Cardiac assistance from skeletal muscle: a reappraisal

Stanley Salmons *

Department of Human Anatomy and Cell Biology, School of Biomedical Sciences, University of Liverpool, The Sherrington Buildings, Ashton Street, Liverpool L69 3GE, UK

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Summary

Cardiac assistance from skeletal muscle offers an attractive surgical solution to the problem of end-stage heart failure, yet it is widely regarded as a failed approach. I argue here that this is an outdated assessment. Systematic progress has been made over the last 25 years in understanding the relevant basic science. In the light of these advances we should be reconsidering the place of skeletal muscle assist in the surgical armamentarium.

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1. Introduction

End-stage heart failure is common, debilitating, and ultimately fatal. The gold standard surgical treatment for advanced cases is heart transplantation. Although the rising prevalence of heart failure in the population creates ever higher demands for transplants, the number performed has declined since the mid-1990s because of a shortage of donors. In the United States, 2192 heart transplants were carried out during 2006 [1]. An estimated 15,000–30,000 patients would have received transplants if enough donor hearts were available [2].

As a result, a patient on a transplant list has a 25—30% chance of dying while awaiting a donor heart. For those who get the operation, the benefits have to be weighed against a high rate of coronary vascular complication and the unwanted side-effects of lifelong immunosuppression, including susceptibility to infection, the risk of renal failure, and various cancers. The cost of the procedures and drug maintenance places a heavy burden on health service provision.

Is there an alternative? Xenografts from transgenic animals could reduce waiting list mortality, but raise ethical issues and add the risk of infection by latent animal viruses to existing problems. Ventricular reduction surgery carries a high perioperative mortality, and surgeons who find it counterintuitive to discard hundreds of grams of functional myocardium will not be surprised by follow-up data indicating that dilatation will recur after 2 years. Mechanical artificial hearts pose problems of biocompatibility, haemocompatibility, and infection, and require an external power supply. They can be used as a bridge-to-transplant, but this lengthens the existing queue.

There is a further possibility: a surgical approach that provides cardiac assistance from one of the patient’s own skeletal muscles. This biological solution is free from the risks, debilitating side-effects, and costs associated with long-term immunosuppression. Donor shortage is not a problem: the patient is the donor. The patient’s own heart is not discarded, but is retained under conditions that offer the potential for myocardial recovery. This is an affordable technology that could reduce transplant waiting lists and ease the burden on health budgets. It is especially appropriate in parts of the world where other approaches, including mechanical pumps, are too costly to implement [3,4], or where there are religious objections to the harvesting or use of donor organs.

It is being ignored. Why?

1.1. The hype cycle

Industry analysts Gartner Inc. have proposed a theory of hype cycles of technological progress (http://www.gartner.com/pages/story.php.id.8795.s.8.jsp). They describe five phases:

(1) The new technology triggers enthusiastic interest and media coverage.
(2) This rises to a ‘peak of inflated and unrealistic expectations’.

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* Corresponding author. Tel.: +44 151 794 5496; fax: +44 151 794 5517.
E-mail address: s.salmons@liverpool.ac.uk.

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(3) It then falls into a ‘trough of disillusionment’ as expectations are not met and the technology becomes unfashionable.

(4) General interest remains low, but steady progress is made in understanding the real potential, limitations, and applications (the ‘slope of enlightenment’).

(5) A plateau is reached at which the technology finds its proper place, according to the benefits and available alternatives.

This cycle describes well the history of cardiac transplantation [2]. It also appears to fit skeletal muscle assist, which currently finds itself in the ‘trough of disillusionment’. Moreover, this trough coincides with what may arguably be described as the early phases, the enthusiastic interest and inflated expectations, of stem cell therapy.

In this article I describe the ‘slope of enlightenment’ that should be preparing us for the clinical re-adoption of some forms of skeletal muscle assist in a more stable and rational manner.

2. Background

2.1. Early work

Although skeletal muscle had been used before as a passive surgical biomaterial, the first attempts to exploit the active properties of muscle for cardiac assistance were made in the 1960s [5–7]. These and subsequent pioneering studies were defeated by the apparently insuperable problem of muscle fatigue.

