Aortic Counterpulsation with a Valved Skeletal Muscle Ventricle: Short-Term Studies of Coronary Flow and Left Ventricular Function

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Abstract

Left ventricular performance, and coronary as well as systemic blood flow, were evaluated in six dogs in whom aortic diastolic counterpulsation was generated by skeletal muscle ventricles (SMVs).

SMVs were constructed from the right latissimus dorsi and placed in the right hemithorax. After a three-week delay, the muscle was conditioned with 2 Hz continuous stimulation for six weeks. At a second operation SMVs were connected between the aortic root and proximal descending thoracic aorta, using a non-valved afferent conduit, and a homograft-valved efferent conduit. The ascending aorta was clamped immediately proximal to its innominate branch to direct blood flow through the SMV. Hemodynamic measurements were taken at an SMV burst stimulation frequency of 25 Hz, and 1:2 (SMV:heart) diastolic synchronization. Measurements were also recorded at 1:1 synchronization, and at 50 Hz burst stimulation frequency.

At an SMV assist setting of 25 Hz, 1:2 ratio, mean coronary flow was not significantly improved. However, effective LV systolic unloading was produced in all animals, with mean LV systolic pressure being reduced, lowering LV stroke work by 15% (1.34 ± 0.12 vs $1.13 \pm 0.12 \times 10^6$ ergs, $p < 0.05$). Systemic perfusion pressure, regional aortic flow and LV stroke volume, were preserved. Both increased burst stimulation frequency and a 1:1 assist mode achieved significant augmentation of coronary flow, and greater LV off-loading, though burst frequency emerged as the more important variable. In four animals, repeated measurements after 1 hour of counterpulsation confirmed a sustained and comparable level of LV assist.

This study has demonstrated that an SMV-counterpulsation system is capable of enhancing left ventricular performance, while preserving systemic perfusion, and augmenting coronary flow.

Key words: Aortic counterpulsation; assisted circulation; skeletal muscle.

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Aortic counterpulsation with the intra-aortic balloon pump (IABP) is a well-established form of cardiac assist. For long-term use, skeletal muscle is being considered as an alternative means for generating circulatory counterpulsation. Since being totally implantable and largely self-sufficient, a muscle-powered system offers obvious advantages over mechanical devices. Various approaches have been described, ranging from aortomyoplasty, in which muscle is wrapped around the ascending [8] or descending [13, 20] thoracic aorta, to various forms of implantable, skeletal muscle-driven counterpulsation pumps [4, 9, 14, 16].

An alternative technique has been to construct skeletal muscle ventricles (SMVs) connected directly in circula-

tion with the thoracic aorta [1, 2, 18]. Effective diastolic pressure augmentation has been documented for up to two years with this configuration, confirming the ability of skeletal muscle to withstand systemic pressure long-term, without thrombo-embolic complications [24].

However, although arterial counterpulsation implies the provision of cardiac assist by afterload reduction, this aspect has not been consistently demonstrated with skeletal muscle-powered techniques. This may represent a deficiency of system design, or alternatively, may be related to the slow relaxation properties of transformed, fatigue-resistant muscle [25]. On the other hand, while the IABP provides unequivocal cardiac assist, it may be at a disadvantage from its intra-aortic position, since impaired renal blood flow has been reported in relation to its use in dogs [22]. The purpose of this study was to assess a new configuration of SMV-aortic counterpulsation, and to evaluate effects on left ventricular function, and coronary and systemic blood flow.

Materials and Methods

Six mongrel dogs weighing between 14 and 20 kg were used for the experiment. Animals were operated in accordance with the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences (NIH publication no. 85-23, revised 1985). Anesthesia was induced with intravenous thiamylal (12-18 mg/kg) and maintained by inhalation of isoflurane (1-2%). Prophylactic antibiotics included intravenous cefazolin (1g) prior to operation, and oral cephalexin (60 mg/kg/day) postoperatively for 7 days. Pain was controlled with parenteral buprenorphine (0.02-0.04 mg/kg). Animals received atenolol (50 mg/day) for 24-48 hours prior to the second operation, in order to control tachycardias during the procedure.

