1. Introduction

Heart failure is a complex syndrome characterized by a wide spectrum of clinical manifestations; multiple etiologies can lead to heart failure with many pathophysiological mechanisms [1,2].

Successful treatment of heart failure is challenging in view of the complexity of the syndrome. Multiple drugs may improve, but do not stop progression of the disease. Surgical procedures have been proposed for the treatment of heart failure, as an additional procedure for progressive heart failure after drug therapy has failed [3,4]. Heart transplantation is the treatment of choice for severe heart failure. However, its application is limited by donor shortage and selection criterion for heart transplantation. Other procedures have been proposed including cardiomyoplasty, partial left ventriculectomy, mitral valve surgery, and ventricular synchronization with pacemaker.

2. Cardiomyoplasty — technical procedure

The left latissimus dorsi muscle has been most commonly used in cardiomyoplasty. In summary, the latissimus dorsi muscle is wrapped around the left ventricle to contract in cardiac systole [5]. Electrical stimulation of the muscle with implanted electrodes is initiated approximately 2 weeks after the surgical procedure. Skeletal muscle fast fatigable type II fibers may be transformed into fatigue resistant type I fibers, after 6–8 weeks of chronic electrical stimulation. The addition of sequential electrical pulses leads to summation of skeletal muscle twitches, increasing the duration and force of contraction. The skeletal muscle may be paced synchronously to every cardiac beat in variable modes from 1:1 to 1:2 or to be turned off during sleep. An epicardial sensing lead is placed over either the left or the right ventricle and connected to the cardiomyostimulator placed in an abdominal subcutaneous or submuscular pocket. A period of 8 weeks is required to ‘train’ the muscle and a so-called vascular delay period of 2 weeks, which is the time between muscle mobilization and recovery of distal muscle blood supply from a single vascular pedicle. Only patients in a stable clinical condition can reasonably be put forward for cardiomyolasty as sicker patients are unlikely to tolerate this prolonged preliminary period. Factors related to surgery such as the acute and chronic electrical stimulation, and the surgical manipulation with ischemia to distal mobilized muscle could damage the latissimus dorsi muscle, with atrophy jeopardizing a successful outcome after dynamic cardiomyoplasty [6]. Expressive increment of creatinokynase enzyme levels with prognostic values that may occur in the immediate post-operative period after the cardiomyoplasty is evidence for surgical skeletal muscle flap ischemia and lesion [7]. The skeletal muscle flap ischemia may lead to partial or total suppression of the muscle flap contraction response to electrical stimulation. The preservation of the latissimus dorsi muscle may be important in the success of dynamic cardiomyoplasty [8]. Also, the muscle fiber type transformation in humans may not be as complete as that observed in animal experiments and associated to partial replacement by fatty tissue and fibrosis [9].
3. Potential mechanisms of action of cardiomyoplasty

Experimental and clinical studies have postulated that dynamic cardiomyoplasty may work as an active as well as a passive support of the damaged myocardium. The effects include, direct synchronized cardiac systolic assistance, reduction of left ventricular stress, change in left ventricular geometry, active or passive support, prevention of progressive ventricular dilation, partial replacement of the heart muscle, reduction of myocardial oxygen consumption, or an increase in blood flow to ischemic myocardium [10–15]. Improvement in the pressure–volume relationship with a better contractile state of the combined ventricular myocardium and wrapped latissimus dorsi muscle has been documented [7]. These effects could reverse some mechanisms of the remodeling process in heart failure. However, beneficial effects of cardiomyoplasty on other complex pathophysiological mechanisms such as increased neurohormonal activity, abnormal baroreflex/chimioreflex, pro-inflamatory process, endothelial dysfunction, hypertrophy, apoptosis, mitral or tricuspid regurgitation, atrial and ventricular arrhythmias, right ventricular function, and oxidative stress have not been well studied or described.

4. Selection criteria

Patients with chronic systolic congestive heart failure due to ischemic or idiopathic dilated cardiomyopathy in persistent New York Heart Association functional class III are candidates for cardiomyoplasty. Additional indices to support the indication are recurrent hospitalizations, peak oxygen consumption during exercise testing < 16 ml/kg per min, left ventricular ejection fraction < 30% (MUGA), cardiac index < 2.5 l/min per m² at rest, high left ventricular filling pressure, and stable condition on medical therapy enough to withstand a waiting time of 2–3 months before effective skeletal muscle flap adaptation or to survive the operation. Also, patients with left ventricular tumor or aneurysms are candidates for dynamic cardiomyoplasty.

5. Contraindications

Patients are not accepted for cardiomyoplasty in the presence of: intravenous inotropic drug support; hemodynamic or clinical instability or both; N.Y.H.A. functional class IV; severe valvular dysfunction; arrhythmia not controlled by medical therapy; resuscitation or sustained ventricular tachycardic episodes; major enlargement of left ventricle with left ventricular end diastolic diameter by echo > 5 cm/m²; chagasic cardiomyopathy; poor lung function with forced vital capacity < 55% of predicted value; drug or alcohol abuse; chronic atrial fibrillation; older age; syncope; irreversible excessive elevation of pulmonary vascular resistance; severe pulmonary hypertension; peak oxygen consumption < 10 ml/kg per min; thrombus in left ventricle; myocarditis; muscle disease; coexistent systemic illness with poor mid-term prognosis; morbid obesity; non-compliance with treatment; coexisting disease with high surgical risk or cardiac cachexia.

