MINIREVIEW

Skeletal Muscle as a Myocardial Substitute

(43232)

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During the past few years there has been an intense worldwide interest in the use of skeletal muscle for cardiac augmentation. To date, more than 100 patients have undergone cardiomyoplasty. The latissimus dorsi muscle is wrapped around the heart and stimulated with a special pacemaker to contract in synchromy with the patient's own failing heart.

We have used a different approach for skeletal muscle cardiac augmentation. Ventricles have been constructed from the latissimus dorsi muscle, connected to the aorta, and then used as diastolic counterpulsators. At present, one dog's skeletal muscle ventricle (SMV) has been pumping blood in the circulation for more than 1 year. There has been no evidence of thromboembolism. This dog is in good health and has no tubes or wires crossing the skin. Thus, the two methods that are currently being investigated for skeletal muscle cardiac assist are cardiomyoplasty and the construction of separate muscle pumping chambers.

History

DeJesus (1) in 1931 was probably the first to use skeletal muscle for a cardiac substitute. He used it to replace a partial defect in the heart from a traumatic injury. Other early investigators in the use of skeletal muscle as a replacement for myocardium were Leriche and Fontaine (2) and Beck (3). Petrovsky (4–6) used skeletal muscle to repair left ventricular aneurysms. The muscle was not stimulated to contract; therefore, any symptomatic improvement was due only to a reduction in paradoxical wall motion rather than an active contribution from the muscle graft.

Kantrowitz and McKinnon (7), in 1959, reported experiments where canine diaphragm was wrapped either around the cardiac ventricles or the descending thoracic aorta. The ventricular wrap had no apparent effect on the mean aortic pressure when the muscle was stimulated to contract around the heart. However, a rise in mean arterial pressure did occur when the muscle wrapped around the aorta was stimulated. The effect lasted 15 sec before fading to control levels, presumably due to fatigue. Following Kantrowitz's lead, many others experimented with skeletal muscle cardiac assist. Among those were Nakamura and Glenn (8) and Sheppard, (9) both of whom conducted experiments in which muscle was wrapped around the right atrium or used to replace a portion of the free wall of the right ventricle. The results were disappointing. In these early studies, it seemed that fatigue was an insurmountable obstacle.

Salmons and Vrbova found that chronic electrical stimulation would effect a change in the fiber population of a muscle (10). Where a muscle was composed of a mix of slow-twitch (Type 1) and fast-twitch (Type 2) fibers, chronic electrical stimulation would, over a period of about 6 weeks, effect a total transformation to a uniformly slow twitch (Type 1) population of fibers. Such muscle showed an increase in capillary density, enzymes of oxidative metabolism, and mitochondrial volume fraction. There was also a switch from the synthesis of fast to the synthesis of slow isoforms of myosin (11). All of these changes resulted in an increased resistance to fatigue. While the electrical stimulus continued the changes in the muscle persisted. It seemed that it might be possible to exploit this phenomenon for skeletal muscle cardiac assist (11–15).

The cardiac myocyte is profoundly fatigue resistant due to a highly efficient aerobic metabolism. A similar efficiency in energy utilization was observed when chronically stimulated skeletal muscle was examined using phosphorous nuclear magnetic resonance (16). The increased resistance to fatigue is attributed to an increased capacity for oxidative phosphorylation linked

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to the increased mitochondrial volume. The decline in phosphocreatine and the rise in ADP and inorganic phosphate usually seen in muscle fatigue was absent. This ability of muscle to adapt to chronic electrical stimulation is essential if skeletal muscle is going to provide continuous cardiac assist.

Another factor critical to a muscle's working efficiency is blood supply. Most attempts to use skeletal muscle for cardiac assist require the muscle to be mobilized on a principal neurovascular pedicle with division of collateral blood vessels. This reduces perfusion of the muscle, making it more fatigue susceptible. Work by Mannion and his colleagues (17, 18) has shown that after ligation of collaterals to the latissimus, there is a recovery of blood supply over the next 3–4 weeks to a level near normal. This period of 3–4 weeks, known as the vascular delay period, is important in the prevention of severe fatigue.

Muscles to Use

Early work concentrated on the diaphragm (7–9) since this was a flat powerful muscle lying in close proximity to the heart. It is accustomed to regular contraction, and so it was thought to be a good candidate for fatigue resistance in a more active setting. Its disadvantage is that while healthy experimental animals tolerate loss of the diaphragm well, the same would not necessarily by true of patients in heart failure. Also, the diaphragm has not shown greater fatigue resistance than other skeletal muscles (19). The use of other muscles, such as the rectus abdominis and the pectoralis major, is limited because they do not have a single major blood and nerve supply, making stimulation via the nerve difficult (20). The most popular muscle at present is the latissimus dorsi which is large, powerful, and nonessential. It has a single major blood supply and a single nerve, making both mobilization and stimulation of the whole muscle relatively easy.

Methods of Use

Systolic Augmentation. The actively contracting muscle may either assist the systolic function of the heart or augment diastole. At present, systolic assist can be achieved by three methods. The first two have been applied clinically.

Substitution technique. The muscle can be used to replace a defect in the wall of the ventricle (3, 4, 8, 9, 14, 20–25) or conceivably to enlarge a hypoplastic ventricle in certain forms of congenital heart disease. Since muscle is so thrombogenic, a thromboresistant surface should be interposed between the ventricular cavity and the muscle. Most of the experimental work has centered on replacing the right ventricle (9, 21–24), although left ventricular aneurysms have been replaced (26). It has been hard thus far in either an experimental or clinical setting to see convincing evidence of cardiac output augmentation by this method.

