Invited Review: Avoiding Ischaemic Damage in Latissimus Dorsi Muscles Redeployed as Functional Grafts

Stanley Salmons

Department of Human Anatomy and Cell Biology, University of Liverpool, Liverpool, UK

Abstract

The success of cardiomyoplasty and other surgical procedures involving the redeployment of the latissimus dorsi muscle (LDM) depends crucially on preserving the long-term viability of the muscle graft. The need to sacrifice perforating arteries during mobilization renders the grafted muscle vulnerable to ischaemic damage when it is subjected to electrical stimulation, a problem that is not adequately addressed by existing protocols. In this review we show how a more complete understanding of the vascular anatomy of the LDM enables us to propose a new and more effective approach. By injecting fluorescent microspheres we demonstrated the existence of arterial anastomoses connecting the vascular territories of the major arterial supplies: the thoracodorsal and perforating arteries. We went on to show that stimulation of the muscle before it was raised as a graft enhanced flow through these anastomoses, allowing the existing vascular networks to be perfused effectively from the thoracodorsal supply alone. Ischaemic damage was thereby reduced. Under closely comparable conditions this prestimulation procedure proved more effective than the comparatively invasive ‘true vascular delay’ procedure widely used in plastic reconstructive surgery. Protocols based on prestimulation not only offer a solution to the problem of distal graft ischaemia but will also allow cardiac assistance to be introduced at an earlier postoperative stage.

Key words: cardiomyoplasty, damage, ischaemia, latissimus dorsi muscle, prestimulation.

Basic Appl Myol 13 (2): 71-81, 2003

A Potential Surgical Solution to the Problem of Heart Failure

Cardiac assistance based on redeployment of the patient’s own skeletal muscle offers an attractive solution to the growing problem of end-stage heart failure. Compared to mechanical artificial hearts and left ventricular assist devices it is permanent, less costly, less prone to infection and problems of haemocompatibility, and does not require an external power supply. Unlike cardiac transplantation, it is free from the risks, debilitating side-effects, and costs associated with life-long immunosuppression; moreover, it is not limited by donor availability and the procedure is confined to a single patient and is therefore less expensive. The patient’s own heart does not have to be discarded or compromised by resection; on the contrary, the reduction in work-load offers some potential for myocardial recovery.

Principle of Cardiac Bioassist

The principle of cardiac assistance from skeletal muscle is that a small amount of energy, needed to stimulate the motor nerve to a skeletal muscle, triggers the release of a much larger amount of energy. That energy, derived ultimately from the normal intake of nutrients and oxygen, is converted with great efficiency into mechanical work, which can be harnessed in various ways to assist a failing circulation [42, 43].

Historical Context

The first attempts to use skeletal muscle in a cardiac assist role date back some 40 years [26, 27, 36]. Skeletal muscle had been employed before that as a passive surgical biomaterial; these pioneers took the novel step of stimulating the muscle electrically in order to exploit its contractile properties. However, these and subsequent attempts were defeated by the problem of muscle fatigue. The current interest in this technique arises from three key developments.

1. It was discovered that, given time, skeletal muscles could change their physiological, biochemical and structural characteristics to accommodate a more demanding pattern of use. In particular, the use of chronic electrical stimulation to induce fatigue-resistant characteristics, a procedure now referred to
Making LDM grafts viable

as ‘conditioning’, enabled the muscle to perform cardiac levels of work [2, 44].

2. Techniques were adapted from reconstructive plastic surgery that enabled a non-essential muscle to be diverted from its normal role, transferred into the chest, and configured appropriately to provide cardiac assistance. A number of muscles have been evaluated for this purpose, including rectus abdominis, pectoralis major, and serratus anterior, but the muscle of choice is most frequently the latissimus dorsi muscle (LDM).

3. Suitable implantable electrical stimulators were designed and marketed. These delivered a train of impulses to the motor nerve in synchrony with the R-wave of the patient’s ECG so that the grafted muscle contracted at the optimal point in the cardiac cycle and for the appropriate duration [21].

