Comparative study of the biomechanical performance of trained and untrained skeletal muscle

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Abstract

Changes in contraction and relaxation parameters during chronic electrical stimulation can exert profound effects on diastolic augmentation during skeletal muscle assistance (SMA) of the circulation, in both short and long term. The physiological properties of latissimus dorsi muscle (LD) performance in a system that mimics the clinical setting has not been adequately studied. Objective: To quantify changes in the biomechanical performance of trained and untrained skeletal muscle in relation to circulatory assistance using an ex-vivo Windkessel mock circulation. Methods: Twelve Welsh Mountain sheep were divided into 2 groups: Group A (n = 6) underwent implantation of intramuscular electrodes into the left LD connected to a myostimulator (Teletronics Pacing Systems, Inc., Colorado) and progressively trained by burst stimulation over a 12-week period using standard stimulation parameters (2.5-5 V, 35 Hz, 6 pulses per burst, 240 µs per pulse); Group B (n = 6) were the untrained controls. At the end of 12 weeks, the LD was mobilised on its neurovascular pedicle and wrapped around a latex rubber aorta connected to two Windkessel chambers pressurised to 70 mmHg and stimulated to contract 40 times per minute continuously for 60 min. Pressure change per contraction (augmentation, ΔP), volume displacement, contraction (C,) and relaxation to 90% (R90) times, and the standardised rate of change of pressure generation (+dP/dt:ΔP) and decay (−dP/dt:ΔP) were determined and assessed for potential clinical efficacy. Results: In Group A, the LD was fatigue-resistant in all 6 animals with a mean pressure augmentation of 13.7 (s.e.m. 1.3) mmHg and mean stroke volume of 12.5 (s.e.m. 1.0) ml. These muscles were slow with a mean C, and +dP/dt:Δmax of 243.2 (s.e.m. 6.1) ms and +6.5 s⁻¹, respectively, and R90 and −dP/dt:Δmax of 261.0 (s.e.m. 4.8) ms and −7.8 s⁻¹, respectively. In contrast, the LD in Group B was fatiguable with a mean pressure augmentation and stroke volume of 24.6 (s.e.m. 0.9) mmHg and 21.1 (s.e.m. 0.7) ml at 1 min and only 5.4 (s.e.m. 0.3) mmHg and 5.2 (s.e.m. 0.3) ml, respectively, at 30 min (P < 0.001). These muscles were faster at all time points compared to group A (P < 0.02). Acute diminution of power output per contraction in Group B coincided with a prolongation in the R90 by 101% compared to the C, which decreased by less than 5% (P < 0.001). The C,/R90 ratio did not significantly change during performance testing in Group A (fatigue-resistant animals) (P > 0.1). Conclusion: Using a mock circulation system, we have identified significant differences in biomechanical properties of trained and untrained skeletal muscle. Optimisation of these parameters during and after electrical training may alter the clinical efficacy of SMA.

Keywords: Skeletal muscle assist; Electrical training; Fatigue; Sheep; Mock circulation

1. Introduction

Skeletal muscle assist is of potential therapeutic value in the management of end-stage heart failure [5,7,17]. The efficacy of this technique depends on many factors, including the power output by the latissimus dorsi muscle (L.D.), the efficiency of mechanical coupling of the muscle to the systemic circulation, the timing of contraction and relaxation, fatigue resistance, and the maintenance of the structural and functional integrity of the muscle. Phenotypic transformation by chronic low-frequency stimulation results in a vital gain of fatigue resistance, but undesirable changes accompany this process such as a profound loss of specific power, although it is estimated that the remaining

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power is more than adequate to assist the failing heart [29]. Other changes, such as a slow contraction and relaxation rate, can compound the problem further by interfering with, rather than augmenting, the systolic and diastolic phases of cardiac function [6,22]. All these factors, either individually or in concert, may contribute to the reported lack of significant improvement in central haemodynamics after cardiomyoplasty [8,9,15].