Reinforcement technique. The muscle can be wrapped around the cardiac ventricles and stimulated to contract synchronously with the ventricle, thereby assisting ventricular ejection (Figs. 1 and 2). This method, termed cardiomyoplasty, has been used clinically in more than 100 patients around the world. Many of the patients have had an improvement in cardiac failure symptoms (27). However, there have not been collective data showing this improvement to be due to an increase in the left ventricular stroke volume. Experimental results have been equivocal (28, 29). Chagas et al. (30) have recently demonstrated experimentally that propranolol-induced heart failure could be improved by cardiomyoplasty. These experiments conducted in dogs were acute studies not exceeding 15 min of continuous stimulation.

We are not aware of any experimental study showing prolonged improvement in chronic heart failure by this method. Nevertheless the clinical improvement cannot be denied, and so this technique deserves continued attention.

Although the precise role of cardiomyoplasty is uncertain, an important report has recently appeared from San Paulo, Brazil (31). Of 29 patients with dilated cardiomyopathy, 13 underwent cardiomyoplasty and 16, who refused the procedure, continued to receive medical treatment. Although this was not a randomized trial, the two study groups were comparable in other respects. Ten of the 13 patients experienced an im-

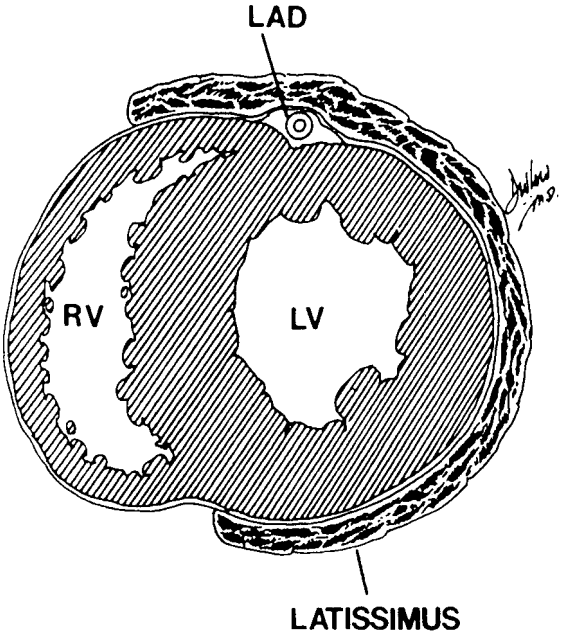

Figure 1. Drawing of cross-sectional representation of the muscle graft as it overlies the left ventricle (LV) and a portion of the right ventricle (RV). LAD, left anterior descending coronary artery (reprinted with permission from Circulation **78**(suppl III):III–181, 1988).

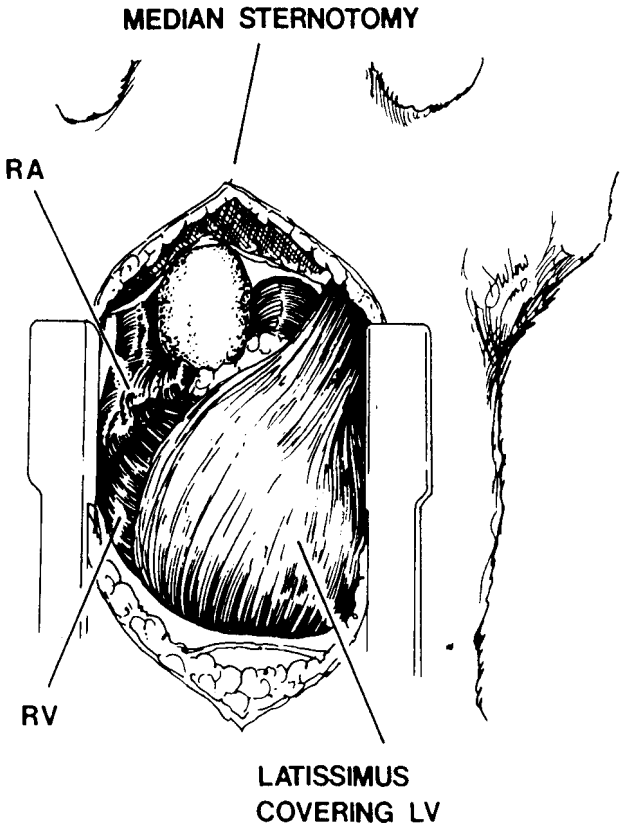

Figure 2. Drawing of muscle graft covering the canine heart as depicted through a midline sternotomy (reprinted with permission from Circulation **78**(suppl III):III–182, 1988).

provement in functional status following cardiomyoplasty (by New York Heart Association classification) and an increase in mean left ventricular ejection fraction of about 30%. However, of particular interest was the finding of improved 18-month actuarial survival in the cardiomyoplasty group, compared with those treated medically (80% vs 31%). This is the first study to suggest such a survival advantage.