Cardiomyoplasty: Interest and Disenchantment

Research interest in the possibilities of skeletal muscle assist was heightened when it achieved clinical application [10]. In this procedure, known as dynamic cardiomyoplasty, the left LDM is raised as an unipedicle graft on the thoracodorsal vessels, taken into the thorax, and wrapped around the failing heart. The wrap is conditioned and then stimulated electrically to contract synchronously with cardiac systole to provide assistance.

Since that time considerable experience has since been gained in something like 1500 clinical cases worldwide, yet there is a widespread perception that cardiomyoplasty has failed to live up to its promise. Although most patients show a distinct postoperative improvement in New York Heart Association functional class, between 15 and 20% derive no benefit from the procedure [17] and the 2-year survival rate is less than 60% [19]. Moreover, symptoms of cardiac insufficiency can return following an initially successful operation. This disappointing outcome can be attributed in many cases to functional deterioration of the muscle wrap, evidence for which comes from both animals [4, 13, 18, 29, 38] and man [24, 34].

Graft Damage: the Role of Ischaemia

What is responsible for deterioration of the grafted muscle? Stimulation alone produces very little damage to an otherwise undisturbed muscle [18, 28]. The conditions responsible for damage must therefore be created by the mobilization of the muscle as a graft. Of the factors involved, ischaemia, particularly of the distal part of the muscle, is increasingly regarded as the most important. The LDM receives its blood supply from two main sources: the thoracodorsal artery and several segmental perforating branches of the posterior intercostal and lumbar arteries [40]. During mobilization of the muscle all of the perforating arteries are divided and only the blood supply from the thoracodorsal artery remains. In this condition the distal portion of the muscle is vulnerable to ischaemic damage. If such a muscle is to perform in a cardiac assist role it must be stimulated electrically, initially to condition the muscle and subsequently to activate it [41]. This imposes a continuous demand for energy which the tissue is unable to meet from aerobic metabolism [18, 23]. The result is a necrotic process in which contractile tissue is replaced by fibrous tissue and fat. This is particularly serious because it is the distal part of the muscle that is used to form the muscle wrap.

Two further factors can exacerbate the ischaemic insult to the mobilized muscle. First, if the neurovascular pedicle is subjected to traction, compression or torsion where it enters the chest, partial occlusion of the thoracodorsal vessels, and even denervation [33], can result. Clearly this is a problem that must be addressed through appropriate surgical technique. Secondly, configuration of the graft for cardiac assistance involves a partial loss of normal physiological tension. This is less easy to avoid: in cardiomyoplasty, for example, the muscle must be wrapped at reduced tension in order to allow unrestricted diastolic filling of the heart. The condition can be simulated experimentally by setting the muscle below its normal resting length; considerable fibre damage is then seen, with a proximodistal gradient that is again suggestive of an ischaemic etiology. Why necrosis, rather than merely atrophy, is seen in these circumstances is not entirely clear, but the explanation may lie in kinking or compression of intramuscular vessels. At all events the effects are exacerbated if reduced tension is combined with loss of the collateral arterial supply or with stimulation [18].

We should not assume that the long-term viability of the graft will be assured if we can overcome the problem of acute ischaemic damage. For example, if the muscle is activated on every cardiac cycle, the sustained intramuscular pressure will prevent reperfusion of the tissue between contractions, resulting again in unsustainable anaerobic conditions [53]. The damage that results when such inappropriate protocols are applied to patients has been clearly demonstrated [24]. It is important, therefore, to pay adequate attention to the steady-state conditions of cardiac bioassist. What is certain, however, is that a graft whose functional integrity has been compromised by ischaemic damage will be incapable of providing adequate cardiac assistance at any subsequent stage. Thus the future progress of cardiac bioassist from skeletal muscle depends crucially on addressing this problem.

