EDITORIAL

## Skeletal Muscle - Cardiac Assist in the Americas

Research groups from North, Central and South America were invited to contribute to this issue of BAM on the subject of skeletal muscle - cardiac assist. It has been eight years since Carpentier and Chachques performed the first cardiomyoplasty in a human [1]. For the next couple of years after their first procedure relatively few cardiomyoplasties were performed. This is in contrast to heart transplantation, where following Christian Barnard's first heart transplant in December 1967, the number of heart transplants done worldwide increased rapidly with more than twenty were performed during some months. Enthusiasm for heart transplants, however, dwindled quickly because of problems with rejection. After 1968, there were only a few centers worldwide where heart transplantation was continued. With the introduction of cyclosporin in the early 1980s, which helped to suppress the rejection process, heart transplants again became a popular procedure for the treatment of endstage disease.
The number of heart transplants performed worldwide increased almost logorithmically during the 1980s. The next stumbling block, however for heart transplantation became a shortage of donors. Because of this, the number of heart transplants being performed has plateaued with about 2000 a year being done in the United States. The waiting list for such procedures has steadily increased so that at some centers, the wait for a heart transplant is currently approaching one year.
In contrast to heart transplants, the enthusiasm for performing cardiomyoplasty has steadily increased over the last five or six years at centers around the world. More than 300 have now been done worldwide, with the number of patients undergoing the cardiomyoplasty procedure each year almost doubling (see Fig. 1 in Furnary's study in this issue). Currently, Phase II clinical trials are being conducted under the supervision of the Food and Drug Administration in the United States, and Phase III clinical trials are expected to start soon. Phase III trials will likely involve as many as ten centers, and these trials will be randomized between medical treatment and cardiomyoplasty.
Despite the growing enthusiasm for cardiomyoplasty, the precise mechanism by which most patients are benefitted is still not fully understood. It is clear in some patients, that the stimulated skeletal muscle wrap actually assists left ventricular systolic ejection, as witnessed by improvements in left ventricular ejection fraction with stimulator On vs. Off and improvements in cardiac output with stimulator On vs. Off. Most patients who undergo cardiomyoplasty and survive the procedure improve one or more NYHA functional classes for heart failure. They feel better and frequently have dramatic improvements in their physical activity. Relatively few, however, have improvements in cardiac output and ejection with stimulator On vs. Off.
Is their improvement a placebo effect?
If the main effect of the latissimus dorsi muscle (LDM) wrap is to give the failing heart a squeeze each time it contracts, then one would expect to see an improvement in cardiac output and/or LV ejection fraction, particularly with stimulator On vs. Off in those patients who are symptomatically improved. Jatene, et al. are the only group to consistently report such clinical findings [5, 9]. In contrast, Delahaye et al. closely followed 11 patients with cardiomyoplasty and found similar improvements in symptoms for heart failure, like Jatene's patients, but no detectable improvement in cardiac output or LV ejection fraction [3]. Carpentier, Magovern and others have noted similar symptomatic improvements in their patients, yet only some have had improvements in cardiac output and/or LV ejection fraction [2, 4, 7, 8]. In this issue of BAM, both Braile and Almada report improvements in ejection fraction after cardiomyoplasty, but have not told us the differences with stimulator On vs. Off. Salmons has suggested that due to the geometry of the muscle wrap and its force-velocity contractile characteristics, the theoretical contribution to cardiac ejection fraction is likely to be small [11].
If we assume that the ventricles are not squeezed by the LDM during systole in most patients who have undergone cardiomyoplasty, then how are these patients benefitted? Could their improvement in symptoms be a placebo effect? In an acute study by Lee et al., another mechanism of action by which cardiomyoplasty benefits cardiac function is suggested [6]. The pressure-volume loops of the ventricle generated after

cardiomyoplasty indicated the myocardial wall stress was reduced, which would result in decreased energy demands of the myocardium. Recent studies of Nakajima, from our group utilizing a sheep LV infarct model to study the chronic effects of cardiomyoplasty indicate that the probable main effect of cardiomyoplasty in sheep with an infarct is active support of the geometry of the damaged heart by the LDM, which reduces wall stress and also prevents ventricular dilatation [10].

