

Skeletal Muscle Ventricle: 1993 Up Date

Susumu Isoda, Hidehiro Nakajima,⁽¹⁾ Robert L. Hammond,⁽¹⁾ Gregory A. Thomas,⁽¹⁾ Huiping Lu,⁽¹⁾ Hisako O. Nakajima,⁽¹⁾ Ali D. Spanta⁽¹⁾ and Larry W. Stephenson⁽¹⁾

First Department of Surgery, Yokohama City University, School of Medicine, Yokohama, Japan and (1) Division of Cardiothoracic Surgery, Department of Surgery, Wayne State University, Detroit, Michigan, U.S.A.

Abstract

Skeletal muscle ventricles (SMVs) constructed from electrically conditioned latissimus dorsi muscle (LDM) may become an alternative for assisting the failing heart. Recent experiments detailing improvements in SMV performance, change in SMV size, application of valved conduits, improvements in blood surface interaction, different circulatory configurations, long term reliability, and low cardiac output models are described. Left and right heart circulatory assist using SMVs has been demonstrated in both acute and chronic settings. For these studies, configurations used to connect SMVs to the circulation have included configurations of left atrial-aortic bypass, left ventricle apico-aortic bypass, aortic counterpulsators, cavo-pulmonary bypass, and right ventricular-pulmonary bypass. One SMV used as an aortic counterpulsator functioned effectively in the circulation for more than 27 months. Thromboembolism, which was an important cause of mortality in early series, is no longer a major lethal complication (mortality 4.5%). However, SMV rupture continues to occur (mortality 34%). Although problems remain to be solved, the goal of the SMV, permanent circulatory assist without the limitation of an external power source, seems within reach.

Keywords: skeletal muscle ventricle, circulatory assist device, heart failure.

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Recent advances with skeletal muscle research for cardiac assists can be divided into two principle areas: cardiomyoplasty and skeletal muscle ventricles (SMVs). Cardiomyoplasty involves wrapping the muscle around the heart and stimulating the graft to contract during cardiac systole in order to reinforce hypokinetic myocardium or repair myocardial defects. This procedure was first applied clinically by Carpentier and Chachques in 1985 in France and by Magovern in the United States in 1986 [14, 35]. Clinical experience with this technique now exceeds 300 patients around the world. The disparity between the wide-spread symptomatic improvement of these patients and the small amount of improvement in objective data in most patients has created much interest in cardiomyoplasty's mechanism of action [6, 9, 42]. Recent studies suggests that the efficiency of myocardial work and oxygen consumption may improve after cardiomyoplasty [26, 30, 44].

SMVs are separate pumps constructed from skeletal muscle which are electrically stimulated to contract synchronously with the heart for circulatory assistance. SMVs are not connected directly to the heart, which makes analysis easier since SMV function can be measured independent from cardiac function. Recent research has been directed toward improving the efficacy of the SMV for assisting the circulation and long-term reliability. This review article is focused on recent developments in SMV research.

SMV Construction

Various skeletal muscles, such as diaphragm, quadriceps femoris, rectus abdominis, and gluteus maximus have been studied for their potential to assist the heart [24, 28, 33, 60]. The LDM is most commonly used because of its bulk, the absence of essential duty for shoulder motion, and the mobility with which this muscle and its neurovascular pedicle can reach into the thorax [58]. Constructing a SMV requires dissection of the muscle and wrapping it around a

mandrel [23, 56]. A stimulating electrode is placed around the thoracodorsal nerve and connected to a neuro-muscular stimulator. The inlet/outlet orifice of the SMV is made of Dacron felt. The completed SMV is positioned either subcutaneously or within the hemithorax.

Vascular Delay

After construction, the SMV is left unstimulated for several weeks to allow recovery of blood perfusion to the muscle. This period has been termed "vascular delay" [3]. Canine and human LDM are perfused principally by the thoracodorsal artery with collateral blood flow from the intercostal arteries. To mobilize a LDM flap, the collaterals must be ligated. Mannion et al. showed recovery of intramuscular blood flow 3 weeks after ligation of collaterals [39]. There is the potential for damage to the ischemic portion of the muscle by electrical stimulation before this period. SMVs after 18 weeks of vascular delay demonstrated better performance than after 4 weeks of vascular delay [56]. This suggests that the development of a vascular network in LDMs might take more than one month.