Early Attempts at Avoiding Ischaemia

Early approaches consisted of introducing a so-called ‘vascular delay’ of several weeks before stimulation was commenced [31]. The rationale for this approach was that it would provide time for neovascularization, extending the area effectively perfused by the thoracodorsal artery. The clinical cardiomyoplasty protocol that has been most widely adopted also includes such a delay. Unfortunately this also postpones the benefit that the patient might otherwise be deriving from the operation. Moreover the effectiveness of the measure is not always assured: even with such a delay it is still possible to demonstrate the additive damaging effects of stimulation and division of...
collateral vessels [18, 23]. This suggests that vascular recovery during the delay period is at best incomplete, so that conditioning of the muscle still has to take place on a background of a compromised blood supply.

New Knowledge

In this review I want to trace the development of a series of studies that have shed new light on the vascular anatomy of the LDM and provided a new solution to the problem of ischaemia in the freshly mobilized graft.

The Vascular Anatomy of the Latissimus Dorsi Muscle

Arterial anastomoses

In 1992, Amanda Craven, who was reading for our B.Sc. Degree in Anatomy and Human Biology, asked if she could do her third year project in our laboratory. We set her the task of using resin injection to create corrosion casts [25] that would demonstrate the two major vascular supplies of the LDM in the rat and the rabbit. With our help she perfused the animals post mortem with physiological saline. Then she cross-clamped the aorta just below the aortic arch and injected a blue-dyed methylmethacrylate resin above and red-dyed resin below the level of the clamp to demonstrate the vascular beds of the thoracodorsal and perforating arteries, respectively. The injection technique worked extremely well but to our surprise all the vessels in the muscle were filled with purple resin. Further experimentation revealed that injection of resin via either route filled the entire vascular network, even though the other route had been ligated [15]. There had to be some communication within the muscle between the vascular trees of the two arteries.

Such a suggestion was by no means new, for there had been earlier reports of anastomotic channels linking the two vascular territories in this muscle in man [32, 38, 50-52] and in the dog [50, 52]. We were, however, excited to rediscover the phenomenon, because it suggested that the distal portion of the mobilized muscle could, in principle, continue to be perfused via the thoracodorsal artery – despite the loss of the perforating arteries – via an existing vascular network.

The observations needed to be subjected to more critical scrutiny, however. It is, for example, difficult on the basis of 2-dimensional radiographs to be completely sure that vessels are in continuity and not merely overlapping. Moreover, resin or radio-opaque materials are viscous and have to be injected under pressure so it was possible that artefactual channels were being opened up that were not present in normal circumstances.

By this time Gus Tang had joined us to pursue research leading to an M.D. We decided he should study the blood supply to the LDM under physiological conditions. The traditional view was that the thoracodorsal artery supplied the proximal two-thirds of the muscle and the so-called collateral arteries (perforating branches of the 9th-11th posterior intercostal and 1st-3rd lumbar arteries) the distal third, so lumbar arteries) the distal third, so the first thing to do was to measure the actual blood flow from these sources. The experiments were conducted on anaesthetized sheep. Building on earlier work in our laboratory by Hans Degens, we measured flow by the method of dye-extraction fluorescent microspheres. The microspheres were introduced directly into the left ventricle via a carotid catheter, a procedure that produces adequate mixing with the circulating blood and that we had validated previously [16, 54]. Before each injection the left LDM was stimulated electrically to elicit intermittent tetanic contractions (30 Hz, on for 0.19 s, off for 1.5 s, for 2 min). This induced a functional hyperaemia, which ensured that blood flow in the muscle was maximal. Flow was calibrated by withdrawing blood at a known constant rate from a catheter in one femoral artery.