Construction of SMV

Through a right flank incision, the latissimus dorsi muscle was mobilized completely, apart from its neurovascular pedicle. A bipolar cuff nerve electrode (Medtronic Inc., Minneapolis, MN) was placed around the right thoracodorsal nerve for subsequent muscle stimulation. The latissimus muscle was then partly folded longitudinally, and wrapped approximately twice around a lightweight, conical plastic mandrel, with a volume of 35-45 ml, basal diameter of 3.0 cm, and length of 6-7 cm. A sewing ring fashioned from Teflon felt (USCI, Billerica, MA) was used to secure each layer of muscle to the base of the mandrel. A 5-6 cm portion of the third rib was excised and the SMV placed within the apex of the right hemithorax, with the base directed ventrally.

A Medtronic Itrel pulse generator (Models 7420/7421, Medtronic Inc., Minneapolis, MN) was connected to the nerve lead, and implanted behind the right rectus muscle. Muscle stimulation was not begun immediately. After a three-week vascular delay period, the stimulator was activated to deliver 2 Hz continuous stimulation, of 210 μsec pulse duration and 1.0-1.5 V amplitude. This was continued for six weeks, to transform the muscle to a more fatigue-resistant form.

Connection to the circulation

At a second operation nine weeks later, a median sternotomy was performed, and the base of the SMV exposed to allow removal of the mandrel. The pericardium was then opened, and the entire aortic arch and proximal descending thoracic aorta mobilized. A 14 mm reinforced polytetrafluoroethylene vascular graft (Gore-Tex; WL Gore & Associates Inc, Flagstaff, AZ) was then anastomosed between the aorta, immediately distal to the left subclavian artery, and the SMV, via an interposed canine aortic valve homograft (Figure 1). A similar conduit, but without a valve, was connected between the ascending aorta and the SMV.

Following administration of 1000 U of sodium heparin intravenously, circulation was established through the SMV, and the ascending aorta was occluded with a clamp immediately proximal to the innominate arterial branch, in order to divert blood flow through the SMV. Two sensing epicardial electrodes (model 6917, Medtronic Inc.) were placed on the left ventricle. The Itrel stimulator was then replaced with a rate-responsive, synchronized pulse train stimulator (Prometheus™, Medtronic Inc.), and this was connected to the nerve lead and cardiac sensing electrodes.

Measurements

Distal aortic pressure was recorded with an 18Ga catheter inserted via the femoral artery, and connected to a fluid-filled transducer. A 5F microtransducer-tipped catheter (Millar Instruments Inc., Houston, TX) was inserted into the afferent SMV conduit to measure aortic root pressure. A similar catheter was inserted through the left ventricular (LV) apex, to record LV pressure changes.

A custom-made, 10-electrode conductance catheter (Webster Laboratories, Baldwin Park, CA), with 8.6 mm interelectrode spacing, was also inserted through the LV apex, and positioned such that its terminal electrode lay just above the native aortic valve. The catheter was connected to a signal conditioner amplifier (Model Sigma 5/DF, Leycom, Oegstgeest, The Netherlands) to compute LV volume, and to record instantaneous LV pressure-volume loops [5]. A second conductance catheter (10 electrode, 6.6 mm spacing) was placed into the SMV cavity, through the site of the SMV-conduit anastomosis, to measure volume changes.

Two 12 mm ultrasonic flow probes (Transonic Systems Inc., Ithaca, NY) were placed around the innominate artery and the distal thoracic aorta, respectively, to measure regional blood flow. A similar 2 mm flow probe was placed around the proximal circumflex coronary artery, to record coronary blood flow.

The Prometheus™ stimulator was programmed to deliver a 25 Hz or 50 Hz burst frequency, at 50-55% R-R delay, 30-35% R-R duration, and 3V amplitude. Measurements were taken with the stimulator *off* and *on*, at both 25 Hz and 50 Hz burst frequencies, and at 1:2 and 1:1 diastolic