Skeletal muscle ventricle. The muscle may be shaped into a pouch known as a skeletal muscle ventricle (32). SMV have been used experimentally for cardiac assist (33, 34). The main problem has been to increase SMV compliance so that it can operate at physiologic preloads. Work from our laboratory has addressed this problem. By introducing stretch during the vascular delay period, it has been possible to make SMV which perform useful cardiac type work at low filling pressures (35). In acute experiments SMV were used to supplant the native right ventricle (34). Cannulas were placed in the inferior and superior vena cavae such that all systemic venous return was routed through the SMV which pumped into the pulmonary artery. With the SMV switched off, blood flowed passively to the lungs and the animal became hypotensive. On activation of the SMV there was an immediate rise in blood pressure. Aortic blood flow could be maintained at approximately 80% of normal over a 4-hr period with SMV contraction. During this period, the CVP rose by 6–7 mm Hg, remaining within the physiologic range. Recently, we have had two animals survive beyond 10 weeks using a right ventricular SMV assist system.

Diastolic Augmentation. Aortic diastolic augmentation, better known as aortic counterpulsation, has been widely used clinically for the last 15 years to support the failing heart, especially in the setting of heart failure after open heart surgery. The device that is most commonly used is the intra-aortic balloon pump. The balloon is inserted into the descending thoracic aorta, usually through the iliac or femoral artery. Then the balloon is connected to a catheter and its inflation and deflation is controlled by an external console. Helium gas is used to inflate the balloon. The balloon is removed after the patient's own cardiac contractility has recovered, which is typically 2 or 3 days after its insertion. About 50% of patients who could not otherwise be weaned from cardiopulmonary bypass can be weaned with the aid of the intra-aortic balloon pump. The counterpulsation works in three ways to benefit the heart. First, blood is pumped when the balloon expands and forces blood in both directions up and down the aorta. Second, since the coronaries are perfused during diastole, there is an increase in coronary blood flow caused by the pumping action of the balloon during diastole. Finally, and most important, the balloon deflates during systole; therefore, when the failing heart contracts, it is pumping against the balloon as it deflates, thus causing a decrease in afterload. Therefore, less work is needed to eject the same

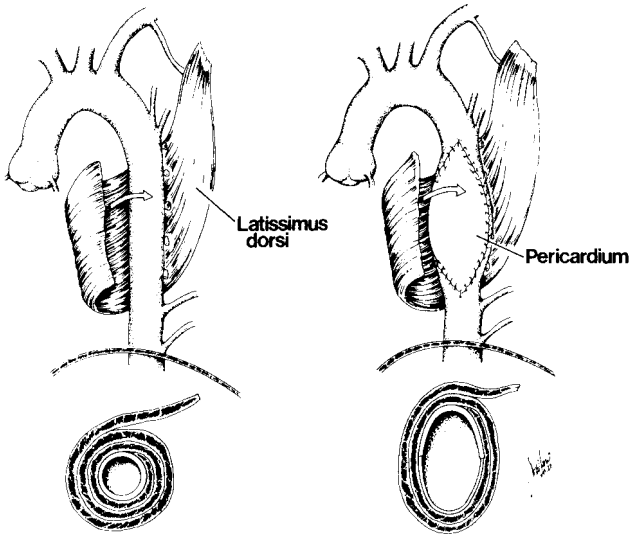

Figure 3. The muscle is fully mobilized and introduced into the thorax where it is wrapped around the descending aorta after division of a number of intercostal branches (left). The aorta is enlarged to increase the volume of blood that is compressed. Pericardium or any flexible material can be used (right).

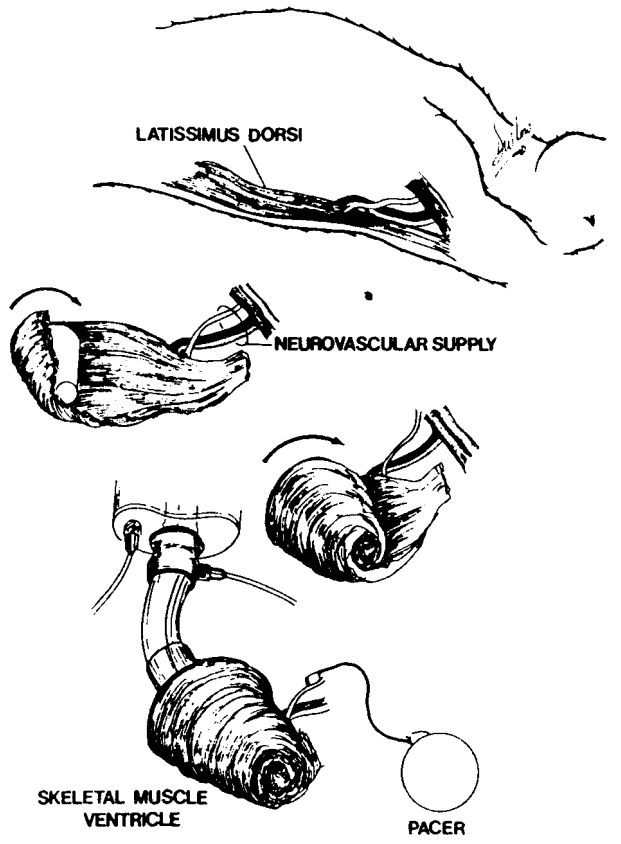

Figure 4. Construction of the SMV (reprinted with permission from The Journal of Thoracic and Cardiovascular Surgery **00**:734, 1990).

