is believed to be between 100.000 and 150.000 patients, and is expected to rise to approximately 195.000 in 2025 (11). These numbers are probably underestimated and lack accuracy due to the absence of a uniform definition for HF. Easier to determine is the number of patients waiting for a donor heart. Eurotransplant is the international collaborative framework responsible for allocation

Abbreviations: BIVAD, biventricular-assist device; BMMNCs, bone marrow-derived mononuclear cells; CSCs, cardiac stem cells; EF, ejection fraction; ESC, European Society of Cardiology; GHs, growth hormones; HF, heart failure; HGF, hepatocyt growth factor; IGF-1, insulin-like growth factor-1; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LV, left ventricle or ventricular; LVAD, left ventricular-assist device; MCS, mechanical circulatory support; MI, myocardial infarction; miRNA, microRNA; VAD, ventricular-assist device.



of donor organs in the Netherlands, Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, and Slovenia. Annual statistics show a rising number of patients on the waiting list, with an actual number of 1250 patients at the end of December 2013, a 2.5-fold increase compared to 2000 (12). With a total of 563 heart transplantations in 2013, the scarcity of donor hearts is evident. In the Netherlands, the same trend is seen. Added up with the progressive decline in the amount of donors, heart transplantation will not relieve the burden of HF on healthcare.

MECHANICAL SUPPORT

As briefly stated in the introduction, MCS with a VAD is a possibility for some patients. VADs can be used as a bridge to transplantation, recovery or decision, and as destination therapy. These mechanical pumps partially or completely take over ventricular function to support circulation. Either the left ventricle (LV), right ventricle (RV), or both ventricles can be unloaded. Predominantly, left ventricular-assist devices (LVADs) are implanted because of disappointing results of biventricular-assist device (BIVAD) support (13). Since the first successful implantation of a VAD in 1966 by DeBakey (14), mechanical support has shown to be of great value in survival of patients with advanced HF. The landmark REMATCH trial (15) compared the long-term use of the first generation, pulsatile LVADs with optimal medical therapy in end-stage HF and showed significantly improved survival with an absolute reduction in mortality rate of 27% at 1 year (16). Two major factors causing a low 2-year survival rate of 23% in the LVAD group were infection and mechanical device-failure (16). Since 2006, continuous-flow assist devices are implanted, with much better results (17). Lahpor et al. (18) explored the outcomes of more than 400 patients with this second generation, continuous-flow device and found no mechanical failure, a low incidence of neurological complications but still major infectious and bleeding complications. Although the mean duration of support was

significantly higher due to the shortage of donor hearts, overall survival is comparable to other studies (17, 18). Permanent mechanical support, or LVAD as destination therapy, is an option for patients with contraindications for heart transplantation, but reimbursement differs per country (19). In addition to the financial aspects, durable LVAD support as a therapy for end-stage HF is still hampered by substantial bleeding (2.69 events/pt-year) and thromboembolic events (0.31 events/pt-year), as well as inflammatory complications (2.34 events/pt-year) (16, 18, 20–22). The fifth Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) analysis demonstrated a sixfold increase of pump exchanges for pump thrombosis between 2011 and 2012, clinically concerning due to the associated higher mortality rates (23, 24). These findings emphasize the importance of restricting long-term support only for those who really need that and stimulating myocardial recovery and device explantation in as many patients as possible. While initially ventricular remodeling in end-stage HF was held to be irreversible, multiple analyses have shown high percentages of “reverse remodeling” but only low numbers of myocardial recovery (1, 2, 25). Although the influence on end-organ perfusion and unloading is similar with pulsatile versus continuous-flow support, conflicting literature exists regarding their influence on recovery (26). In the current clinical setting, LVADs infrequently lead to sufficient myocardial recovery to allow device explantation, i.e., function as a bridge to recovery (BTR). In a retrospective review with patients receiving MCS as a bridge to transplantation, recovery occurred in less than 5% of patients (27). An explantation rate of 9% was described by the LVAD working group, mostly in younger patients with recent onset HF of non-ischemic origin (2). These results correspond to prior data showing higher percentages of myocardial recovery in patients with non-ischemic cardiomyopathy (28). Yacoub et al. aimed at the process of “physiological hypertrophy” and “reverse remodeling” to maximize the rate of cardiac recovery by using LVAD

