Counterpulsation From the Skeletal Muscle Ventricle and the Intraaortic Balloon Pump in the Normal and Failing Circulations

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Background—The intra-aortic balloon pump (IABP) is the device that is in most common use to provide cardiovascular support. A skeletal muscle ventricle (SMV) was configured to produce counterpulsation in the thoracic aorta similar to that obtained with an IABP. The hemodynamic effects of an IABP and a SMV in the same animal and in both normal and failing circulations were assessed.

Methods and Results—SMVs were connected to and IABPs were placed in the thoracic aorta of 12 anesthetized pigs. Hemodynamic parameters during the IABP- or the SMV-assisted beat were compared with those during the preassist beat. Acute heart failure was induced in 6 of the pigs by snaring the left anterior descending coronary artery (LAD). The hemodynamic effects of the IABP and the SMV were then reassessed. In the assisted cycles, SMV activation increased the mean aortic diastolic pressure (MADP) by 26.5±3.5%, the mean diastolic LAD flow by 48.4±7.2%, and endocardial viability ratio (EVR) by 31.6±3.8% (P<0.0001). In the same animals, IABP assist increased MADP by 19.8±2.3%, mean diastolic LAD flow by 37.2±3.9%, and EVR by 21.4±3.0% (P<0.0001). Under acute heart failure conditions, both SMV and IABP assist significantly increased MADP, mean diastolic LAD flow, and EVR.

Conclusions—In both the normal and failing circulations, the SMV was an effective counterpulsator, providing cardiac assist that was at least equal to that available from an IABP. The SMV may therefore provide the proven benefits of an IABP in ambulant patients. (Circulation. 2006;114[suppl I]:I-10–I-15.)

Key Words: balloon ■ heart-assist device ■ heart failure ■ hemodynamics ■ skeletal muscle ventricle

The decrease in the number of donor hearts available for transplantation has led to a decline in the number of heart transplant operations.¹ This has highlighted the need for alternative approaches to the long-term treatment of end-stage heart failure. Xenotransplantation poses a risk of viral infection and also requires life-long immunosuppression. Despite the development of improved synthetic materials and transcutaneous power supplies, mechanical assist devices continue to pose problems of cost, bleeding, thrombosis, and infection. The use of transposed skeletal muscle to provide cardiac assist is therefore attractive because it is relatively inexpensive and requires neither immunosuppression nor externally mounted apparatus.

The intra-aortic balloon pump (IABP) is the clinical device most commonly used during severe ventricular dysfunction. It unloads the heart in systole and increases the diastolic blood pressure, augmenting coronary blood flow. A skeletal muscle ventricle (SMV) can be configured to unload the heart by filling during systole and ejecting during diastole; it should then provide counterpulsation similar in effect to an IABP.

This proposition was examined in a porcine model by configuring SMVs within the chest and introducing IABPs in the same animals. The hemodynamic effects in acute heart failure brought about by coronary artery occlusion were also investigated.

The introduction of a single-limbed conduit, a single anastomosis, intrathoracic SMV placement, and use of a homograft lining represents progress toward a clinically applicable SMV. In situ muscle training before SMV construction was used to enable the SMV to provide cardiac assistance immediately after connection to the circulation in a single thoracic operation.

Materials and Methods

All animals were cared for and operated on in strict accordance with the Animals (Scientific Procedures) Act of 1986, which governs experimental animal research in the United Kingdom. SMV design and construction have been described before,² but a more detailed description follows. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.
Anesthetic Technique: Implantation of Stimulator

Twelve female adult Large White pigs were premedicated with 2 mg/kg of intramuscular azaperone (Janssen Animal Health). General anesthesia was induced by a 50:50 mixture of oxygen and nitrous oxide and 1% to 3% isoflurane (Abbott, Wiesbaden, Germany). An intravenous injection of propofol 2 mg/kg (Propofol-Lipuro; Braun, Melsungen, Germany) was followed by intubation. Anesthesia was maintained by a 50:50 mixture of oxygen and nitrous oxide and 1% to 3% isoflurane administered through a rebreathing anesthetic circuit (Ohmeda, Essex, UK). The ECG and peripheral oxygen saturations (Kontron, Chichester, UK) were monitored. A single intramuscular dose of lincomycin hydrochloride (Lincomycin; Upjohn Ltd, Crawley, UK) 22 mg/kg was used as antibiotic prophylaxis.

The lateral border of the left latissimus dorsi muscle (LDM) was exposed via a flank incision and was carefully reflected to reveal the thoracodorsal neurovascular bundle on its deep surface. The single electrode was custom made and consisted of a polyvinyl chloride-coated stainless steel wire with its terminal end deinsulated and placed on a silicone rubber backing. This electrode was placed across the thoracodorsal neurovascular bundle and connected to a programmable monopolar neuromuscular stimulator (Irel SP 7421; Medtronic, Minneapolis, Minn), which was implanted subcutaneously in the flank.

