# Changes in Lower Limb Skeletal Muscle and Mechanisms of Fatigue in Chronic Heart Failure

Andrew L. Clark and Andrew J.S. Coats

*Department of Cardiac Medicine, National Heart & Lung Institute, London, UK*

**Abstract**

Lower limb skeletal muscle becomes abnormal in chronic heart failure. There is reduced blood flow to the legs during exercise, and function is reduced in terms of both isometric force production and increased fatiguability. There is loss of muscle bulk, and a shift towards early anaerobic metabolism associated with histological and enzymatic changes. These changes are associated with both an increased ventilatory response to exercise and a reduction in exercise tolerance, with fatigue and breathlessness as prominent limiting symptoms.

To tie these phenomena together, it is attractive to postulate a central role for muscle ergoreceptors that become abnormally active in response to the abnormal skeletal muscle. The receptors may be excessively stimulated by a variety of stimuli, so that leg blood flow, muscle bulk or intracellular pH or potassium may not of themselves be the unique stimulus. An enhanced ergoreflex has the merit of helping to explain the excessive sympathetic activity of CHF which is poorly explained by invoking reduced perfusion pressure of the baroreceptors: the baroreflex gain is greatly reduced in CHF [21, 67, 83].

In therapeutic terms, this hypothesis emphasises the importance of leg skeletal muscle changes in CHF. Therapies aimed at interrupting the vicious circle of declining muscle function, such as exercise training, anabolic steroids or $\beta_2$ adrenoceptor agonists [54] may improve the functional status of patients where the traditional approaches aimed at squeezing the failing myocardium harder [23, 69, 92] or reducing vasoconstriction have failed to improve outcome.

**Key words**: chronic heart failure, exercise, skeletal muscle, fatigue, magnetic resonance spectroscopy.

*BAM 5 (4): 349-358, 1995*

Chronic heart failure (CHF) is characterised as a clinical disorder by exercise intolerance. The symptom causing a subject to stop exercising is usually given as shortness of breath or fatigue. During exercise, there is an early and prolonged release of lactate from exercising muscle in patients with CHF, even during light exercise [76]. The concept of a lactate threshold corresponding with a measurable ventilatory anaerobic threshold has become widespread, and has consistently been found to occur at a lower level of exercise in CHF [34, 95]. At first sight, fatigue may be thought simply to be due to failure of perfusion of the exercising musculature and the consequent early onset of intramuscular acidosis; however, evidence increasingly points to there being intrinsic abnormalities of muscle metabolism and structure in patients with CHF. In this article, we will review these changes, and discuss the genesis of limiting symptoms.

## Peripheral haemodynamics in CHF

Exercise tolerance in chronic heart failure has traditionally been tested by incremental exercise protocols with measurement of metabolic gas exchange to determine peak oxygen consumption (peak $\dot{V}O_2$). Peak $\dot{V}O_2$ correlates poorly with indices of central haemodynamic function [22, 24, 96], and attention has turned to the periphery as an explanation for exercise limitation. The observation that increasing the exercising muscle bulk by the addition of arm exercise at peak leg exercise results in increased peak $\dot{V}O_2$ in CHF patients, but not in controls, strongly suggests that some aspect of skeletal muscle behaviour is an important determinant of exercise tolerance in CHF rather than a limitation of cardiac output.

Wilson *et al.* found a reduction in blood flow using thermodilution to exercising leg muscle compared with controls [102]. The delayed improvement in exercise capacity seen after treatment with angiotensin converting

enzyme inhibitors is correlated closely with the increase in leg blood flow [16]. There is near-maximal oxygen extraction by exercising muscle [44], and the widened arteriovenous oxygen difference [16, 32] suggesting that the exercising muscles' activity is being limited by the capacity of the circulation to deliver oxygen.

A decrease in blood flow to the periphery might be explained by abnormalities of vasomotor tone [105], with a reduced response to endogenous vasodilatory stimuli [41, 43], and to infused hyperosmolar solutions [3]. Alternatively an increase in circulating levels of the vasoconstrictor endothelin may contribute [61]. An increase in the arterial wall sodium has been reported in an experimental model [104], which could result in smooth muscle contraction within arterial walls. LeJemtel showed that the peripheral resistance is greatly elevated in CHF [45].

