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Alternatives to heart transplantation: integration of biology with surgery

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1. ABSTRACT

Chronic heart failure is one of the major health care issues in terms of increasing number of patients, rate of hospitalizations and costs. Heart transplantation is the best established therapy for patients with severe heart failure. However, the number of donors limits the activity to 5000 heart transplants performed annually worldwide. This limitation has generated alternative treatments. The increase of the interest in the reversibility of the heart failure and the application of new biological alternatives has generated therapeutic strategies designed to integrate biology and medical technologies in order to act to the biomechanical, the molecular and the neurohormonal mechanisms of heart failure. These treatments include cellular cardiomyoplasty, tissue engineering, surgical left ventricular restoration as well as passive and active mechanical ventricular assistance as destination therapy, bridge to recovery or bridge to transplantation. The integrated development of these approaches could offer hopeful treatments, although there is still much to be learned regarding the optimal use of these strategies.

2. INTRODUCTION

Chronic heart failure is one of the major health care issues in terms of increasing the number of patients, rate of hospitalization and costs. The prevalence in the USA is 5 million patients, almost 400,000 new cases/year and 300,000 deceased/year (1, 2). The etiology is ischemic cardiomyopathy in two-third of cases. The dilation of the left ventricle (LV) occurs in 20% of the patients with a transmural acute myocardial infarction (AMI), despite the successful early revascularization and the prognosis is more closely related to the increase in LV volume than to reduction of ejection fraction (LVEF) (3). The remodeling is a complex phenomenon with the participation of neurohormonal, molecular, genetic and biomechanical processes.

A 5% of the patients are very symptomatic, need frequent hospitalizations and survival is lower than the 30% after 12 months (4). In these patients with chronic heart failure class D, the medical therapy acting against neurohormonal activation is ineffective. The increase in ventricular volume and the normal elliptical shape that

becomes spherical are responsible for the progression of heart failure (5). These geometric changes lead to structural changes of the myocytes and the extracellular matrix, which worsen cardiac function and increase neurohormonal activation. The treatment must act on this biomechanical mechanism of heart failure.

Heart transplantation is the best established therapy for patients with severe heart failure. The transplant half-life for the entire cohort of adult and pediatric heart transplant recipients is currently 10 years, according to the Registry of the International Society for Heart and Lung Transplantation (6). However, the number of donors limits the activity to 5000 heart transplants performed annually worldwide, with a decreasing transplant procedure volumes in many countries (6). This limitation has generated alternative treatments in these patients. The recent therapeutic strategies are designed to integrate biology and mechanical technologies in order to act to the biomechanical, molecular and neurohormonal mechanims of heart failure. These treatments include surgical ventricular restoration (SVR), mechanical ventricular assistance as destination therapy or bridging to recovery, passive ventricular constraint, immunoadsorption and tissue engineering.

3. LEFT VENTRICULAR REMODELING PROCESS

The chronic effect of the compensatory changes to heart failure is known as¨remodeling¨. This process includes ventricular dilation and neurohormonal activation. The left ventricle dilation increase wall stress according to Laplace´s Law: wall tension = 3D x P/2H (D= diameter, P= intracardiac pressure, H= ventricular wall thickness). The increase of the wall stress secondary to the ventricular dilation results in increased oxygen consumption, decreased subendocardial blood flow and reduced systolic shortening (7). The prognosis in the patients keeps a straight relation with dilation and the patients with left ventricular end systolic volume index > 40 mL/ m^2 are more symptomatic and has a worse prognosis (8).

The dilation of the ventricle is associated to a change from elliptical to spherical shape and normal systolic torsion is reduced. The normal myofibril shortening of 15% generates an EF of 30% in spherical ventricles and 60% in elliptical ventricles (9). In ischemic cardiomyopathy, the curvature increases after infarction with loss of the EF in the non-infarcted myocardium and the adverse effects are similar for akinesia and dyskinesia (10). The increase of the wall stress induces changes in gene expression and stimulation of neurohormonal activity with promotion of myocyte apoptosis and adverse effects on the extracellular matrix (11): increase of p21ras, c-fos, p38α/βMAP kinase and decrease of Ca^{2+} ATPase/phospholamban (12)

The treatment for these patients must consider the biomechanical model of heart failure and the therapeutic approach of the neurohormonal activation, myocyte apoptosis and changes in the extracellular matrix. In order to reach these objectives, the therapeutic strategy must integrate the surgical reduction of the volume and restoration of the geometry of the ventricle, by surgical ventricular restoration (SVR) or passive ventricular constraint, together with immunoadsorption or cardiac tissue engineering.