Long-term damage and atrophy of the LD is now becoming a well-recognised complication of cardiomyoplasty [19,21]. The mechanism of this damage is probably multifactorial and includes ischaemia as well as excessive stimulation. The hallmark of muscle overstimulation is an acute reduction in power output, or fatigue, and is associated with intracellular changes that are characteristic of metabolic stress [11]. At present, it is likely that the development of early fatigue in patients undergoing progressive training goes undetected with the likelihood that stimulation parameters are increased at a time when the muscle is stressed. Identifying a marker(s) of early fatigue by a simple and non-invasive means would help guide the training process and thus avoid over-stimulation and long-term damage.

Optimisation of early and long-term results of skeletal muscle assistance requires accurate characterisation, and possibly modulation of factors relating to muscle performance. Most of our knowledge on the physiological properties (e.g., power output and twitch speed) of electrically transformed muscle has come from studies on linear performance of lower limb muscles in small animals [3]. Little is known, however, of the behaviour of the LD when it is working continuously either in vivo or ex vivo in a manner that mimics the loading conditions and wrap configuration in aorto- or cardiomyoplasty.

The aim of this study was to quantify some of the biomechanical properties of trained and untrained skeletal muscle in a mock circulation system that simulates the clinical setting of aortomyoplasty.

2. Methods

Twelve Welsh Mountain ewes with a mean body weight of 34 (range 28–37) kg were studied and cared for in accordance with guidelines laid down by the Home Office of Great Britain and Northern Ireland. All animals were housed in a 12 h light–dark cycle and given feed and water ad libitum. After 1–2 weeks of settlement they were randomly assigned to 2 groups. In group A (n = 6) 2 intramuscular electrodes were implanted into the left LD and a myostimulator (Telelectronics Pacing Systems Inc., Colorado) placed into a subcutaneous pocket in the interscapular region under general anaesthesia. Only the proximal portion of the LD was mobilised without ligation of major or perforating blood vessels to the muscle. The proximal (cathode) and distal (anode) electrodes were inserted 5 cm apart into the proximal portion of the muscle by threading the leads through a smooth-ended metal stylet (external diameter of 1.5 mm) that was pre-positioned by insinuating it between the visible branches of the thoracodorsal nerve. The stylet was then removed and the electrode secured to the edges of the LD with 4-0 sutures. We have found this method of insertion to be safer than the needle and suture technique which can result in neurovascular injury. Prophylactic antibiotics (Amfipen, 500 mg i.m.) were administered from the time of induction to 48 h post-operatively. Progressive training for fast-to-slow transformation over a 12-week period was commenced at this time using the stimulation parameters outlined in Table 1. The burst frequency was constant at 35 Hz throughout the period of training and shown to provide supra-maximal stimulation of the muscle (Fig. 1). The LD twitch remained visible and/or palpable in all 6 sheep throughout this period. Group B (n = 6), the untrained controls, were housed under similar conditions but did not have a myostimulator implanted. After 12 weeks, all animals underwent evaluation of linear and wrap performance of the left LD under general anaesthesia. Pre-medication was with ketamine (1 mg/kg) and diazepam (0.5 mg/kg) administered intramuscularly and anaesthesia maintained with a gas mixture of oxygen (8–10 l/min), halothane (0.5–3%) and nitrous oxide (2 l/min). Muscle relaxants were omitted. The ruminant stomach was decompressed using a 12-bore oro-gastric tube. Intravenous fluid mainte-
trance was administered at a rate of 100 ml/h. Arterial oxygen saturation was monitored with a pulse oximeter and maintained at 96-100%. Core temperature was measured with a rectal thermistor probe. In view of the long duration of each experiment (4-5 h) and the ex-vivo nature of the preparation, a separate group of animals acted as controls rather than evaluating the performance of both the left and right LD in the same group of animals in a cross-over fashion. Sham operations (i.e., implantation of myostimulation equipment without switching on the burst stimulator) on control animals were not performed due to the limited number of devices and leads available to us.