support in combination with a specific sequence of pharmacological therapy, including beta-2-agonist Clenbuterol (29). A small cohort of 15 patients receiving MCS for non-ischemic cardiomyopathy without acute myocarditis, were treated with the particular sequence of medication that resulted in sufficient recovery to meet explantation criteria in 11 patients (73%). In most cases, improvement maintained for more than 4 years (30). Long-term outcomes of patients bridged to recovery versus bridged to transplantation were investigated (31) to review the results of an aggressive attempt at stimulating myocardial recovery. Particularly patients with non-ischemic cardiomyopathy profit from aggressively inducing reversal of HF. The rate of device explantation was 20.5%, much higher than other data so far (2, 31, 32).

EXPERIMENTAL REGENERATIVE THERAPIES

A concise concept of different regenerative approaches, present experience, and associated hurdles for clinical application will be discussed. Experimental pharmacological therapies (33) are beyond the scope of this review.

CELL THERAPY

Various cell populations and delivery strategies have been examined for their cardiac repair and regenerative capacity in the last decades. Stem cells can be derived from blood, bone marrow, skeletal muscle, adipose tissue, embryonic sources, or cardiac tissue (34, 35). Initially, stem cells were presumed to replace damaged cardiomyocytes. Instead, currently, the major mechanism of action is assumed to be through paracrine factors leading to decreased neurohormonal activation and apoptosis, better Ca^{2+} -handling, stimulation of neovascularization, and activation of endogenous cardiac-resident cells (36–38). Most clinical experience with cell therapy is gained in ischemic heart disease with unselected bone marrow-derived mononuclear cells (BMMNCs). Results in clinical setting are modest but significant with greatest improvements in the lowest LV ejection fraction (EF) at baseline (34, 38–45). The discordance with preclinical data is not fully explained, but poor cell retention and survival plus possible malfunctioning of bone marrow-derived cells in patients with HF are alleged to play a role in these somewhat disappointing findings (34, 46–48). The discovery of so-called endogenous cardiac stem cells (CSCs) (49) and evidence that cardiomyocytes have renewal capacity (49–51) have provided a new therapeutic approach, to stimulate the endogenous CSCs since these cells are programmed to reconstitute cardiac tissue. Encouraging results were shown in the SCIPIO trial (autologous CSCs) (52) and in the CADUCEUS trial (autologous cardiosphere-derived cells) (53). Compared to ischemic heart disease, limited clinical data is available regarding efficacy of cell therapy in dilated cardiomyopathy. Results in this population seem mostly positive, though heterogeneity of the population, procedures, and outcome parameters prohibit extrapolation (54). A novel cell-based technology in which somatic cells (all cells in the body except germ cells) are modified or reprogramed into a special type of stem cell, called induced pluripotent stem cell (iPS), is in development (35, 55). This technique is already applied for other purposes but is fairly unknown as therapeutic. To improve clinical success of cell therapy, better understanding of the primary mechanism and best cell type are fundamental (10, 36, 38, 41). In addition, knowledge

about optimal timing, dosing, and delivery strategies, including better cell retention and survival, is essential (35, 46, 56).