4. THERAPEUTIC STRATEGIES

4.1. Immunoadsorption (IA)

Disturbances in humoral and cellular immunity have been described in cases of myocarditis and idiopathic dilated cardiomyopathy (DCM) (13, 14). In DCM patients, immunohistological methods have been successfully introduced for diagnosis of myocardial inflammation. Among the phenomena encountered in DCM, infiltration with lymphocytes and mononuclear cells, increased expression of cell-adhesion molecules, as well as human leukocyte antigen (HLA) upregulation are the most frequent (15, 16). These findings support the hypothesis that the immune process remains active.

Various autoantibodies have been detected in DCM patients, including antibodies against mitochondrial proteins (17), cardiac myosin (18), cardiac β_1-adrenergic receptors (19), muscarinergic receptors (20), and the sarcolemmal Na–K–ATPase (21). Despite the functional role of these cardiac autoantibodies in DCM still remains unclear, experimental data indicate that they may play a causal response in development of DCM. Active immunization of rabbits with peptides derived either from cardiovascular G-protein coupled receptors or to the human M_2 acetylcholine receptor may induce morphological changes of the myocardial tissue resembling DCM (22, 23). Publications in recent time have demonstrated that rats immunized against the second extracellular loop of cardiac β_1-receptor develop progressive left ventricular dilatation and dysfunction (24).

It has been thereby hypothesized that cardiac autoantiboides play an active role in pathogenesis of DCM, by virtue of triggering the disease process, or by aggravating myocardial contractile malfunction after the onset of the disease (25). Under this hypothesis, one would expect that their elimination could improve the haemodynamics of DCM patients. Immunoadsorption (IA) makes it possible to extract cardiac antibodies. Immunoadsorption is a treatment option that removes circulating immunoglobulins from the patient's blood. Highly specific polyclonal antibodies immobilized within sepharose adsorbers can bind and retain a predefined amount of immunoglobulins and immune complexes.

Dörfflerb (26) conducted the first trial to characterize the short-term haemodynamic effects of IA in patients with DCM and severe heart failure. Extraction by anti-IgG columns of circulating IgGs from the plasma of these patients induced significant increase in cardiac index (CI), accompanied by simultaneous fall in systemic vascular resistance. These data suggested that removal of antibodies may improve the haemodynamics in DCM. A subsequent open randomized study was aimed to evaluate the haemodynamic influence of IA as a therapeutic option

of patients in DCM (NYHA III-IV, LVEF<30%, CI<2.5. L/min/m^2) (27). In the IA group, IVIg was infused to reduce the infection risk following IgG depletion, and to block the so called 'immunological rebound' of antibody production in B cells. Both CI and SVI rose significantly (30%) in the treatment group, and accompanied by parallel reduction in SVR. IA followed by IgG substitution enhances cardiovascular function in DCM patients, since LVEF and CI increased more than 30% and systemic vascular resistance decrease significantly in the treatment group. In contrast, haemodynamics and LVEF did not change in the control group.

Müller (28) performed IA for 5 consecutive days, without IgG substitution. LVEF increased from 22 to 40% after IA therapy over one year, differing from the control group where no enhancement was achieved. Even though no relapse of cardiac autoantibodies took place, it was seemingly unclear to explain the prolonged effect of IA – only a 5-day course without repetition- over one-year follow-up. It could be elucidated that the IA sessions were performed with specific anti-Ig adsorbers, obtaining a better long-term efficacy.