The solution came from an unexpected quarter. I had developed an implantable muscle stimulator [8], and used it to study the effect of augmenting muscle activity in unrestrained laboratory animals for weeks and months. Under these conditions the muscles underwent a transformation even more profound than that induced by sustained endurance exercise [9–11]. Among the changes was a marked increase in fatigue resistance [10].

Although I attempted to point out the clinical relevance of the discovery [12], it was several years before it was picked up by Dr J. Macoviak, working in Dr L.W. Stephenson’s laboratory. This led to a productive and long-lasting collaboration between Stephenson, then at Philadelphia, and my group, then at Birmingham, UK.

The initial idea was to enlarge a hypotrophic right ventricle with a graft of skeletal muscle. The innovative aspect was the use of chronic electrical stimulation to induce fatigue-resistant characteristics in the graft. Stephenson called it ‘conditioning’ (not to be confused with ischaemic preconditioning) and the term stuck [13]. Macoviak and Stephenson presented the concept at the International Society for Artificial Organs in Paris in July 1981, where it attracted considerable attention. The work sparked interest in other laboratories, leading to a series of mini-symposia and seminars in Philadelphia (hosted by L.W. Stephenson, 1982), Montreal (hosted by R.-C. J. Chiu, 1984), and Birmingham (hosted by S. Salmons, 1985).

The proximity of the diaphragm made it a logical source of skeletal muscle for grafting to the heart. However, the focus soon switched to the latissimus dorsi muscle (LDM). This had a number of advantages. It was a large, flat sheet of muscle, thicker than diaphragm and non-essential, and could be mobilized on a single neurovascular pedicle. Although the LDM was on the outside of the chest wall, it could be internalized by resecting a rib and ‘posting’ it into the thorax. Other muscles have been investigated, including rectus abdominis, pectoralis major, serratus anterior, and psoas major, but the LDM remains the preferred choice.

2.2. The skeletal muscle ventricle

In Stephenson’s group, the idea evolved of using the LDM as an auxiliary heart, or skeletal muscle ventricle (SMV). This was formed by winding the muscle around a mandrel, which was then removed. The device was connected to the descending aorta and operated in counterpulsation with the host heart. By 1985 the technique was sufficiently well established experimentally for the U.S. National Institutes of Health to award a grant of nearly $1 million to Stephenson and myself to develop it further. We soon showed that a muscle conditioned and configured in this way could sustain cardiac levels of work indefinitely [14–16].

2.3. Cardiomyoplasty

Meanwhile a more conservative solution emerged from Paris. In the first successful case of dynamic cardiomyoplasty, Carpentier and Chachques removed a 1.4 kg fibroma and reinforced the thinned heart wall with a stimulated LDM [17]. Muscle contraction probably contributed little, because the conventional pacemaker used would have elicited only single twitches. It took a paper from Chiu’s laboratory [18] to remind the cardiac fraternity of something known to physiologists since the beginning of the 20th century: skeletal muscle, unlike cardiac muscle, develops significant force only when stimulated repetitively. Medtronic then developed an R-wave-triggered implantable stimulator, which enabled a train of impulses to be delivered to the muscle at the right point of the cardiac cycle.

Medtronic’s support was heavily instrumental in the technique progressing to FDA approval and clinical trials. Initially the LDM was used as a substitute for resected myocardium, but soon the muscle was being applied to the failing intact heart as a reinforcing wrap. Some 2000 such operations were performed. Aortomyoplasty, in which the muscle was wrapped around the ascending or descending aorta, was also done, on a more limited scale.

2.4. Decline and fall

There is now a widespread perception that the approach failed to live up to its promise. Why is this?

First, a limited grasp of how cardiomyoplasty actually worked led to unrealistic expectations of the haemodynamic benefits. Second, a conditioning protocol was widely adopted that produced an undesirable muscle phenotype. Third, the graft was partially ischaemic, because the blood supply was imperfectly understood. Fourth, protocols implemented in some centres created working conditions that the muscle grafts could not survive. Fifth, premature commercial
exploitation, the drive to meet regulatory requirements, and a
certain rigidity on the part of some of the personalities
involved, discouraged evolution of the recommended proto-
col, isolating clinical practice from progress in the underlying
science. Finally, withdrawal of the cardiomyostimulators
made by Medtronic Inc. left surgeons without a clinically
acceptable device.