The relationship between leg blood flow and exercise capacity is, however, more complex than these findings suggest. Wilson *et al.* used dobutamine to increase cardiac output, thereby causing an acute improvement in leg blood flow [101]. At any given work load, the lactate response to exercise was unchanged, drawing attention to the possible distinction between blood flow and "nutritive flow". In a further study, Wilson reported a subset of heart failure patients with normal femoral blood flow on exercise, but who had abnormal leg muscle as lactate production was increased compared with normals [98]. There therefore appear to be abnormalities of leg muscle that are independent of changes in blood flow. These abnormalities may be at the level of histological changes or ultrastructurally, and if skeletal muscle abnormalities are important determinants of exercise capacity should result in disordered muscle performance.

### Muscle performance and bulk

Lower limb skeletal muscle performance is disordered in CHF. Data from our institution initially suggested that *quadriceps* muscle strength is reduced [47], and in a small study we showed a relationship between *quadriceps* strength and exercise performance assessed by peak oxygen consumption during an incremental exercise test [7]. Minotti and colleagues have reported that there was no reduction in skeletal muscle strength in CHF [62, 65]. This apparent contradiction may be resolved by the observation that in our original study, mean force per unit area was within the normal range, implying that myofibril force production was normal, but that loss of skeletal muscle bulk was an important determinant of *quadriceps* strength [47].

From a functional point of view, the ability to perform repeated submaximal exercise is more important than peak force generation, and early *quadriceps* fatiguability has been reported by both sets of investigators [47, 65]. The reduction in endurance correlates with exercise performance, and has been found by others investigators [100]. In that there is no change with acute circulatory occlusion to the exercising limb, fatigue appears independent of acute changes in blood flow [62, 65] and of central factors [100]. Buller found fatiguability in a very small muscle group in which blood flow is unlikely to be limited by cardiac reserve [7]. This suggests intrinsic muscle factors mediate fatiguability of muscle. Minotti [65] also emphasised the importance of intrinsic muscle changes to the sensation of fatigue, finding no evidence of abnormal central motor drive or neuromuscular transmission in his patients.

Muscle wasting in chronic heart failure has been recognised since ancient times [40]. Decreased muscle bulk could potentially explain many of the observed lower limb abnormalities seen in CHF; an increase in fatigue and decrease in exercise tolerance as a result of increase load per unit myofibril; and a proportionate reduction in leg blood flow. The increased peripheral vascular resistance might result from the decreased vascular conductance. Using anthropometric methods and 24 hour urinary creatinine excretion, Mancini showed that muscle wasting occurred in even mild heart failure [51]. Further, she showed that peak exercise capacity correlated with calf muscle volume. We studied the influence of leg blood flow, leg muscle bulk and *quadriceps* strength on exercise capacity in CHF. Although we used a relatively crude measure of muscle mass, a single computed tomography scan slice at the level of mid femur, we have shown that exercise capacity correlates well with both strength and mass, and that reduced leg blood flow may be a consequence of muscle wasting [93]. There was no relationship between exercise capacity and blood flow, measured either at rest or following exercise and ischaemia as a measure of peak blood flow. We used venous occlusion plethysmography to determine flow which measures flow per unit muscle volume; the implication being that flow *per unit muscle bulk is* not a determinant of exercise capacity.

Minotti *et al.* have extended these findings using magnetic resonance imaging to determine maximal thigh cross sectional area [66]. In 21 patients muscle size was reduced, as were muscle strength (although not significantly) and endurance. Maximal force per unit of muscle remained unchanged. These observations lend further support to the idea that muscle wasting may be the key event, so that strength may be reduced whilst maximal force per unit muscle is not impaired. Nevertheless, there appears in addition to be a qualitative difference between normal and heart failure lower limb muscle as fatigue was not fully explained by the reduction in muscle size. This may be related to muscle quality, or may be related to alterations in gross structure, such as intramuscular fat content.