It is possible that IA not only enhances haemodynamics, but likewise makes an influence on myocardial inflammation in DCM patients. In Staudt´s study (29), IA was performed in four courses, at 1-month intervals. Right ventricular biopsies were obtained from all patients at baseline and after 3 months. In those patients with no immunomodulatory treatment, the number of lymphocytes (CD3, CD4 and CD8) as well as the number of leukocyte common antigen (LCA)-positive cells in the myocardium remained stable during all the study period. Differently, IA therapy and subsequent IgG injection reduced the amount of lymphocytes and LCA-positive cells. Furthermore, this behavior was accompanied by significant decline of the HLA class-II antigen expression, whereas this pattern was unchangeable in the control group. In addition, it has been recently published that IA may influence a variety of changes in the myocardial gene expression of a cytoskeletal filament desmin that is known to be upregulated in patients with DCM and heart failure (30).

Further confirmation of the therapeutic benefit of IA in DCM has been experimentally revealed because of the improved cardiac structure and function achieved after the specific removal of anti-β_1-adrenoreceptor autoantibodies in rabbits with autoimmune cardiomyopathy induced by immunization with a β1-adrenoceptor peptide (31). However, the contribution of a particular antibody to myocardial damage in DCM remains to be elucidated. Experimental models have shown that both antibodies against β_1-adrenergig receptor and against troponin I (32, 33) actually induce myocardial dysfunction and left ventricular dilatation resembling DCM. A recent study has demonstrated that autoantibodies removed by IA from DCM patients induce positive chronotropic effects and exhibit complement-dependent cytotoxicity in neonatal rat cardiomyocytes (34).

Detection of cardiodepressant antibodies may be of essential therapeutic relevance, since the contribution of humoral activity, with production of cardiodepressant antibodies, may differ among DCM patients. Since IA successfully removes cardiac autoantibodies from plasma, this technique enables assessment of the role played by the humoral immune system in cardiac dysfunction among DCM patients. It has been lately confirmed that the presence of cardiodepressant antibodies serves as predictor of acute and long-lasting hemodynamic benefits during IA (35).

Immunological differences prevail throughout IgG subclasses. For instance, complement activation is more active with IgG-3 (36). Furthermore, IgG-3 antibodies are more efficient than IgG-1 as mediators of antibody dependent cellular cytotoxicity. It was recently shown that DCM patients have elevated levels of IgG-3 antibodies against a- and b-myosin heavy chains. The level of these antibodies correlates with the degree of left ventricular dysfunction (37). Some studies have investigated the role of antibodies belonging to various IgG subclasses with respect to cardiac dysfunction in DCM, and concluded that the negative inotropic effect of antibodies obtained from DCM patients is primarily attributable to antibodies belonging to IgG-3 subclass (38). The acute and prolonged efficacy of IA therapy for DCM patients will be depending on the capacity of the effective removal IgG subclass 3 antibodies (38, 39). Therefore, removal of IgG-3 may represent the essential mechanism of IA in DCM. However, not all the IA techniques have shown the same efficacy at time to deplete this subclass of IgG. Immunoadsorption columns constituted by polyclonal antibodies conjugated to sepharose retain all classes of immunoglobulins, including IgG-3.

The results from the studies cited above suggest that activation of the humoral immune system, simultaneous to the production of cardiac autoantibodies, could play a functional role of the cardiac dysfunction occurred in DCM patients. Influencing the humoral immune system through IA could then offer a hopeful treatment approach for intervention into the autoimmune process in DCM patients with symptomatic heart failure and severe reduction of LVEF.

4.2. Cardiac tissue engineering and cellular cardiomyoplasty

Stem cell therapy, as a strategy to regenerate injured tissues, has emerged as one of the most promising areas for the treatment of illnesses with reduced cure expectations (with low possibilities of treatment). The heart failure, mainly of ischemic etiology, is one of the diseases that more can benefit from this therapeutic strategy, called cellular cardiomyoplasty (CCMP). The aim is to regenerate the muscle, reduce apoptosis, increase the expression of the collagen and get an effective production of new vessels. This very attractive approach is undergoing in vitro and in vivo studies with a variety of myogenic and angiogenic cells (40, 41): skeletal myoblasts; mononuclear bone marrow cells; circulating blood-derived progenitors; mesenchymal stem cells from bone marrow, endometrial or

adipose-derived stromal cells, mesothelial cells and induced pluripotent stem cells (iPSC).

