

Accessory Skeletal Muscle Ventricles for Circulatory Support: Early Experience with SMV's in Continuity with the Circulation

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Abstract

Skeletal muscle ventricles were constructed in five dogs by wrapping the latissimus dorsi muscle around a mock circulation device which allowed performance of volume work during a six week conditioning period of pulse-train stimulation via a direct 360 nerve cuff electrode. In a second survival operation, the SMV was interposed into the descending aorta in a configuration obligating all flow to pass through the SMV. A specific interrupted, pledgeted suture technique was developed to accomplish a secure anastomosis between dacron inflow and outflow conduits and the SMV. No lining other than the native fibrous tissue inside the conditioned SMV was used, thus exposing the SMV directly to the bloodstream. Good diastolic augmentation was accomplished in all cases, with survival up to one week. Histologic examination of the blood-SMV interface revealed only a thin layer of thrombus lining the "pseudo-intima" of the SMV.

Key words: Skeletal Muscle Ventricle.

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Congestive heart failure is a health care problem of tremendous proportions affecting millions of people. Approximately 100,000 patients per year die in the United States of end-stage heart failure [1]. Several promising therapeutic modalities have been developed beyond conventional methods to deal with this burgeoning problem. Transplantation offers significant promise, however the number of donor organs appears limited to a maximum of 2000 per year. As well, orthotopic transplantation can be complicated by cellular rejection and opportunistic infections which limit the long-term survival. The artificial heart, while theoretically attractive, is still in its developmental stages with infections and thromboembolic events complicating early clinical implantations. [2]

Skeletal muscle, on the other hand, offers a biologic alternative to assist the failing heart. Skeletal muscle has been demonstrated by a number of investigators to perform volume and pressure work in mock circulatory systems [3]. These advances have been based upon the basic observation that skeletal muscle can be transformed to perform "cardiac-like" fatigue-resistant work when subjected to continuous low frequency stimulation over six weeks. These transformations have been demonstrated by biochemical and microscopic markers [4].

The potential applications of skeletal muscle to assist the failing heart are multiple. In the cardiomyoplasty procedure, muscle is directly applied to the heart to assist in contractions [5]. In the aortic counterpulsation procedure, the muscle is wrapped around the ascending aorta and stimulated to contract during diastole. This technique has been shown to increase coronary perfusion pressure and therefore augment coronary blood flow [6].

Perhaps the most promising potential application has been the creation of a neo-ventricle which functions as a ventricular replacement or circulatory assist. A few authors have reported sporadic success in survival experiments placing these neo-ventricles in continuity with the descending aorta [7]. Acker et al utilized a PTFE bladder to line the muscle tube, thus exposing the graft material to the blood. Thromboembolic events were common in this series leading to morbid complications in 33% of animals. Anastomotic complications at the SMV - conduit anastomosis led to fatal hemorrhage in 50% of the animals.

In this paper, we present our early experience with accessory skeletal muscle ventricles placed in continuity with the circulation. These experiments were performed with latissimus dorsi muscle which was conditioned to perform volume work over a 6 week period. The ventricles were connected to the descending aorta without inner chamber linings using a specific interrupted pledgeted suture technique for anastomosis of the inflow and outflow conduits to the skeletal muscle ventricle. Each of these maneuvers served to address important problems identified in previous studies to improve the potential for direct cardiac replacement or assistance by skeletal muscle ventricles.