### Lower limb histology in chronic heart failure

A variety of histological skeletal muscle changes have been reported in chronic heart failure from a variety of biopsy sites, and a consistent pattern has been slow to emerge. Lipkin *et al.* reported results of *quadriceps* muscle needle biopsies in 9 patients with severe chronic heart failure [47]. A range of histological abnormalities was found with an increase in muscle fibre size variance, and

a shift towards type II fibres. Atrophic fibres were found, as well as intracellular lipid droplets. There was no change in capillary density, nor change in cytochrome oxidase or succinate cytochrome c reductase activity.

In a study of 22 patients with 8 controls, Mancini *et al.* studied the histology of *gastrocnemius* biopsies quantitatively [49], reporting a shift towards type IIb fibres and atrophy of type IIa fibres, and the presence of type IIc fibres. In this study, type I fibres were not found to be significantly reduced. Capillary density per fibre was unchanged compared with controls, but was increased in heart failure when expressed per $mm^2$. Citrate synthase, lactate dehydrogenase and phosphofructokinase activities were normal. An enzyme mediating the β-oxidation of fatty acids, β-hydroxyacyl CoA dehydrogenase activity was reduced. Changes were similar regardless of aetiology of heart failure. There was no correlation between the biopsy results and a measure of muscle aerobic metabolism*. A preliminary study also reported a reduction in capillary density in *vastus lateralis* biopsies but decreased capillary to muscle fibre ratio [103]. Type II fibres appeared to be increased in number but decreased in size, and succinate dehydrogenase activity was reduced.

A fourth study examined needle biopsies from *vastus lateralis* in 11 patients and 9 controls [85]. Type I fibres were found to be reduced, and type IIb to be increased. Type IIc were seen in 1 control subject only. The type IIb fibres were smaller than in controls. The ratio of capillaries to fibre cross-sectional area was unchanged; as the fibres were smaller than normal, the number of capillaries per fibre was reduced. Sullivan also reported a range of enzymatic analyses. The measured glycolytic enzymes (phophorylase, phosphofructokinase, pyruvate kinase and lactate dehydrogenase) were all present on normal concentrations. Succinate dehydrogenase and citrate synthetase, enzymes of the Krebs' cycle, were reduced, as was the concentration of hydroxyacyl CoA dehydrogenase. Extending the study with this type of patient, Sullivan *et al.* reported the results of biopsies taken during submaximal and maximal exercise [84]. Glycolysis and glycogenolysis were accelerated compared with controls, but lactate accumulation and phosphocreatine (PCr) depletion were decreased at peak exercise. The reasons for this when NMR spectroscopy studies suggest early acidosis, depletion of ATP and lactate generation in CHF [49, 50, 52] are not clear (see below).

Drexler and colleagues have examined the possible contribution of mitochondrial abnormalities to the myopathy of chronic heart failure. Needle biopsies from *vastus lateralis* were obtained from 57 patients and 18 controls [17]. Type I fibres were reduced and type II relatively increased (subtypes of type II fibres were not measured). The volume density of mitochondria and surface density of cristae were reduced, a finding more marked in the more severely exercise limited subjects. In addition, there was a reduction in cytochrome oxidase activity in the patients, more marked with increasing severity. In a subset of patients, capillary length density (a measure of the length of blood capillaries per unit volume of muscle tissue) was reduced. Other workers have confirmed the reduction in citrate synthase, succinate dehydrogenase and cytochrome oxidase in *vastus lateralis* [75]. Broqvist [6] reported a series of 22 patients with clinically severe CHF who had needle biopsies from the lateral aspect of *quadriceps femoris*. In these patients, there were significant reductions in high energy metabolic substrates (ATP, PCr and glycogen). These findings were in contrast to Sullivan's earlier report [85] that ATP and creatine phosphate were unchanged. Diet had been carefully controlled prior to the biopsies in Broqvist's study, which also reported on patients with clinically severe heart failure: Sullivan included only 1 patient with New York Heart Association class IV symptoms.