We made four determinations of flow, using microspheres labelled with different fluorescent dyes: normal flow (blue microspheres), flow with the thoracodorsal artery clamped (blue-green microspheres), flow with the thoracodorsal artery patent after dividing all perforating vessels and dividing and resuturing all truncal attachments (yellow-green microspheres), and finally flow after again cross-clamping the thoracodorsal artery (orange microspheres). This last injection was designed to measure residual blood flow from any other source. During pilot experiments it revealed an inconstant accessory supply from the scapula; in the definitive experiments it was insignificant, confirming to our satisfaction that we had accounted for all sources of blood supply to the muscle.

Figure 1 illustrates the mean of three such experiments [45]. It shows that blood flow contributed by the thoracodorsal artery diminishes from proximal to distal, whereas blood flow contributed by the perforating arteries diminishes from distal to proximal. This much could have been anticipated. The surprising and significant observation was that the proximal portion of the muscle derives more than a third of its blood flow from the perforating arteries, and the distal portion derives more than a third of its blood flow from the thoracodorsal artery. In other words the territory of both arterial sources extends over the entire muscle. The term ‘collateral’ used in relation to the dorsal perforating branches of intercostal and lumbar arteries was clearly inappropriate, and will not be used again here.

On the basis of these results, the traditional idea that the territories of the thoracodorsal and perforating arteries were contiguous but nonoverlapping could be rejected. The flow distribution illustrated in Figure 1 would be consistent with anastomotic connections between the networks. However, it could equally have resulted from a substantial degree of overlap of the territories without any continuity between them.

To distinguish between these two possibilities we conducted a microscopic examination of frozen samples that had been removed from the muscles used in
Making LDM grafts viable

these experiments. Full thickness cryostat sections were fixed in methanol and treated for the demonstration of capillaries by an antibody to von Willebrand factor. The sections were then viewed under epifluorescence illumination at wavelengths that allowed visualization of both the capillaries and the fluorescent microspheres trapped within them.

Figure 2 illustrates the principle of the experiment. Blue-green microspheres were injected after cross-clamping the thoracodorsal artery and could thus arrive in the muscle only via the perforating arteries. Yellow-green microspheres were injected after dividing all collaterals and dividing and resuturing the aponeurotic attachments of the muscle; they could have arrived only via the thoracodorsal artery. If blue-green and yellow-green microspheres occurred together within a single capillary this would be irrefutable evidence that the vascular networks of these two arteries were in direct communication at a precapillary level. In fact we found a number of examples in which microspheres of both colours were present in the same capillary, and they occurred at about the expected frequency [45]. This confirmed the presence, under normal physiological conditions, of arterial anastomoses that connect the major arterial trees of the LDM.

Surgical implications

This revised view of the anatomy of the vascular supply to the LDM suggests a new way of overcoming the distal ischaemia that threatens the viability of the muscle when it is used in a cardiac assist role.

As already mentioned, the existing approach is to allow 2-3 weeks to elapse between the lifting of the graft and the commencement of stimulation, the so-called ‘vascular delay’ [31]. Better results have been obtained by implementing a ‘true vascular delay’, in which the perforating vessels are divided but the LDM is left in situ for approximately 2 weeks before elevating it as a graft [3, 12]. This true vascular delay, which is commonly used in plastic reconstructive surgery, differs from the so-called ‘vascular delay’ in that the muscle is not reconfigured as a functional graft immediately after the division of the perforating vessels but only some 2 weeks later [20]. Both of these strategies are based on the notion that restoring the blood supply to the distal region can take place only by extension of the proximal vascular tree, a process that depends on the formation of new vessels (illustrated schematically in Figures 3A, B). The existence of functional anastomotic channels connecting the proximal and distal arterial territories changes things dramatically, because it opens up the possibility that perfusion of the distal muscle could be maintained via existing vascular networks (Figures 3C, D).

The question then arises: why should muscle viability be compromised at all by mobilization? Should not the territory abandoned by the perforating arteries continue to be perfused from the thoracodorsal artery via the anastomotic connections? The answer seems to be that

Figure 1. Blood flow in proximal, middle and distal regions of the sheep latissimus dorsi muscle (LDM), measured individually for the thoracodorsal artery and perforating arteries and expressed as a percentage of the combined flow. Filled columns, flow contributed by the thoracodorsal artery (TDA). Hatched columns, flow contributed by the perforating arteries. Error bars, SEM. *, flow significantly different in proximal and distal regions (P < 0.02).