Construction of SMV Linings

Homograft pulmonary artery and descending aorta were obtained from fresh porcine cadavers. The pulmonary artery branches were ligated, and the valve was excised. A double layer of running 5-0 polypropylene suture was used to anastomose the pulmonary artery annulus to a cylindrical conduit made from the descending aorta; this completed the SMV lining. The linings were stored at 4°C in an antibiotic mixture (Alder Hey Children’s Hospital homograft bank protocol) for <1 week before use.

Muscle Conditioning

The pigs were allowed to recover for 1 week, and then the stimulator was switched on. The left LDM was subjected to continuous electric stimulation with amplitude of 1.5 to 2.5 V at 30 Hz for 0.19 second on and 6 seconds off. Voltage was adjusted to the minimum that produced palpable stimulation of the entire LDM. This conditioning protocol lasted for 35.8 ± 2.7 days.

Acute Experiment: Anesthetic Technique

At the end of the conditioning period, the pigs, which by now weighed between 56 and 95 kg, were anesthetized for a second operation with the same anesthetic protocol. A median sternotomy was performed. A pressure catheter (Gaeltec, Isle of Skye, Scotland) was introduced to monitor the aortic pressures. Ultrasound cuffs (Transonic Systems Inc, Ithaca, NY) were placed around the ascending aorta, and a needle within the SMV recorded pressure (Gaeltec, Isle of Skye, Scotland).

A left flank incision with extraperitoneal dissection was performed to free the abdominal aorta. A 25-cm³ intra-aortic balloon was introduced into the abdominal aorta and positioned in the descending aorta with its tip just proximal to the crossing of the hemiazygos vein, as confirmed by palpation. It was connected to a System 98 IABP (Datascope, Fairfield, NJ).

The SMV was stimulated by a bench-top pulse generator and isolated stimulator (model DS2A; Digitimer Ltd, Hertfordshire, UK). Contraction was timed to occur in every third cardiac cycle during diastole. The stimulating voltage was at 3 times the threshold, with a pulse width of 0.2 ms and delivered at a frequency of 30 Hz. The SMV was clamped off during periods in which the IABP was in operation. The IABP was then set to inflate at maximum augmentation during every third cardiac cycle. Hemodynamic parameters were recorded during periods in which either the SMV or the IABP (Figure 2) was active.

In 6 pigs, snares were placed around the LAD distal to the ultrasound flow probe. Blood flow in the LAD was controlled by

Figure 1. Schematic diagram of SMV.

Figure 2. Tracings derived from the recording of hemodynamic data during SMV activity (a) and IABP activation (b) in every third cardiac cycle.
adjusting the snare to a degree that would produce cardiac ischemia sufficient to reduce the cardiac output. The hemodynamic effects of SMV and IABP assist were then evaluated in the compromised system.

A Sonos 5500 (Phillips, Surrey, UK) device was used to provide ultrasound imaging of the heart and SMV. Probes were placed over the heart and the SMV from within and outside the chest cavity.

At the end of the experiment, animals were given a lethal dose of intravenous sodium pentobarbital (Rhone-Merieux, Harlow, UK).

Data Analysis
Windaq software (Dataq Instruments, Akron, Ohio) was used for offline postacquisition processing of hemodynamic data. To reduce interanimal variation, the hemodynamic data acquired during an SMV- or an IABP-assisted beat (Assist) were compared with data acquired during the preceding beat (Preassist). For each pig, hemodynamic data were accumulated during a minimum of 6 assisted cycles after a period of at least 1 minute of assist to allow the circulation to reach equilibrium. Student paired t test was performed between Preassist and Assist values (InStat version 3 for Macintosh, Graphpad Software). A 95% confidence limit was chosen as the criterion of statistical significance (P<0.05).