A summary of the findings of the histological and biochemical findings is presented in table 1. The findings are not definitive. Although it may appear that glycolysis is unaffected, other investigators have found a reduction on phosphofructokinase activity in CHF patients [91]. Other potential biochemical changes as determinants of exercise tolerance have as yet only been lightly touched upon. The sodium-potassium ATP-ase appears to be reduced in *vastus lateralis* muscle biopsies [68]. Some other abnormality of membrane channel, receptor [79] or of the contractile apparatus could prove more important.

### Phosphocreatine metabolism in exercising muscle

The net result of the abnormalities of lower limb skeletal muscle and blood flow appears to be the early onset of intramuscular acidosis and excessive lactate production. This can be measured as an increase in arterial and venous lactates at a given workload in heart failure patients [88, 89, 94]. However, Katz *et al.* found that during 30 minutes of submaximal exercise (at two thirds of the previously determined peak $\dot{V}O_2$), femoral venous and arterial lactate levels were unchanged although lactate turnover was twice that at rest [42]. The implication is that simple measures of arterial or venous lactate are only poorly related to the metabolic state of the exercising muscle.

Using $^{31}P$ nuclear magnetic resonance spectroscopy allows the internal state of the exercising muscle itself to be explored. The analysis of phosphorus spectra allows the relative concentrations of inorganic phosphate ($P_i$), phos-

* Since the relationship between oxygen consumption ($\dot{V}O_2$) and ADP production is linear, the slope of the relationship of $\dot{V}O_2$ to the inorganic phosphate/phosphocreatine ratio derived from magnetic resonance spectroscopy gives an index of aerobic metabolism. It is typically steeper in patients with heart failure.

*Table 1. Summary of skeletal muscle changes. There is a generalised shift away from type I (slow twitch, aerobic) fibres towards type II (fast twitch, anaerobic) fibres. Whilst the glycolytic pathway appears unaffected, there is a reduction in oxidative capacity, including that for β-oxidation of fatty acids. There is a generalised reduction in capillary density, although whether there is a reduction per muscle fibre remains unclear.*

| | Lipkin [47] | Mancini [49] | Yancy [103] | Sullivan [85] | Drexler [17] | Ralston [75] | Broqvist [6] |
|---|---|---|---|---|---|---|---|
| Fibre type-I | ↓ | ↔ | ↓ | ↓ | ↓ | | |
| IIa | | ↓ | | ↔ | | | |
| IIb | (↑) | ↑ | (↑) | ↑ | (↑) | | |
| IIc | | ↑ | | ↔ | | | |
| Glycolytic pathway | | ↔ | ↔ | ↔ | | | |
| Krebs' cycle | | ↔ | ↓ | ↓ | | ↓ | |
| Lipid oxidn | | ↓ | | ↓ | | | |
| Ox phos | ↔ | | | | ↓ | ↓ | |
| ATP/CrP | | | | ↔ | | | ↓ |
| Mitochondria | | | | | ↓ volume<br>↓ cristae | | |
| Cap dens /fibre | | ↔ | ↓ | ↓ | | | |
| / mm$^2$ | | ↑ | ↓ | ↔ | ↓ | | |
| | intracellular lipid, fibre atrophy | Type II fibre size ↓ | Type II fibre size ↓ | Type II fibre size ↓ | | | |

Under fibre types, an arrow in brackets (↑) means that fibre subtypes were not reported. Lipid oxidn refers to hydroxyacyl CoA dehydrogenase activity. CrP is creatine phosphate. Cap dens is capillary density expressed either per fibre or per unit area of muscle.

phocreatine and ATP to be determined. In addition, pH can be calculated. Initial work examining the response of arm muscle to exercise demonstrated more rapid depletion of PCr in CHF patients [56, 57, 97]. Whilst these observations in themselves are interesting, they needed to be extended to weight-bearing musculature of the lower limb. Mancini *et al.* [50] used circulatory occlusion to "freeze" the metabolic state of the muscle after exercise to allow the patient to be transferred to the magnet [31]. She showed that the slope of the increase in $P_i$/PCr relative to $\dot{V}O_2$ was increased in calf muscle in CHF patients, that is, at any given workload (corresponding to $\dot{V}O_2$), there was greater depletion of PCr. The study also showed that the intramuscular pH fell unlike in normals. In addition, the recovery rate (the rate at which PCr was resynthesised) was slower in patients.