2.1. Evaluation of linear isometric force

The linear isometric performance of the intact (pre-mobilisation) left LD was determined in all animals for a short period before evaluation of wrap performance on the mock circulation system. Following calibration, an isometric force transducer (Logan-Research Ltd, Kent, UK) was fixed to the head-end of the operating table. Each animal was positioned in the right lateral position and the left forelimb tied securely in the abducted-flexed position to the arm of the force transducer in line with the origin and insertion of the LD. The resting tension was adjusted by altering the distance between the transducer and the whole sheep until a baseline force of 10 N was obtained. For animals in which a myostimulator was already in situ (Group A) the device remained programmed on the 'ON' mode and the linear isometric force generated with each contraction amplified and recorded (Fylde Electronics Ltd, London) for a period of 30 s. Animals in Group B required electrodes and myostimulator to be implanted before evaluation of linear performance could take place.

2.2. Evaluation of wrap performance

After linear performance testing, the left LD was carefully mobilised off the chest wall with the proximal neurovascular pedicle and tendon remaining intact. The resultant muscle flap was then wrapped around the latex aorta of the mock circulation system (vide infra) and sutured securely onto itself using superficially placed continuous sutures at the 2 free margins.

2.3. Mock circulation system

The mock circulation system used to assess the wrap performance of the LD in this study (Fig. 2) was a modification of the original Windkessel dual compliance chamber system developed by us [2] and is different in 3 aspects: (1) The size of each compliance chamber is smaller (18 × 8 cm), thus making the whole system easier to handle and position above the chest wall of the sheep. (2) Since changes in temperature strongly affect contraction and relaxation of muscle, a heating coil was included to enable the water within the chambers and mock aorta to be heated. This enabled the temperature of the muscle wrap to be maintained within the physiological range of 37.5–39.5°C. (3) Water was used as the blood analogue for the system instead of aqueous glycerol because it was assumed that it was reasonable to ignore the effects of fluid viscosity. Both fluids are Newtonian compared to whole blood (non-Newtonian fluid) although this difference is unlikely to be significant in the context of counterpulsation, which is concerned with flow through large vessels. The compliance chambers were linked by a mock aorta made from a latex rubber tube (Dipro Ltd, UK) measuring 30 mm (internal diameter) × 100 mm (length) × 0.5 mm (wall thickness). The static pressure in the system was maintained at 60–80 mmHg for all experiments (vide infra).

The total volume of air in the Windkessel chambers was 900 ml and corresponds to the compliance of the system. This was calculated as follows:

\[ pV^n = \text{constant} \]  

(1)

where \( p \) is pressure in mmHg, \( V \) is the volume of air in ml and \( n \) is the adiabatic constant = 1.2 (determined experimentally).

Since compliance (C) is defined as the change in volume (dV) per unit change in pressure (dp), therefore:

\[ C = \frac{dV}{dp} \]  

(2)

The total compliance of the arterial system in normal subjects has been calculated to be 1.07 ml/mmHg [31]. Assuming a 10% reduction (approx.) due to advanced age, hypertension and atherosclerosis, the corresponding value in a population of patients likely to undergo cardiac assist is expected to be 0.9 ml/mmHg. Thus, to simulate the arterial compliance of a patient with a mean diastolic blood pressure of 70 mmHg, the total volume of air...
required in the compliance chambers (V) is calculated by rearrangement and differentiation of Eqs. (1) and (2):
\[ \frac{dV}{dp} = -\frac{1}{n} \times V/p \]
\[ V = 0.9 \times 1.2 \times (70 + 760) = 896.4 \text{ ml} \]  

Since mean work done and the fluid pressure generated per muscle contraction may vary with the compliance of the system, we carried out validation experiments in 3 sheep to determine this relationship. These results illustrated in Fig. 3 show that small perturbations in the compliance of the system (e.g., due to air leak) away from the 900 ml value were unlikely to produce significant changes in total power and pressure augmentation.

Once connected to the rig, the LD was stimulated to contract 40 times per minute at 5 V, 35 Hz and with a burst duration of 210 ms, and pressure waveforms were recorded at 1, 5, 15 and 15 min thereafter for a total period of 60 min. The first measurement included a determination of the relationship between aortic pressure (muscle wrap preload) and peak pressure generated per contraction (which is analogous to the ‘length–tension relationship’). In most situations, peak pressure generated did not vary significantly with changes in aortic pressure within the range 15–100 mmHg (see Fig. 4). The resting pressure in the latex tube was maintained at 70 mmHg throughout the period of muscle performance testing. The temperature of the muscle was measured regularly with a needle-mounted thermistor and maintained between 37.5 and 39.5°C. When the peak pressure generated per contraction fell by more than 50% of the initial value (fatigue point), the muscle was allowed to rest for 30 min and stimulation re-commenced in order to demonstrate recovery. At the end of the experiment, a lethal dose of anaesthetic was administered and the left and right LDs were dissected out and weighed. Biopsies were taken for histological examination.