6. Risks of surgery

The post-operative intra-hospital mortality rate is between 0 and 23%. Medtronic worldwide experience demonstrates in-hospital mortality of 17% [16,17]. The most important factors associated with high immediate mortality are New York Functional Class IV; left ventricular ejection fraction < 10% (MUGA), and peak oxygen consumption during maximal exercise < 10 ml/kg per min. In the C-Smart study hospital mortality was 4%. The causes of in-hospital deaths are mainly related to primary ventricular failure, arrhythmias and surgical procedure [18]. Isolated cardiomyoplasty carries a mortality rate of up to 10%; however, it is associated with a mortality of between 20 and 30% when combined with coronary artery bypass, valvular surgery or other procedure.

7. Clinical effects of cardiomyoplasty

Several centers have combined cardiomyoplasty with aneurysmectomy, coronary artery bypass grafting, and valve replacement or repair, making improvement from the cardiomyoplasty procedure itself difficult to evaluate. Most previous trials of cardiomyoplasty have not compared in a randomized fashion the results of the operation with standard medical therapy for heart failure or cardiac transplantation. Non-randomized data suggest that cardiomyoplasty may improve functional class and quality of life, reducing the need for drug therapy. In the Medtronic Multicenter trial cardiomyoplasty improved the functional class in most patients [12]. Improvement in quality of life after cardiomyoplasty has been observed for daily activities, social activities, quality of interaction, and mental health. In addition, cardiomyoplasty improved physical activity, sleep pattern, food pattern, perception and expectations about the treatment.

Modest effects on left ventricular ejection fraction have been consistently reported in most clinical studies [19–21]. Regional left ventricular function im-
proved in anterolateral, apical, diaphragmatic and posterobasal regions [18]. It was observed that cardiomyoplasty may improve left ventricular diastolic function, reducing chamber stiffness and significantly decreasing Doppler E/A ratio [7,22]. Hemodynamical benefits are less consistent. Improvement in stroke volume and stroke work indices was observed, with a reduction in pulmonary pressures [23,24]. Improvement in stroke volume of between 20 and 30% was observed using stimulated and non-stimulated beats [25].

Cardiomyoplasty may improve peak oxygen exercise consumption and total exercise time in patients with a maximal exercise capacity of less than 14 ml/kg per min [26]. Evidence of the beneficial hemodynamic effects of cardiomyoplasty, with an increase in cardiac output and a reduction in pulmonary pressures has been documented at peak treadmill exercise test in patients with dilated cardiomyopathy [27].

The absence of completed randomized trials precludes conclusions about the influence of cardiomyoplasty on long-term survival in patients with heart failure. In a historical comparison of survival after cardiomyoplasty, heart transplantation or medical treatment, improved survival was observed after cardiomyoplasty compared with medical treatment, however, the survival rate was worse than that for heart transplantation [28]. The overall survival rates for cardiomyoplasty at 1 and 2 years range from 72 to 78%, and from 57 to 60%, respectively [12,29]. The late mortality is 5.5% each year and at 5 years the survival rate is approximately 40%. The causes of late mortality are mainly progressive heart failure and sudden death. Heart failure can be associated with many other factors such as progression of the underlying disease, evidence of skeletal muscle ischemia in the immediate post-operative period, late degeneration of the chronic stimulated latissimus muscle, and presence of precipitating causes of decompensation. Despite initial beneficial effects after cardiomyoplasty, fatty degeneration of the latissimus dorsi muscle and fibrous connective tissue replacement associated with progression of congestive heart failure was observed in patients on late follow-up [30]. Cardiomyoplasty does not modify atrial and ventricular arrhythmias. The risk of sudden death remains after cardiomyoplasty, even in patients with improved left ventricular function [31]. However, for patients in whom the cardiomyoplasty has failed, cardiac transplantation can be performed safely and successfully [32]. Recently, the first randomized study (C-SMART) comparing cardiomyoplasty with medical treatment, which planned to recruit 400 patients, was interrupted due to difficulty in recruiting patients [33]. Analysis of data from 51 patients who underwent cardiomyoplasty compared with 52 patients on medical treatment, demonstrated an improvement in a 6-min walk test distance, N.Y.H.A. functional class and some parameters of quality of life (Minnesota Living with Heart Failure) in the cardiomyoplasty group. There was no observed difference in survival (86% for cardiomyoplasty and 84% for medical treatment at 6 months), peak $V_O$, or in left ventricular ejection fraction improvement.

8. Limitations for cardiomyoplasty

Based on the selection criteria of candidates for cardiomyoplasty, the procedure may potentially benefit just a small percentage of patients with heart failure. Post-operative ischemia, the progression of underlying disease, and the reported fatty degeneration of the muscle and fibrous connective tissue replacement are all obstacles to long-term clinical benefits of cardiomyoplasty. The persistent risk of sudden death is a challenge to improve survival after cardiomyoplasty.

9. Future perspectives and directions

The main focus of research efforts to overcome the limitations of cardiomyoplasty should concentrate on the following: concomitant use of cardioverter/de-fibrillators and pacemakers, preservation of the latissimus dorsi muscle during surgery, improvement in surgical technique with less invasive procedures and reduction in the duration of surgery (mini-invasive techniques), the use of growth factors to enhance muscle vascularization, identification of stimulation protocols to optimize cardiac performance and preserve chronically the flap muscle and consequently changes in restricted criteria selection for a widespread indication. In addition, more basic science studies are required to improve clinical application of cardiomyoplasty.

10. Conclusion

In humans, heart failure is a complex syndrome with multiple clinical manifestations and pathophysiological mechanisms. Many different etiologies may lead to heart failure. Despite all basic research and various clinical investigations, the role of cardiomyoplasty in the treatment of heart failure remains unclear. The challenge for clinical application of cardiomyoplasty is that it is a major surgical procedure and the benefits obtained are limited. Based on available results of small clinical trials and of an interrupted randomized trial, cardiomyoplasty seems to be
a procedure for patients with moderately symptomatic heart failure. Randomized trials should provide answers to the question.

References