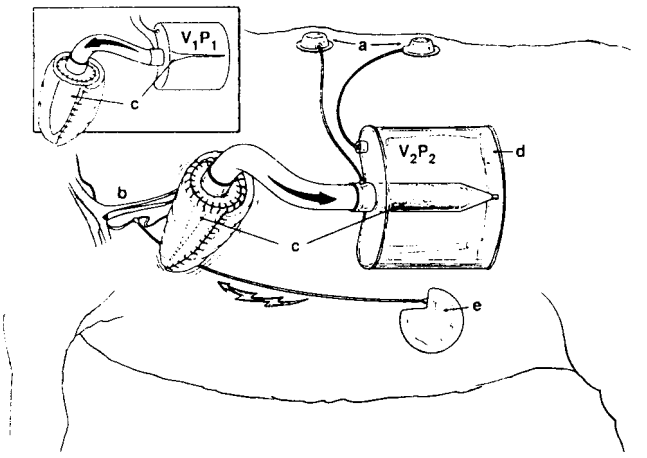

Figure 5. Diagram showing the SMV mock circulation system. The inset depicts the SMV during diastole; the main figure depicts the SMV during systole. a, vascular access ports; b, neurovascular bundle; c, bladders; d, pressurized cannister, e, electrical stimulator. The cannister had a fixed volume (V_1; between 155 and 175 ml) determined for each device at the time of construction. At completion of the contraction of the SMV, the air within the cannister had a new, smaller volume (V_2) and a new higher pressure (P_2). Since V_1 was known, and both P_1 and P_2 could be measured directly, V_2 could be determined according to Boyle's law ($P_1V_1 = P_2V_2$ at constant temperature). The ambient atmospheric pressure was added at both P_1 and P_2 so that:

$$V_2 = V_1(P_1 + P_{atm}) \cdot (P_2 + P_{atm})^{-1}$$

The stroke volume of the SMV was simply $(V_1 - V_2)$·(reprinted with permission from The Journal of Thoracic and Cardiovascular Surgery **00**:000, 1990).

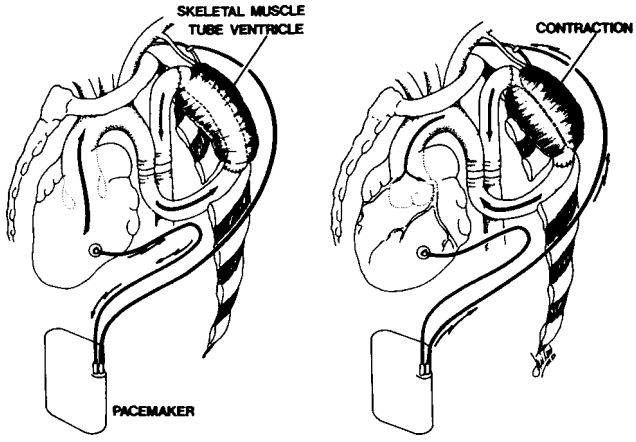

Figure 6. Skeletal muscle tube ventricle.

amount of blood and therefore less oxygen is consumed (36). The aortic diastolic counterpulsation concept is one of the techniques that has been used with the skeletal muscle ventricles.

The latissimus dorsi muscle can be left *in situ* except for its humeral insertion which is reimplanted on the first or second rib. A bladder is inserted under the muscle next to the chest wall (37). This bladder is linked to the aorta such that contraction of the muscle compresses the bladder which displaces a volume of blood in the aorta. The system may have a pneumatic or hydraulic link to the displacement chamber placed in series with the aorta. Alternatively, blood may be allowed to fill the bladder directly. This system has the advantage of avoiding extensive muscle dissection and division of collateral blood vessels to the muscle and is technically simple to perform. However, the system is mechanically inefficient, and any hydraulic or pneumatic drive will absorb energy. We know of no prosthetic biocompatible material which will contain gases or fluids on a long-term basis; using the presently available materials the system would need regular "top up." Allowing the blood to enter the bladder directly introduces major risks of thrombosis.

The muscle may be fully mobilized and wrapped around a bladder connected to the circulation as described above (38, 39). This is mechanically more efficient in transmitting a longitudinal force into compression, but has the same potential drawbacks of thrombosis and energy loss.

Kantrowitz and McKinnon (7), in their original work in this field, wrapped the muscle around the descending aorta. The advantages of this method are that it avoids the risk of thrombosis and dispenses with any need for an indirect drive system. The main drawback is that the volume of blood displaced depends on