2.4. Data acquisition, storage and analysis

Validation studies showed that pressure changes in the fluid compartment at the level of the aorta were linearly related to those in the air compartment. A pressure transducer in the air compartment was used to assess muscle performance after an appropriate manometric correction had been applied. The pressure signal was converted from analogue to digital form and was visualised on the monitor of a PC loaded with a data acquisition/analysis programme (Spike 2, Cambridge Electronic Design, Cambridge, UK). This interactive software package allowed the determination of mean pressure augmentation (i.e., increase in pressure from the resting value of 70 mmHg, \( \Delta P \)), volume displacement (stroke volume), contraction time (i.e., time to peak pressure, \( C_t \)) and relaxation time (i.e., time to 90% fall in peak pressure, \( R_{90} \)). The maximum rate of change of fluid pressure was calculated from the maximum gradient of the contraction (+dP/dt) and relaxation (-dP/dt) phases of the LD wrap performing on the mock circulation. These values were then normalised for \( \Delta P \). In addition, the energy (\( \varepsilon \)) conferred to the circulation (i.e., external work) during the contraction phase was calculated from the product of mean \( \Delta P \) and stroke volume. We avoided measurement of peak energy per contraction as this parameter greatly over-estimates the true performance of the muscle. The average power output per muscle contraction was then calculated from \( \varepsilon /C_t \) and refers to the mean power during contraction and not the...
average power level measured over the entire contraction/relaxation cycle.

The mean and standard error for all these parameters were calculated from 6-8 individual waves at each phase of the procedure.

2.5. Immunocytochemistry

Biopsies from both muscles were taken from standard sites (1 cm distal to the site of penetration of the middle branch of the thoracodorsal nerve on the costal surface) in view of the known regional variation in fibre type frequency within the LD [30]. These were immediately frozen in liquid isopentane cooled by liquid nitrogen. Cross-sections, 8 μm thick, were then cut at −25°C in a cryostat and mounted on glass slides for immunocytochemical staining. Monoclonal antibodies for fast myosin (1:300 dilution) and slow myosin (1:100 dilution) were used to determine the relative frequencies of fast (type II) and slow (type I) fibres. An antibody for spectrin (1:200

![Graphs](image_url)
dilution) was also used for non-fibre-selective staining of the sarcolemma and thus delineate the cells more clearly when seen in cross-section. All antibodies were purchased from Novocastra Laboratories Ltd (Newcastle-upon-Tyne, UK).

2.6. Statistics

A two-tailed Student’s t-test for normally distributed unpaired data was performed for the statistical analyses of various parameters of LD performance. All data are presented as mean ± standard error of mean (s.e.m.) and results were considered significant at P-values of less than 0.05.

3. Results

3.1. Surgical

There were no significant differences between control and test groups with regard to body growth during the 12 week training period (P > 0.1). There were no cases of device failure or sepsis, although one animal developed a seroma in the subcutaneous pocket holding the myostimulator necessitating two aspirations and pressure dressings. All animals survived and remained stable during the 3 h period of anaesthesia for the assessment of the linear and wrap performance of the left LD. The mean weight of the left LD was 152.8 (s.e.m. 12.1) g and 156.8 (s.e.m. 11.8) g for the untrained and trained groups, respectively (P > 0.8).

3.2. Linear performance

The peak isometric force generated was standardised for LD weight to give specific force. The trained muscles in group A produced a mean specific force of 86.3 N/kg compared to 159.5 N/kg for the controls in group B (P < 0.001). Therefore, electrical training of the skeletal muscle for 12 weeks using the stimulation protocol outlined (vide supra) was associated with a reduction in specific force by 46%. There was no evidence of fatigue in either group during this short period (30 s) of performance testing.

