Dynamic Training of Skeletal Muscle Ventricles
A Method To Increase Muscular Power for Cardiac Assistance

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Background Skeletal muscle can be used for cardiac assistance after electrical stimulation over a period of several weeks. This will adapt it to do chronic work with no resulting fatigue. The result of this procedure, however, is a reduction of 80% in muscle power, >60% in muscle mass, and ≈85% in contractile speed. To minimize these disadvantages, the following study was done to develop and test a method to dynamically train skeletal muscle ventricles (SMVs).

Methods and Results Barrel-shaped SMVs were tested in 15 Jersey calves. They were made from the latissimus dorsi muscle, which was wrapped around an elastic silicone training device. Six SMVs were used extrathoracically in a single layer and nine intrathoracically in a double layer. With dynamic training preserving contractile speed, the output increased to ≈5 L/min, the systolic pressure increased to >200 mm Hg, and power developed to ≈10 W after 3 months of dynamic training. The contractile speed of dynamically trained SMVs was between 250 and 700 mm/s. The diameter of the latissimus dorsi muscle increased to three times that of the corresponding contralateral muscle.

Conclusions The combination of electrical conditioning with dynamic training of the SMVs resulted in a strong muscle pump that did not develop fatigue. Dynamic training for skeletal muscle represents a new and promising method for providing powerful autologous cardiac assist. (Circulation. 1994;89:1032-1040.)

Key Words • muscles • contraction • electric stimulation

There have been many reports on cardiac assistance from autologous skeletal muscle that describe experimental and clinical procedures.1,27 A technique that links skeletal muscle contraction directly to the circulation, such as skeletal muscle ventricles (SMVs), would be more efficient and less expensive.38

However, there is a considerable loss of power, muscle mass, and contractile speed when skeletal muscle or SMVs have been trained to do chronic work by electrical conditioning. The aim of this study was to develop and test a method of dynamically training muscle to overcome these disadvantages and obtain strong muscular blood pumps that do not develop fatigue.

Methods
Experiments were carried out on 15 Jersey calves weighing between 56 and 140 kg. Extrathoracic SMVs were performed on 6 calves and intrathoracic SMVs on nine. They were kept under veterinary care at the Animal Department of the RW Technische Hochschule Aachen and the Free University of Brussels. A representative of the Society for the Prevention of Cruelty to Animals supervised the animals in Aachen. In Brussels, the supervision was carried out by a veterinarian of the University.

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FIG 1. Diagrams and graphs. Extrathoracic skeletal muscle ventricles (SMVs) in calves wrapped around a training device to be trained against a resistance tube (a) and an elastic bladder with a high contractile speed (b). Adjusting the heart valves at both ends of the pumping chamber (heart valve closed, heart valve open) altered the flow direction in the mock system. The pressure was measured at points P1 and P2. When output and daily energy of the SMVs in five calves with resistance training (c, e) were compared with training against an elastic workload (d, f), the results showed that training against an elastic workload was much more effective than resistance training.

Daily Energy

FIG 2. Schematic of the pump function of the skeletal muscle ventricle around the training device, Frog. Volume was shifted from the central chamber into the side bladders.

FIG 3. Topographic view of an intrathoracic, double-layered skeletal muscle ventricle in a calf, wrapped around the Frog training device.

Definitions and calculations: The output of the pumping chamber (Fig 1c) was defined as the volume shift per minute (Fig 4). Pressure in the extrathoracic mock circulation system was measured with fluid columns in plastic tubes. The measurements were taken at points P1 and P2 between a resistance tube (Fig 1, a and b). In the intrathoracic model, a tip pressure gauge (Geltec model CTC-L 1B, Geltec Co, Danvegen, Scotland) transferred the pressure data to the data logger of a computer (ISIS 286 SPCM MKI).

In the extrathoracic mock system, the relation between flow through the resistance tube and the pressure gradient between P1 and P2 was documented by a characteristic curve. It was determined before surgery. A pressure gradient in the implanted mock system between P1 and P2 was combined with a defined flow, the output of the pumping chamber. The power and daily energy were calculated from the mathematical product of flow (output), pressure (P1 minus P2), and corresponding time by using a specially designed computer program with an 802 CPU 80287 mathematical coprocessor.

In the intrathoracic device during an SMV contraction, pressure (Pm) was measured in a side bladder of the Frog. The pressure curve (Figs 5 and 6) showed a contraction time (t_con) and a relaxation time (t_rel). Contraction time was the sum of the dynamic contraction time (t_d) and the static contraction time...
Contraction Rate and Afterload
Calf No 6

Fig 4. Bar graph showing dynamic training achieved in two steps: first, by increasing the contraction rate and maintaining a low afterload for around 3 months; second, by increasing and varying the afterload in intervals and having about 50 to 60 contractions per minute for around 2.5 months.