The current indications concern patients with ischemic cardiomyopathy and previous AMI, DCM, Chagas heart disease (American Trypanosomiasis), ischemic mitral regurgitation and diabetic cardiomyopathy. The approaches for cell implantation are surgical performing the main implantation in the infarct and peri-infarct areas (42), intracoronary and endoventricular catheter-based cell delivery. The percentage of cells grafted into the myocardium is less than 10% and the high mortality is probably linked to the injection itself and the poor vascular supply of the scars. In patients with ischemic cardiomyopathy, the best results seem to be obtained in patients presenting a heterogeneous infarct area, a mixture of viable myocardial tissue and multiple small scars (42). Cell therapy is being recognized as a viable strategy with a dose-dependent improvement in heart function (43). Determining optimal delivery methods raises issues not only for dosing, but also of timing. The development of new catheter-based cell implantation procedures and repeated cell injections seem to improve the efficiency of cell therapy (44).

The proposed mechanisms of action are reduction of the size and fibrosis of infarct scars, improvement of myocardial viability, limitation of ventricular remodeling, improvement of ventricular compliance and paracrine effects (41). However, the results of clinical trials have reported only limited improvement in systolic ventricular function and remodeling (40, 41, 45,. 46) This poor effect in systolic function without participation of the implanted cells in the force generation, could be due to the lack of electrophysiologic connections between the implanted cells and the myocardium and the gap junction protein (connexin 43) (47, 48). Combined cellular transplantation with atrial synchronized biventricular pacing induces synchronous contraction of the transplanted cells and the host myocardium, improving myocardial function (48, 49). When cellular cardiomyoplasty was performed using skeletal myoblasts, the differentiation in myotubes and enhanced expression of slow myosin heavy chain was observed in the electrostimulated group (48).

The development of strategies for improving cell survival and differentiation should be encouraged, such as preconditioning procedures with cell electrostimulation or by using tissue engineering. The cell niche provides crucial support needed for cell maintenance. Cell transplantation associated with tissue-engineering approaches would be beneficial to create a myocardial repair procedure. The scaffolds used for tissue engineering have the following objectives (41): deliver and retain cells and biochemical factors, enable diffusion of vital cell nutrients and expressed products, exert mechanical and biological influences to modify the behavior of the cell phase.

The extracellular heart matrix is composed mainly of collagen with smaller amounts of elastin, laminin and fibronectin. In normal hearts, collagen type I represents 80% and collagen type III 10% of the extracellular myocardial matrix. In heart failure or after a myocardial infarction, the extracellular matrix is modified with collagen type I, decreasing from 80% to 40% (50, 51). It could be important to associate a procedure aiming at regenerating myocardial cells and the extracellular matrix (50). Preclinical investigations showed that this approach might contribute to improve the efficiency of cellular therapy. Stem cells promote secretion of angiogenic factors and the paracrine signaling, rather than cell incorporation, that promotes functional recovery (52). The association of stem cells and matrices seeded cells may release growth factor that may preserve extracellular matrix and promote the recruitment of cardiac stem cells that would provide a new endogenous pool of contractile cells (53). The research in specific biomaterials is of great interest to develop the optimal microenvironment to induce the release of angiogenic factors of control cellular adhesion or mechanical function (41). It seems logical the association of a cellularized matrix as a supplement to intramyocardial cell therapy.

The association of a collagen matrix and stem cells is an interesting approach to adjust the proportion of collagen type I and III in the scar zone and in the adjacent and remote zones (49). The first clinical study, MAGNUM trial, has demonstrated that this tissue-engineered approach is feasible, safe and improves the efficiency of the cellular transplantation. The association of a collagen type I matrix to mononuclear bone marrow cells in patients with ischemic myocardial scars, increases the thickness of the infarct scar with viable tissues and helps to normalize wall stress and myocardial viability in injured regions, limiting ventricular remodeling and improving diastolic function. The results of the MAGNUM trial show a higher increase of LVEF, ventricular filling deceleration time and a bigger reduction of left ventricular end diastolic volume and diameter (LVEDV and LVEDD) in collagen matrix + bone marrow cells group than en bone marrow cells group (53, 55). The improvement of the remodeling with a reduction of the LVEDV > 20% has not been published in any clinical study of cell therapy alone (55).