Electrical Conditioning

The fatiguable character of skeletal muscle is changed into one of fatigue resistance via low frequency electrical stimulation for several weeks. Enhanced cardiac type work capacity is obtained through an aerobic dominant metabolism [40, 53, 57]. The electrical stimulation is done after the vascular delay period. Mannion et al. showed phenotypic changes in canine LDMs from a fatiguable to fatigue resistant state after electrical conditioning for 6 weeks at either 2 or 10 Hz [37]. Clark et al. showed increased

oxidative capacity of conditioned canine LDM using phosphorus-31 nuclear magnetic resonance after conditioning for 8 weeks at 25 Hz [17].

Performance of SMV

After vascular delay and electrical conditioning, the SMV is ready to assist the circulation. Performance of the various types of SMVs have been investigated in a mock circulation and in the systemic circulation. Among the factors that regulate performance of the SMV are the relationships between preload and afterload, volume size, and position.

1. Performance studies

The performance of canine SMVs evaluated previously are summarized in Table 1. The stroke work of the SMVs ranged from 40 mJ to 92 mJ and the power output ranged from 36 mW to 84 mW. The stroke work ranged from 1/3 to 2/3 of that of the left ventricle and from 2 to 4 times that of the right ventricle. The power output ranged from 1/9 to 1/2 of that of the left ventricle [4, 10, 22, 32, 38].

2. Volume Size of SMV

The size of the SMV effects the performance with respect to preload and afterload. Assuming a thin walled cylindrical shape for the SMV, Laplace's equation states that $P = T/R$ (P : transmural pressure, T : Tension in the wall, R : radius of SMV). For example, halving the radius and thereby doubling the wrap layers, results in a 4-fold development of transmural pressure with one quarter of the original volume ($V = \pi R^2 L$). Thus, the pressure generation capability and the chamber size are inversely propositional. Oda et al. demonstrated that canine, non-condi-

Table 1. Performance of SMVs.

Test	BW	Size	Stroke Work	Power Output	AL/PL	VD/EC	others
circulation ³⁸	13.1 ± 1.5 kg	16 ml	65 ± 24 mJ (LV183 mJ, RV22 mJ)	60 ± 22 mW (LV540 mW, RV60 mW)	120/ 30mmHg	3 w/ 2 Hz; 6 w	extra @ 25 Hz
mock circuit ⁴	9-13 kg	17 ml	40 ± 14 mJ	36 ± 13 mW	80+/ 40mmHg	4-6 w/ 25 Hz; 2 w	extra @ 25 Hz
mock circuit ¹⁰	16.7 ± 1.4 kg	69 ml	68 ± 14 mJ	37 ± 8 mW	80+/ 15 mmHg	2-3 w/ 2 Hz; 6-8 w	extra @ 25 Hz
mock circuit ²²	10.6 ± 0.4 kg	25 ml	44 ± 5 mJ (LV57 mJ, RV20 mJ)	44 ± 5 mW (LV114 mW, RV40 mW)	80+/ 10 mmHg	3w/ 2 Hz; 6 w	intra @ 33 Hz
circulation ³²	16-20 kg	2.5 ml /kg	92 ± 35 mJ (LV101 mJ)	84 ± 32 mW (LV185 mW)	90/ 90 mmHg	3w/ 2 Hz; 6 w	intra @ 33 Hz

Notes: BW = body weight, Size = volume of mandrel, AL/PL = afterload / preload, VD/EC = vascular delay / frequency and duration of electrical conditioning, LV = left ventricle, RV = right ventricle, intra = intrathoracic position, extra = extrathoracic position, @ indicates stimulation frequency, 1erg = 1 g x cm²/sec², 1 J = 1 kg x m²/sec², 10⁴ erg = 1 mJ, 1 mW = 1 mJ/sec.

tioned, large SMVs (4 ml/BW kg) provided higher stroke work under lower preloads and afterloads, while they provided a lower ejection fraction than small SMVs (1 ml/BW kg) [51]. Hammond et al. showed better performance with large canine conditioned SMVs (45 ml) than with small ones (17 ml) [20].