GROWTH FACTORS

Growth hormones (GHs) are essential for normal myocardial and endothelium development, and for the maintenance of function (57, 58). Endogenous CSCs can be activated by growth factors in the infarcted heart as shown in rodents (59) and in a porcine model (60) of acute MI (34, 59–61). Vascular endothelial growth factor (VEGF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) augment levels of endothelial progenitor cells (EPCs) and improve neovascularization (34). Hepatocyte growth factor (HGF) promotes cell migration, insulin-like growth factor-1 (IGF-1) is mitogenic and antiapoptotic, stimulates myocyte formation, and reduces myocyte death after infarction (59). GH therapy in chronic setting seems rational since part of the neurohormonal disturbances in HF lies in the GH/IGF-1 signaling axis (58). Whereas animal studies demonstrate beneficial effects of growth factor therapy (34, 62), clinical data about the efficacy of growth factors in HF patients is conflicting (58). In a small group of patients ($n = 13$) with severe coronary artery disease and refractory angina, treatment with high doses of VEGF temporarily enhanced myocardial perfusion (63). A preliminary study by Fazio et al. (64) showed improved cardiac output in seven patients with dilated cardiomyopathy treated with GH, whilst other studies examining the effects of exogenous GH in HF yielded no beneficial effects on cardiac function (65–68). A more recent clinical trial (69) with granulocyte-colony-stimulating factor after MI, although appearing to improve LV function, was terminated because of high incidence of in-stent restenosis in this treated group. A safety and efficacy trial with IGF-1 is currently recruiting patients with acute MI (Clinical trial info: NCT 01438086).

GENE THERAPY

Interest for experimental gene therapy in cardiovascular disease has grown in the last 10 years. The most relevant systems targeted to restore function of failing cardiomyocytes are (1) the B-adrenergic system, (2) Ca^{2+} cycling proteins, (3) homing stem cells, and (4) cell death (70). The first clinical, phase 2A safety study (CUPID), with adeno-associated virus (AAV) type 1/sarcoplasmic reticulum Ca^{2+} -ATPase (SERCA2a) suggests a positive effect on LV function (71), but the therapeutic potential will become apparent as a phase 2b trial is ongoing (clinicaltrials.gov: NCT 01643330) (72). Other targets that have been taken forward toward clinical trials include adenylyl cyclase type 6 (clinicaltrials.gov: NCT 00787059) and stromal cell-derived factor-1 (SDF-1) (clinicaltrials.gov: NCT 01082094) (70). As more molecular targets associated with HF are discovered, more effective gene therapy is expected to emerge (70). Another concept in gene therapy for HF concerns microRNA (miRNA). These are small non-coding RNAs that bind to specific target mRNAs, thereby suppressing protein expression (73, 74). The capacity to manipulate miRNA expression and function, together with the fact that their function is heightened under pathophysiological conditions, make them attractive candidates for therapeutic manipulation. Either inhibitors (antimiR) or mimics of miRNA are of interest (73). Several small and large animal studies have targeted relevant miRNA

(-families) (73). For example, miRNA-208a (cardiac remodeling), miRNA-21 (cardiac hypertrophy and fibrosis), miRNA-15 (cardiomyocyte apoptosis and regeneration), and miRNA-92a (angiogenesis and regeneration) have been found to play a role in cardiovascular pathology (74–77). Hinkel et al. demonstrated improved recovery after ischemia/reperfusion injury by inhibiting miR-92a by LNA-based miRNA inhibitor in a pig model (74). Challenges in miRNA therapy essentially concern the pleiotropy and multiplicity of miRNA that needs intensive research, since only target tissue is examined in all studies. Next to that, feasibility of adequate dosing has to be assessed (70).

EXOSOMES

These small membrane vesicles (40–100 nm), endosomal-derived and extracellularly released by many cells, are involved in intercellular communication (78, 79). Although discovered 30 years ago (80), major interest in exosomes and their function in regenerative medicine recently emerged. In response to injury, extracellular microvesicles are released from activated platelets and apoptotic endothelial cells, suggesting not only therapeutic but also diagnostic value (81). Special attention for exosomes derived from cardiac progenitor cells has originated from the postulated paracrine effects of cell-based therapy, mainly regarding the release of growth factors, cytokines, and chemokines (78, 81). Exosomes derived from cardiomyocyte progenitor cells are proposed to play a role in cardiac protection (78). In mice as well as in a porcine model of ischemia/reperfusion injury, mesenchymal stromal cell-derived exosomes reduced myocardial damage (78, 82). While acknowledged to target via transfer of proteins or genetic materials, the role of exosomes in cardiac injury is far from clear (79). Further research on the production and content sorting of exosomes and their effect on target (and non-target) cells is crucial (79, 81).