Future approaches are the application of mesenchymal stem cells as “universal donor cells” or human cells reprogrammed to iPSC, the preconditioning of the cells to improve the efficiency and the developments of nanotechnologies and bioengineered platforms with bioactive membranes made of two types of nanofiber matrix to promote local angiogenesis in the necrotic tissue as well as its regeneration (41).

4.3. Biomechanical approaches

4.3.1. Surgical ventricular reconstruction

According to the biomechanical model of chronic heart failure, the geometric changes in volume and shape of the ventricle are responsible of the changes in myocytes and extracellular matrix (5, 56). This concept introduces the need for surgical therapies that reduce the LV volume and improve geometry (57).

Surgical ventricular reconstruction includes surgical procedures that reduces LV volume and restore the elliptical shape. The surgical approaches can be

summarized in left ventricular reconstruction through surgical treatment of mitral insufficiency, partial left ventriculectomy and surgical ventricular restoration associated to coronary artery bypass graft (CABG) in ischemic cardiomyopathy.

4.3.2. Mitral valve repair or replacement

Mitral insufficiency in dilated cardiomyopathy is secondary to the interaction of several factors as the segmental alterations in contractility, dilation of the mitral annulus, papillary muscle dysfunction and geometric change of the ventricle from an elliptical to a spherical shape (57, 58). The objectives of surgical treatment are the correction of the mitral regurgitation and the restoration of the LV geometry.

The restrictive mitral annuloplasty repairs the regurgitation and contributes to reverse the remodeling of the LV with LVESD < 50 mm and LVEDD < 65 mm (58, 59). The implantation of a mitral prosthesis that is smaller than the annulus, and preservation and traction of the papillary muscles to reduce sphericity of the ventricle is a simple and reproducible technique to correct mitral regurgitation and rebuild the ventricular shape in ischemic and dilated cardiomyopathy (57).

4.3.3. Partial left ventriculectomy (Batista operation)

The Batista Operation consists of the resection of a slice of the lateral wall of the left ventricle between the two papillary muscles, from the apex to the mitral annulus and closure with a single suture with or without mitral annuloplasty (60, 61). The objective is to reduce the ventricular volume, intraventricular pressure and wall tension. The high mortality and the results with no documented benefits at long term make that the procedure is not included nowas a valid and safe strategy. The resection of the lateral ventricular wall is made in an unsuitable region. It is not taken in account neither the viability of those segments nor the lesions of branches of the circumflex artery. Therefore this procedure can induce acute myocardial infarctions and malignant arrhythmias. The conceptual mistake in the Batista operation is not the Laplace's Law application, but the vulneration of the basic principles of anatomy and the physiology of the cardiac function.

4.3.4. Surgical ventricular restoration (SVR)

Vincent Dor developed the endoventricular plastia in order to treat both dyskinesias and big akinetic areas (62). This technique has been developed by surgeons from twelve hospitals wich formed the RESTORE Group[7]. The technique has been modified by several groups and the bigger refinement has been the introduction by Menicanti et al. of the mannequin TRISVR to optimize size and shape of the new ventricle (63).

Torrent-Guasp´s model of the helical heart consider that cardiac muscular structures produces two loops that start at the pulmonary artery and end in aorta (64, 65), forming a descending and ascending segment of the apical loop with an apical vortex. Basing on this helical heart model, on the Laplace´s law and on the elliptical shape of the ventricle, Buffolo (66) and Trainini (67), have developed a surgical technique for ischemic and dilated cardiomyopathy, named *pacopexy* (65). The advantages of this technique are 1) the preservation of the muscle by acting in an area without vessels limited by the descending and ascending segments that are far away from each other in heart failure, 2) the recovery of the elliptical shape, and, 3) the absence of implanted synthetic materials.

The results of the RESTORE study (7, 10, 63, 66) associating SVR to CABG in patients with antecedents of AMI, NYHA class III-IV, LVESV > 60 mL/m^2, regional asynergic LV circumference > 35% and EF < 35%, show a hospitalization mortality < 6% and a five-year survival between 68% and 89%, just needing re-hospitalization the 80% of the patients (7, 63). These results seems to be better than those published with isolated CABG which show five-year survivals lower than 60% with persistent signals of cardiac insufficiency in the majority of the patients (68).