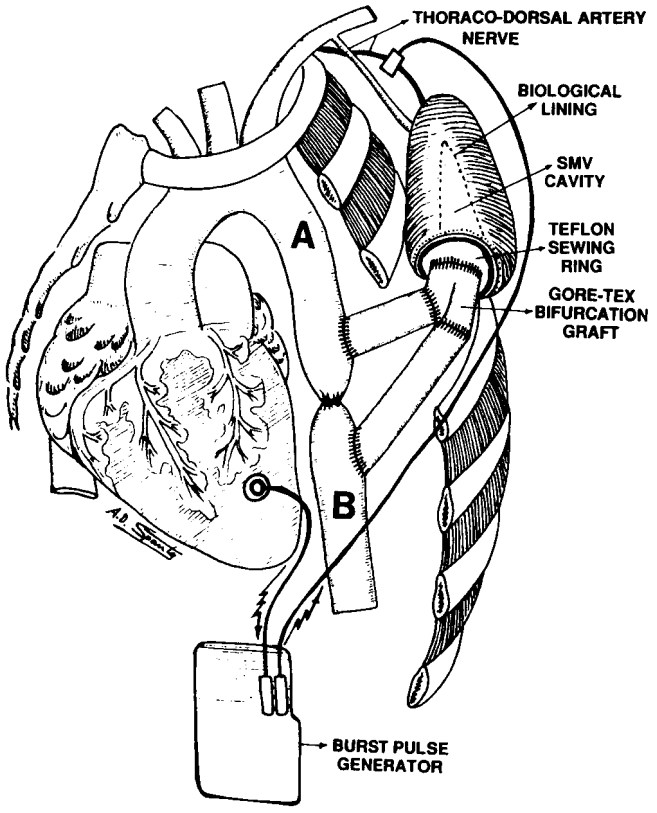

Figure 7. Diagram of SMV configuration. The SMV is on the outside of the chest wall. The limbs of the bifurcation graft have been divided, tailored, and rejoined to prevent kinking. Flow probes were placed around the aorta at points A and B.

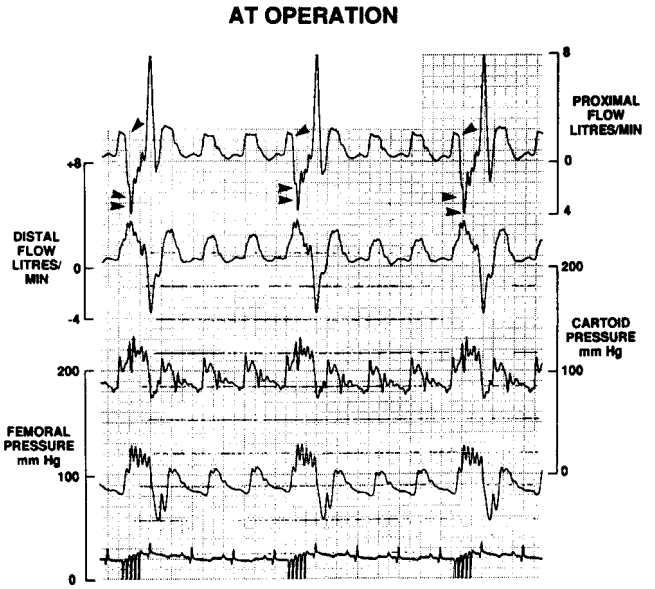

Figure 8. Recordings of ultrasonic flow and pressure taken at operation in the longest surviving dog. Topmost trace is flow measured at point A (Fig. 1) and demonstrates a sudden cutoff in the flow curve of the cardiac ejection (single arrowhead) when the SMV begins to contract and then reversal of blood flow toward the aortic arch (double arrowheads). Below that is flow at B (Fig. 1) showing increased distal aortic flow followed by passive reflux. Below, the carotid and femoral pressure traces show the increase in diastolic pressure as the SMV contracts. The burst of stimuli activating the thoracodorsal nerve can be seen superimposed on the ECG at the bottom.

the length and diameter of aorta encompassed. It also depends on the width of the muscle. In order to maximize the length, several sets of intracostal branches must be divided, and this may cause spinal ischemia. Volume may be increased by enlarging the aorta using an inlay patch (Fig. 3). Many of the patients needing cardiac assist have degenerative calcified aortas not suitable for rhythmic compression or enlargement.

In our laboratory SMV are constructed by wrapping the latissimus dorsi muscle around a Teflon mandrel to create a muscle pouch or tube (12). The mandrel is removed after a period of 3–4 weeks (Fig. 4). This allows for recovery of blood supply, formation of adhesions between the layers of the muscle wrap, and development of a smooth inner lining (32.

Experimental development of SMV. In our initial canine experiments we electrically preconditioned the SMV after the vascular delay period, so that the SMV would be totally transformed into a slow, fatigue-resistant muscle before performing cardiac work. In acute studies these conditioned SMV were connected to the descending thoracic aorta and stimulated to contract during cardiac diastole (40). These SMV were capable of generating significant pressures (110 ± 1.5 mm Hg) and outputs (330 ± 10 ml/min), which for several hours approximated 20% of the total cardiac output. Anemia, hypoxia, and hypotension eventually caused deterioration of SMV function in these acute studies.

To determine whether SMV were capable of continuous and chronic work in an awake animal, we constructed SMV and connected them to a totally implantable mock circulation device. No tubes or wires crossed the skin barrier (Fig. 5). The animals moved about freely without apparent discomfort or locomotor deficit.

This system allowed independent control over preload (filling pressure) and afterload (resistance the SMV pumped against). Measurement of pressure and flow could be obtained independent of the circulation (41). The SMV, which had been electrically preconditioned, pumped continuously against a pressure of 80 mm Hg with a preload of 40 mm Hg at a rate of 54 times/min for up to 9 weeks. After 2 weeks of continuous pumping, the systolic pressure generated by the SMV was 104 ± 1 mm Hg, and fluid displacement was 206 ± 16 ml/min.