Methods

Creation and Training of Skeletal Muscle Ventricles

Five mongrel dogs underwent creation of skeletal muscle ventricles (SMV) during a preliminary procedure under general anesthesia (Halothane 5%) with endotracheal intubation. The left latissimus dorsi muscle was taken down from its thoracic and humeral attachments. The proximal thoracodorsal

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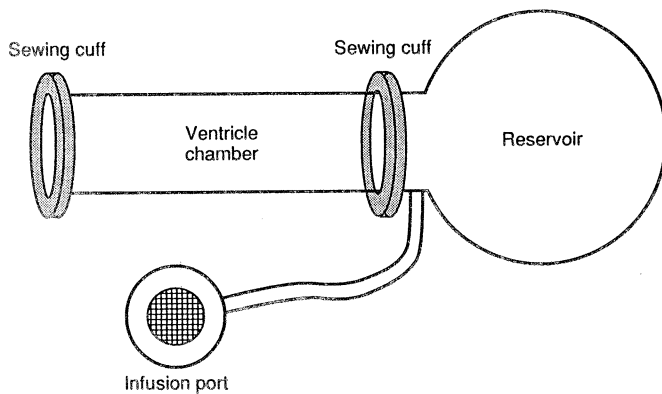


Figure 1. Mock circulation device.

sal nerve was isolated and a 360° nerve cuff was placed around the nerve and secured to the underlying muscle with care not to injure the nerve. The muscle ventricle was then fashioned by wrapping the muscle around the mock circulation device (Dow Corning), securing the muscle to the proximal and distal teflon sewing cuff with interrupted nonabsorbable suture (see figure 1). The muscle was wrapped two and one half times around the mock circulation device. One animal had a pouch SMV created by wrapping the muscle around the mock circulation with only one sewing cuff.

The mock circulation device is a silastic system constructed to provide a bladder chamber filled with sterile water which ejects into a bulb reservoir when the muscle ventricle is stimulated to contract. During relaxation, the ventricle chamber is automatically refilled by the reservoir. At the time of ventricle construction, mock circulation volumes, resting chamber pressures, and average pressures during contraction were obtained to construct a pressure volume relationship for all ventricles.

After the muscle ventricle was constructed, an Itrel programmable pacemaker (Medtronic, Inc. Neuro Division, Minneapolis, MN) was implanted in a subcutaneous pocket to chronically stimulate the muscle ventricle. Pacing parameters were set to provide a low frequency stimulation to induce muscle fiber transformation. After a two week healing period, nerve stimulation was initiated with pacing parameters as follows: the duty cycle was set with a 210 msec. on phase, followed by a 2 sec. off phase; burst frequency was 10 hz, pulse width was 150 micro secs. with an initial voltage of 1 to 1.5 volts. Voltages were adjusted to provide contraction of the muscle chamber as assessed by daily palpation. The conditioning program continued for a scheduled six weeks with incremental changes in the pacing parameters to increase the number of muscle contractions per minute by decreasing the on and off stimulation time. The SMV was able to contract approximately 70-80 times per minute by the completion of training.

Diastolic Counterpulsation in Continuity With the Circulation

At the completion of the conditioning period, the animals were prepared for connection of the SMV in continuity with the circulation. Each animal was pre-treated with 325 mg of aspirin to minimize potential thrombus formation. The animals were intubated, ventilated, and anesthetized with Halothane and Phenobarbital. A femoral pressure line was inserted to monitor systemic perfusion pressure. The skeletal muscle ventricle was dissected within the subcutaneous pocket with care not to disrupt the thoracodorsal nerve and the vascular supply to the muscle. An antero-lateral thoracotomy was performed through the fifth intercostal space and the descending aorta was isolated with care not to disrupt the intercostal vessels. Test occlusion of the descending aorta was performed using a side-biting vascular clamp to ensure adequate peripheral perfusion to maintain an average pressure of 50 mm Hg. Double velour dacron grafts were then anastomosed end-to-side with 5-0 prolene sutures to the proximal and distal aorta. These grafts were then brought out through small thoracotomy incisions two rib spaces above and below the thoracotomy. Additional rib resections were performed when necessary to prevent kinking of the grafts. The mock circulation system was removed from the skeletal muscle ventricle to prepare it for anastomosis to the dacron grafts. An interrupted, pledgited suture technique with 2'0 Ethibond was then utilized to perform the SMV graft anastomosis. (See Figure 2)