Recently has been published the Hypotheses 2 of the STICH trial that is: if SVR when added to CABG would decrease the rate of death or hospitalization as compared with CABG alone (69). The results show that the association of SVR does improve neither the mortality nor the functional capacity. These results question the previous experience published of studies with thousands of patients and a very rigorous methodology, although they haven't been randomized studies (62, 63, 66, 67, 70, 71, 72). The reasons for these contradictions are due to some features of the STICH (69): a) Features of the patients with a 52% in class I-II of the NYHA, 49% with angina II-IV of the CCS, 13% without clinical history of previous acute myocardial infarction and 26% of patients didn't have significant lesions of the left descending coronary artery; b) The number of randomized patients was less than 20% of eligible patients. The 80% of eligible patients was treated with SVR because the clinical evidence of the superiority of this procedure; c) The surgical technique is crucial in determining the final result. In the STICH study took part 127 hospitals from 26 countries. The variability of the technique experience is shown by the scarce reduction of the LVEDV; if the 318 patients would be selected from Canada and West Europe, the benefits of SVR would be better (69).

4.3.5. Passive ventricular constraint

Passive containment is designed to provide diastolic ventricular support that helps to stop the progressive HF remodeling. As it reduced wall stress, it promotes down regulation of increased local neurohormonal activity and reduction of cardiomyocyte maladaptative gene expression (12, 73). The Acorn CorCap^{TM} is a mesh like jacket that is easily slipped around the heart and adjusted to provide ventricular support. It provides circumferential support to the heart, relieving wall stress while preventing further dilation without compromising beat to beat dynamics. The clinical studies in patients with idiopathic or ischemic DCM, associated or not to other procedures like CABG or restrictive mitral anuuloplasty (74), have demonstrated reduction in LVEDV and LVESV, improvement in EF, recover of an elliptical shape (74-76), and reversal of remodeling on a cellular

level (single myocyte studies) and on a molecular level (decrease in stretch protein levels, improvement in Ca^{2+} cycling and better NT-pro. BNP) (77). In acute infarct models, the Acorn CorCap™ device has shown limitation of infarct expansion, improvement of myocardial energetics and attenuation of the expression of cellular determinants of the remodeling process (73). However, long-term evolution of diastolic filling and ventricular contractility are not clearly improved with this approach. This fact represents a drawback for large clinical application.

4.4. Left ventricular assist devices (LVAD)

The most common indication for LVAD is as bridge to transplantation that represents 80% of all implants, whereas as destination therapy or as bridge to recovery are less frequents indications (78). The indications of LVAD according the INTERMACS levels to classify the stage D heart failure are (79) cardiogenic shock and patients declining the response to inotropes (INTERMACS levels 1 and 2). The goal is to rescue potential heart transplantation whereas destination therapy should be reserved for stable patients as an elective surgery. Heart transplantation and LVAD have shown to provide the greatest survival benefit at this stage of INTERMACS level 3. The criteria for LVAD implantation is considered if patient´s condition worsens, in patients with anticipated long waiting time to heart transplantation and as destination therapy in non transplant candidates. Although the quality of life of patients in INTERMACS levels 4, 5 and 6 is severely compromised, the right timing of LVAD remains an area of controversy.

Several risk factors have been identified to correlate with increased operative risk of LVAD and scores have been developed to predict the outcome of patients with LVAD as bridge to transplantation or destination therapy (80, 81). The patients with a Destination Therapy Risk Score < 16 achieved 1-year survival ranging between 71% and 80% (82, 83), superior to even those of medical therapy in the REMATCH study with 1-year survival of 28% (84). Outcomes for LVAD destination therapy in patients with chronic end-stage heart failure have improved in the post-REMATCH era. In groups of selected patients, 2-year survival may exceed that reported for heart transplantation in an older population (85). The emerging HeartMate II technology, using an axial-flow pump, illustrates the changes in technologies and the timing of destination therapy that shift to earlier stages of heart failure (86).

