Skeletal Muscle Ventricles: a Potential Treatment for Heart Failure

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Abstract

Heart failure continues to cause major morbidity and mortality in the United States and worldwide. As operative techniques and immunosuppression have improved over the last several decades, orthotopic cardiac transplantation has become the preferred alternative for treatment of end-stage heart failure. However, a lack of an adequate supply of donors, the problems of chronic rejection, as well as continued high costs have kept the application of this procedure limited. This has fostered the development of several artificial devices, many of which are currently undergoing clinical trials. Rather than using an artificial mechanical device, our laboratory has developed and studied pumping chambers constructed from latissimus dorsi muscle which we term skeletal muscle ventricles or SMVs. This report will focus on two effective applications of SMVs- the diastolic aortic counterpulsator model and the left ventricular apex-to-aorta model.

Key words: muscles, heart failure, heart-assist device, transplantation.

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History

Beginning in the 1930's, several investigators grafted skeletal muscle directly to the surface of ischemic myocardium to attempt to promote vascular ingrowth [2, 13]. In the late 1950's, diaphragmatic muscle was wrapped around the descending aorta in an animal model and stimulated to act as a diastolic counterpulsator [6]. These muscles fatigued after a few minutes of stimulation. It was soon shown that the stimulation characteristics of the innervating nerve could influence the muscle fiber characteristics [3, 4, 14]. This knowledge made it possible to convert a fast-twitch (fatigue sensitive) muscle fiber to a slow-twitch (fatigue resistant) muscle fiber with repetitive stimulation.

Beginning in 1979, our laboratory began looking at the potential application of skeletal muscle to treat heart failure. We developed an implantable mock circulation device which was able to independently vary preload and afterload, and it was shown that SMVs were able to generate a work equivalent to approximately half of the native left ventricle. These pumping chambers were tested in small dogs and were also able to produce a flow rate of 464 ml/min with the afterload set at 80 mmHg and the preload set to 40-50 mmHg [10]. From these studies, it was concluded that these skeletal muscle chambers had the possibility of providing a large share of the work required to support the circulation.

Construction of Skeletal Muscle Ventricles

Although other investigators have used other skeletal muscles such as the rectus abdominis or gluteal muscles, our laboratory has focused on the use of the latissimus dorsi for SMV construction [5, 7, 15]. This muscle has the advantages of a single major neural and vascular innervation (the thoracodorsal nerve and artery, respectively) and an ease in harvesting. There is also no significant clinical detriment associated with its use.

The latissimus is a broad, flat muscle that originates at the proximal humerus and inserts onto the posterior thoracolumbar spinous processes and the lower ribs. In addition to the above-mentioned thoracodorsal nerve, the muscle receives some collateral blood supply from the overlying platysma muscle and the underlying chest wall. Initially, the muscle is mobilized through a flank incision that extends from the axilla to the eleventh rib. The collateral blood supply from the platysma and chest wall is divided. The thoracodorsal nerve is then isolated proximally, with care taken to avoid injury to it and its neighboring artery. A specialized pacing lead is then placed around the nerve and connected to an implantable stimulator. The muscle pouch is formed by wrapping the mobilized muscle around...
Figure 1. Construction of the pumping chamber. The latissimus dorsi muscle is fully mobilized and the neurovascular supply is isolated. An electrode is used to encircle the nerve, while the muscle is wrapped around a Teflon mandrel and attached to a Dacron sewing ring. The electrode is then connected to a temporary nerve stimulator for electrical preconditioning.

Skeletal muscle ventricle

A Teflon or plastic mandrel with a volume of 1.5 to 2 ml/kg and is encircled by a felt collar (figure 1). The muscle is sutured to the collar and to the chest wall to prevent migration. After a three week period to allow for recovery from ischemia caused by division of the collateral blood supply, the stimulator is activated to deliver a regular pulse at a rate of 40-50 per minute. This conditioning period is continued for 5 to 6 weeks. A second operation is then performed where the mandrel is removed and the SMV can be coupled to the circulation in a variety of configurations.

Skeletal Muscle Ventricles as Diastolic Counterpulsators

This is the most-studied configuration in our laboratory. The SMV is connected by means of a bifurcated Gore-tex (W.L. Gore and Associates, Inc, Flagstaff, AZ) tube graft to the descending aorta in two places. The aorta is then ligated between the limbs to obligate flow through the circuit (figure 2). The muscle is then stimulated to contract in cardiac diastole, which serves several beneficial purposes. First, blood is pumped proximally and distally from the descending aorta. Second, since the coronary arteries are perfused in diastole, the coronary flow is improved. Lastly, the relaxation of the chamber at the end of diastole provides for afterload reduction and decreases the work required by the heart to eject blood. These actions are