The grafts and SMV were flushed to prevent thrombus formation and air embolism and the system was allowed to fill in continuity with the circulation. After hemostasis was obtained, the descending aorta was ligated by an umbilical tape between the proximal and distal anastomoses in order to obligate flow through the accessory system. (See Figure 3) Test stimulation of the SMV via the thoracodorsal nerve cuff was then performed and the amplitude of diastolic augmentation was recorded from the femoral pressure tracing. A screw-in left ventricular electrode was then implanted to sense the left ventricular EKG. This left ventricular sensing electrode was then connected to an SP 1005 Cardiomyostimulator (Medtronic, Inc.) and counterpulsation was synchronized to occur in diastole. A chest tube was placed in the left thoracic cavity and the thoracotomies were closed with care not to occlude or kink the Dacron conduits. The Cardiomyostimulator and SMV were placed in the subcutaneous pocket and the skin incision was closed in layers. The animals received transfusions of whole blood as necessary during the perioperative period. The animals were extubated when awake and able to ventilate adequately. Postoperative pain control was facilitated by intercostal nerve blocks with Marcaine (2%) injection prior to closing the thoracotomy. The chest tube was removed within eight hours when chest drainage decreased. Anti-platelet therapy was continued in the postoperative period (325 mg ASA/daily).

Results

Pressure-Volume Relationships

During the preliminary procedure to create the skeletal muscle ventricle, the filling volumes, static pressures and contraction pressures generated by the SMV were measured by the mock circulation infusion port (see Figure 4). The pre-contraction volume represents the preload on the skeletal muscle

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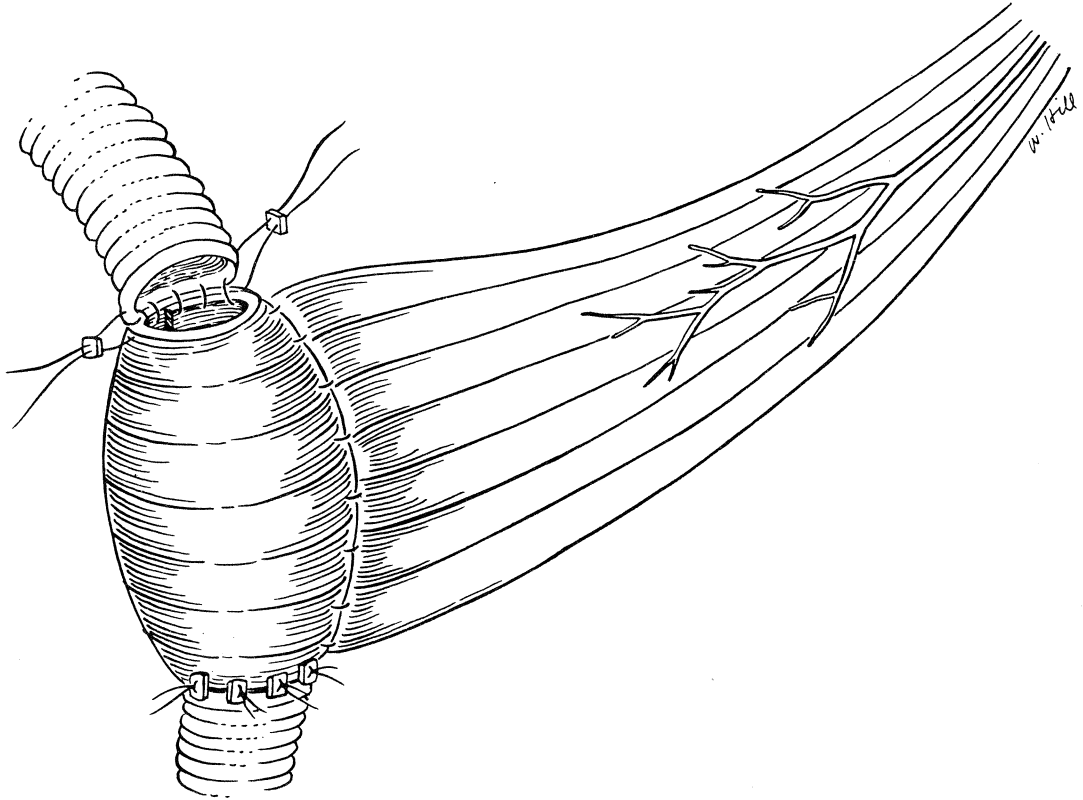