These problems, and their solutions, will now be
considered in more detail.

3. Harnessing the power of skeletal muscle for cardiac
assistance

3.1. The problem

Most cells have some capacity for changing shape. In
muscle cells the packing and alignment of contractile
proteins is so highly developed that orientated assemblages
of these cells can perform external work. It does not follow,
however, that such work can be delivered under all
conditions. The actual configuration has a profound influence
on the work that can be transferred from a muscle graft to
the circulation.

3.2. Cardiomyoplasty

In cardiomyoplasty, the LDM is wrapped around a failing
heart. This has the advantage that it does not place
new surfaces in contact with the blood. However, the
persuasive notion that the wrap provides a more forceful
ventricular contraction runs counter to elementary muscle
mechanics. Because the muscle is heavily loaded, it
contracts isometrically, or at best shortens slowly, operat-
ing far from the peak of its power curve [19]. Rather than a
beat-to-beat action, the wrap has a longer term effect as a
“ratcheting girdle” [20]. This relieves initial wall stress and
limits or even reverses dilatation. Reluctance to abandon
the concept of a ‘systolic squeeze’ was a disservice to
cardiologists and surgeons, who were unable to obtain
consistent evidence of systolic enhancement (augmenta-
tion of cardiac output, systemic arterial pressure, pulmon-
ary capillary wedge pressure, and ejection fraction) and
assumed the procedure had been unsuccessful.

3.3. Aortomyoplasty

Like cardiomyoplasty, aortomyoplasty creates no new
blood-contacting surfaces. Although the smaller diameter of
the wrap creates more favourable working conditions for the
muscle, there are anatomical difficulties. On the ascending
aorta the LDM must be split to accommodate major branches;
on the descending aorta only a small stroke volume can be
achieved, unless the diameter is enlarged surgically or a
greater length is wrapped. The latter requires the sacrifice of
spinal arteries, with the risk of causing paraplegia.

3.4. Skeletal muscle ventricle

An SMV is not constrained by the geometry of existing
structures. The muscle can therefore be configured so that it
operates close to the peak of its power curve. From an
energetic point of view, this is undoubtedly the most efficient
way of harnessing muscle power for cardiac assist. Used in
counterpulsation, the SMV reduces left ventricular stroke
work during its filling phase; subsequent SMV ejection, with
the aortic valve closed, elevates diastolic pressure, enhan-
cing coronary perfusion as well as systemic flow. The host
heart therefore experiences a reduced metabolic demand
coupled with an improved delivery of oxygen and substrates,
a formula conducive to myocardial recovery.

A disadvantage is that the SMV places a new surface in
contact with the blood, posing a risk of thrombogenesis.
Pericardium may be used to line the auxiliary ventricle, and
the connection with the aorta made with a bifurcated
conduit; partial ligation of the aorta between the limbs of the
graft then generates obligatory flow through the SMV. Such
SMVs have pumped in circulation for up to 4 years
[21].

Alternatively, a preformed lining can be used. This enables
the SMV to be constructed, placed inside the thoracic cavity,
and connected to the aorta in a single-stage procedure [22].
Use of a single conduit avoids the need for aortic ligation, but
requires careful attention to the geometry of the conduit and
graft to ensure adequate mixing and exchange. As in the
native heart, travelling vortices within the SMV then wash all
surfaces and stasis is avoided [23–26]. In pigs, such SMVs
produced 63 (21–184)% of the power output of left
ventricular ejection in the same animal [27], and provided
cardiac assist at least equal to that of an intra-aortic balloon
pump [28].

Other SMV configurations have been investigated [29–32].

3.5. Hybrid devices

Progress has been made towards using skeletal muscle as
the power source for a mechanical pump [33,34]. The main
problems are the overall efficiency of energy conversion,
cost, haemocompatibility, connective tissue investment, and
the risk of infection associated with multiple implanted
devices.