Figure 2. Drawing illustrating schematically the hypothetical outcomes when blue-green microspheres (black spheres) were injected via the perforating arterial route and yellow-green microspheres (white spheres) were injected via the thoracodorsal route. In A, the arterial territories overlap but do not communicate. A single capillary can contain only microspheres of one colour. In B, the two arterial territories communicate through anastomotic connections. A single capillary can contain microspheres of either colour. In practice blue-green and yellow-green microspheres were found to occur together within a single capillary, irrefutable evidence that the vascular networks were in communication.
there are several ways in which the arterial anastomoses can be rendered ineffective. Cooling and handling of the LDM and use of electrocautery during surgical mobilization could induce vasospasm. Reduction in resting tension could bring about distortion or collapse of vessels, which would explain the apparently ischaemic nature of the damage that results when the muscle is fixed at less than its physiological resting length. The normal blood-carrying capacity of the thoracodorsal artery could be insufficient to perfuse the entire vascular network in every case, or it could be insufficient to reperfuse vessels that have constricted or collapsed through one of the mechanisms already mentioned.

Can this be prevented? Is there some way in which flow through the arterial anastomoses could be maintained or even enhanced in spite of all the trauma of mobilization?

**The effects of prestimulation**

It is well known that the vascularity of skeletal muscle is markedly enhanced by chronic electrical stimulation; for example, stimulation produces an increase in capillary density [8], capillary-to-fibre ratio [5], and collateral blood flow from an LDM wrap to ischaemic myocardium [6]. Would chronic stimulation of the LDM enhance the anastomotic connections between its two vascular territories?

To answer this question we returned to the fluorescent microsphere technique described earlier. We looked at the effects of surgical mobilization on regional blood flow in the LDM of two groups of sheep. In both groups a stimulator was implanted and connected to an open bipolar electrode cuff secured across the main trunk of the thoracodorsal nerve. The LDM remained in situ and was disturbed as little as possible. The animals were allowed to recover for 1 week. Then in one group the stimulators were activated to deliver supramaximal stimulation at a frequency of 2 Hz for 24 h/day; the stimulators in the other group remained quiescent. Two weeks later we measured the regional blood flow in the LDM of each sheep before and after mobilization [48].

In the unstimulated sheep the results confirmed the earlier findings: the territory supplied by the thoracodorsal artery extended over the whole LDM, but diminished from proximal to distal; the territory supplied by the perforating arteries also extended over the whole muscle, but diminished from distal to proximal. In the stimulated sheep, however, this proximodistal gradient in blood flow was abolished. This pointed to a reduced resistance to blood flow in the middle of the muscle, consistent with enlargement of the anastomotic connections between the two vascular territories. The net result was a substantial benefit in distal blood flow when the muscle was acutely elevated on the thoracodorsal pedicle alone.

We took this further in a subsequent experiment, also performed on the LDM in sheep. Again the measurements were performed with and without prior stimulation of the muscles. This time, in addition to mobilizing the LDM, we deliberately manipulated and cooled the muscle and then reattached it at a reduced resting length to simulate the effects of surgical redeployment in applications such as cardiomyoplasty. An additional recovery stage was also introduced, allowing us to examine the changes in regional blood flow not only immediately after mobilization but also 5 days later [49].

When the unstimulated muscles were mobilized, handled and reattached at reduced length, blood flow declined throughout the muscle but particularly in the distal region. Five days later regional blood flows throughout the LDM remained at less than half the baseline levels measured before intervention (Figure 4). In the stimulated muscles, the acute effects of mobilization and reattachment were much smaller, and were distributed uniformly across the muscle. Five days later blood flow had recovered to baseline levels (Figure 4). These
results suggest that stimulation not only enlarges the anastomotic bridges between the two arterial territories but renders the vascular network more resistant to the acute generalized collapse or constriction brought about by mobilization and manipulation of the muscle.