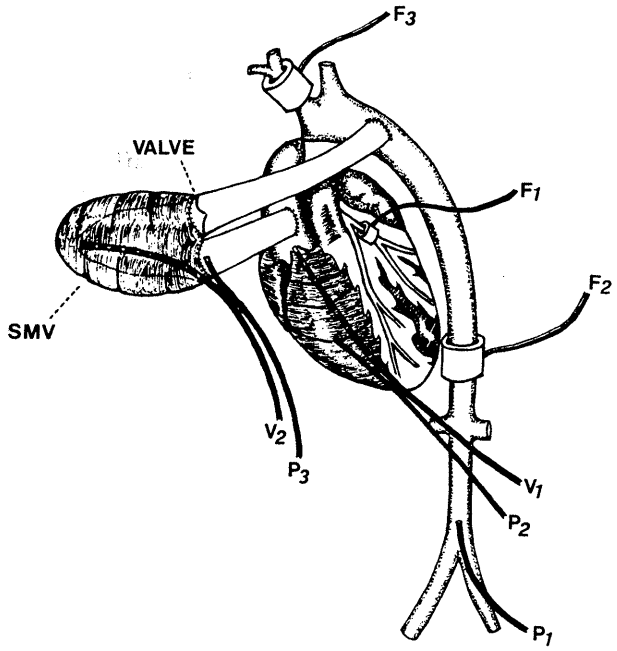

Figure 1. Schematic drawing to demonstrate the SMV configuration used, and the positioning of flow probes, and volume and pressure catheters. (F1- circumflex coronary artery flow probe, F2- distal thoracic aortic flow probe, F3- innominate artery flow probe, V1- LV volume catheter, V2-SMV volume catheter, P1- distal aortic pressure, P2- left ventricular pressure, P3- aortic root pressure).

synchronization modes. In four of the six animals, measurements were repeated after sixty minutes of continuous SMV counterpulsation at 25 Hz stimulation and 1:2 synchronization.

Data Analysis

Data was collected on computer (Model 386-20, Northgate Computer Systems, Plymouth, MN) using CODAS real-time data acquisition software (Dataq Instruments, Akron, Ohio), and analyzed with Advanced CODAS Post-Acquisition software. LV pressure-volume signals were analysed using Leycom software (Conduct PC, Leycom, Oegstgeest, The Netherlands), to derive stroke volume and stroke work. Subendocardial Viability Index (SVI) was calculated as the ratio of diastolic pressure-time index (mean aortic diastolic pressure multiplied by diastolic time), to systolic pressure-time index (mean LV systolic pressure multiplied by systolic time).

Table 1. Hemodynamic parameters recorded at the various stimulation protocols. (Ao dia- mean aortic root diastolic pressure, LV sys- mean left ventricular systolic pressure, SVI- Subendocardial Viability Index, LVedp- left ventricular end-diastolic pressure, LVsv- left ventricular stroke volume).

	Pacer	1:2 mode		1:1 mode	
	off	25 Hz	50 Hz	25 Hz	50 Hz
Ao dia mmHg	60.3 ±2.9	62.1 ±2.5	63.7 ±2.7	64.3 ±2.0	65.7 ±2.6
LV sys mmHg	77.4 ±3.2	65.7 ±1.8	59.6 ±2.8	61.2 ±1.7	56.8 ±2.0
"SVI"	1.8 ±0.2	2.1 ±0.2	2.4 ±0.2	2.4 ±0.2	2.6 ±0.2
LV edp mmHg	6.8 ±0.3	6.7 ±0.3	6.8 ±0.3	6.8 ±0.3	6.7 ±0.3
LV sv ml	17.4 ±1.5	17.5 ±1.5	17.3 ±1.5	17.6 ±1.3	17.7 ±1.2

All data is given as the mean ± standard error. Statistical analysis was by paired t-test, and by two-way analysis of variance, with covariate and repeated measures, using SPSS-PC software (SPSS Inc., Chicago, IL). Statistical significance was set at the $p < 0.05$ level for all analyses.

Results

Representative pressure and flow recordings taken with the stimulator *off*, and *on* at the various assist settings, are shown in Figure 2. Relevant hemodynamic measurements are shown in Table 1, and Figures 3-5. Animal heart rates varied from 90 to 135 per minute during experiments, but did not change during individual recordings.

Stimulator off versus 25 Hz 1:2 assist

During SMV counterpulsation, a biphasic response in aortic root diastolic pressure was observed, with an early augmentation of diastolic pressure being largely offset by an end-diastolic fall related to SMV filling. As a result, mean aortic diastolic pressure was only modestly elevated (60.3 ± 2.9 mm Hg with stimulator *off*; 62.1 ± 2.5 at 25 Hz, 1:2 mode; $p < 0.05$). The pattern of coronary blood flow mirrored that of aortic root pressure changes, with a degree of flow reversal being evident at end-diastole. As a result, at this lowest assist setting, effective mean flow was not significantly improved (*off* 28.9 ± 3.7, *on* 29.9 ± 3.8 ml/min, p=ns).