Indices of the Effectiveness of Counterpulsation
The SMV was configured to fill during systole and to eject blood into the descending aorta during diastole. LDM electric stimulation was set to commence at the dicrotic notch from the aortic pressure waveform and to continue for 80% of the duration of diastole. We have found in previous unpublished studies (PhD thesis submitted by M.C. to Medical Faculty, University of Liverpool, April 2006) that this timing allows the maximum benefit from the SMV. LDM relaxation would then allow the SMV to fill passively and to reduce the cardiac afterload during the following cardiac systole. This mode of operation, known as counterpulsation, increases diastolic aortic blood pressure and decreases cardiac work. IABP produces the same effects.3

The mean aortic diastolic pressure (MADP) and the endocardial viability ratio (EVR; also known as diastolic augmentation index) were used to assess the degree of assist provided by counterpulsation. The EVR was calculated from the following formula:

\[
\text{endocardial viability ratio} = \frac{\text{mean diastolic pressure} \times \text{diastolic time}}{\text{mean systolic pressure} \times \text{systolic time}}
\]

This simplified version of the ratio of the diastolic pressure time index (DPTI) to the tension time index (TTI) reflects the potential benefit of the increased myocardial blood flow (DPTI) balanced by an estimate of left ventricular work (TTI).4 It has been used extensively in the assessment of cardiac assist devices.5

Another potential benefit of an increased MADP is an improvement in coronary artery blood flow. The mean diastolic blood flow through the left anterior descending coronary artery was therefore measured.

Results

SMV Design
Cardiac assist from skeletal muscle was first classified by Salmons and Jarvis6 into category 1 assist, in which the

Discussion

SMV and IABP Assist During Acute Cardiac Failure
In 6 pigs, the distal LAD was partially occluded by snaring. The cardiac output dropped from 7.8±0.8 to 5.5±0.5 L/min (P=0.003; Figure 5). Under these conditions of acute heart failure, SMV assist increased the MADP by 19.0±5.8% (P=0.01), mean diastolic LAD flow by 45.4±17.5% (P=0.003), and EVR by 16.7±5.9% (P=0.01). Two pigs developed refractory ventricular fibrillation and died before the IABP could be used. In the other 4 pigs, IABP assist increased MADP by 22.2±5.0% (P=0.03), mean diastolic LAD flow by 100.3±41.7% (P<0.05), and EVR by 19.7±4.4% (P=0.02).
natural endothelial lining of the patient is preserved, and
category 2 assist, in which an independent structure is
connected to the patient’s circulation that presents an additional
surface to the blood. Cardiomyoplasty and aortomyoplasty provide
category 1 assist, but the geometry of the structure wrapped by the muscle (the heart and aorta, respectively) does not allow for optimum use of the available muscle power.6 SMVs provide category 2 assist, and the
hemodynamic performance of several configurations has been demonstrated.

Previous SMV models have used linings made from
synthetic materials, autologous pericardium, or aortic homograft.12 The current model includes a lining made from pulmonary artery homograft.2 Human pulmonary homograft has minimal thrombogenic potential and is in extensive use in many cardiac surgical procedures. The porcine homograft lining proved to be quite strong, was easy to work with, and formed a blood-tight surface. The lining protects the innermost muscular layers of the SMV from direct exposure to systemic blood pressure and avoids possible compromise of the nutritional blood flow to the wall. The inherent elasticity of the pulmonary artery also serves to reduce the effective preload pressure on the muscle of the SMV wall.13

Earlier SMV configurations used an inflow and an
outflow that required 2 vascular anastomoses. Blood
circulated through the device in parallel with the systemic
circulation. The SMV had a higher resistance to flow than
the aorta, limiting flow through it and increasing the risk of
thrombus formation. Valved conduits were used to encourage
flow through the device, but the successful recovery
model required ligature of the descending aorta between
the SMV limbs to provide adequate blood flow. Although
this SMV functioned successfully in circulation for up to 4
years, aortic ligation is not likely to be acceptable in human application. The advantage of the single-limb SMV
is the single vascular anastomosis required, rendering aortic ligation unnecessary.

Previous SMV models were located outside the chest. The intrathoracic SMV location allowed the use of shorter conduits, maximizing the mixing of blood within the device.15 The intrathoracic location also provides protection within the rib cage and the prospect for clinical application. The disadvantage is that there may be a corresponding loss of lung volume and risk of external pressure on the heart itself. This is more of a risk in the sharply tapering thoracic cavities of quadrupeds than in humans.

The SMV fills passively and behaves like a capacitance vessel attached to the circulation. A blind-ending pouch design can pose problems of stasis, particularly in the apex. Salmons et al conducted an in vitro assessment of this SMV model and demonstrated that, under the right conditions, a vortex forms at the apex and propagates along the length of the SMV. This flow structure promotes mixing of blood and minimizes the problem of stasis within the pouch. Design rules were also developed to ensure adequate exchange with circulating blood by limiting the volume of the connecting arterial conduit. The model was based on an estimate of 40% for SMV ejection fraction. In the current sequence of experiments, SMV ejection fractions in the region of 70% to 95% were obtained. Therefore, the risk of thrombosis in the chronic model would be even less than predicted by the conservative model.