In view of these findings the absolute regional blood flows in the undisturbed LDM might have been expected to be higher in the muscles subjected to 2 weeks of stimulation. They were, however, lower. This may seem paradoxical but it must be recalled that all blood flows were measured under hyperaemic conditions, so that a decline could represent a reduction in either the resting flow or the hyperaemic response of a muscle that is adapted for more efficient oxygen extraction [1]. Previous work indicates that both resting and hyperaemic flows may have been affected [31]. It is safe to assume that blood flow in the undisturbed muscle was equal to its physiological needs, so it makes sense to use this as the baseline with which to compare the flow following mobilization and recovery (Figure 4).

The benefits of improved vascularity

We had shown that prestimulation of the LDM in situ improved significantly the blood flow in the vulnerable distal portion of the muscle after mobilization. Using an amperometric microelectrode technique [22], Barron and coworkers examined the influence of prestimulation on regional perfusion and oxygenation in the rabbit LDM. Muscles that had been prestimulated for 2 weeks at 2.5 Hz showed enhanced perfusion of all regions both before and after mobilization. In a fatigue test consisting of a sustained series of contractions, these prestimulated muscles behaved quite differently from controls: they were significantly more resistant to fatigue and were capable of maintaining pO2 in the distal regions without decrement [7].

It would be reasonable to suppose that enhancement of blood flow, tissue perfusion and oxygenation, coupled with improved oxygen extraction, would be reflected in improved survival of the muscle after mobilization. However, formal evidence for this was lacking until recently, when Edwin Woo conducted the necessary experiments as part of his M.D. research supervised jointly by ourselves and Manchester.

For this study we used the rat LDM. This muscle is similar in shape to the human LDM but is thin enough to lend itself to quantitative macrohistochemical mapping of damage. Acute mobilization of the muscle as a single-pedicle flap based on the thoracodorsal artery had been shown to result in substantial necrosis of the distal region after only 24 hours, making this a useful model of ischaemic LDM injury [46, 47]. Viable tissue was demonstrated by incubating the LDM in the vital stain nitroblue tetrazolium, a technique that had already been used successfully to identify early muscle necrosis in ischaemic skeletal muscle [37]. The intact muscles were photographed and the images digitized for computer-based analysis by a single observer who was blind to their identity. The results were clear. Electrical prestimulation (5 weeks at 10 Hz) had no noticeable effect on the small amount of non-viable tissue found in the proximal and middle regions of rat LDM muscles 24 hours after surgical mobilization, but it significantly reduced the larger amount of non-viable tissue found in the distal region (from $18.5 \pm 2.2\%$ to $11.2 \pm 3.6\%, P < 0.006$) [56].

How does prestimulation work?

Prestimulation enhances flow through vascular anastomoses that connect the two major arterial networks supplying the LDM. It is reasonable to assume that this action is related to the general increase in vascularity that is associated with chronic stimulation, but the signalling pathways that underlie this response have yet to be elucidated. There is evidence that chronic stimulation of skeletal muscle upregulates the expression of Fibroblast Growth Factor (FGF), a known angiogenetic substance [35]. FGF has been administered in conjunction with stimulation or vascular delay to improve perfusion of the LDM after it has been mobilized as a graft, with encouraging results [11, 30]. These studies would have been predicated on the need for neoangiogenesis (Figure 3A, B) although the results may have been at least partly due to a response in the anastomotic vessels. If prestimulation works in a similar way it should be more effective than exogenous administration, because the growth factors would be released locally and continuously over a period of weeks.
Making LDM grafts viable

Prestimulation or vascular delay?