Using a larger coil allowing exercise to take place inside the magnet, Arnolda *et al.* showed a 7 times greater fall in the PCr/(PCr+$P_i$) ratio in heart failure patients during the early stages of plantar flexion exercise [2]. At peak exercise, PCr/(PCr+$P_i$) ratio and pH were lower than in controls. In this small study (7 patients), recovery of PCr after exercise was not significantly slower in CHF patients. By simultaneously measuring leg blood flow by plethysmography, Arnolda was able to show that blood flows at a given level of exercise were the same in both patients and controls, a further indication that blood flow *per se* is not a determinant of muscle metabolism, at least in the acute situation, when expressed per unit leg volume.

Extending this work, Mancini showed no relationship between histological and biochemical abnormalities and magnetic resonance spectroscopic variables [49]. This later finding suggests that the observed histological and biochemical changes do not closely predict the abnormal metabolic response. Marie *et al.* [52] found that the load taken to achieve a given level of PCr depletion during calf exercise was about one-third of that in normals. A further study by Mancini and co-workers [51] analysed the time

constant of recovery for PCr. This variable is said to be independent of work load and muscle mass used. The time constant of recovery correlated better with work slope than did measures of muscle mass, which has been interpreted as suggesting that intrinsic alterations of muscle fibres rather than atrophy (at least as far as external muscle size is concerned) are the dominant mechanisms for reduced exercise tolerance [18].

Some of these findings apparently contradict Sullivan's findings of less lactate generation and less PCr decline at peak exercise on muscle biopsy studies [84]. This may be because in Sullivan's study maximal exercise using a cycle protocol was used, whereas in the magnetic resonance spectroscopy studies, smaller muscle groups were used, which would not challenge the capacity of the cardiovascular system to deliver oxygen to the exercising tissue. With a small muscle group, exercise may be determined by the metabolic capacity of the muscle alone, whereas with cycle exercise to exhaustion, other limiting factors such as cardiac output, muscle blood flow and the ventilatory response may become more important determinants of exercise capacity.

### Potassium handling and release from skeletal muscle

In normal subjects, potassium is released from exercising muscle, and rises in arterial potassium closely parallel rises in ventilation [71, 72]. It has been suggested that the behaviour of potassium at the level of the myocyte cell membrane may be responsible for the sensation of fatigue; intracellular calcium rises during exercise, causing an increase in potassium conductance, leading in turn to an inactivated membrane. This potential protective mechanism, preventing an excessive rise in intracellular calcium during excessive work, may equate with fatigue [82]. Handling of potassium may be abnormal in chronic heart failure, and has been reported to be higher at matched workloads in CHF [4]. We have shown that potassium is unlikely to be important as a circulating determinant of the ventilatory response to exercise [12]; nevertheless, as a local intramuscular mediator, potassium may be important.

### The origins of muscle change

The lower limb skeletal muscle of patients with chronic heart failure thus has a combination of abnormalities that appear, at least in some studies, to be partially independent of each other. There are biochemical and histological changes suggesting a move from aerobic towards anaerobic metabolism. These are accompanied by changes in metabolism during exercise of rapid early decline in PCr and a fall in intracellular pH, coupled with excess lactate turnover. The muscle function is reduced; there is at least a tendency towards decreased isometric power, and an increase in fatiguability. Muscle bulk itself appears to be reduced, and there is a reduction in femoral blood flow. How do these changes arise?