![Figure 2. Skeletal muscle ventricle in place as a diastolic counterpulsator. Two sensing leads have been placed on the myocardium and connected to a permanent stimulator to synchronize muscle contraction. Two conduits connect the SMV to the aorta, which is ligated to obligate flow through the circuit.](image)

![Figure 3. Electrocardiogram and femoral pressure tracing of one animal with the SMV connected as a diastolic counterpulsator. Data shown are at time of implant (A) and after twelve months of continuous pumping in the circulation (B). Dots indicate diastolic augmentation with muscle contraction.](image)
Skeletal muscle ventricle

Figure 4. Skeletal muscle ventricle in place in the left ventricular apex-to-aorta configuration. Valved conduits are used to connect the left ventricular apex to the SMV and from the SMV to the descending aorta. Sensing leads are placed on the myocardium to synchronize muscle contraction.

similar to those of the intraaortic balloon pump, which has been in clinical use for three decades.

Early investigators were able to show that circulatory augmentation with this model was possible. Mannion noted that preconditioned SMVs were able to provide a power output of $0.68 \times 10^7$ ergs in acute experiments [9]. This was approximately half the output of the left ventricle in the same animal. Later, Acker showed that SMVs were capable of pumping effectively in the circulation for up to eleven weeks [1]. The longest-surviving animals in this series, however, demonstrated multiple splenic and renal thromboemboli at autopsy.

Improvements in design allowed longer survival with less complications. Mocek reported in 1992 on a series of four dogs that survived for greater than six months with functional SMVs [11]. The longest-surviving animal lived for 836 days, but had evidence of thrombus formation in the chamber at the time of its death. Thomas then investigated the use of autologous lining (pleura and pericardium) within the SMV chamber as a method of decreasing the incidence of thrombus formation. Although there was no thrombus formation seen in either the experimental or the control group (without autologous lining), the lined group had a significantly lower incidence of chamber rupture (63% in the control group vs. 0% in the lined group) [20]. They concluded this lining improved the structural integrity of the chamber. One of these animals is currently living.

Figure 5. Representative tracing from one animal with a skeletal muscle ventricle in the left ventricular apex-to-aorta configuration at implant and at 3 days post-op. Effective diastolic counterpulsation is achieved. There is also effective left ventricular unloading, as demonstrated by the reduction in the area under the left ventricular pressure curve following relaxation of the muscle pump. ECG - electrocardiogram. SMV = skeletal muscle ventricle. LV = left ventricle.
The most effective configuration of cardiac assistance studied involves connecting the SMV from the left ventricular (LV) apex to the descending aorta with two valved conduits. The afferent valved conduit carries blood from the LV apex to the SMV while the second conduit carries blood from the SMV to the descending aorta (figure 4). This model has potential advantages over the diastolic counterpulsation model. The series of valved conduits protect the SMV chamber from a high systemic pressure. With these valves functional, there is a substantial period of time during the cardiac cycle when the pressure inside the SMV approximates the left ventricular end-diastolic pressure. This provides better blood supply to the layers of the muscle, which may otherwise be compromised by high intraluminal pressure. The close proximity to the left ventricle also provides very effective unloading properties, thus reducing the work requirement of the native heart. Lastly, the model does not require ligation of the descending aorta, which would be advantageous in patients with atherosclerosis or calcified aorta.

Lu from our laboratory has reported on acute studies with this model in which the SMV pumped 47% of the cardiac output initially (the remainder being ejected through the aortic valve) and 40% after three hours of pumping blood in the circulation [8, 12]. Mean diastolic pressure was also very effectively augmented, with an increase of 58% initially and 73% at three hours. The left ventricular tension-time index (an indirect measurement of left ventricular oxygen consumption) was decreased by 25% initially and by 26% at three hours. This indicates that a substantial portion of the work required to maintain the circulation effectively was being performed by the SMV. A representative data tracing from one of these animals at implant and again at three days post-op is shown in figure 5. Recently, design modifications have made survival beyond the acute setting possible. Five animals have survived with functioning SMVs from 10 to 76 days, and it is likely that with continued refinement of construction techniques long-term survival similar to that found with the diastolic counterpulsation model will be achieved. Figure 6 demonstrates maintenance of diastolic pressure augmentation in one of these animals.

Conclusion

Skeletal muscle pumps offer an attractive potential alternative for the treatment of end-stage heart failure. The problems of donor availability and the necessity for long-term immunosuppression, which are an inherent problem with cardiac transplantation, are avoided. Previously, thromboembolism and rupture have been major obstacles, however continued progression of our research, including the addition of autologous lining and continued evolution of our operative model have largely overcome these problems. Clinical application of this technology may only be a few years away, and may someday provide an attractive and effective treatment for end-stage heart failure.

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References