4. Conditioning and activation

4.1. The problem

‘Conditioning’ of a skeletal muscle by electrical stimula-
tion induces the adaptive changes that enable it to perform
cardiac work. The clinical protocol adopted for cardiomyo-
plasty escalated over time, culminating in short bursts of
stimulation at 30 Hz [35]. This protocol was largely intuitive,
rather than scientifically based. It was certainly far from
optimal, for it took 8 postoperative weeks. Worse still, by the
end of this time the muscle had acquired an undesirable
phenotype.

Fig. 1 illustrates the point. Shortening velocity and power
(force × shortening velocity) vary according to the loading
conditions and the conditioning régime. This example
happens to come from experimental work in the rat. It
shows that peak power, obtained under optimum loading
conditions, declined by 90% as a result of conditioning to a
4.2. Fast, fatigue-resistant muscle

Early adopters of skeletal muscle assist seem to have thought that slowness and fatigue resistance are inseparable. This was a misconception. Fatigue resistance depends on energy metabolism, which can be changed with a stimulation regime that does not induce slow myosin expression [40–44]. The resultant muscle has a ‘2A’ phenotype, with the necessary fatigue resistance allied to fast contractile characteristics. We have argued for many years that this should be the proper goal of conditioning for cardiac assistance [45–49].

To induce fast, rather than slow, fatigue-resistant properties, the muscle must receive a smaller aggregate amount of impulse activity, irrespective of pattern or frequency [44,50–52]. However, results obtained in small laboratory animals cannot be used as a guide to the necessary clinical protocols, because adaptive changes in larger species require less stimulation [52,53]. This is intuitively reasonable, because the muscles of small mammals have inherently faster contractile characteristics, and these are matched to higher motor unit firing frequencies. The phenomena that occur at one frequency in the smaller species therefore tend to occur over a lower frequency range in the larger species. Thus rabbit muscles stimulated continuously at 2 Hz acquire stable fast, fatigue-resistant characteristics (type 2A fibres); the same pattern in the dog or sheep results in slow, fatigue-resistant characteristics (type 1 fibres). For humans, the most useful comparator is the pig, which has a similar body size. In this species a burst pattern equivalent to continuous stimulation at about 1 Hz conditioned the muscle to type 2A in about 6 weeks. Even then the proportion of type 1 fibres continued to increase slowly [54]. The so-called ‘Paris protocol’ [35] delivered between 3 and 8 times as much stimulation as this.

4.3. Reducing aggregate impulse activity

Thus, to maintain stable fast, fatigue-resistant properties under clinical conditions, the final stimulation regime must deliver less stimulation, and certainly not more than the daily equivalent of continuous 0.5 Hz. How may this be achieved?

4.3.1. Stimulation with optimised bursts

Stimulus bursts containing a high-frequency component are the most effective for maintaining the mass and force-generating capacity of the muscle [51,55–57]. Instead of conventional constant, high-frequency bursts, it is more physiological to use bursts in which the interpulse intervals are optimised for maximum force [58]. The same performance may then be achieved with fewer pulses.

4.3.2. Heart synchronisation ratio

The predominant action in cardiomyoplasty is a girdling, not a beat-to-beat, effect. Nevertheless, the value of having an active, rather than a passive, wrap has been convincingly demonstrated [59,60]. This effect could be achieved equally well by activating the muscle wrap on a smaller proportion of cardiac cycles. In Russia, heart synchronisation ratios were usually set between 1:4 and 1:16, apparently without compromising the clinical benefits [61].

It is certainly important to set the ratio at less than 1:2. During a strong contraction, intramuscular pressure is high enough to stop blood entering the muscle; time must be allowed for relaxation and reperfusion. If this is not done, and instead the muscle is stimulated on every cardiac cycle, there is a rise in venous lactate; unequivocal evidence of anaerobic, and therefore unsustainable, working conditions [62]. Unfortunately some clinical centres implemented this 1:1 régime [35,63], and reports of the resultant damage led to the general impression that deterioration of the graft could not be avoided.