Bridges et al. developed a mathematical model for SMVs using wall thickness as part of the equation. He estimated that a size of approximately 50 ml was an adequate volume for a 15 kg dog with 100 gram LDM pumping with a preload of 20 mmHg and an afterload of 80 mmHg [12]. The large canine SMVs (69 ml) performed well with a low preload of 5 to 15 mmHg (Table 1) [10]. In recent applications of SMVs in circulation, a size of 2.5 ml/kg of body weight has generally been used [19, 23, 32, 45]. This ratio is based on canine experiments and may change in accordance with LDMs in other species or different applications.

3. Position of SMV

For clinical application, it may be preferential to place SMVs inside the thorax to avoid external compression and also for cosmetic reasons. In our experimental models, extrathoracic SMVs have been used for both ease of construction and subsequent ease of evaluation. Intrathoracic SMVs provide easier surgical access for connection to the heart and great vessels [23]. At a preload of 10 mmHg, the stroke work of intrathoracic SMVs was approximately half of that of the left ventricle [22] (Table 1). When connected to a mock circulation device, intrathoracic SMVs provided higher stroke work than extrathoracic SMVs against low preloads (5 to 10 mmHg) and an afterload of 30 mmHg [48]. The combination of suitable size and intrathoracic position make it possible to apply SMVs in low pressure systems like the left atrium [23]. We feel that the advantages of intrathoracic SMVs are 1) need for shorter conduits to connect to the circulation, 2) less adhesions to non-mobile tissue which may restrain the SMV wall movement and 3) protection from external compression. A disadvantage is the possibility of pulmonary compression resulting in decreased pulmonary function [43, 46].

4. Performance Evaluation during Low Cardiac Output.

SMV function has been evaluated during pharmacologically induced low cardiac output. Administration of a β -blocker causes temporally low cardiac output, hypotension and high LV end-diastolic pressure [19, 60]. SMVs have demonstrated a relatively greater degree of cardiac assist during the periods of low output than when the cardiac function is normal. The percent changes in systolic unloading, diastolic augmentation and cardiac output secondary to SMV contraction were greater during pharmacologically induced low cardiac output than with normal cardiac function.

Connecting SMVs to the Circulation

Various configurations have been investigated for connecting SMVs to the circulation. To assist the right heart, SMVs have been interposed between the vena cavae and pulmonary artery, the right atrium and the pulmonary

artery, and the right ventricle and pulmonary artery. To assist the systemic circulation, SMVs have been interposed between the aorta and the aorta as aortic counterpulsators, the left atrium and the aorta, and the left ventricle and the aorta.

1. Applications to Right Heart Assist

In 1987, Macoviak et al. constructed canine, conditioned, tubular shaped SMVs with valves to pump blood from the right atrium to the pulmonary artery and ligated the right coronary artery. The animals survived with functioning SMVs for up to 20 hours [34]. Bridges et al. used conditioned SMVs interposed between the inferior and superior vena cavae and the pulmonary artery [11]. Complete right heart bypass was maintained for 4 hours with a central venous pressure of 13 mmHg. Watanabe et al. also reported cavo-pulmonary bypass using canine conditioned SMVs. He observed a 2-fold increase in cardiac output in an acute experiment [62]. Niinami et al. used conditioned SMVs with valved conduits as pulmonary counterpulsators. These SMVs were between the right ventricle and the pulmonary artery, resulting in effective assistance of right ventricular function for 4 hours [50]. Cardiac output was increased by 30% after 3 hours with counterpulsation by the SMV. Niinami et al. also applied this configuration in a chronic setting [49]. Cardiac output increased at 3 weeks by 11% during SMV counterpulsation. One animal survived for 18 weeks. Reduction in the size of the SMV over time hindered long-term SMV function in this configuration. It is possible that pressures of the normal pulmonary circulation are too low to maintain appropriate resting muscle fiber length and these low pressures result in reduction of chamber size.

2. Applications for Left Heart Assist

During SMV performance as a left heart assist device not only is stroke work generated directly by the SMV, but also "phase transfer" occurs. This refers to the amount of stroke work delivered to the SMV during a cardiac systole. During SMV contraction this work is then transferred back to the circulation. While this may not result in work generation by itself, it does contribute significantly to myocardial perfusion and left ventricular systolic unloading. Several indicators are commonly used to evaluate left heart assist by counterpulsation. The tension time index (TTI), which is the area under the systolic portion of left ventricular pressure trace, is representative of myocardial oxygen consumption. Left ventricular systolic unloading is indicated by a decrease in the TTI. Increase in peak or mean diastolic pressure represents diastolic augmentation. The diastolic pressure time index (DPTI), which is the area under the diastolic portion of arterial pressure, correlates with oxygen availability for myocardium. The endocardial viability ratio (EVR) = $DPTI / TTI$, representative of myocardial oxygen supply and demand, is improved by both diastolic augmentation and systolic unloading [54].