There is increasing interest in LVAD as bridge to myocardial recovery. It may be feasible to use LVAD to bridge selected patients to myocardial recovery, reducing the need for heart transplantation. LVAD induces LV reverse functional and structural remodeling. It was observed: reduction of total collagen content as well as collagen type I and III (87, 88); increase in adrenoreceptors and relocation of specific receptor subtypes with differences in the distribution of β_2 and α_1-receptors and in α_{1A} subtypes (88), disappearance of A-β_1-AAB (89), decrease of myocyte size (87, 88), decrease of intracardiac tumor necrosis factor-α, a protein capable of producing hypertrophy and fibrosis (87), increase in sarcomeric and non-sarcomeric cytoskeletal proteins (myosin heavy chain, sarcomeric actin, troponin C, αII spectrin, troponin T, cytoskeletal actinin and smooth muscle α-actin) (90), reverse of the increase of desmin and β-tubulin (91) and decline of natriuretic peptides (NT-proBNP, BNP, MR-proANP) (92, 93).

There is still much to be learned regarding optimal use of LVAD for ventricular recovery. The rate of recovery in patients with non ischemic cardiomyopathy receiving an LVAD is between 8% and 70% (89, 94-98). The actuarial survival rates are similar to transplanted patients, 90%-86% and 81%-77% at 1 and 5 years after explantation (94-96) and the quality of life is better than the transplant patients (99). The results indicate that, although recovery is seen in patients with myocarditis in a few weeks (100), patients with DCM need several months of LVAD before weaning (94). Studies of explanted human hearts have indicated that reverse remodeling is complete by 40 days and these data support the clinical results that waiting two months would capture half of the patients, and waiting up to three months would capture 80% of patients who would recover ventricular function followed by successful device removal (95, 101).

A short history of heart failure, less than three months (95), EF > 40% and LVEDD < 50 mm after LVAD (89), [are] favorable prognostic criteria for recovery. Identifying predictive parameters for possible recovery is difficult, without differences in pre-operative clinical and hemodynamic values. Except for the EF and LVEDD, no echocardiographic parameters have a predictor value in patients with the LVAD switched on. However, monitoring recovery prior the LVAD explantation is mandatory. Switching off the device for 15 minutes, followed by exercise under echocardiographic monitoring, is a safe procedure under full heparinization, and provides a method to assess the inotropic reserve (97). After weaning from LVAD, more than 80% of the weaned patients are freedom from recurrent heart failure (89, 94). An index of Liang (89) < 0 (prognostic index = - 10.1.0 + 0.2.08 x years of heart failure + 0.1.73x pre-explantation LVEDD in millimeters) is the best value to predict long-term heart function (89).

5. PERSPECTIVES

Heart transplantation is a consolidated treatment. Currently, more than 25.0.00 patients in the United States could benefit from heart transplantation. However, the donor pool limits the number to 2.3.00 per year (6). Furthermore, the incidence of heart failure and the disproportion with the number of heart donors makes necessary to restrict cardiac transplant to patients with no other treatment possibilities and develop alternatives such as CABG, treatment of mitral regurgitation, LVAD as destination therapy or bridge to recovery, SVR, regeneration therapy and immunoadsorption.

The percentage of patients with DCM weaning from LVAD is low and the strategy of combined LVAD

and pharmacologic therapy with the β_1 agonist clenbuteral used to stimulate physiologic hypertrophy has failed the initial expectations (104). On the other hand, HF patients (stage D and INTERMACS level 3 to 6) treated with cellular cardiomyoplasty showed limited improvements in systolic function and in ventricular remodeling, thus this treatment is insufficient for this HF population. Therefore, it is necessary to develop strategies designed to integrate biological and biomechanical approaches.

Based on the physiopathology of the stage D heart failure, and the preliminary results of the mentioned treatments, we are involved in the design and development of clinical trials that integrate biological and mechanical approaches. Some of these clinical trials are in a stage of clinical evaluation, while other trials are still in a stage of design, approval of the Ethic Committees or management of financing. The proposals to confirm our hypothesis are the following:

6. THERAPEUTIC PROPOSALS USING COMBINED PROCEDURES

6.1. Acute ischemic cardiomyopathy

In acute myocardial infarction (AMI), percutaneous coronary revascularization associated to intracoronary mononuclear bone marrow cells is a well-established treatment.