4.3.3. Demand stimulation

Stimulation could be restricted to waking hours or times of increased demand. Clinical studies provide clear evidence of increased contractile speed (and therefore power) of the grafted muscle when stimulation is switched from the conventional to the intermittent ‘demand’ régime, and over the longer term this is associated with enhanced clinical benefits and improved survival [64–66].

A combination of these strategies would limit the aggregate impulse activity and maintain the desired fast, fatigue-resistant properties in the graft.
5. Preserving the viability of the muscle graft

5.1. The problem

Although claims that cardiomyoplasty had a beat-to-beat effect were unfounded, many patients experienced considerable symptomatic benefit [35,52,65–73], presumably because the muscle wrap halted or reversed ventricular dilatation and provided some collateral blood flow to the myocardium [20,74,75]. However, 15–20% of patients showed no improvement [68]. Furthermore, a review of 127 patients over a 10-year period reported a 2-year survival rate of less than 60% [70]. Although the procedure could be used as a bridge-to-transplant [76,77], this was clearly not the primary intention, and the procedure is considered unimportant. This was a mistake. The perforating vessels make a major contribution to the blood supply of the muscle [82–84]. Their vascular territory covers as much as two-thirds of the muscle, including the middle and distal thirds, precisely that part used by surgeons to wrap the heart. Without these vessels the muscle cannot sustain the increased metabolic demands imposed by electrical stimulation [80,81].

5.2. Vascular delay

Mannion et al., working in Stephenson’s group, recognised this problem and delayed the onset of stimulation [85]. The idea was to provide time for neovascularisation, extending the area perfused by the surviving thoracodorsal artery. Such a delay was incorporated into the cardiomyoplasty protocol, although it was shortened to 2 weeks [35]. Unfortunately this approach postpones the benefit a sick patient should be deriving from major surgery. It is also unreliable [81]. Better results can be achieved with a true vascular delay, in which the perforating vessels are divided but the muscle is left in situ for about 2 weeks before elevating it as a graft [83,86–88]. This, however, involves an additional invasive procedure, and the extensive dissection creates adhesions that could interfere with subsequent surgery.

5.3. Prestimulation

Fortunately there is a better solution. Several authors have described arterial anastomoses linking the vascular trees of the thoracodorsal artery and perforating arteries in the LDM [82]. During mobilisation of the muscle, these vascular bridges presumably collapse or go into spasm because of handling, cooling, and loss of normal resting tension. We have shown that stimulation in situ (‘prestimulation’) dilates the vessels, and the thoracodorsal artery then maintains continuity with the vascular tree of the perforating arteries, even after the latter have been divided (Fig. 2). It then perfuses the whole of the grafted muscle [89,90]. This is associated with enhanced muscle function and viability [42,91].

In a direct comparison between true vascular delay and prestimulation, both procedures ameliorated the fall in distal blood flow that normally follows mobilisation, but prestimulation had the more positive effect [92]. Compared to true vascular delay, prestimulation is less invasive, less traumatic for the patient, and less likely to complicate subsequent surgery. It also initiates conditioning, so that the muscle has the capacity for cardiac levels of work even before it is moved into the chest.

Clinical cardiomyoplasty initially resulted in a high mortality during the 8-week postoperative delay. This had to be overcome by selecting patients rigorously. Clearly, careful patient selection is still needed for an invasive procedure. However, prestimulation could broaden the candidate group, since a degree of assistance would be available from the time of surgery.

6. Devices

6.1. The problem

When Medtronic Inc. withdrew support for cardiomyoplasty for commercial reasons, it was taken as a vote of no confidence in the technique. Without a clinically acceptable...
device, operations were no longer performed, and the judgment of failure became self-fulfilling.

6.2. Solutions

The impasse may be overcome by new devices, such as the LD-PACE II, a synchronous cardiomystimulator from pace-maker manufacturer CCC Uruguay [93]. The lack of an FDA-approved device in North America could create an opening for niche services in areas such as the Caribbean, where benefits to the local population would be enhanced by referrals, and their associated income, from outside the region [4]. Devices certified by European standards commissions would require a fresh commitment from manufacturers, but the potential market is very large.