Protocols that have been used previously for skeletal muscle assist have incorporated a period of recovery (of up to 2 weeks) before the commencement of muscle training (typically an additional 4 weeks). The benefits of cardiac assist would therefore not be available for a considerable time after a major surgical procedure in patients already experiencing cardiovascular compromise.

### Hemodynamic Effects

<table>
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<th></th>
<th>Preassist, mm Hg</th>
<th>Assist, mm Hg</th>
<th>P</th>
<th>Preassist, ml/min</th>
<th>Assist, ml/min</th>
<th>P</th>
<th>% Change</th>
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<tr>
<td>SMV (n=12)</td>
<td>43.4±3.8</td>
<td>54.9±5.0</td>
<td>&lt;0.0001</td>
<td>43.4±4.4</td>
<td>63.4±6.1</td>
<td>&lt;0.0001</td>
<td>31.6±3.8</td>
<td>&lt;0.0001</td>
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<tr>
<td>IABP (n=12)</td>
<td>42.9±3.8</td>
<td>51.6±4.8</td>
<td>&lt;0.0001</td>
<td>43.6±4.4</td>
<td>59.6±6.5</td>
<td>&lt;0.0001</td>
<td>21.4±3.0</td>
<td>&lt;0.0001</td>
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<tr>
<td>P, SMV vs IABP</td>
<td>0.89</td>
<td>0.46</td>
<td></td>
<td>0.94</td>
<td>0.46</td>
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**Figures:**

- **Figure 5.** Hemodynamic benefits of the SMV (6 pigs) and the IABP (4 pigs) in the acutely failing circulation. Values shown are mean with 1 SD. *P*<0.05 for the comparison Preassist vs Assist. a, Effect on mean arterial blood pressure. b, Effect on mean diastolic LAD flow. c, Effect on EVR.
The electric stimulation protocol in the present study was designed to harness the benefits of electric prestimulation18 over vascular delay, benefits that include better blood flow in the distal SMV wall and enhanced muscle viability. The combination of this protocol with the use of the preformed lining would provide a muscle-powered cardiac-assist device that could provide immediate hemodynamic benefit and improve postoperative recovery. Our experience is that, provided that care is taken to ensure that blood flow is not restricted where the muscle passes through the thoracic wall or during construction of the pumping chamber, substantial pumping effort is available from the moment of anastomosis. The SMV requires no external power source, only a pulse generator the size of a normal pacemaker, which would be far less expensive than mechanical assist devices.19

**Hemodynamic Benefits**

The SMVs in this series ejected volumes of blood of approximately half the left ventricular stroke volume against systemic arterial pressure. These volumes in turn are similar to the volume displacements achieved by inflation and deflation of the typical IABP. The indices of counterpulsation produced by both SMV and IABP were strikingly comparable. Thus, the SMV clearly and consistently reproduced the known beneficial hemodynamic effects of the IABP.

The SMV was not set to provide cardiac assist in each cardiac cycle because this obliges the skeletal muscle to recruit anaerobic production of ATP, which is not sustainable.20 LDM stimulation at 1:1 was almost certainly responsible for the muscle ischemia, injury, long-term fatty degeneration, and demise reported by some authors.20,21 In routine clinical use an IABP would, of course, be operated at a frequency of 1:1. Therefore, this study should not be regarded as a direct comparison of the merits of assist by SMV or by IABP. It demonstrates, however, the potential use of the IABP as a screening tool to determine which patients could derive benefit from SMV support under fully ambulant conditions and demonstrates that a substantial level of continuous cardiac assist is potentially available from the SMV. Moreover, short periods of SMV assist at 1:2 or even 1:1 should be possible, provided that subsequent rest is sufficient to allow anaerobic reserves to be replenished and that the total number of impulses delivered to the assisting graft does not exceed the threshold above which the muscle would become slow.22

**Acute Heart Failure Model**

SMVs have been shown to provide hemodynamic benefits in chronic heart failure.23 Both the SMV and the IABP continued to provide appreciable augmentation of diastolic pressure and EVR in the compromised system. Although it has been shown previously that SMV assist can increase coronary blood flow in chronic heart failure,23 we have demonstrated in the present study that the IABP and SMV both significantly increased the blood flow in vessels with distal obstruction to flow. Therefore, the SMV has the potential to augment coronary artery blood flow to ischemic myocardium even when its own blood supply is potentially compromised in a low-output syndrome. Patients with ischemic cardiomyopathy who have coronary artery disease that is not suitable for revascularization may prove to be the group most suitable for SMV assist. This is the rationale behind the use of enhanced external counterpulsation,24 which is already in widespread use.

In conclusion, this study shows that a SMV can provide counterpulsation in the normal and failing circulations. The design represents progress toward a clinically applicable SMV.

**Acknowledgment**

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**Disclosures**

None.

**References**


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