a. Aortic Counterpulsator

Skeletal muscle has been investigated as an aortic counterpulsator using three different approaches: 1) aortic wrap, 2) muscle powered assist devices, and 3) SMVs. The aortic wrap with skeletal muscle was introduced by Kantrowitz in 1959 [25]. Recently Chachques et al. and Pattison et al. reported wrapping muscle around the aorta with non-conditioned goat and sheep LDM [15, 52]. Muscle powered assist devices are mechanical pumping chambers energized by skeletal muscle. In 1987, Chiu et al. placed a polyurethane surfaced chamber beneath the canine LDM and connected it to the aorta as an aortic counterpulsator [16]. Kochamba et al. constructed an aortic counterpulsator hydraulically powered by the non-conditioned LDM [27]. Anderson et al. constructed pneumatically driven counterpulsators energized by canine SMVs [7]. The animals survived for 2 to 4 weeks during continuous pumping. Half of the animals died from thromboembolic complications. Muscle powered assist devices have an advantage of flexibility for both their positioning and design geometry. The disadvantages are thromboembolism, power transfer loss, and the necessity of frequent gas or fluid adjustments in their closed systems.

In 1987, Acker et al. used non-conditioned, tube-shaped SMVs as aortic counterpulsators [2]. The animals tolerated SMV counterpulsation for up to 11 weeks. The mean diastolic pressure increased by 20 mmHg. Short axis echocardiography at the middle portion of the SMV demonstrated a 70% decrease in cross sectional area during SMV

contraction in one animal. Anderson et al. connected canine conditioned SMVs to the descending aorta with e-PTFE (expanded polytetrafluoroethylene) bifurcation grafts. The aorta was ligated between the two limbs of the graft to obtain obligatory flow through the SMV [5]. In this study, diastolic peak pressure increased by 30% after 40 weeks of continuous pumping. One animal in the series survived for 27 1/2 months during continuous aortic counterpulsation with the SMV (Figure 1). There was an increase in diastolic peak pressure of 20 mmHg on post-operative day 836 of SMV functioning. This is the longest survival of any laboratory animal or human with a functional circulatory assist device [41]. In another study, Pochettino connected non-conditioned SMVs to the descending aorta [55]. One animal in his study, demonstrated a 39% increase in diastolic peak pressure at 28 weeks.

Valved-SMV's have also been used as aortic counterpulsators (Figure 2). In 1986, Mannion et al. developed a model that controlled filling pressure with a valved device. He connected the SMV as an aortic counterpulsator in an acute setting [36, 38]. Fietsam et al. connected canine, conditioned single-valved SMVs to the descending aorta as aortic counterpulsators and followed them for several months. He demonstrated a 24.2% increase in diastolic mean pressure [19]. Under -blocker induced low cardiac output, the SMV demonstrated marked circulatory assist. Cardiac output increased by 16.3%, left ventricular systolic unloading (TTI) was 14.9% and the myocardial supply/demand ratio (EVR) increased 34.1%. Hooper et al.



Figure 1. Hemodynamic recording of one animal one year after the SMV was connected to the descending aorta as a counterpulsator. The SMV continuously pumped at a ratio of 1:2 during cardiac diastole. Asteriks (*) mark diastolic augmentation.