In a subsequent experiment, we found that electrical preconditioning was not absolutely necessary for SMV to perform sustained work. Six SMV were constructed, allowed a period of vascular delay, but not electrically conditioned (42). After 2 weeks of continuous pumping into the mock circulation, these SMV, without the benefit of electrical preconditioning, gen-

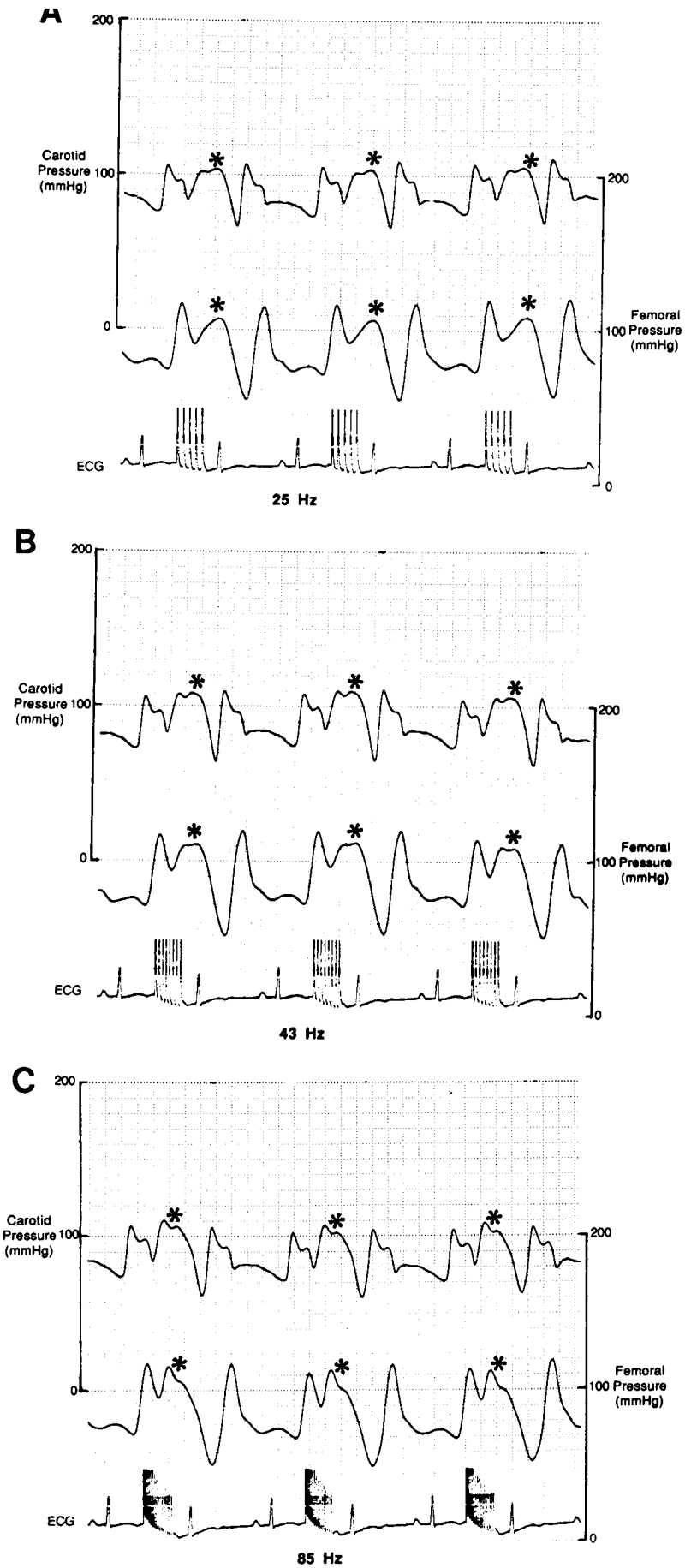

Figure 9. Arterial pressure and electrocardiogram traces taken at 1 year in the dog reported in Figure 8 whose SMV had been pumping continuously in the circulation for that length of time. Arterial pressures and electrocardiograms at pulse trains of 25, 43, and 85 Hz are shown in A, B, and C, respectively. Asterisks mark diastolic augmentation. The synchronization ration is 1:2. The stimulator was set chronically at an R-wave delay of 175–250 msec, burst duration of 185–240 msec, 25-Hz burst, 2.5-V voltage, and 2:1 mode synchronization ratio (varying from 1:4, 1:3, or 1:2 depending on the native heart rate).