Some form of continuous stimulation of the LDM may be necessary in all patients undergoing this procedure to provide dynamic tone to the muscle. There have been numerous anecdotal reports at national meetings, where a patient was improved after cardiomyoplasty, but no difference in hemodynamics could be detected with stimulator On vs. Off, yet when the pacemaker system malfunctioned, the patient's heart failure symptoms worsened over several days and improved again after the pacemaker system was repaired [3, 4]. This could explain why some reports claim patients to be symptomatically improved when the graft is only stimulated at a 1:6 or 1:8 ratio with the heart [6]. The dynamic tone concept would also help to explain the results from other reports, including that of Almada et al. in this issue of BAM that claim symptomatic improvement in patients when the muscle graft was stimulated with only a single impulse [1, 7]. A single impulse would result in very little force being generated when compared with a burst of electrical stimuli [2]. In this issue of BAM, George et al. present a comprehensive review of possible mechanisms of action of cardiomyoplasty.

Does wrapping the LDM around the cardiac ventricles acutely impair LV diastolic function? This probably depends on how much the skeletal muscle is stretched when it is wrapped around the heart. If the LDM is stretched with much force during the muscle wrap, then intuitively one would expect to see both a slower rate of LV relaxation and a slower maximal rate of diastolic pressure decay, but probably less effect on LV systolic function. These issues are addressed in detail in this issue of BAM by Lazzara et al., who review both the clinical and experimental effects of the unstimulated right latissimus dorsi cardiomyoplasty on left ventricular function. Furnary and his associates, in this issue of BAM also review possible mechanisms of action of cardiomyoplasty and discuss future directions that this procedure may take, and in addition, discuss some of the limitations that have been placed on the development of this procedure by the FDA in the United States.

In this issue of BAM, Lavine et al. point out some of the difficulties in the assessment of cardiac function in patients after cardiomyoplasty. Dr. Blood and his associates present an excellent historical review on the indirect myocardial revascularization using skeletal muscle and other tissues. They indicate that one of the mechanisms by which the cardiomyoplasty procedure may benefit patients, particularly those with ischemic myocardopathy, is by improving the blood supply to the ischemic myocardium. Dr. Greentree and his associates from McGill University cover a subject that is beyond skeletal muscle transformation. In their review, they discuss the potential use of skeletal muscle satellite cells to replace damaged myocardium.

Isoda, from our group reviews a different approach to skeletal muscle cardiac assist, the use of skeletal muscle ventricles (SMVs). Although the results with skeletal muscle ventricles have been promising, this procedure has not yet been tested clinically. With this procedure, the latissimus dorsi muscle is used to form a separate pumping chamber as opposed to cardiomyoplasty, where the muscle is wrapped directly around the heart. These SMV pumping chambers have been connected to both the pulmonary and systemic circulations and used successfully to pump blood. In chronic experiments, SMVs have pumped blood effectively for more than two years. Currently, three issues need to be resolved before these pumps can be used clinically. First, there has been a 30% incidence of SMV rupture which occurs between the muscle and Dacron outlet cap of the SMV. Rupture occurs from the first to fourth week while these SMVs are pumping blood in the circulation. Recently, the incidence of rupture has decreased. In fact, the problem with rupture may even be solved, but longer follow-up is necessary in a larger number of animals before this can be determined. The second problem is that thrombus forms in some of the SMVs over time. Fortunately, the thrombus usually stays within the SMV and does not embolize. When thrombus occurs, usually it only involves a small portion (less than 5%) of the SMV pumping chamber. The third issue

that needs to be resolved before SMVs can be used clinically, is which configuration is best for connecting them to the systemic circulation. Should they be connected from the left ventricular apex to the aorta, from the aorta to aorta, or from left atrium to aorta? This issue is currently being evaluated.
In summary skeletal muscle cardiac assist research has come a long way during the last decade. Although cardiomyoplasty should still be considered an experimental procedure, clinical results to date are encouraging. If the number of cardiomyoplasty procedures continues to increase at the current rate, within another five years, more cardiomyoplastics will be performed each year than heart transplants. Skeletal muscle ventricles also show promise for treatment of heart failure, but are not yet ready for clinical use.

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