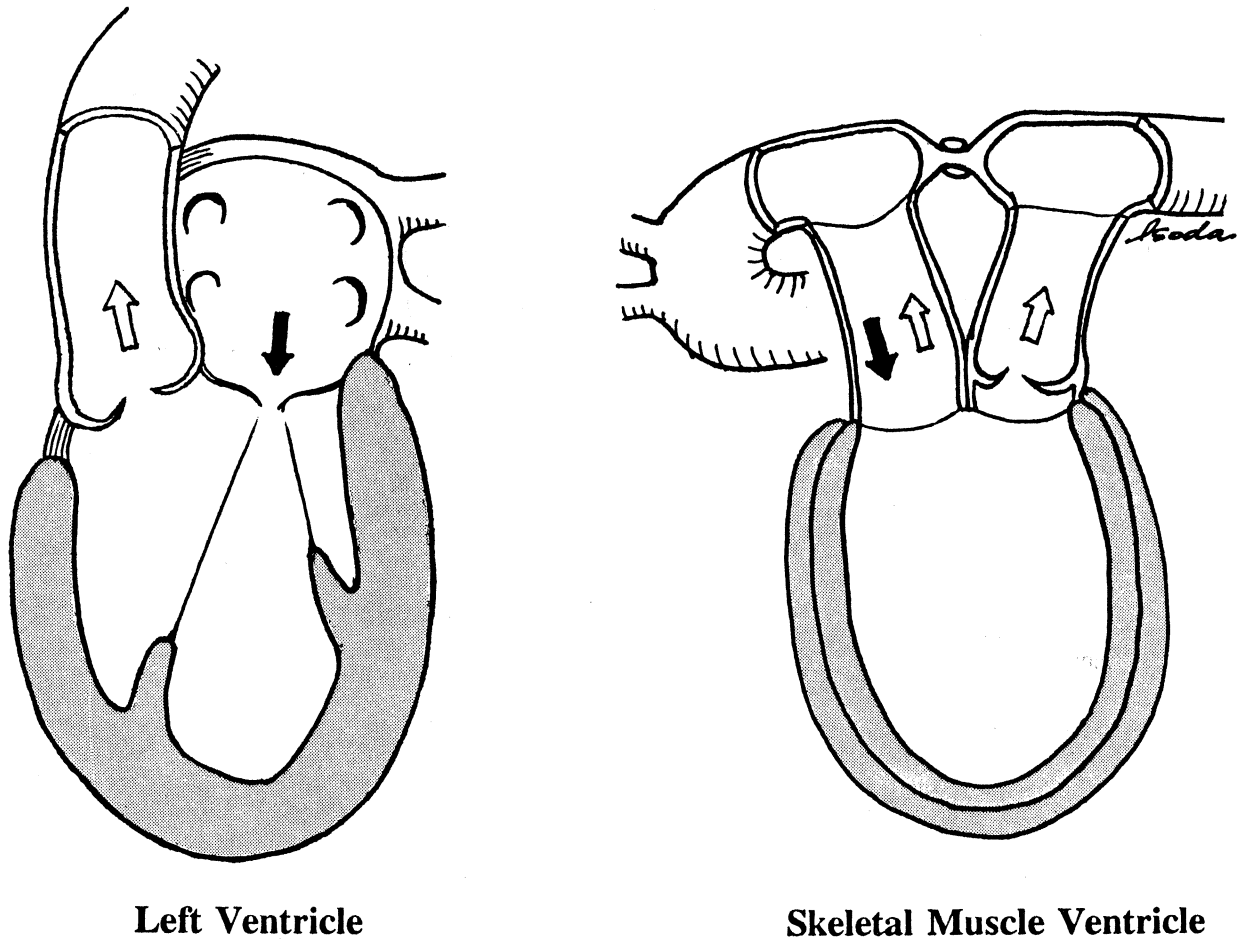


Figure 2. Schematic drawing of left ventricle and skeletal muscle ventricle (SMV). The SMV is connected to the aorta using two conduits. The distal conduit has a valve to prevent regurgitant flow from the distal aorta. SMV contraction provides both proximal and distal flow, resulting in diastolic augmentation with an increase in coronary flow. SMV filling from the proximal conduit provides left ventricular systolic unloading.

studied intrathoracic, single-valved SMVs as counterpulsators in an acute setting [21]. These SMVs demonstrated marked systolic unloading (left ventricular stroke work decreased by 15%). The diastolic peak pressure increased, exceeding systolic peak pressure, and there was a marked increase in coronary flow velocity. Nakajima et al. connected an intrathoracic, single-valved SMV to the descending aorta. One animal in the series survived for 216 days [43]. The SMV demonstrated systolic unloading (TTI decreased 19.9%), diastolic augmentation (DPTI increased 9.9%), and improvements in myocardial oxygen supply/demand (EVR increased 32.4%). While non-valved SMVs have rapid filling and regurgitant flow during the relaxation period, valved-SMV prevent distal regurgitant flow and provide slower filling. By these mechanisms, more efficacious SMV function can be provided.