A reduction in mean LV systolic pressure was achieved

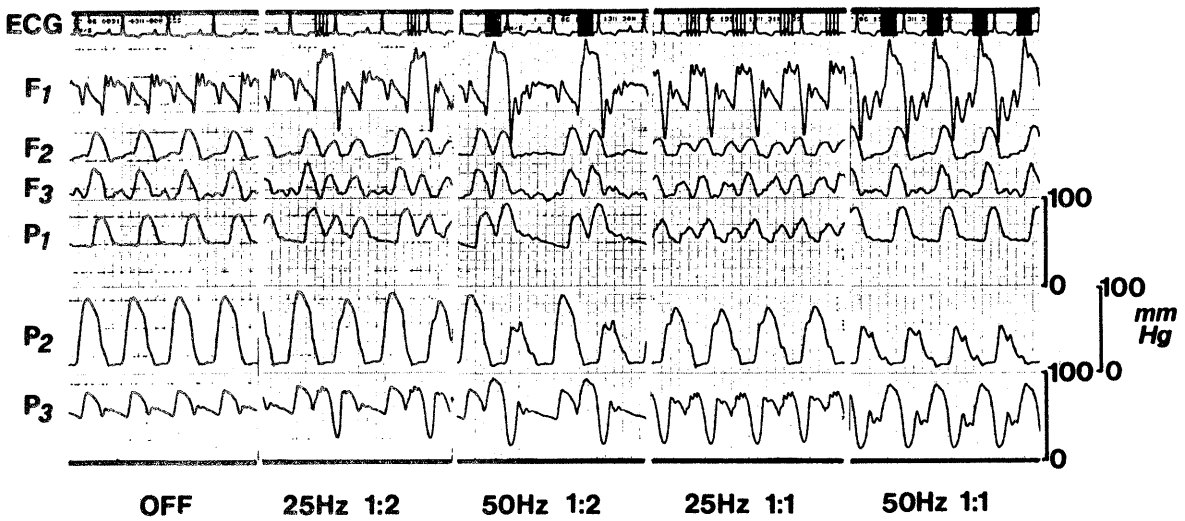

Figure 2. Representative tracings taken from one animal after 1 hour of continuous SMV counterpulsation, at each SMV stimulation setting. Flow axes have been omitted for clarity. (Abbreviations correspond to those in Figure 1).

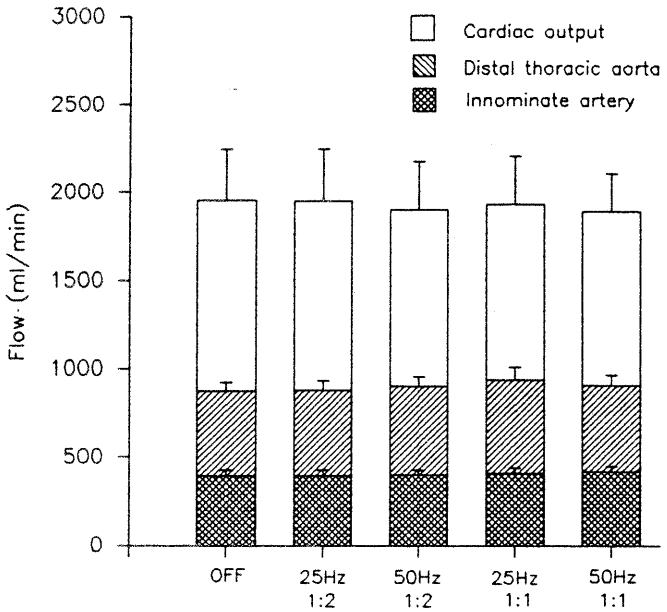

Figure 3. Regional aortic blood flow measurements, at the various SMV stimulation settings.

during assist (*off* 77.4 ± 3.2 mm Hg, *on* 65.7 ± 1.8, $p < 0.05$). As a consequence, calculated LV stroke work was lowered by 15% (*off* 1.34 ± 0.12, *on* 1.13 ± 0.12 x 10^6 ergs, $p < 0.05$). This, together with aortic diastolic augmentation, was reflected in a 17% increase in the Subendocardial Viability Index (SVI). No changes were observed in LV stroke volume, and measured flows in the innominate artery and distal thoracic aorta also remained unchanged (Figure 3).