3.3. Wrap performance

3.3.1. Peak pressure augmentation

The mean peak pressure change generated by the trained LD (group A) was 19.9 (s.e.m. 2.4) mmHg at the start and 12.5 (s.e.m. 1.1) mmHg after 15 min and was maintained at this level throughout the 60 min of testing, consistent with fatigue-resistant work. In contrast, the initial mean peak pressure in the control group (A) was 24.6 (s.e.m.

Fig. 6. Pressure tracings from an untrained LD performing on the mock circulation demonstrate the almost total recovery in pressure augmentation 28 min after resting the muscle. This confirms the decline at 20 min to be due to fatigue.
Control Trained Control Trained

Fig. 7. The transformed muscle generates a significantly lower rate of pressure generation (a) and pressure decay (b) after 60 min of testing compared to the untrained muscle. Mean values and standard error bars are shown.

0.9) mmHg although this higher level of augmentation could not be maintained beyond the first 5 min of continuous work due to the rapid development of fatigue. By 15 min, the mean augmentation declined to 25% of its initial value (P < 0.001) (see Fig. 5a). Allowing the muscle to rest for 30 min resulted in an almost total recovery in its performance (Fig. 6).

3.3.2. Stroke volume (SV)

As with pressure augmentation, there was an acute drop in SV in the control group from 21.1 (s.e.m. 0.7) to 7.9 ml (s.e.m. 1.4) in the first 15 min of continuous activity (P < 0.01). By 60 min, the mean SV was only 4.8 ml in this group compared to the trained group of muscles which gave 11 ml (±1.3) per contraction (P < 0.02).

3.3.3. Specific stroke power

The average power output per contraction was normalised to LD weight and found to be 0.969 (s.e.m. 0.06) W/kg in the trained group at the start of testing compared to 2.677 (s.e.m. 0.2) W/kg in the prefatigued controls (P < 0.005), representing a 64% decrease. Although the isometric force generated per contraction fell to a lesser degree (46%) with training, it is inappropriate to correlate this with wrap performance as the former is related to isometric muscle action whereas the latter is produced by

Fig. 8. Serial transverse sections of control LD showing the minority of fibres to be positively immunoreactive to slow myosin (a) and the majority to stain positive for fast myosin (b). In contrast, almost all cells become positive for slow myosin after 12 weeks of electrical training (c) with absence of staining for fast myosin (d).
the muscle working isotonically in a profoundly altered configuration (i.e., aortomyoplasty wrap). Moreover, the former parameter, in contrast to the latter, does not assess external power.

3.3.4. Contraction (C,) and relaxation (R,) times

The mean C, and R,, at the beginning of the test were 243.2 (s.e.m. 6.1) and 249 (s.e.m. 35.2) ms, respectively for the trained group (A) of LDs consistent with the slow-twitch characteristics of an electrically transformed muscle. The C,/R,, ratio was 1.05 (s.e.m. 0.13) at the start of performance testing and remained relatively unchanged throughout the 60 min period of testing (P > 0.2).

In the untrained LDs (group B), however, the C, and R,, were 135.3 (s.e.m. 8.8) and 115.3 (s.e.m. 7.2) ms, respectively at the start of testing. By 5 min, however, coincident with the onset of fatigue, the R,, significantly increased to 231 (s.e.m. 18.9) ms (P < 0.001) although the C, remained relatively unchanged at 132.7 (s.e.m. 12.1) ms (P > 0.5). Consequently, the C,/R,, ratio decreased by 50.3% during the first 5 min (P < 0.001) (see Fig. 5b,c,d).

3.3.5. + dP / dt and - dP / dt

As expected, the trained muscles in group A had low values for +dP/dt:ΔP (ranging from +6.5 to 7.4 s⁻¹) and for -dP/dt:ΔP (ranging from -7.8 to -9.5 s⁻¹) and remained relatively unchanged during the 1 h period of testing (P > 0.1). In contrast, the controls were intrinsically faster at all time points studied (P < 0.02). The development of fatigue in these muscles coincided with a dramatic fall in -dP/dt:Δmax by 51% but not in +dP/dt:Δmax (P < 0.01) (see Fig. 7a,b).