The origins of skeletal muscle wasting and biochemical change may be related to inactivity. The changes seen are similar to those seen in normal subjects undergoing "detraining", with skeletal muscle wasting and depletion of oxidative enzymes [36, 77], and activation of the sympathetic [15] and renin-angiotensin [33] systems. Some authors have suggested that malnutrition may contribute significantly to muscle wasting [5, 8]. In the case of patients with ischaemic heart disease, skeletal muscle ischaemia may be an additional factor [74]. Although some studies of abnormal skeletal muscle have been careful to include only those patients with intact peripheral pulses [47, 49], intramuscular small vessel arterial disease may contribute. Chronic hypoxia causes a reduction in fibre size and a decrease in aerobic enzymes [28]. However, studies of detraining have shown generalised fibre wasting and not a change in the distribution of muscle fibre types [29, 70], although *training* can result in a shift towards type I and IIa fibres [35]. However, as Arnolda has pointed out [2], the fact that changes are seen in small arm muscles (the finger flexors [56, 57]) suggests that simple disuse is unlikely to be the only contributor to the muscle changes.

The generalised activation of the sympathetic system seen in CHF could act as a further mediator of skeletal muscle change, together with a possible contribution from catabolic factors. Tumour necrosis factor has been found to be elevated [46, 60]. Insulin resistance is also present in patients with CHF [90], and the insulin resistance found may contribute to muscle catabolism. The existence of ergo- [38] or metabolo- [78] receptors, sensitive to muscle work and transmitting to the central nervous system via small unmyelinated nerve fibres [59] suggests the possibility of a "vicious cycle": chemically sensitive afferents from muscle drive blood pressure responses and increase sympathetic activity in normal subjects [25, 37, 53], and the presence of increased ergoreceptor activity in CHF [74] might maintain the increased sympathetic outflow, increasing peripheral resistance and decreasing skeletal muscle perfusion [3, 41, 43, 45, 61, 104, 105]. In turn, the skeletal muscle may deteriorate further.

### The evidence from exercise training

Acute corrective changes in haemodynamics in CHF, such as inotropic support [55], vasodilation [16, 58], or cardiac transplantation [80, 81], may result in improved leg perfusion, but are not accompanied by acute increases in exercise capacity. Exercise training regimes have, however, been shown to have beneficial effects on exercise capacity [13, 14, 87]. There appears to be an improvement in cardiac performance with training [19]. Minotti has shown improvements in forearm metabolic capacity [64]. Sullivan demonstrated increased leg blood flow secondary to a reduction in leg vascular resistance following training [87], together with a decrease in the lactate rise during exercise associated with an increase in the ventilatory anaerobic threshold [86]. Adamopoulos [1] has shown improvements in the leg metabolic abnormalities

measured by $^{31}P$ magnetic resonance spectroscopy with training. The improvements in exercise capacity appear to occur largely in the absence of improvements in central haemodynamic function [39, 63].

These findings together argue strongly for the importance of skeletal muscle in determining exercise capacity in CHF. The abnormal muscle, however it arises, takes time to recover as a result of training, and the improvements in muscle rather than changes in haemodynamics and blood flow determine the improvements in exercise capacity.

### Origin of fatigue and the termination of exercise

Ultimately, incremental exercise stops with a voluntary decision made by the exerciser in response to unwelcome symptoms, usually fatigue or breathlessness. Most studies of exercise capacity have used cycle exercise, particularly in the USA, and cycle exercise is usually terminated by fatigue [22]. Treadmill exercise, more common in the UK, is more frequently terminated by shortness of breath [11]. The same patient may complain of different symptoms depending upon the type of exercise undertaken [48]. We have shown [11] that there is no difference in cardiac function and ventilatory response between those patients stopping due to breathlessness and those stopping due to fatigue. It is not clear that fatigue is a discrete phenomenon.

It might be thought that fatigue should be related to the metabolic state of the muscles and particularly to lactate accumulation. However, in normal subjects, reducing the blood flow to the exercising leg results in early anaerobic metabolism, but a lower than usual lactate at peak exercise [20]. Lactate accumulation cannot be responsible for the fatigue that terminates exercise. In CHF, lactate reduction using an infusion of dichloroacetate results in no change in leg blood flow or exercise capacity [99], again suggesting that lactate is not an important mediator of fatigue. The sensation appears not to be related to PCr usage - chronic hypoxia leads to less PCr reduction at the same level of fatigue [27]. Other possible sites for the generation of fatigue have been identified, including intramuscular potassium [82]. The possibility that the sensation of fatigue is generated as a central mechanism to protect against hypoxic damage to essential organs [26, 30] is attractive.