(td). Two facts had to be taken into consideration when calculating the output and power of the Frog. First, the Frog was a closed system filled with incompressible fluid, and second, the fluid was expelled into the side bladders during muscle contraction and flowed back into the central bladder during muscle relaxation. A relation between the volume added \( (V_n-V_{n-1}) \) into the elastic side bladders and the increased pressure \( (P_n-P_{n-1}) \) showed a characteristic curve, as in Fig 7. The characteristic curves changed during implant of the Frog. Consequently, they had to be determined for each measurement. With the help of a characteristic curve, the pressure increase up to its maximum pressure \( (P_n) \) in the Frog caused by an SMV contraction allowed the stroke volume \( (V_i) \) to be calculated:

\[
V_i = \frac{V_n - V_{n-1}}{P_n - P_{n-1}}
\]

The stroke work is the numerical integration \((A I + A II)\) of the pressure increase \((P_n - P_{n-1})\) and the added volume \((V_n - V_{n-1})\), as shown in Fig 8. Power (in watts) was determined by dividing work by the dynamic contraction time \((t_d)\).

During an SMV contraction, a known volume of fluid, the stroke volume, shifted from the central chamber into the side bladders of the Frog. The diastolic \((V_d)\) and systolic \((V_s)\) volumes of the SMV cavity were calculated from the formula for the volume, \(V\), of a geometric barrel:

\[
V = \frac{\pi}{3} \left( D^2 \times d^2 \right)
\]

With a constant minimum diameter, \(d\), and a given length, \(l\), the difference in the inner diameters \(D_1 - D_2\), as well as the difference in the circumferences \(C_2 - C_1\), could be calculated:

\[
C_2 - C_1 = \pi (D_1 - D_2)
\]

The difference in circumferences \(C_2 - C_1\) reflects the contractility of the SMV. The contractile speed was calculated by dividing this difference in circumferences by the time of maximum contraction, \(T_d\), in seconds (Figs 5 and 6; Table 1).

The dynamic training was done in two steps. First, the muscle was trained by increasing its contractions from 1 to \(\geq 60\) per minute over a period of about 3 months. Then the afterload was increased by gradually filling the Frog with fluid up to the diastolic systemic pressure (Figs 4 and 6).

The diameters of the trained and contralateral untrained latissimus dorsi in the six calves with extrathoracic SMV and the three calves with intrathoracic SMVs were compared at the end of the training. The animals were killed, and a histological study using hematoxylin-eosin staining was done on the trained latissimus dorsi muscle and untrained contralateral latissimus dorsi muscle.

Results

The surgical procedure of constructing the SMVs was well tolerated by all 15 calves. The animals were able to move around freely with no physical impairment or discomfort. In all 6 extrathoracic models, infection caused by skin perforations occurred between 16 and 64 days after surgery. When this happened, the animals were killed immediately.

The constructed SMVs were allowed to recover with no electrical stimulation or artificially induced contractions applied. The vascular delay lasted 8 to 14 days in all extrathoracic SMVs without any problems. In the first two double-folded intrathoracic SMVs, however, no contraction could be induced after a vascular delay of 8 and 11 days. In the autopsy, the SMVs were found to have degenerated. For calves 3 to 9, the frequency training was carried out first. In calves 4, 5, 6, and 9, this was followed by an afterload training (Figs 6 and 9, calf 6). Table 2 shows the final diastolic pressure of calves 3, 4, 5, 6, 7, and 9. A fractured electrode was found in two intrathoracic double-folded SMVs in calves 4 and 8. In calves 3 through 9, none of the SMVs showed fatigue with a 24-h/d stimulation.

As reported elsewhere, the systolic pressure in the single-layered extrathoracic SMV with a low preload...
never reached half of the animal's average systolic pressure. Less than 50 mm Hg was measured. The output of the single-layered SMVs was measured at <0.5 L/min when used against a resistance tube (Fig 1a). The training with an elastic bladder (Fig 1b), however, was highly effective. Output increased nearly four times (Fig 1c), and the daily energy was six times higher than that obtained with the resistance training (Fig 1f) against the resistance tube between P1 and P2 (Fig 1a).

Because of severe subcutaneous infections caused by the extrathoracic training device, this device was abandoned in favor of the intrathoracic apparatus, the Frog (Figs 2 and 3), which had a very compliant workload (elastic bladders).

Use of the Frog in the intrathoracic system permitted the pressure, output, contractile speed, and power to be measured. Even with a low afterload of between 0 and 5 mm Hg, it was possible to obtain systolic pressure up to systemic and suprasystemic pressure levels in the Frog (Fig 9). Furthermore, increasing the afterload intermittently increased the systolic pressure (Fig 9) and power (Fig 10). In calf 7, a Frog that had been implanted twice burst on the 59th postoperative day after systolic pressures >300 mm Hg had been measured (Table 2, Fig 10).