3.4. Histology

Macroscopic evidence of muscle damage was absent although areas of fibrosis could be seen in close proximity to the electrode tracks in the trained LD muscles. Immunocytochemical staining showed the majority of fibres (approximately 75%) to be immunoreactive to fast myosin and confirmed the completeness of fast-to-slow transformation that occurred 12 weeks after electrical training (Fig. 8a–d).

4. Discussion

This study demonstrates the potential mismatch between the physiological characteristics of the trained LD and the requirements for its use in SMA. The characterisation of trained and untrained muscle performance using an ex-vivo preparation that mimics the loading conditions of in vivo aortomyoplasty has not yet been reported. Using such a system we have measured important differences in parameters of contraction and relaxation during a continuous period of LD performance. Furthermore, we have identified a potentially useful parameter for monitoring fatigue. These observations may have implications in clinical aortomyoplasty.

Several techniques have been developed utilising conditioned skeletal muscle to provide circulatory assistance and include: ventricular wrapping (cardiomyoplasty) [4,5], wrapping the aorta for counterpulsation (aortomyoplasty) [7] and shaping the muscle into a neoventricle [17]. Others have advocated the use of the LD in the linear configuration to power a hydraulic piston coupled to the circulation [13]. A major limitation common to all these techniques, however, is the low power output of the LD principally due to a reduction in specific power inherent in the training process. Other factors may also contribute like poor mechanical coupling and long-term atrophy. There is consistent evidence, based on linear isometric force measurements, showing that electrically transformed skeletal muscle retains approximately half its original isometric power [29]. We have confirmed this by showing a 46% decline in specific isometric force with training. It is generally accepted, however, that the maximum force measured by this means and from force–velocity curves greatly overestimates the total power available from a muscle during continuous and repetitive action, as in locomotion, flight and, indeed, skeletal muscle assist [16]. Furthermore, changes in muscle configuration may significantly alter overall performance so that predicting wrap performance from a linear assessment is probably invalid. Consequently, we have adopted a method that allows measurement of repetitive power output, as well as mimicking the conditions under which the muscle might operate in vivo. The mock circulation system with the LD working as an extra-aortic counterpulsator provides a ‘work loop’ method for the measurement of sustained mechanical power output by including both the positive work done during shortening and negative work during lengthening, as well as allowing for changing muscle velocity and degree of activation throughout a cycle [18]. The mean external work done per unit time (i.e., specific stroke power) during continuous activity of the trained muscle, under the conditions described for the mock circulation, was found to be 64% lower than for the pre-fatigued untrained muscle. Such a profound loss of power output resulted in a mean pressure augmentation of only 13.7 mmHg, which is probably too low for effective cardiac assistance. Based on clinical experience with the intra-aortic balloon pump (IABP), we believe that diastolic augmentation should be greater than 20 mmHg to be of clinical benefit. The human LD, however, would be expected to generate a greater total power output owing to its larger size, although up to 60% atrophy can occur as a long-term complication of cardiomyoplasty [19].

Our data on twitch duration throughout the 60 min of continuous action clearly demonstrate the slow character of the trained LD (C, between 222 and 243 ms, and R,,...
between 249 and 284 ms). The normal left ventricle (LV), however, requires a much shorter period for contraction and relaxation, particularly at heart rates above 100 min\(^{-1}\), and may consequently experience a restrictive physiology when coupled to a more hypokinetic layer of skeletal muscle. Similarly, the \(-dP/dt\) of normal left ventricular pressure decay is approximately \(-2000 \text{ mmHg s}^{-1}\) \([14]\) which, with a peak LV pressure change of 100 mmHg, equates to a \(-dP/dt:\Delta P\) of \(-20 \text{ s}^{-1}\). This is significantly faster than that measured for the fatigue-resistant muscle (mean value of \(-8.6 \text{ s}^{-1}\)). Our findings therefore support, albeit indirectly, the evidence that dynamic cardiomyoplasty acutely impairs left ventricular diastolic function \([6]\). Similarly, the potential efficacy of aortomyoplasty may be limited since rapid relaxation (similar to the deflation rate of an intra-aortic balloon pump which occurs almost instantaneously) is an essential requirement to achieve a reduction in left ventricular afterload. These findings support the need to develop strategies to optimise the performance of the electrically transformed LD. The use of myotrophic agents such as anabolic steroids \([12,28]\) and \(\beta_2\)-agonists \([26,27]\) have been suggested in an endeavour to preserve the power and/or twitch speed. The mock circulation system could potentially be used to determine experimentally the functional benefits, if any, of such a 'pharmaco-electrical' approach to LD training.