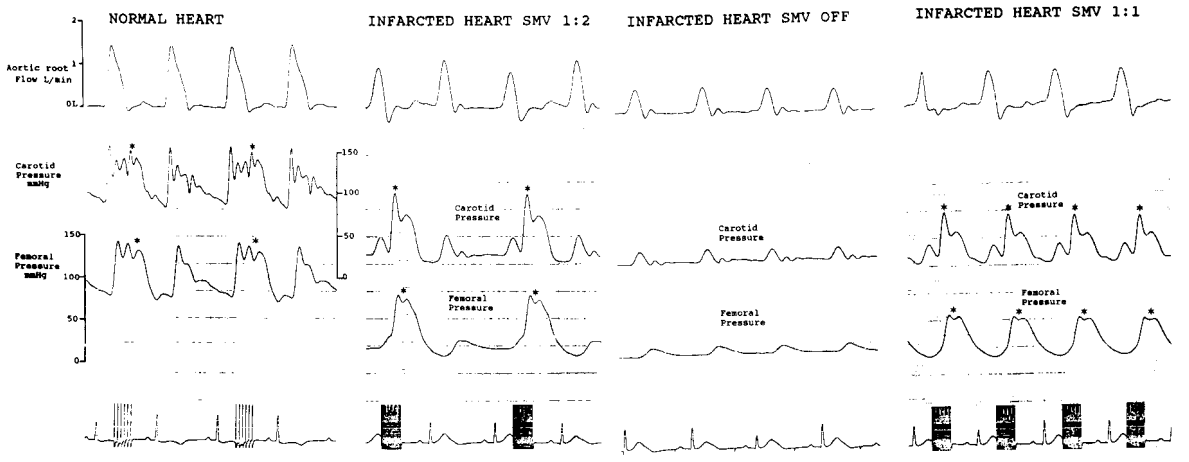

Figure 10. Pressure and flow tracing from one dog before and after introducing myocardial infarction. There is a drop in pressure and aortic root ultrasonic flow. In 1:2 ratio there is increased velocity and volume of flow of the ejection following SMV contraction. Diastolic blood pressure is augmented (*) to exceed the cardiac systolic pressure. With the SMV off, there is a severe drop in stroke volume and systolic pressure. When the SMV is activated at 1:1, both the stroke volume and pressure increase.

erated stroke work of 0.04 ± 0.014 J at the baseline settings (25 Hz, preload 40 mm Hg, afterload 80 mm Hg). When the burst frequency was increased to 85 Hz at the same preload and afterload, the stroke work increased to 0.078 ± 0.04 J (excluding one SMV that generated stroke work of 0.205 J). This compares favorably with the measured stroke work of the canine left and right cardiac ventricles of 0.183 and 0.022 J, respectively (38). The results described above indicated that canine skeletal muscle could perform continuous work while simultaneously undergoing adaptive transformation. Although the SMV pumped continuously against the mock circulation at preloads of 40 mm Hg, significant stroke work was produced at physiologic preloads as low as 10–20 mm Hg. This suggested that it might be possible to construct SMV with a compliance similar to that of the left ventricle (42).

Next, SMV that pumped blood within the systemic circulation were tested for several weeks. The skeletal muscle ventricle was modified to a flow-through design and connected to the descending thoracic aorta with an interposition graft (Fig. 6). The SMV were stimulated to contract synchronously during cardiac diastole (43). The SMV was stimulated via its motor nerve using an implantable prototype R-wave synchronous burst stimulator. Awake dogs tolerated these contracting SMV well and ambulated without apparent difficulty. No tubes or wires crossed the skin.

This configuration provided effective diastolic augmentation over periods of up to 11 weeks but failure was eventually due to either rupture of the aortic anastomoses or to renal failure. Even though the SMV had been lined with the relatively thromboresistant polytetrafluroethylene, thromboembolism was responsible for the renal failure.

Subsequent SMV have been lined with autogenously derived tissues in hopes of finding a more thromboresistant surface (44). SMV were linked with a free graft of autogenously derived pericardium or pleura (Fig. 7). As a control, some had no specific lining other than the normal fibrous reaction induced by the Teflon mandrel over a 3- to 4-week period. These SMV were cone shaped. After a 4-week delay, but without electrical preconditioning, they were connected to the descending aorta using a Gore-Tex bifurcation graft.

The aorta was ligated between the two limbs of the graft such that there was obligatory flow of blood through the SMV. When the SMV contracted, blood was ejected both cephalad and caudad (Fig. 8). The SMV were stimulated to pump continuously as diastolic counterpulsators. Pressure and flow measurements were made at operation and then at regular intervals over the survival periods. The SMV were examined for function and evidence of thrombus using ultrasound. Presently, one animal continues to do well after 1 year with no ultrasonic evidence of thrombus in the SMV, no clinical evidence of thromboembolism, and good diastolic augmentation (Fig. 9).

No dog has shown clinical evidence of thromboembolism or renal dysfunction. We are presently unable to conclude that any one autogenous lining has an advantage over the others. The surviving dog continues to demonstrate a 25% or greater increase in peak diastolic pressure at the standard stimulation setting. The increase in pressure correlates with increased blood flow as determined by Doppler interrogation at the femoral artery.

Heart Failure Experiment

The experiments described above were conducted in the context of a normal heart. As yet no study has been reported on the effect of chronic SMV counterpulsation in the context of heart failure. An acute heart