Figure 2. Interrupted, pledgeted suture technique for Dacron conduit-SMV anastomosis.

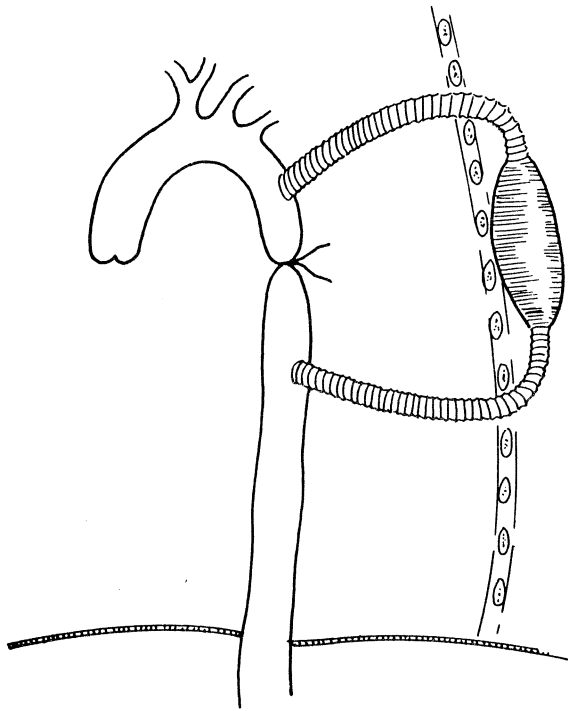


Figure 3. Skeletal muscle ventricle in continuity with the circulation.

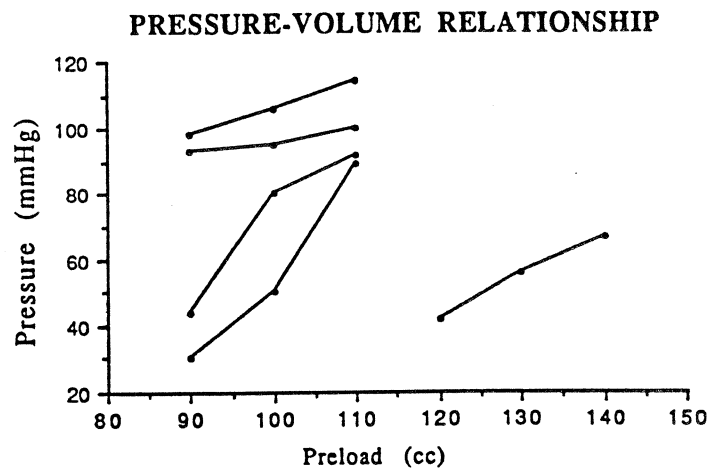


Figure 4. Pressure-Volume relationship of skeletal muscle ventricles.

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fibers. As the preload increased, the pressure generated by the SMV increased consistent with the Frank Starling principles.