Influence of altering pattern of SMV stimulation

Both a 50 Hz burst stimulation frequency and a 1:1 assist mode achieved a significant increase in coronary flow, up to 16% higher than with stimulator *off* (Figure 4). The extent of LV off-loading was also increased in a progressive manner with more intense stimulation protocols, with a maximal reduction in LV stroke work of 34% being achieved (Figure 5). The relative influence of altering SMV burst stimulation frequency and/or synchronization

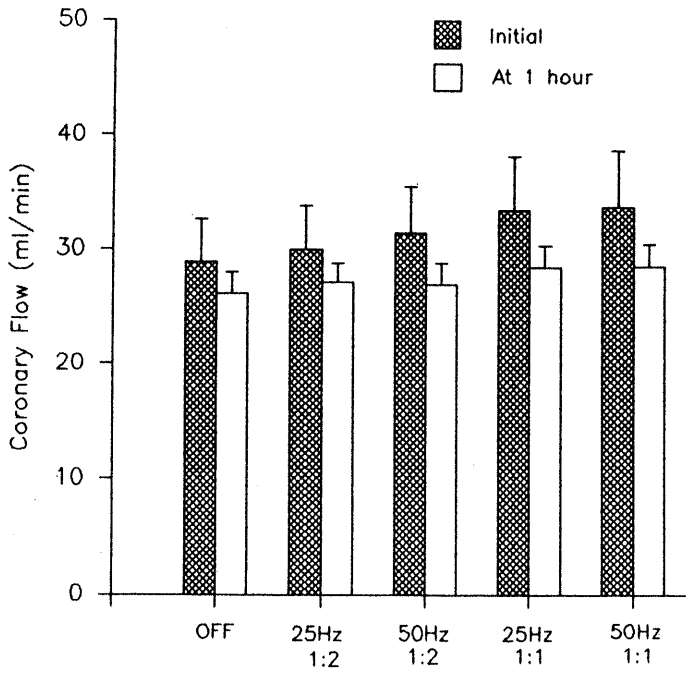

Figure 4. Coronary flow measurements, both initial and after 1 hour of counterpulsation.

rate on LV off-loading and coronary flow, was analyzed by two-way analysis of variance. Burst frequency, rather than synchronization ratio (1:2 vs 1:1), emerged as the significant variable influencing both coronary flow and LV off-loading ($p < 0.05$). Distal aortic pressure changes highlighted the influence of SMV counterpulsation on the systemic circulation (Figure 6). With increasing SMV stimulation, progressive systolic unloading of the LV resulted in a 13%-27% fall in peak systolic pressure. This was accompanied by a reciprocal rise in mean diastolic pressure of from 10%-24%, such that mean perfusion pressure was preserved at all assist settings. The influence of burst stimulation frequency on SMV function is illustrated in Figure 7. As expected, SMV stroke volume was greater at 50 Hz stimulation (5.3 ± 0.3 ml at 25Hz vs 7.9 ± 0.8 ml at 50 Hz, $p < 0.05$).

Measurements after 1 hour of pumping

After 60 minutes of continuous counterpulsation, SMV function was relatively stable (Figure 7). Although the numbers in this group were small ($n = 4$), the degree of LV stroke work reduction continued to be significant ($p < 0.05$), and was comparable with that achieved initially (Figure 5). The extent of LV off-loading is well illustrated by the pressure-volume loops shown in Figure 8, taken from one animal after 1 hour of counterpulsation. The modest changes in coronary flow seen initially were no longer evident after 1 hour (Figure 4).

Discussion

Physiologic benefit from aortic diastolic counterpulsation with the IABP is believed to derive from a combination of systolic unloading, which reduces myocardial work, and diastolic augmentation, which enhances coronary blood flow [7, 21, 23]. The present study has demonstrated that SMVs connected in circulation with the thoracic aorta can reproduce both features of IABP assist, thereby favorably influencing the myocardial oxygen supply/demand ratio.