b. Left Atrium - Aorta Bypass

Hooper et al. constructed canine, conditioned, intrathoracic, double-valved SMVs which were connected be-

tween the left atrium and the descending aorta [23]. In this acute study, 21% of total systemic flow was bypassed through the SMV and was pumped to the aorta during diastole, generating a peak pressure of 71 mmHg at a left atrial pressure of 12 mmHg. After 4 hours of continuous pumping, bypass flow was maintained, equaling 70% of the starting value. This study demonstrated that SMVs can function in the systemic circulation at physiologic preloads.

c. Left Ventricle - Aorta Bypass

Drinkwater et al. and Neilson et al. interposed distensible chambers wrapped with non-conditioned, canine rectus abdominis muscle between the left ventricle and the aorta [18, 47]. Stevens et al. also connected non-conditioned SMVs in a left ventricle - aorta configuration. They demonstrated that cardiac output increased by 31% under β -blocker induced low cardiac output [60]. Lu et al. constructed canine, intrathoracic, double-valved SMVs, which had been electrically conditioned and connected between the left ventricular apex and descending aorta

[32]. After 3 hours of continuous pumping, 40% of the systemic blood flow was pumped by the SMVs. There was a 73% increase in diastolic mean-pressure. EVR increased by 63%. The advantage of this configuration is its marked systolic unloading and diastolic augmentation. The disadvantage may be an increased rate of thromboembolism because of the absence of obligatory flow and also the potential for damage to the myocardium where the left ventricular conduit is connected.

Future Prospect for SMVs

At present, the long term course of SMVs in circulation has uncovered complications such as SMV rupture and thromboembolism which were not apparent in acute studies. Investigation is under way to solve these problems so that SMVs can be used clinically.

1. SMV Orifice Connection

After connection of SMVs to the systemic circulation, the most frequent fatal complication is SMV rupture. SMV rupture occurred a 34% [15/44] of dogs in a recent series [46]. The mechanism of SMV rupture is not yet clear. Rupture has generally occurred at the suture line between the muscle edge and the Dacron felt attached to the base of the SMV. Possible causes include surgical technique, ischemia of the muscle, mechanical stress between the orifice of the SMV and the vascular prosthesis and infection. SMV rupture may not be secondary to muscle weakness, but rather the operative technique since the middle and the apical portions of the SMV wall rarely rupture [46]. It is expected that SMV rupture may be prevented by modification of the operative procedure.

2. Blood Surface Interaction

The major thrombogenic factors can be grouped into three categories: the blood vessels, aberrant blood flow, and the constituents of the blood [29]. Interaction between blood and the SMV surface also can be grouped according to three factors (Table 2). Several approaches have been tested to obtain better blood-contacting surface of the SMVs (Table 3).

a. Blood Surface Material

Synthetic material linings, autogenous linings, and fibrous linings have been utilized as blood contacting surface for SMVs. Application of e-PTFE to the pumping surface of the SMV resulted in a 40% incidence of lethal thromboembolism [2]. Subsequently, autogenous linings, either pleura or pericardium were compared to a fibrous lining. No lethal thromboembolism occurred in any of the autogenous and fibrous lining groups [5]. In regard to thrombus formation in the SMVs, pleura demonstrated a slightly lower incidence of thrombus, whereas there was no difference between pericardium and fibrous linings. Recent series of fibrous-lined SMVs showed a low rate of lethal thromboembolism (4.5%, 2/44), but a relatively high rate of thrombus formation within the SMV (55%, 24/44) [46]. Fibrous-lined surfaces are composed of a thin layer (1 mm) of reactive connective tissue that develops between the muscle and the mandrel [43]. This fibrous lining, which

Table 2. Interaction between SMVs and blood.

1. Surface Material Factors
synthetic surface (e-PTFE ² , polyurethane ^{16,60})
autogenous lining (pericardium, pleura ⁵)
fibrous lining ^{5,55}
endothelial seeding ^{31,61}
2. Hemodynamic Factors
compulsory flow (connection in series ⁵)
geometry (shape ⁵⁵)
ejection fraction, regional contractility
general status (cardiac output)
surgical technique (stenoses)
3. Constituents of Blood
coagulation control (warfarin ⁴⁹ , heparin)
platelet function (aspirin ⁵)
thrombolytic system

is still autogenous tissue, may have potential as a thrombo-resistant surface [8]. An endothelial layer is perhaps the most thrombo-resistant surface. Lelkes et al. and Thomas et al. have applied endothelial seeding to SMVs with promising results [31, 61]. Questions about adherence of endothelial cells and a possible "washout" phenomenon after connection to the circulation are currently being studied.