Nevertheless, leg muscle factors do appear important as determinants of exercise. In contrast to haemodynamic variables, Mancini [51], Minotti [66] and ourselves have found muscle bulk to be a good predictor of peak $\dot{V}O_2$. This again raises the possibility that the ergoreceptors may be important. There is some evidence that increased ergoreceptor activity is related to an increased ventilatory response [9, 10], and it may be that these receptors are also responsible for mediating the sensation of fatigue, and perhaps even of dyspnoea.

**Address correspondence to:**

Andrew JS Coats, DM, FRACP, Department of Cardiac Medicine, National Heart & Lung Institute, Dovehouse Street, London SW3 6LY, tel. 071352 8121 extn. 8164.

### References

[1] Adamopoulos S, Coats AJS, Brunotte F, Arnolda L, Meyer T, Thompson CH, Dunn JF, Stratton J, Kemp GJ, Radda GK, Rajagopalan B: Physical training improves skeletal muscle metabolic abnormalities in patients with chronic heart failure. *J Am Coll Cardiol* 1993; 23: 1101-1106.

[2] Arnolda L, Conway M, Dolecki M, Sharif H, Rajagopalan J, Ledingham JGG, Sleight P, Radda GK: Skeletal muscle metabolism in heart failure: a $^{31}P$ nuclear magnetic resonance spectroscopy study of leg muscle. *Clin Sci* 1990; 79: 583-589.

[3] Bank AJ, Rector TS, Burke MN, Tschumperlin LK, Kubo SH: Impaired forearm vasodilation to hyperosmolal stimuli in patients with congestive heart failure secondary to idiopathic dilated cardiomyopathy or to ischemic cardiomyopathy. *Am J Cardiol* 1992; 70: 1315-1319.

[4] Barlow CW, Qayyum MS, Davey PP, Conway J, Paterson DJ, Robbins PA: Effect of physical training on exercise-induced hyperkalemia in chronic heart failure: relation with ventilation and catecholamines. *Circulation* 1994; 89: 1144-1152.

[5] Blackburn G, Gibbons G, Bothe A, Benotti P, Harken D, McEnany T: Nutritional support in cardiac cachexia. *J Thorac Cardiovasc Surg* 1977; 73: 489-496.

[6] Broqvist M, Dahlström U, Karlsson E, Larsson J: Muscle energy metabolism in severe chronic congestive heart failure - effect of treatment with enalapril. *Eur Heart J* 1992; 13: 1217-1224.

[7] Buller NP, Jones D, Poole-Wilson PA: Direct measurements of skeletal muscle fatigue in patients with chronic heart failure. *Br Heart J* 1991; 65: 20-24.

[8] Carr J, Stevenson L, Walden J, Heber D: Prevalence and haemodynamic correlates of malnutrition in severe congestive heart failure secondary to ischaemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1989; 63: 709-713.

[9] Clark AL, Piepoli M, Coats AJ: Evidence for skeletal muscle metabolic receptors driving ventilation on exercise. *Circulation* 1993; 88 (suppl): I-415.

[10] Clark AL, Piepoli M, Coats AJS: The skeletal muscle signal to ventilation on exercise is a function of muscle bulk used. *Br Heart J* 1994; 71(suppl): 181.

[11] Clark AL, Sparrow JL, Coats AJS: Muscle fatigue and dyspnoea in chronic heart failure: two sides of the same coin? *Eur Heart J* 1995; 16: 49-52.

[12] Clark AL, Volterrani M, Cerquetani E, Ludman PF, Swan JW, Poole-Wilson PA, Coats AJS: The Relationship between arterial potassium and ventilation during exercise in patients with chronic heart failure. *J Cardiac Failure* 1994: 1: 133-141.

[13] Coats AJS, Adamopoulos S, Meyer T, Conway J, Sleight P: Physical training in chronic heart failure. *Lancet* 1990; 335: 63-66.