Various techniques for generating counterpulsation with skeletal muscle have been reported previously. One proposal has been to wrap the thoracic aorta with muscle [8, 13, 20], such that, when appropriately stimulated, diastolic counterpulsation is achieved by intermittent compression of the aorta. While blood-surface interactions are avoided with this method, a serious limitation is imposed by the relatively small blood volume displacement achieved. This problem has been addressed by enlarging the aorta with a patch [8], and significant diastolic augmentation has been reported in short-term studies. However, the effect was only transient, since unconditioned muscle was used, and muscle fatigue intervened after a few minutes. However, Pattison et al [20] reported effective diastolic pressure augmentation for up to 28 days in sheep, when the latissimus muscle was wrapped around the descending thoracic aorta and stimulated every fourth cardiac cycle. Sub-endocardial Viability Index (SVI), which has been used clinically during aortic counterpulsation as a reflection of myocardial oxygen supply/demand balance, was increased by 12-89% on each augmented beat. However, evidence of left ventricular systolic unloading was not provided.

An alternative approach has been to develop a skeletal muscle-driven counterpulsation assist device, connected in parallel with the thoracic aorta, and powered either pneumatically or hydraulically by a pouch placed beneath the intact latissimus dorsi muscle [14, 16]. Peak diastolic pressure augmentation of 69% has been achieved, with an

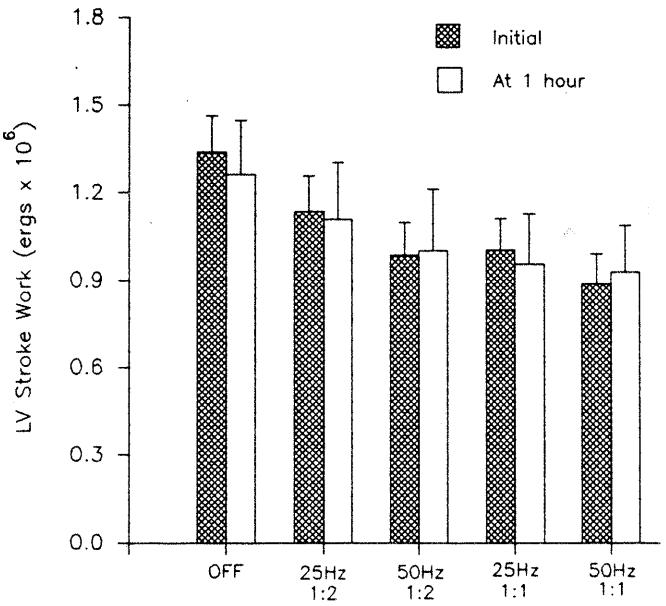

Figure 5. Left ventricular (LV) stroke work, both initial and after 1 hour of counterpulsation.

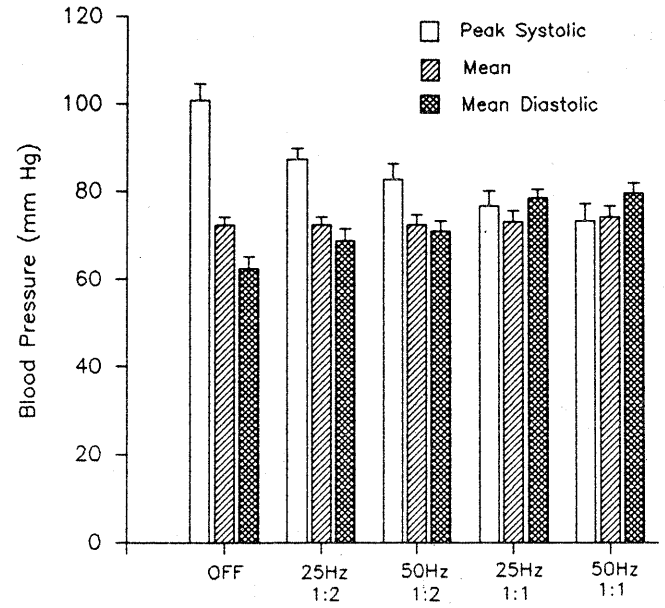

Figure 6. Distal aortic pressure measurements, at the various stimulation settings.

accompanying systolic pressure reduction of 11%, and increase in SVI of around 53%. However, in these studies aortic end-diastolic pressure reduction was not consistently achieved, and measurements of left ventricular performance were not reported. A pneumatic-powered device appeared to be the more effective, but continual leakage of air or fluid from such a system may pose problems for long-term use.