In AMI and cardiogenic shock, despite coronary revascularization, inotropes and IABP (INTERMACS level 1 and 2 of the stage D of heart failure) (78), the results of the "Refractory Shock post-AMI. AB5000 Registry", justify the indication of LVAD as a bridge to recovery. The 67% of the patients recovered and were weaning of the LVAD without transplantation (105). During the surgical procedure of LVAD implant, the association of tissue engineering with bone marrow CMP-cell seeded collagen matrix is a safe and feasible approach that could potentiate the benefit of the LVAD in terms of improvement of the systolic function and remodeling.

6.2. Chronic ischemic cardiomyopathy

Mitral valve regurgitation must be repaired. The objectives of surgical treatment (restrictive mitral annuloplasty or replacement with Buffolo technique) (57), are the correction of mitral valve regurgitation and the restoration of left ventricular geometry.

SVR (endoventricular plasty of Dor or the *pacopexy technique,* based on Torrent-Guasp´s model of the helical heart) associated to CABG is the technique of election in patients with previous AMI, NYHA class III-IV, LVESV > 60 mL/m^2, regional asynergic LV circumference > 35% and EF < 35%. It seems logic and feasible to propose the association of CCMP (cellular cardiomyoplasty) or CCMP associated with cell seeded collagen matrix to induce regeneration of the remaining myocardium. The immunoadsorption with fibrinogen membranes, instead IgG membrane, improves ischemia in patients with coronary chronic disease. This association of fibrinogen immunoadsorption is safe and feasible.

A second approach in patients with extremely dilated LV and morphology type III of Di Donato classification (106) can be passive ventricular constraint associated to CCMP and cell seeded matrix to add or replace SVR. The group of Chachques in Georges Pompidou Hospital (Paris) has demonstrated that in ischemic models, stem cells associated with a collagen matrix and Acorn CorCap ventricular constraint, improves EF and diastolic function, inducing also myocardial regeneration.

6.3. Idiopathic dilated cardiomyopathy

Mitral valve regurgitation must be repaired as in chronic ischemic cardiomyopathy, performing restrictive mitral annuloplasty or valve replacement with Buffolo technique (57). There is increasing interest in the reversibility of certain forms of end-stage heart failure during support with LVAD, but there is still much to be learned regarding optimal use of LVAD for ventricular recovery. A short history of heart failure and a limited dilatation of the LV are favorable predictors for LVAD as bridge to recovery:

In patients with a history of heart failure < 3 years and LVEDD < 60 mm, the proposition is LVAD as bridge to recovery associated to immunoadsorption and the possibility to add CCMP and cell seeded collagen matrix.

In patients with a longer history of heart failure or more dilated LV, the ventricular constraint Acorn CorCap associated to CCMP-cell seeded matrix should be added to the treatment with LVAD + immunoadsorption.

6.4. Chagas disease cardiopathy

Although heart transplantation has been successfully performed in Chagas disease, the infectious etiology demands to exhaust other approaches. The intracoronary delivery of mononuclear bone marrow cells has shown its efficiency with the improvement of the NYHA class, increase of the EF and decrease of LV volumes. The therapeutic strategy can be related to the benefit of associated surgical procedures:

In patients without mitral regurgitation and LVESV < 60 mL/m^2, the association of intracoronary cellular CMP with immunoadsorption, can potentiate the efficiency of each treatment.

In patients with severe mitral valve regurgitation and/or LVESV > 60 mL/m^2, immunoadsorption treatment can be associated with ventricular constraint Acorn CorCap + CCMP-cell seeded matrix. In addition, the correction of mitral regurgitation can be considered.

7. CONCLUSIONS

In conclusion, the number of donors that limits the activity of heart transplants performed annually has generated the development of alternative therapeutic approaches. There is an increasing interest in the reversibility of certain forms of end-stage heart failure and the application of biological procedures for the treatment of

these patients. The therapeutic strategies which integrate biological approaches with mechanical assist devices could offer hopeful treatment approaches. Great interest exists in the revival of Cardiac Bioassist procedures (108) (e.g.: latissimus dorsi dynamic cardiomyoplasty) and new devices are under development (e.g. Parachute intraventricular device). However, there is still much to be learned regarding the choice of strategies, optimal use and opportunities.

8. REFERENCES

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