BIOMATERIALS

Another recent topic in regenerative therapy for cardiovascular disease is the use of biomaterials. Multiple scaffolds, naturally derived and synthetic, are used. Therapeutic ability is suggested for MI, prevention of remodeling, and in consequence prevention of ischemic HF in small and large animal models (83–85). Whilst originally tissue-engineered cardiac patches were of interest, research in the area of injectable biomaterials is rapidly evolving (47, 61, 83, 86, 87). The prospective profit of biomaterials is two-sided, either to stimulate endogenous repair and regeneration or to provide a vehicle to support delivery of other therapeutics (e.g., cells, growth factors), generating greater cell retention and survival (47, 86). Gelatin microspheres have been shown to be a feasible carrier for cardiomyocyte progenitor cells and growth factors, resulting in improved engraftment and cell survival in mice (Feyen. Thesis: Strategies to improve cardiac cell therapy. Chapter 8: Gelatin microspheres as carriers for cardiac progenitor cell and growth factor to the ischemic myocardium, unpublished, 2014). Dai et al. studied the effect of non-cellular hydrogels versus cell therapy in a rat model of chronic ischemia and showed similar increases in EF and thereby potential of hydrogels alone (84). No clinical trials have yet been performed with biomaterials. The challenge of this therapy is the delivery, mainly relating to the

solubility during the procedure while the hydrogel has to become gel-like after injection in the myocardium.

COMBINED MECHANICAL SUPPORT AND REGENERATIVE THERAPIES

Following unloading of the ventricle, a complex network of changes on molecular, cellular, tissue, and organ level arises (32, 88–94). Although the exact mechanism of reversal of HF during LVAD support is unclear, the effect of ventricular volume and pressure unloading together with improved neurohormonal and cytokine activation are thought to induce reverse remodeling (1, 92, 95). In a study comparing isolated human myocytes of failing hearts with and without prior LVAD showed increased contractile properties and beta-adrenergic responsiveness after LVAD support (96). Immunohistochemical analysis of the contractile myofilaments after LVAD implantation uncovered improved staining pattern of all thin contractile proteins and titin, however structural myocyte damage was persisting (89). Significant improvement of the proliferation/apoptosis balance by ventricular unloading has been shown in a mouse model of ischemic HF (95). Also, specific changes in gene expression of cytoskeletal proteins after LVAD support have been seen in recovered versus non-recovered myocardium (91). The beneficial effect on LV function appears to deteriorate over time (2), suggesting that combining mechanical support with other, regenerative, therapeutic strategies like GHs, gene therapy, or cell therapy might hold the key to better long-term results (92). The unloaded ventricle provides a less hostile milieu and thereby a potentially more appropriate platform for different regenerative therapies. Along the same lines, the combined approach of biventricular pacing and BMMNCs in ischemic HF indicated a significant and clinically relevant improvement in cardiac function in comparison with BMMNCs alone, while CRT showed no impact on perfusion (97). The rationale for this approach is that electrical stimulation might promote cell differentiation.