Recently, Lee and co-workers [15] have stressed the importance of documenting a reduction in left ventricular systolic work, rather than simply diastolic pressure augmentation, during arterial counterpulsation. They have evaluated left ventricular performance in dogs during skeletal muscle-powered, extraaortic counterpulsation, and reported a mean reduction in systolic left ventricular wall stress of 29%. However, unconditioned muscle was used in these experiments, and thus readings were taken for only 15 seconds to avoid muscle fatigue. The precise

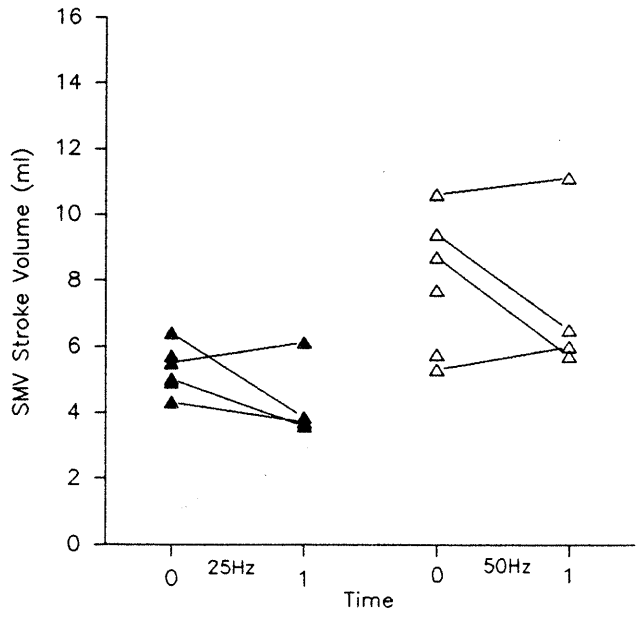

Figure 7. SMV stroke volume of individual animals, at 25 Hz and 50 Hz stimulation frequencies, and after 1 hour of counterpulsation.

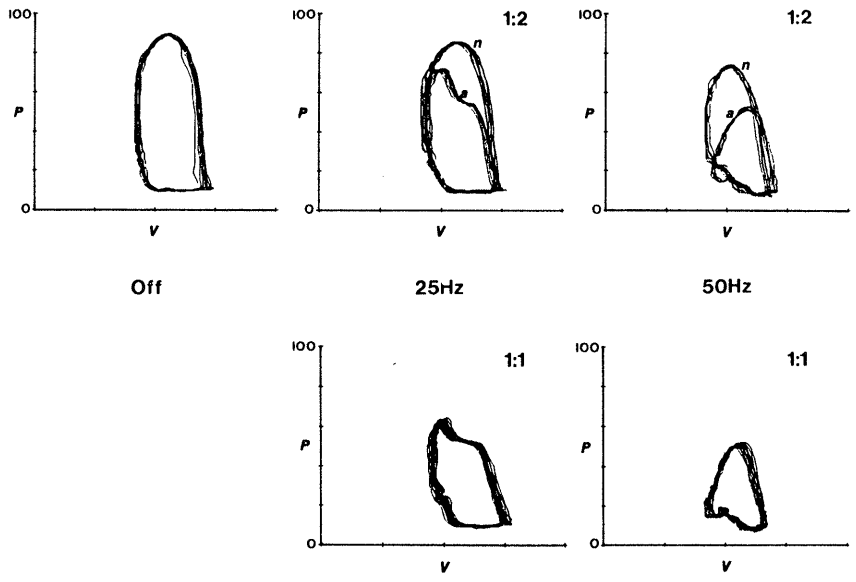

Figure 8. Pressure-volume (P-V) loops taken from one animal after 1 hour of counterpulsation, to show the influence of differing stimulation protocols on LV performance. At 1:2 assist mode, assisted (a) and non-assisted (n) beats are labelled. LV stroke work is represented by the area enclosed by the loop. Pressure units are mm Hg, and relative volume change is given by each interval on the volume axis, which represents 15 ml.

relevance of these findings to a clinical setting is questionable, however, since muscle transformation to a fatigue-resistant state, necessary for long-term use, is associated with appreciable reductions in both contractile force and speed [25].