Cardiac arrhythmia was a significant cause of mortality in cardiomyoplasty patients. This could be inherent in the patient group, or a consequence of the procedure itself. Future stimulators could, with advantage, incorporate a defibrillation capability.

7. Cell-based alternatives

7.1. Cellular cardiomyoplasty

So far we have considered biological approaches to the treatment of heart failure that involve the surgical transposition of autologous skeletal muscle. There is an understandable desire to seek less invasive options. The fashionable trend for regenerative medicine has led to the notion of injecting stem cells into infarcted or peri-infarcted regions of myocardium, or into the coronary circulation. This has been referred to as 'cellular cardiomyoplasty'. Progress has been reviewed [94] and potential problems discussed [95—98].

In the general excitement some of the fundamental issues tend to be overlooked, and are worth restating briefly.

(Since we are concerned with functional augmentation of a failing heart resulting from the introduction, survival, differentiation, and integration of contractile tissue, we do not consider here solutions based purely on attempts to revascularise the infarcted area, or to derive benefits from paracrine secretions from the implanted cells.)

7.1.1. Amount

Tissue-based techniques, such as the SMV and cardiomyoplasty, involve the surgical redeployment of hundreds of grams of existing, mature contractile tissue. This contrasts with the few milligrams made available by current cell-based techniques.

7.1.2. Candidate cells

It is wrong to assume, although such a belief persists in some quarters, that any cells implanted into a cardiac environment will automatically become cardiomyocytes; indeed, in some circumstances they may actually contribute more scar tissue. The sources of potentially useful cells are therefore limited [99,100].

Autologous skeletal muscle myoblasts may be harvested and expanded in vitro [101]. However, myoblasts become muscle cells, not cardiomyocytes, and they are not integrated into existing myocardium. Their presence may even prejudice normal cardiac rhythmicity [102]. Furthermore, in the absence of innervation the regenerated tissue would be expected to suffer the atrophy and necrosis encountered in any denervated muscle.

Few suitable precursor cells can be derived from bone marrow. They may not generate cardiomyocytes [103] or even be retained to any significant extent in the heart when injected into the coronary circulation [104].

Embryonic stem cells are a potential source of cardiomyocytic precursors. However, they may become immunogenic, and may retain their potential for unlimited division or for generating other, unwanted, tissues [105]. A small population of autologous cardiac progenitor cells exists, but there are doubts about their capacity for expansion in vitro and their ability to integrate electrically and mechanically with uninjured myocardium.

7.1.3. Candidate routes

If an appropriate volume of suitable cells became available, how would it be delivered?

Introducing the cells surgically into the infarcted area risks placing the cells in an environment that is either unsupportive, because of local ischaemia, or hostile, promoting inflammation and apoptosis. Injection into the coronary circulation depends on extravasation and migration of the cells, and may cause embolism.

7.1.4. Function

Cellular cardiomyoplasty with autologous skeletal myoblasts has been claimed to improve the function of experimentally infarcted hearts, but it is difficult to see how a small, unstimulated island of tissue, isolated electrically and mechanically from myocardium, can contribute actively to cardiac performance. Any improvement is more likely to have been the result of local vasculogenesis and/or increased compliance of the scar.

7.1.5. Comment

It would be foolish to pretend that these and other problems will not be overcome eventually. Nevertheless, further research is needed before such techniques become safe and beneficial. It seems quite extraordinary that they are already on offer in some centres as a therapeutic procedure. As Taylor has stated: 'The promise for cell transplantation is too great to be spoiled by ill-designed attempts that forget to account for the biology of both the cells and the myocardium.' [95].

7.2. Tissue engineering

The alternative to introducing suspensions of isolated or cultured cells is to replace infarcted myocardium by tissue constructs, created ex vivo [106—113]. The problems of selecting suitable candidate cells are the same (see Section 7.1.2 above), but such an approach could generate a larger tissue mass with better organisation and more predictable function than could be achieved by cell suspensions. Tissue engineering of this type is an exciting concept, and this accounts for the enormous growth and
investment in this field since it was formalised as an entity in the late 1980s.