PRECLINICAL EXPERIENCE

Up to date, a representative large animal model of chronic HF with myocardial unloading is lacking. The majority of LVAD studies was performed in healthy animals with only a few studies in chronically failing models (98). Preclinical experience consists of several (b)ovine ischemic HF models, induced by either coronary microembolization, coronary ligation, or ameroid constriction (99–103). Non-ischemic HF models include a pressure and volume overload model caused by aortic constriction, respectively, mitral regurgitation via chordae rupture (98, 104). Last-mentioned models have the disadvantage of required thoracotomy, undesirable in case of future device implantation. Other methods like pacing, pharmacotherapeutic induced (doxorubicin), direct shock, and cardiotoxins are not reflective of human HF (98). Recreating a model similar to human etiology remains a challenge. To advance innovative and clinically applicable strategies for cardiac regeneration, suitable preclinical research is inevitable. Not only to test combined unloading and regenerative therapies, but also to direct future mechanical support and treatment of earlier stage HF. Thereafter, different regenerative therapies must be evaluated in such a model.

Table 1 | Clinical experience of LVAD combined with cell therapy.

Study type (Reference)	n	Etiology CMP	Cell type (and timing)	Clinical outcome	Measured effect
Phase I (111)	20	Ischemic and non-ischemic	Allogeneic MPCs (concomitant)	Increased weaning frequency and duration	Safe/efficacy
Case report (105)	1	Dilated	Autologous skeletal myoblasts (+16 months)	LVAD explantation	LVEF increased
Phase I (110)	4	Ischemic	Autologous skeletal myoblasts (concomitant)	1 LVAD explantation, 3 non-cardiac deaths	n = 2 LVEF increased
Case series (108)	2	Ischemic	Autologous BMMNCs (concomitant)	1 Improved perfusion, 1 unknown	Perfusion improved
Case report (107)	1	Ischemic	Autologous skeletal myoblasts (+3 months)	Death + 466 days (sepsis)	Increased EF
Case series (109)	10	Ischemic	Autologous BMMNCs (concomitant)	1 LVAD explantation, 3 HTx, 2 deaths	n = 1 increased EF
Case report (106)	1	Ischemic	Autologous BMMNCs (+99 days)	LVAD explantation	Increased EF and perfusion
Phase I (40)	6	Ischemic	Autologous skeletal myoblasts (concomitant)	4 HTx, 3 deaths	Safe/feasible
Phase I (39)	5	Ischemic	Autologous skeletal myoblasts (concomitant)	3 HTx, 1 DT, 1 death	Safe/feasible

CMP, cardiomyopathy; MPCs, mesenchymal progenitor cells; BMMNCs, bone marrow-derived mononuclear cells; HTx, heart transplantation; DT, destination therapy. Systematic search LVAD/SCT: search detail: "heart-assist devices" [MeSH Terms] OR ("heart-assist devices" [MeSH Terms] OR ("heart-assist" [All Fields] AND "devices" [All Fields]) OR "heart-assist devices" [All Fields] OR ("heart" [All Fields] AND "assist" [All Fields] AND "device"[All Fields]) OR "heart-assist device" [All Fields]) AND ("cell- and tissue-based therapy" [MeSH Terms] OR ("cell-" [All Fields] AND "tissue-based" [All Fields] AND "therapy" [All Fields]) OR "cell- and tissue-based therapy" [All Fields] OR ("cell" [All Fields] AND "therapy" [All Fields]) OR "cell therapy" [All Fields]).

In total: 195 hits, excluding review/animal/Japanese/no combination → 9 included articles.