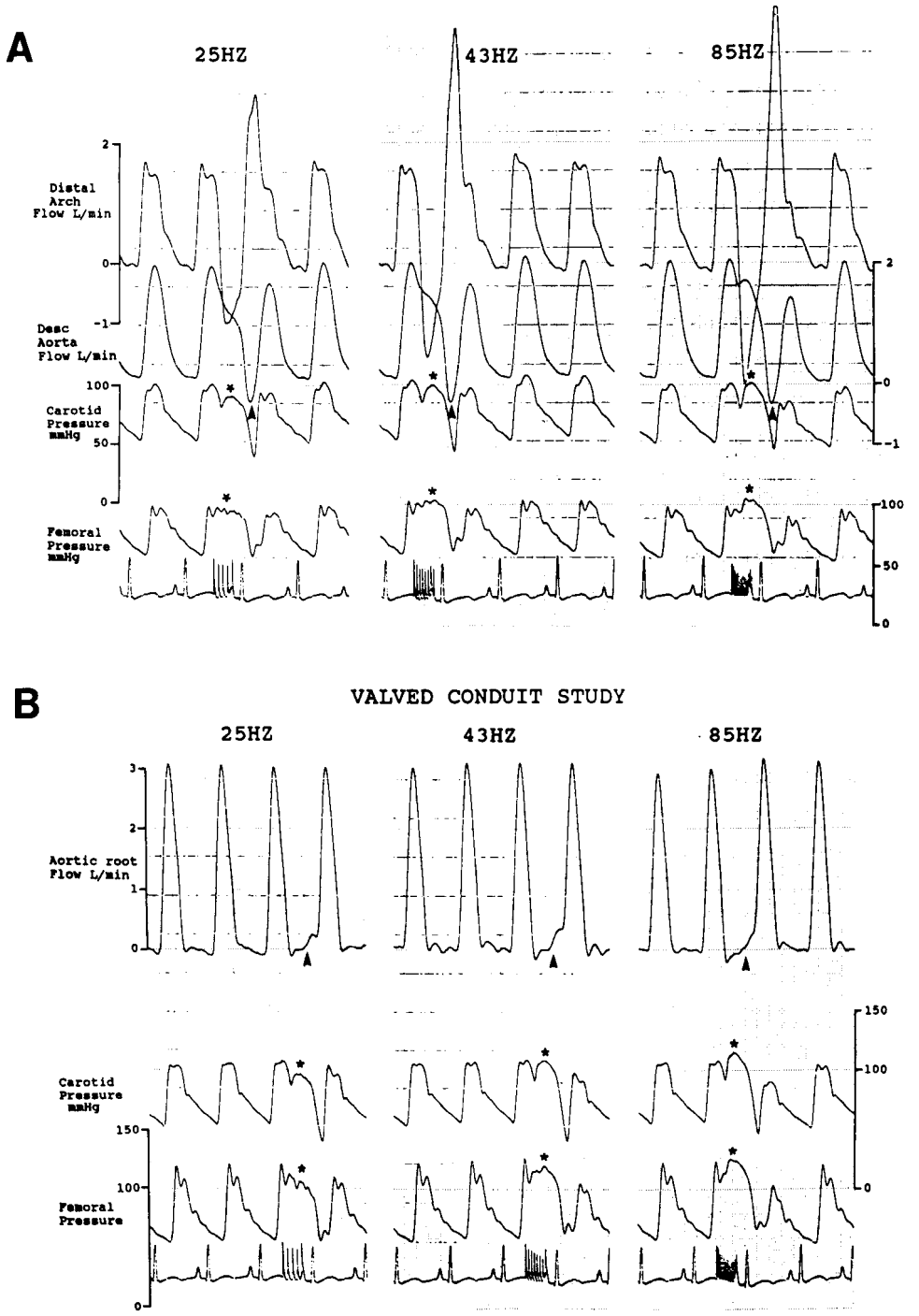

Figure 11. (A) An aortic homograft valve has been placed in the limb of the bifurcation graft leading to the distal aorta. Diastolic pressure augmentation (*) is similar to that seen in Figure 8 but the relative volume of reflux (arrowheads) from the distal aorta is much less. The increased velocity and volume of forward flow in the distal arch can also be seen. This increases as the intensity of the stimulation frequency increases, possibly indicating greater offloading of the left ventricle. (B) The aortic root flow shows presystolic flow (arrowheads).

failure experiment was performed in a dog whose SMV had been pumping continuously for 7 weeks, producing very effective diastolic augmentation. A terminal experiment was performed where blood pressure was recorded in the femoral and carotid arteries. Ultrasonic flow probes were placed around the aorta, above and below the SMV and also around the aortic root, just above the coronaries. The aortic root probe gave a beat to beat measure of cardiac output. Baseline measurements were made and recorded (Fig. 10). The left anterior descending coronary artery was cannulated near its origin and then embolized with 30-μm microspheres. This caused generalized infarction in the distribution of the artery and prevented reperfusion from

collaterals. There was a profound drop in systolic blood pressure to approximately 40–50 mm Hg coinciding with a dramatic reduction in cardiac output as observed by the aortic root flow probe (Fig. 10). The SMV was then switched on and an immediate rise in systemic blood pressure was observed due to a greatly enhanced diastolic pressure (up to 100 mm Hg). The cardiac output also rose, confirming cardiac assist. (Compare aortic root flow in third panel with fourth panel [Fig. 10].)

Valved Conduit Experiment

An aortic homograft valve was placed into the outflow limb of an SMV (i.e., that leading to the distal thoracic aorta). This meant that the SMV could refill only from the proximal limb instead of receiving some refluxed blood from the distal aorta. This experiment was conducted in an animal with a normal heart. Enhanced afterload reduction was demonstrated as evidenced by increased volume and velocity of blood flow in the proximal aorta after an augmented diastole (Fig. 11). At the same time, presystolic flow was observed at the aortic root which we believe is further evidence of afterload reduction and cardiac assist. This experiment indicates that the efficiency of the SMV can be increased in the aortic diastolic counterpulsation mode by placing an efferent valve.

Summary

Although skeletal muscle currently offers a realistic means for providing functional support of the failing myocardium, more research is required to define the optimal mode of assist. The mechanism by which cardiomyoplasty augments cardiac function is unclear, although symptomatic improvement following the procedure is being increasingly reported.

Skeletal muscle ventricles, on the other hand, have the potential to replace left ventricular function and have pumped effectively in the circulation for more than 1 year. With continued improvements in SMV design, the future for this mode of support is optimistic. The efficacy of some other forms of circulatory support using skeletal muscle remains to be elucidated.

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