The construction of SMVs as auxiliary blood pumps is a further option which has been pursued by this laboratory over the last few years. Due to the contractile characteristics of skeletal muscle, which differ from those of cardiac muscle, preloads of 50-150 mm Hg have been shown to be necessary to extract optimal performance [26]. It is probably for this reason that SMVs have proved most successful in circulation as arterial counterpulsators, since their high preload requirements are met by systemic blood

pressure. Earlier, we had reported that, when connected to the thoracic aorta, SMVs were capable of generating diastolic counterpulsation for several weeks in dogs, though repeated thrombo-embolic complications ultimately caused death from renal failure [1]. Later experience with SMVs lined with autogenous pleura or pericardium demonstrated that thrombo-embolism could be avoided, resulting in survival for many months [2]. In one animal an autogenously-lined SMV provided diastolic counterpulsation for over two years [19, 24]. More recently, experimentation with a new mandrel design appears to have reduced embolic complications further, without the need for artificial linings or formal anticoagulation (unpublished data). Although we have previously characterized SMV performance during aortic counterpulsation [18], the impact on left ventricular performance has received little attention. Effective aortic diastolic pressure augmentation *per se* does not necessarily signify the provision of left heart assist, particularly as systolic unloading of the heart has not been a consistent observation in previous experiments. One reason may be related to the SMV configuration used. Because SMVs have previously been connected to the descending thoracic aorta, at a distance from the aortic valve, pressure changes associated with SMV filling may be dispersed to some extent by the elasticity of the intervening aortic wall. Furthermore, because previous configurations have allowed SMV filling to occur from both proximal and distal aortic segments, the resulting degree of afterload reduction may have been attenuated.

In the present study, both the proximal location of the SMV on the aorta, and the inclusion of a valved conduit to focus afterload reduction close to the native aortic valve, have resulted in clear evidence of cardiac assist. At a stimulator setting of 25 Hz and 1:2 contraction rate, known to be well-tolerated by SMVs during long-term use [2, 4, 24], left ventricular stroke work was reduced by 15%. SVI was increased by 17%, comparable with that reported for the IABP [21]. A higher burst stimulation frequency (50 Hz) further augmented the degree of cardiac assist achieved, to an extent greater than that achieved by a 1:1 synchronization mode. Although it is difficult to draw conclusions from this finding, in view of the small number of animals used, it is possible that the slow contractile properties of conditioned skeletal muscle may have prejudiced both SMV ejection and filling within the short R-R interval associated with 1:1 assist. This may prove less relevant for a human application, since, with a heart rate of approximately half that of dogs, a 1:1 synchronization may be better tolerated. However, it is currently unclear what maximal level of stimulation will prove appropriate for long-term assist, since there is evidence to suggest that skeletal muscle may fatigue more readily under more intense stimulation conditions [6].

While left ventricular stroke work was appreciably reduced by counterpulsation, stroke volume did not change during the brief period of recording. Systemic perfusion pressure also remained stable. Moreover, since this SMV configuration did not disturb regional aortic blood flow, it is likely that renal flow was preserved. This contrasts with a recent report of experimental IABP counterpulsation in dogs, where balloon inflation was associated with a redistribution of thoracic aortic blood flow in favour of the arch vessels, and to the detriment of renal blood flow [22].

The marginal improvement in coronary blood flow associated with SMV counterpulsation may represent a potential limitation of the stimulator used. Mean diastolic pressure in the aortic root, a major determinant of coronary blood flow, is related not only to the SMV-generated diastolic peak, but also to the trough associated with SMV filling, and responsible for left ventricular off-loading. To some extent the two influences can be balanced by adjusting the stimulator settings, but in the present study the sharp reduction in aortic end-diastolic pressure invariably resulted in some reversal of coronary flow, largely offsetting an initial increase. The stimulator used did not permit timing manipulations beyond 90% of the R-R interval, limiting the extent to which coronary flow reversal could be minimized. It is worth bearing in mind, however, that the increase in coronary flow produced by the IABP has been reported by some workers to be modest, ranging from 5-15% [12, 23].

In conclusion, at a time when some other forms of skeletal muscle assist, such as cardiomyoplasty, have failed to demonstrate consistent hemodynamic improvement [3, 10, 11, 17], this study has illustrated the potential of an SMV-counterpulsation system for enhancing left ventricular performance, improving coronary flow, and preserving systemic perfusion.

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