During dynamic training, the stroke volume increased from the start. For example, in the SMV of calf 6, it increased from 20 to 84 mL (Fig 11). End-stage stroke volume was dependent on the quality of training. It was between 21 and 84 mL (Table 1). The maximum output per minute in calf 6 was measured and found to be nearly 5 L by the end of the training session (Fig 11).

The final contractile speed varied between 234 and 715 mm/s. A contractile speed of about 500 mm/s in calf 7 was added to the highest determined power (Table 1, Fig 10).

Comparing the power developed in the intrathoracic SMVs in seven calves showed completely different results. The final power varied between 1.3 and 9.6 W (Tables 1 and 2, Fig 10). For example, Fig 10 shows the power developed in calves 6, 7, and 8. The power curve of calf 7 shows that the largest power measured was about 10 W. This training device, however, burst on the 59th postoperative day, having measured a pressure >300 mm Hg (Table 2). In calf 6, the frequency training lasted nearly 3 months (Fig 4). It can be seen that the power level for the subsequent months changed by 5 to 7 W as a result of altering the afterload (Fig 10). A similar behavior for the maximal pressure by a modified afterload is documented in Fig 9. There was no significant power increase in the SMV for calf 8 because of a fractured electrode.

The muscular thickness was thinner than that of untrained contralateral muscle in the five extrathoracic SMVs trained against a resistance. However, in one extrathoracic calf trained against a compliant workload, the muscular thickness increased to 19 mm (Fig 1b), compared with 10 mm for the control untrained muscle.
The increase in the double-layered intrathoracic SMVs was more impressive. The thickness of the untrained contralateral muscle versus the trained muscle was, for calf 3, 9 versus 20 mm; for calf 6, 9 versus 28 mm (Fig 12); and for calf 9, 14 versus 32 mm.

Discussion

Autologous cardiac assistance using cardiomyoplasty has been done on around 320 patients worldwide for more than 8 years, yet it has not been shown to be hemodynamically effective. One reason may be that there is a 50% loss in muscle bulk of the latissimus dorsi muscle when performing heavy, continuous work and with further loss due to the process used. The original muscle mass decreases from 600 to about 225 g.38 Furthermore, contractile speed drops to a minimum with electrical conditioning, so it is difficult to achieve efficient work, as explained later. A third handicap is the large diameter of a heart during the final stages of heart failure. According to Laplace's law, a considerable amount of energy is required to compress such a heart.

Even when the geometry of the constructed SMV is optimally suited to pump blood, it is still judged necessary to dynamically train the muscle to preserve its mass, contractile speed, and power.

Jersey calves were used in the study because they are nearly the same weight as an adult man. The latissimus dorsi muscles in both men and calves are similar in size, anatomy, and topography. This means that the same intrathoracic training device could be used in both, which is convenient for any clinical studies that may be done later.

In the last calf of the extrathoracic training, the heart valves of the pumping chamber were changed (Fig 1, a and b). This caused the flow direction to change too, resulting in an elastic compliant afterload. The SMVs then became six times more effective. The daily energy increased from around 1 to about 6 kW. The output increased from 0.5 to nearly 2 L/min. This could be explained by the power-velocity relation of contracting muscles, as described by Salmons and Jarvis.38,39 With a higher contractile speed within defined limits, more power could be achieved. In a single-layered extrathoracic SMV, the systolic pressure obtained was only half that of the animal's own circulation. It was unable to transport blood from the SMV to the aorta. The use of a stronger or multilayered SMV was therefore deemed necessary.

Two of the intrathoracic SMVs failed. A possible reason was that the muscle was wrapped around the Frog in a double layer and fixed into place with two felt rings. These may have become too tight, causing swelling and producing a compartment-like effect. Consequently, we can consider that there may be a risk of a vascular delay with this operating procedure when a double-layered SMV is used. Squeezing the SMV im-

<p>| TABLE 1. End-Stage Training Data of Dynamically Trained Skeletal Muscle Ventricles, 1 |
|-----------------------------------|----------------|----------------------------|-----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Calf</th>
<th>Stroke Volume, mL</th>
<th>Contractile Path, mm</th>
<th>Dynamic Contraction Time, ms</th>
<th>Contractile Speed, mm/s</th>
<th>Power, W</th>
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</thead>
<tbody>
<tr>
<td>6</td>
<td>84</td>
<td>89.4</td>
<td>125</td>
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<td>6.8</td>
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<td>7</td>
<td>58</td>
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<td>133</td>
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<td>9.6</td>
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<tr>
<td>9</td>
<td>42</td>
<td>50.7</td>
<td>156</td>
<td>321</td>
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<tr>
<td>3</td>
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<td>358</td>
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<tr>
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<td>277</td>
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<td>26</td>
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The amount of data exceeds the table format.