We have seen that prestimulation offers a potential solution to the problem of graft viability. We have also mentioned an alternative approach, true vascular delay, in which vessels other than the main thoracodorsal artery are divided 2 weeks before elevating the LDM as a graft. Plastic and reconstructive surgeons have used this technique for many years to improve survival of the skeletal muscle flap [9]. How does it compare to prestimulation?

In dogs, prestimulation had been found to compare unfavourably with vascular delay [3]. In that study, however, neither blood flow nor muscle viability were assessed; the outcome measure was the haemodynamic performance of the muscle as a cardiomyoplasty wrap. The 4-week stimulation protocol that was used for prestimulation would certainly have reduced the contractile speed of the prestimulated muscle, and this, rather than any difference in viability, could have accounted for the difference in mechanical performance that was observed. We therefore decided to conduct a new side-to-side comparison between vascular delay and prestimulation under conditions that were carefully matched, and with regional blood flow as the outcome measure.

The study was performed in the pig because it is closer to man in terms of the anatomy of the thoracic cavity, organs and muscles and has, for this reason, become our preferred animal model for in-circulation studies of cardiac assistance from skeletal muscle. Since the previous experiments had been conducted in sheep we had to confirm at the outset that the main features of the blood supply to the LDM were the same. The pig differed only in the extent of functional overlap between the arterial territories. For example, the thoracodorsal artery supported only about 15% of total blood flow in the distal region of the LDM, as opposed to 35% in the sheep [55]. Either the arterial anastomoses have a lower flow capacity in the pig than in the sheep or they are more sensitive to surgical disturbance. For our purposes this could only be an advantage, for the greater dependence of distal blood flow on the perforating arteries in the pig would constitute a more critical test of techniques designed to maintain flow when this blood supply was interrupted during mobilization.

The design of the main experiment is illustrated in Figure 5. In Figure 6 the results are again expressed as a percentage of the baseline blood flow. Both prestimulation and vascular delay had a beneficial effect on distal blood flow in the mobilized LDM. However, blood flow throughout the prestimulated muscles continued to equal or exceed baseline values, whereas distal blood flow in muscles of the vascular delay group was nearly 50% below baseline immediately after mobilization, and remained more than 30% below baseline even after a further 2 days [55].

Figure 5. Design of an experiment to compare the effects on regional blood flow of true vascular delay and prestimulation. Stimulators were implanted in two groups of 10 pigs. In one group, the prestimulation group, they were programmed 24 hours later to activate the left LDM in situ at 2 Hz, 24 h/day. In the other group, the vascular delay group, the stimulators remained quiescent but the perforating arteries were divided at the time of implanting the stimulators. Two weeks later, regional hyperaemic blood flows were determined in the undisturbed LDM (baseline), in the acute phase immediately after mobilizing the muscle, and after recovery for 2 days.

How May Prestimulation Be Achieved in Practice?

The benefits of prestimulation for the viability of the grafted LDM will be of only theoretical interest unless there are practical ways of achieving it in a clinical setting.

Stimulation via surface electrodes

As always, the problem with stimulation of motor nerve branches via surface electrodes is that stimulation also excites nerve endings in the skin. It is therefore difficult to recruit the whole of the muscle at stimulation levels that can be tolerated by the patient. Substantial vascular benefits of prestimulation may be achievable with submaximal surface stimulation. However, muscle fibres that are not recruited will fail to undergo metabolic adaptation and could therefore be susceptible to fatigue and damage when supramaximal stimulation is applied at a later stage. Prestimulation via surface electrodes may therefore be inadequate on its own; it would be advisable to condition the whole muscle further when it has been reconfigured as a graft.

Stimulation via implanted electrodes

Prestimulation could be achieved most effectively by implanting both the electrodes and stimulator in a separate procedure at least 2 weeks before elevating the muscle. A suitably designed stimulator could be used both for prestimulation and for activating the muscle subsequently in cardiac assist mode. The obvious disadvantage of this
approach is that it subjects sick patients to the risk of a second operation under general anaesthesia.