CLINICAL EXPERIENCE

Combined mechanical unloading and regenerative therapy in clinical setting has only been examined with cell therapy. The results of these studies were systematically reviewed as shown in **Table 1** (39, 40, 105–111). A total of 50 patients have been treated with the combinational strategy. The limited data illustrate that in all cases that LVAD was explanted, an extracorporeal device was used. Usually, percutaneous support is initiated when myocardial recovery is expected. However, Sawa et al. (105) describe a case where a patient with idiopathic dilated cardiomyopathy did not show enough improvement in LVEF for explantation 7 months after starting MCS. After additional cell transplantation, LV improved to a reasonable function that sustained for at least 1.5 years. All studies, except Ascheim et al., used autologous cells, either bone marrow-derived or skeletal myoblasts, mainly in patients with ischemic cardiomyopathy. The first and only randomized trial with allogeneic mesenchymal precursor cells in ischemic and non-ischemic HF shows encouraging results when it comes to efficacy, but safety regarding sensitization is concerning, especially when the aim is to increase the amount of cells in future studies (111). No results of the combination of SERCA gene therapy and MCS have yet been reported (clinicaltrials.gov: NCT 000534703). Accordingly, the combination of MCS and cell therapy is promising as both therapies share action mechanisms and might possess synergistic effects (39, 40, 92, 105, 107–111). Focusing on this combination provides not only a point of reference to gain more success in bridging to recovery but also the unique opportunity to analyze the myocardium in case of heart transplantation, which can broaden understanding in the process of ventricular reverse remodeling and myocardial recovery. In patients awaiting heart

transplantation, allogeneic cell therapy should only be considered with great precaution because of immunologic sensitization (111).

FUTURE PERSPECTIVE

The rapidly developing field of regenerative therapies enables various combinations with LVAD support (e.g., hydrogel loaded with exosomes or growth factors combined with microspheres). Considering the different etiologies of HF, the most pronounced effect of combined cell therapy, biomaterials, and mechanical unloading could be expected in patients with ischemic HF. The rationale is that the ischemic myocardium will benefit most from the paracrine effects leading to angiogenesis. The combination with biomaterials might positively enlarge efficacy by higher retention rates, and perhaps through a direct therapeutic effect of the biomaterial. Gene therapy in combination with (biomaterials and) MCS is more probable to enhance myocardial function of patients with dilated cardiomyopathy. The advancements in assist devices will help to uncover the most optimal technology to stimulate recovery and reduce adverse events. Cheng et al. suggest that pulsatile flow support might have better results with regard to recovery, due to the less affected vascular reactivity in the presence of a pulse pressure (26). The absence of arterial pulsatility leads to stiff unresponsive arteries (102). Moreover, the development of algorithms for continuous-flow-LVADs to generate a pulse pressure is very intriguing, also for the possible influence on adverse events (26). The increasing rate of permanent LVAD support will lead to more clinical data regarding recovery rates and adverse events. However, the small number of patients included in LVAD trials and the lack of an illustrative preclinical model, makes moving forward to clinical application time-consuming. Besides testing of combined

therapeutic strategies, preclinical research is also inevitable to gain more understanding of the types of support in the setting of myocardial recovery.

CONCLUSION

Since heart transplantation, the gold standard therapy for end-stage HF, is not sufficiently available, other advanced therapeutic approaches are crucial. LVADs provide a bridge for patients awaiting heart transplantation or myocardial recovery. Rates of successful and durable recovery are very low, but this can be stimulated pharmacologically. Better-sustained results could be expected from combining LVADs with regenerative therapies such as gene therapy, biomaterials, and cell-based therapies. Especially, cell therapy for the treatment of heart disease has been extensively studied, showing promising results. The small number of LVAD patients does not allow clinical testing of the numerous potential combinations of therapies. A clinically relevant animal model of unloading should be established for preclinical testing of these regenerative approaches. Regarding current experience in the reversal of HF with combined LVAD and cell therapy, future clinical research should focus on placebo-controlled studies in patients undergoing LVAD implantation.

ACKNOWLEDGMENTS

This work was funded by ICIN – Netherlands Heart Institute, www.icin.nl.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 02 November 2014; paper pending published: 25 January 2015; accepted: 07 March 2015; published online: 07 April 2015.

Citation: Tseng CCS, Ramjankhan FZ, de Jonge N and Chamuleau SAJ (2015) Advanced strategies for end-stage heart failure: combining regenerative approaches with LVAD, a new horizon? *Front. Surg.* **2**:10. doi: 10.3389/fsurg.2015.00010

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