7.2.1. Scaffolds and matrices
The selected cells need to be assembled into a three-dimensional tissue of the required size, architecture, and function. One way is to seed the cells into a porous polymeric scaffold [114—116]. In addition to supporting cell attachment and growth, the polymer used must be biocompatible, bioabsorbable, and non-immunogenic when implanted. Synthetic polymers provide the best control of material properties such as strength, degradation time, porosity, and microstructure [116]. However, they lack the signals present in normally developing tissues, in which the intracellular pathways that govern proliferation, differentiation, and cell metabolism are influenced by interaction with cellular and non-cellular components of the extracellular matrix (ECM). This problem may be addressed by modifying the polymer chemically or by coating or otherwise incorporating the necessary growth factors into the matrix. Alternatively the scaffold may be made with biopolymers from the outset [117]. Other researchers have departed from the scaffold-based approach altogether, and engineer tissue from a combination of the desired precursor cells and ECM components [112].

7.2.2. Vascularisation
To have any value, a myocardial construct needs to be of some thickness. Reliance on diffusion alone for the delivery of oxygen and nutrients and the removal of metabolites would limit the thickness to 200 μm. It is therefore necessary to vascularise the construct in some way. One strategy is to incorporate angiogenic factors, or to seed with endothelial cells, in the expectation that angiogenesis will occur after implantation. A more positive approach is to ensure subsequent survival by prevascularising the construct, either in vivo [118] or in vitro [117]. It has been suggested that pulsatile tissue perfusion is needed to promote viability [119].

7.2.3. Orientation
If the engineered tissue is to contribute usefully to the contractile function of the heart, the cells must be aligned in a suitable orientation. This may be achieved by growing the cells under conditions of progressive or cyclic mechanical stretch [108,110,112,120] or by subjecting them to electrical stimulation [121].

7.2.4. Comment
In summary, the tissue-engineering approach to cardiac assistance depends on the growth and differentiation of suitable, non-immunogenic cardiomyocytic precursors, in a well-orientated, suitably vascularised (and therefore viable) construct that is of the appropriate size and has the requisite electrical and mechanical characteristics for augmenting systolic and diastolic function. Moreover, it must integrate with existing myocardium without constituting a locus for arrhythmia. These are considerable challenges, which are proving difficult to meet [113].

If the problems can be solved, tissue constructs of this type will undoubtedly be useful in research and initial drug evaluation, reducing the requirement for animal testing [107]. Their application in vivo remains a more distant prospect; indeed, the practicality and economic viability of tissue engineering as a therapeutic approach has been questioned [111].

8. Conclusion
Cardiomyoplasty has fallen into disuse largely as a result of erroneous ideas about the mechanism of action, over-conditioning of the grafted muscle, and procedures that compromised graft survival. These shortcomings in the implementation of the technique were made known, and should have been addressed, at the time. It is not too late. The scientific advances of the past 25 years now put us in a strong position to exploit the potential of skeletal muscle assist. With our present knowledge of the vascular anatomy of the LDM and the adaptive response of muscle to electrical stimulation we can prepare a graft that is both viable and powerful. Cardiomyoplasty performed with the revised protocol could well provide a reduction of systolic wall stress and actual beat-to-beat assistance in the short term, together with reverse remodelling and extramyocardial revascularisation in the long term. Used in this way it could offer an effective long-term solution to the problem of end-stage heart failure. It would not replace cardiac transplantation but could shorten the queue, enabling scarce donor hearts to be directed to those in greatest need.

The re-emergence of cardiomyoplasty would also re-ignite interest in other modalities, including SMVs, which harness the pumping power of skeletal muscle with greater efficiency.

The current investment of time and resources in stem cells and tissue engineering should not be allowed to eclipse the potential of techniques based on skeletal muscle. In those terms, a skeletal muscle graft is a large, well vascularised and fully populated tissue construct. Unlike engineered myocardium, it is a functional, but not a structural replacement, and it does require an implantable stimulator. On the other hand, it is available now.

The rising prevalence of heart failure has created a pressing need for alternatives to transplantation. Cardiac assist from skeletal muscle offers such an alternative. There appears to be no other technique on the immediate horizon with comparable maturity and promise.

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