It would be less invasive if the nerve electrodes, at least, were placed endoscopically. Such a procedure has been tried in Cleveland for stimulation of the phrenic nerve. Although the thoracodorsal pedicle is less accessible, the possibility is worth considering.

Magnetic stimulation

Magnetic stimulation would have unique advantages in this application because it enables deep nervous structures to be stimulated non-invasively without associated excitation of cutaneous pain afferents. The technology has been used mainly for neurological diagnosis, an application that requires only single or double pulse outputs (reviewed in [39]). In 1993, before we were aware of the potential of prestimulation for promoting graft survival, Tim Hooper and I entered into discussions with The Magstim Company Limited (Whitland, Wales) about the possibility of using magnetic stimulation to achieve preoperative conditioning in cardiomyoplasty patients. The company then successfully applied for a Small Firms Merit Award for Research and Technology (SMART) from the UK Department of Trade and Industry and developed the necessary technology with the help of the two academic research teams. Adapting the techniques for chronic neuromuscular stimulation demanded innovative solutions to the problems posed, such as the number of impulses to be delivered, the aggregate power requirements and the need for a suitable user interface for the more complex protocols.

Machines of this type have since been used for other applications [14], but because of a lack of grant support the technique was never brought to fruition as we had intended. There is, however, no technical reason why it should not be used in the context of cardiac assistance. The instrument, antenna and connecting cable are heavy so we envisaged building them into a chair, in which the patient would be stimulated for a minimum of 1 hour at a time and for at least 2 sessions a day. We would expect excellent compliance from this group of patients, who are, by the nature of their condition, not very physically active and could well derive psychological benefit from an undemanding daily routine that contributes to the success of their operation.

Conclusion

Mobilization of the LDM for cardiac assist applications renders the distal region vulnerable to ischaemic damage. Prestimulation allows distal perfusion to be re-established via the existing vascular networks. Prestimulation therefore obviates the need to wait for neoangiogenesis; in the experiments described here the protective effects of prestimulation had developed after only 2 weeks. Prestimulation has other advantages. The true vascular delay procedure involves extensive dissection of the deep surface of the LDM. Prestimulation, on the other hand, requires access only to the thoracodorsal nerve where it enters the muscle close to the humeral insertion, and is therefore less likely to create adhesions that would interfere with the subsequent redeployment of the muscle. It may even prove possible to stimulate the LDM non-invasively. Prestimulation has the further merit that it initiates metabolic conditioning and the associated increase in fatigue resistance at a pre-operative stage. A muscle that receives prestimulation of a few weeks’ duration should therefore be capable of sustaining cardiac levels of work almost immediately after mobilization.

The material surveyed in this review therefore makes a substantial case for prestimulating the LDM before raising it as a graft for use in cardiomyoplasty and other forms of cardiac assistance. The procedure...
minimizes ischaemic damage in the LDM graft by ensuring that blood flow is maintained at physiologically adequate levels in all regions of the muscle. It is more effective in this respect, as well as less invasive, than vascular delay. Finally inclusion of pre-operative stimulation in the protocol would enable a patient to receive the benefits of sustainable cardiac assistance at a much earlier post-operative stage.

Acknowledgements

The author wishes to acknowledge the vital part played in all this work by his colleagues, in particular Dr J.C. Jarvis, Mr A.T.M. Tang, Mr E.B.-C. Woo, and Miss H. Sutherland. Some of the research was conducted in collaboration with Mr T.L. Hooper (Wythenshawe Hospital, Manchester), Dr L.W. Stephenson (Harper Hospitals, Detroit), and Mr J.R. Pepper (National Heart and Lung Institute, London). We thank The British Heart Foundation and the European Community for research support.

Address correspondence to:
Professor S. Salmons, Department of Human Anatomy and Cell Biology, University of Liverpool, The Sherrington Buildings, Ashton Street, Liverpool L69 3GE, UK, Email s.salmons@liverpool.ac.uk.

References

Making LDM grafts viable


Making LDM grafts viable