b. Hemodynamic Factors

To avoid blood stagnation inside the SMVs, compulsory flow has proven to be an effective approach [5]. When connected to the circulation in series, there is a higher flow velocity through the SMV than when connected in parallel. The geometry of the SMV seems to be another important factor. An ovoid shape for an SMV was reported to have a more favourable geometry than a long cone shape, which tended to promote thrombus formation at the "hindend" of the SMV [55]. Ejection fraction and regional surface contractility of SMVs may be factors that counteract blood stagnation and thrombus formation. SMVs actively eject blood, while vascular prostheses do not contract by itself. A higher ejection fraction of SMVs should also help to prevent blood stagnation [29]. For further improvements in the geometry of SMVs and to obtain better hemodynamics, comprehensive rheological studies are needed [13].

c. Constituents of Blood

Thromboembolism is also related to the constituents of the blood including clotting factors, platelet function, and the thrombolytic system [29]. Anticoagulants and anti-platelet agents are generally used to prevent thromboembolism for patients with prosthetic blood surfaces [1]. SMVs in the systemic circulation have generally been maintained with aspirin only [5, 55]. SMVs in the pulmonary circulation long-term were maintained with warfarin [49].

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Table 3. Thromboembolism in SMVs.

Configura- tion	Medication	Mandrel Shape	Type Connection	Lining	Thrombus	Embolism	Duration
<i>Left Heart Assist</i>							
Ao-Ao ²	aspirin 350 mg/d	1 = 120, d = 22, cone	tubular, series	e-PTFE	40% (2/5)	40% (2/5)	1-11 w
			saccular, T-connect	fibrous	100% (1/1)	0% (0/1)	8d
Ao-Ao ⁵	aspirin 75 mg/d	1 = 75, d = 22, cone	saccular series	pleura	50% (3/6)	0% (0/6)	3 d - 40 w
				pericardium	100% (3/3)	0% (0/3)	10 d - 12 w
				fibrous	100% (6/6)	0% (0/6)	1 d - 2 w
Ao-Ao ⁵⁵	aspirin 81 mg/d	1 =63, d = 43, ovoid	saccular, series	fibrous	25% (3/12)	17% (2/12)	1 w - 28 w
Ao-Ao ¹⁹	aspirin 75 mg/2d	1 = 45-55, d = 34	saccular, series	fibrous	not given	0% (0/7)	1 d - 18 w
Ao-Ao ⁴⁶	aspirin 75 mg/2d	1 = 45-55, d = 34, or 1 = 63, d = 43, ovoid	saccular, series	fibrous	54% (24/44)	4.5% (2/44)	1 d - 31 w
<i>Right Heart Assist</i>							
RV-PA ⁴⁹	warfarin 4 mg/d	1 = 90-100, d = 22, cone	saccular, series	fibrous	25% (2/8)	0% (0/8)	1 w / 17 w

Notes: Configuration; Ao = aorta, RV = right ventricle, PA = pulmonary artery, Shape; 1 = length (mm), d = diameter (mm), Thrombus, thrombus in SMV, Embolism; postmortem or clinical findings, Duration: period after SMV connection to the circulation.

Conclusion

From cumulative investigations in animal models, SMVs constructed of electrically conditioned LDMs show promise as tether-free circulatory assist devices without the need for an external energy source. Performance studies demonstrate that the SMVs can effectively assist both systemic and pulmonary circulations long term. The SMV of one animal continuously pumped for 27 1/2 months as an aortic counterpulsator. This is the longest reported living laboratory animal or human with a functioning heart assist device. The goal for SMVs is not merely as a bridge to the heart transplantation, but rather as a permanent alternative for the treatment of cardiac failure. Recent improvements in SMV research include variation in sizes, positions, valve utilization and circulatory configurations. Thromboembolism, the major complication in the early stages of development, is no longer a lethal problem. For clinical application, the rupture problem still needs to be improved upon.

Address correspondence to:

Larry W. Stephenson, Chief, Division of Cardiothoracic Surgery, Department of Surgery, Wayne State University,

Harper Professional Building, Suit 228, Detroit, Michigan, 48225 U.S.A.

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