The optimal electrical stimulation regimens have not yet been established in the field of skeletal muscle assistance. However, any regimen is a balance between muscle power output and transformation that avoids fatigue and muscle fibre damage. Although the current stimulation protocol for cardiomyoplasty patients is gradual and progressive \([4]\), the lack of detection of early fatigue during the training period increases the likelihood of over-stimulation. Chronic over-stimulation of skeletal muscle is probably an important determinant of the long-term damage and atrophy that is increasingly becoming recognised as a complication in skeletal muscle assist. For example, it has recently been shown using MRI scanning that the distal LD atrophies by more than 60% in patients 2-4 years after cardiomyoplasty \([19]\). This was associated with increased signal brightness, characteristic of fibrosis and lipomatosis. Similarly, in a sheep model of aortomyoplasty, marked damage to the trained LD was reported using a synchronisation ratio of 1:1 compared to muscles subjected to the less stressful 1:2 and 1:4 modes \([25]\). In addition, other workers have demonstrated the direct relationship between excessive electrical stimulation and muscle damage \([20]\).

We have shown that slowing of relaxation and depression in peak rates of tension development (+dP/dt) and relaxation (-dP/dt) both occur as early events in the fatigue process. Prolongation of relaxation coincident with the onset of fatigue has also been observed during in vivo exercise in humans as well as in isolated muscles contracting in situ or in vitro \([1,3,23,24]\). Furthermore, accompanying this, in vivo is a decline in motorneurone discharge, thus completing a physiological response known as 'muscle wisdom' \([10]\). This is believed to optimise the force generated by the stressed muscle and to ensure a more economic activation by the central nervous system. The mechanism underlying this compensatory response is unknown.

We postulate that a reduction in the level of stimulation (e.g., amplitude, frequency, number of contractions per minute) at the onset of early fatigue could help mimic 'muscle wisdom' when stimulating a muscle extrinsically. Respecting this physiological principle may lessen the long-term damage of the LD in cardiomyoplasty patients and, in turn, improve the level of cardiac assistance.

The acute reduction in peak twitch tension of the LD that occurs with fatigue in cardiomyoplasty patients can only be detected indirectly using invasive techniques—e.g., measuring acute drop in haemodynamic parameters (e.g., cardiac index, left ventricular end-diastolic pressure, pulmonary artery wedge pressure) with intravascular catheters. It may be feasible to measure the \(C_T/R_{90}\) ratio in patients under fluoroscopy using the excursion made by radiopaque markers (e.g., the intramuscular electrodes, surgical clips) or implantable ultrasound crystals with each contraction. This relatively non-invasive investigation could be performed every time the stimulation parameters were increased to compare the \(C_T/R_{90}\) ratios. This approach could help prevent long-term muscle damage and warrants further investigation, particularly with regard to long-term feasibility.

In conclusion, we have used a mock circulation system to evaluate the performance of the electrically trained and untrained LD in sheep during continuous activity. The power output of the former group performing in the wrap configuration was found to be 64% lower than for pre-fatigue values attained by the untrained muscles and corresponded to a pressure augmentation and stroke volume of only 13.9 mmHg and 12.5 ml, respectively. This, in combination with slow rates of contraction and relaxation, may greatly limit the efficacy of skeletal muscle assist. Optimising these parameters pharmacologically or by different stimulation protocols may help improve early and long-term clinical results. Finally, the development of fatigue in control muscles was accompanied by prolonged relaxation time, which may be of value in monitoring the LD during chronic electrical training by serving as an indirect marker of fatigue.

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