Skeletal Muscle Ventricle Connection to the Circulation

The skeletal muscle ventricles were connected to the thoracic aorta without technical problems, however there was a modest blood loss when the anastomoses were checked and the grafts were flushed. After hemostasis was obtained, the SMV-Dacron conduit anastomosis was performed with an interrupted, pledgetted 2'0 Ethibond suture technique similar to that used for a valve prosthesis. Each skeletal muscle ventricle demonstrated excellent diastolic augmentation by femoral arterial tracings (See Figure 5). This augmentation was achieved by stimulation of the thoracodorsal nerve with an average amplitude of 2 volts, a pulse width of 150 microseconds and a 25 Hz electrical burst. The SP1 005 Cardiomyostimulator provided SMV stimulation synchronized with the EKG at a ratio of 1:2 or 1:3. Two of the five animals survived beyond the immediate postoperative period for 4 and 7 days respectively (see Table 1). The SMVs in each animal functioned until their deaths. These two animals expired secondary to hemorrhage at the SMV-conduit anastomosis without plegeted technique. Each episode of hemorrhage occurred after the animals became more active in their runs. Three dogs did not survive beyond the post-operative period because of respiratory complications. Respiratory function was improved in later experiments with intercostal nerve blocks for better pain control.

Pathology

On gross examination, the skeletal muscle ventricles were composed of two concentric layers of hypertrophied muscle with relatively normal architecture. There was a fibrous connective tissue layer interspersed between the muscle layers and between the muscle and the lumen. The inner surface of the SMV was a smooth, white layer which covered the muscle uniformly. Examination of the tube SMVs at the time of animal

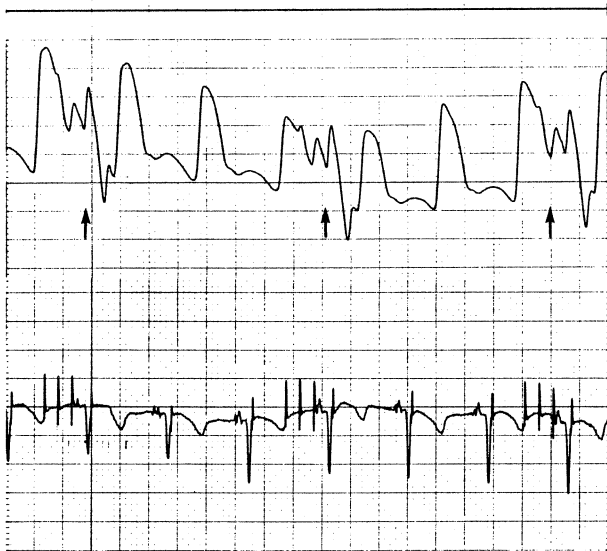


Figure 5. Femoral pressure tracing demonstrating diastolic augmentation.

death demonstrated no significant thrombus formation in the inner ventricle chamber. The pouch SMV did, however, have a concentric layer of thrombus adherent to the inner surface at the blind end. There was no evidence of thrombus formation in the Dacron grafts or in the native aorta at the time of examination. Each of the specimens was thoroughly sectioned. Slides were prepared and stained with hematoxylin and eosin. These showed a thin layer of red blood cells and fibrin thrombus on the inner most aspect of the SMV chamber. Surrounding this innermost membrane was a foreign body type of intense inflammatory response characterized by histiocytes and fibroblasts (see Figure 6). Surrounding this inflammatory response was a dense layer of scar with organization consistent with the six to seven weeks duration of the structure. The concentric layers of muscle demonstrated essentially normal histology on the hematoxylin and eosin stained slides. A fibrous connective tissue layer between the muscle layers had the histologic appearance of fascia rather than of scar.

Discussion

Congestive heart failure leads to significant morbidity and mortality throughout Europe, South and Central America and the United States each year. Conventional therapy to treat the patient with end-stage cardiac failure is often inadequate. Higher levels of therapy including mechanical circulatory support may offer some improvement in cardiac function, however, long-term support has not been easily obtained. Potential cardiac replacement either by cardiac allotransplantation, xenografting or the total artificial heart holds significant promise, but their application is limited by donor organ shortage, imperfect immunosuppression, opportunistic infections, and rejection. The total artificial heart is still in its developmental stages.