<p>| TABLE 2. End-Stage Training Data of Dynamic Trained Skeletal Muscle Ventricles, 2 |
|-----------------------------------|----------------|----------------|-----------------|----------------|</p>
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<tr>
<th>Calf</th>
<th>Training Time, d</th>
<th>Stimulation Rate, bpm</th>
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<th>Stroke Work, J</th>
<th>Power, W</th>
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</tr>
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</table>

bpm indicates beats per minute.
mediately after surgery could perhaps prevent a swelling. Another reason for the failure observed could have been nerveal or vascular damage of the muscular pedicle.

Dynamic training was performed in two steps. Frequency training should condition the cellular biochemistry of the muscle to a chronic beat frequency similar to the heart. Afterload training increased by intervals (Figs 4 and 9) should adapt the SMV to chronic afterload, as found in the aorta.

Since the skeletal muscle normally shortens by around 30%, stroke volumes of about 75 mL were theoretically achievable. In practice, the maximum stroke volume obtained was 84 mL in calf 6. Increasing the maximum diameter of the pumping chamber to 70 mm could in theory produce a stroke volume of 120 mL. Assuming a contraction rate of 80 beats per minute, an output of nearly 10 L/min would be obtained.

A contractile speed between 234 and 715 mm/s could be achieved, depending on the quality of training (Table 1). The quality of training, however, can be influenced by several factors, such as fracture of the electrode, the location and kind of electrode, the training procedure, and the bladder compliance of the Frog. If we take the contractile speed of a skeletal muscle, such as the musculus rectus abdominis, to be about 700 mm/s, that of the heart to be 200 mm/s, and that of an electrically conditioned muscle to be only around 40 mm/s, the potential of preserving contractile speed by this method is seen. The relation between contractile speed, power, and stroke volume is shown in Table 1. The highest contractile speeds of about 500 and 700 mm/s are combined with the highest power (9.6 and 6.8 W) and stroke volumes (84 and 58 mL). Preserving contractile speed is the key to producing powerful cardiac assist.

After optimal training of the SMVs dynamically over several months, as in calves 3, 6, 7, and 9 (Fig 10), a power of 6 to 9 W can be obtained. The maximum
power measured in the SMV of calf 7 was around 10 W. This may have been caused by the myoelectrode being too close to the proximal branches of the nervus thoracodorsalis. To get an idea what 6 to 9 W means, it is worthwhile to compare it to the power produced by a left heart ventricle. Values of human hearts are easily available.25 A human left ventricle does a stroke work of around 0.8 J25,38 in 250 to 300 milliseconds. This is a maximal power of 2.6 to 3.2 W. In other words, the SMV in calf 7 produced three times more power than a human heart.

The largest increases in the muscle wall diameter in the dynamically trained SMV were found in calves 6 (Fig 12) and 9. The SMV of calf 7 was not examined. Fig 12 shows that the muscular wall of the SMV became two to three times thicker during dynamic training compared with the contralateral untrained latissimus dorsi muscle. The histological findings were difficult to interpret. There were no signs of hypertrophy in the muscle fiber. It is likely, however, that hyperplasty occurred even though histometric methods were used in calves 6 and 9. Further investigations may show whether this phenomenon can be repeated and whether it is a result of cell splitting or the transformation of satellite cells.41,42

Skeletal muscle in dogs has already been tested on extrathoracic mock systems with a high afterload of around 80 mm Hg and a preload of around 40 mm Hg at the start of training.1 Such a method differs fundamentally from that described here. Training against a high afterload does not guarantee the preservation of a high contractile speed, which is needed to create considerable power.38,39 Dynamical training against a high afterload from the start is comparable to training against high resistance. Such a technique has been shown to be ineffective (Fig 1).

The output and power calculation of the SMVs used in different configurations are shown. Investigations done on autologous cardiac assistance by other investi-
gators* did not use dynamic preconditioning against a highly compliant workload to preserve a high contractile speed. In an aorto-aortic configuration by counterpulsation, about 20% to 25% of left ventricle output was achieved.43 The power and output data of the dynamic training detailed in this article were not applied to circulation.

Even allowing for a loss of power as a result of an integration into the circulation, as shown in the training data, dynamically trained SMVs should be very effective.

Once the electrical and dynamic training has been completed, the elastic training device is removed. It is then possible to integrate the skeletal muscle ventricle as a left or right heart assist device into the circulation.

The initial dynamic training of the skeletal muscle, resulting in the preservation of its contractile speed, power, and increased muscle mass, is a promising technique for powerful autologous cardiac assistance.

Acknowledgments

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