Skeletal muscle augmentation of the failing heart is a concept which has been explored by several investigators during the past 25 years. The recent surge of excitement in this field has been stimulated by observations about the "plasticity" of skeletal muscle, which can be "transformed" to perform cardiac-like fatigue resistant work [8]. This transformation occurs in an orderly, well documented fashion under the influence of chronic low frequency stimulation of the nerve trunk supplying a particular muscle. During the training period, metabolic changes occur in the muscle consisting of an increase in enzymatic activity for aerobic metabolism. After long-term stimulation, the maximum velocity of muscle fiber shortening is significantly reduced and these changes are consistent with measurements of calcium-activated myosin ATPase activity. A number of ultrastructural changes occur accompanying these physiologic and biochemical changes, which lead to the development of a muscle flap able to assist the failing heart [4].

A second major advance has been the development of the pacing technology necessary to stimulate skeletal muscle, led by Dr. William W. L. Glenn and associates at Yale. Our experience with artificial stimulation of the diaphragm has led to the realization that stimulation of the skeletal muscle requires a train of stimuli rather than the simple single stimulus required for cardiac pacing. [9] This burst-train stimulation leads to a controlled summation of muscle contraction suitable for cardiac assistance.

Carpentier was among the first to apply these concepts in clinical investigations performing the "cardiomyoplasty" procedure to assist the failing left ventricle in 1985 [10]. These

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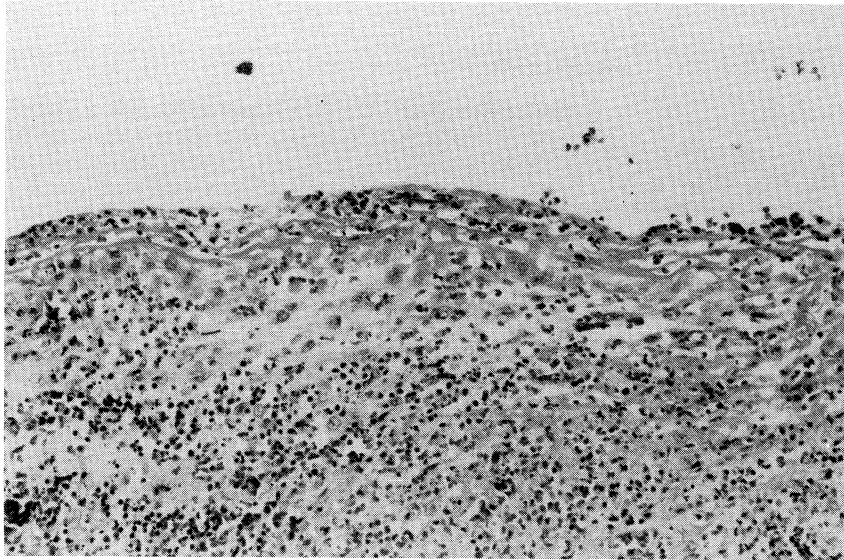


Figure 6. Microscopic view of innermost membrane with intense inflammatory response.

cardiomyoplasty procedures continue to be performed by his group and a few other specialized centers [11]. The creation of a "neo-ventricle" to provide assistance or even to replace the heart would represent a more advanced realization of the potential use of skeletal muscle to assist the heart.

A number of studies in this area have demonstrated that transformed skeletal muscle can perform pressure and volume work in mock circulation systems for extended periods of time [12,13]. In 1987, Acker and associates reported their experience in 5 mongrel dogs who had skeletal muscle ventricles created and placed within the arterial circulation for several weeks [7]. These ventricles did not undergo conditioning prior to hook up, however, they did provide diastolic counterpulsation for up to 11 weeks. In our series, the muscle was conditioned prior to connection in the circulation.

The mock circulation device allowed the ventricle to perform pressure and volume work. The pressure within the system during relaxation simulated diastolic pressures and preload volume. As the volume within the mock circulation was increased, the pressures generated with contraction were increased consistent with the Frank Starling principles. When the

ventricles were connected to the circulation, they were able to provide excellent diastolic augmentation. The muscle ventricles were indeed fatigue resistant with sustained diastolic augmentation throughout the experimental period as demonstrated by muscle contraction until the death of the animals.

The inner membrane of these ventricles exposed to the blood elements is of paramount importance. In other studies, these ventricles were created with a Dracon graft sewn to the inner ventricle chamber. This eventually led to thromboembolic events from thrombus which formed on the Dracon material. In our ventricles, no inner graft material was sewn in place prior to connection to the circulation. We did, however, find a smooth glistening, whitish, inner tissue layer when the mock circulations were removed. In the two animals who survived for 5 and 7 days with the SMV in connection with the circulation, there was no evidence of gross thrombus formation except for a thin layer of red cells and thrombin seen histologically on the inner muscle layer. There was no evidence of distal emboli or thrombus in the Dracon grafts. This inner layer of the SMV appeared to be an intense inflammatory response to

Table 1. Accessory Skeletal Muscle Ventricles: Early Experience with SMV's in Continuity with the Circulation.

Animal	Procedure	Augmentation	Cause of Death
1	pouch SMV	good	exsanguination at 6 days; muscle functioning well
2	tube SMV	good	died at 10 hrs due to respiratory failure; muscle functioning well
3	tube SMV	good	exsanguination at 5 days muscle functioning well
4	tube SMV	good	died at 15 hrs secondary to respiratory failure; muscle functioning well
5	tube SMV	good	died at 5 hrs secondary to respiratory failure; muscle functioning well

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the mock circulation characterized by histiocytes and fibroblasts.

Extended survival experiments with this inner membrane exposed to the blood elements will be necessary to determine the long-term interaction of this lining with the blood. The pouch SMV did have thrombus at its blind end, however, there was no evidence of distal emboli in this dog either.

Long-term survival in most series has been limited by thromboembolic events and anastomotic disruptions at the SMV-conduit anastomosis. We did not observe any significant thrombus in our tube SMV nor did we find any evidence of emboli on postmortem study. Fatal hemorrhage at the anastomotic suture line was a significant problem in our preliminary experiments, but during the course of these studies, we developed an interrupted pledgetted suture technique which greatly reduced the number of anastomotic problems. This technique was similar to that used for valve surgery and involved full thickness suture placement through the SMV wall incorporating the inner "pseudo-intima".

Respiratory complications were also an important factor limiting extended survival in our experimental animals. It was evident in the postoperative period that certain dogs did not tolerate the thoracotomy and rib resections on the same side very well. In spite of intercostal blockade with long-acting local anesthetics and postoperative pain control, they did not demonstrate normal respiratory mechanics throughout the postoperative period. On postmortem examination, the left lung was noted to be atelectatic in some cases. In the future, it may be appropriate to stage the procedures by placing the conduits on the skeletal muscle ventricle and placing it into the thoracic cavity through a small rib resection at the preliminary procedure. This would allow a healing period for the rib resections and decrease the operative time of the second "hook up" procedure.

Summary

We report our early experience in 5 mongrel dogs who underwent creation and training of a skeletal muscle ventricle. These ventricles were placed in continuity with the descending aorta for circulatory support in survival experiments. The ventricles were conditioned to perform volume work using a fluid-filled mock circulation system. All ventricles provided effective diastolic augmentation in a fatigue resistant manner throughout the experiments. A pledgetted suture technique was developed to prevent anastomotic bleeding complications in the post-operative period. The SMV were constructed without artificial inner chamber materials exposed to the blood elements and there were no thromboembolic events.

These preliminary results confirm the potential benefit of skeletal muscle ventricles in support of the failing heart. We are presently investigating additional applications of this model in survival experiments including direct left ventricular systolic support and right ventricular assistance using a right atrial to pulmonary arterial accessory conduit with interposed skeletal muscle ventricles.

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