[14] Coats AJS, Adamopoulos S, Radaelli A, McCance A, Meyer TE, Bernardi L, Solda PL, Davey P, Ormerod O, Forfar C, Conway J, Sleight P: Controlled trial of physical training in chronic heart failure: exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation* 1992; 85: 2119-2131.

[15] Cooksey JD, Reilly P, Brown S, Bomze H, Cryer PE: Exercise training and plasma catecholamines in patients with ischemic heart disease. *Am J Cardiol* 1978; 42: 372-376.

[16] Drexler H, Banhardt U, Meinertz T, Wollschläger H, Lehmann M, Just H: Contrasting peripheral short-term and long-term effects of converting enzyme inhibition in patients with congestive heart failure. A double-blind, placebo-controlled trial. *Circulation* 1989; 79: 491-502.

[17] Drexler H, Riede U, Münzel T, König H, Funke E, Just H: Alterations of skeletal muscle in chronic heart failure. *Circulation* 1992; 85: 1751-1759.

[18] Drexler H: Skeletal muscle failure in heart failure. *Circulation* 1992; 85: 1621-1623.

[19] Ehansi AA: Adaptations to training in patients with exercise-induced left ventricular dysfunction. *Adv Cardiol* 1986; 34: 148-155.

[20] Eiken O, Bjurstedt H: Dynamic exercise in man as influenced by experimental restriction of blood flow in the working muscles. *Acta Physiol Scand* 1987; 131: 339-345.

[21] Ellenbogen KA, Mohanty PK, Szentpetery S, Thames MD: Arterial baroreflex abnormalities in heart failure: reversal after orthotopic cardiac transplantation. *Circulation* 1989; 79: 51-58.

[22] Fink LI, Wilson JR, Ferraro N: Exercise ventilation and pulmonary artery wedge pressure in chronic stable congestive heart failure. *Am J Cardiol* 1986; 57: 249-253.

[23] Flosequinan for chronic heart failure. *Drugs Ther Bull* 1993; 31: 47-48.

[24] Franciosa JA, Park M, Levine TB: Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. *Am J Cardiol* 1981; 47: 33-39.

[25] Gandevia SC, Hobbs SF: Cardiovascular responses to static exercise in man: central and reflex contributions. *J Physiol* 1990; 430: 105-117.

[26] Garner SH, Sutton JR, Burse RL, McComas AJ, Cymerman A, Houston CS: Operation Everest II: neuromuscular performance under conditions of extreme simulated altitude. *J Appl Physiol* 1990; 68: 1167-1172.

[27] Green HJ, Sutton J Cymerman A, Young PM, Houston CS: Operation Everest II: muscle energetics during maximal exhaustive exercise. *J Appl Physiol* 1989; 66: 142-150.

[28] Green HJ, Sutton JR, Cymerman A, Young PM, Houston CS: Operation Everest II: adaptations in human skeletal muscle. *J Appl Physiol* 1989; 66: 2454-2461.

[29] Green HJ, Thomson JA, Daub BD, Ranney DA: Biochemical and histochemical alterations in skeletal muscle in man during a period of reduced activity. *Can J Physiol Pharmacol* 1980; 58: 1311-1316.

[30] Green HJ: Manifestations and sites of neuromuscular fatigue. *Biochem Exer* 1990; 21: 13-35.

[31] Harris R, Edwards R, Hultman E, Nordesjo L, Nylind B, Sahlin K: The time course of phosphorylcreatine resynthesis during recovery of the quadriceps muscle in man. *Eur J Physiol* 1976; 367: 137-142.

[32] Herrlin B, Sylvén C: Increased arterial oxygen content - an important compensatory mechanism in chronic moderate heart failure. *Cardiovasc Res* 1991; 25: 384-390.

[33] Hespel P, Lijnen P, Faggard R, Van Hoof R, Goossens W, Lissens W, Moerman E, Amery A: Effects of physical endurance training on the plasma renin-angiotensin-aldosterone system in normal man. *J Endocr* 1988; 116: 443-449.

[34] Hoh H, Taniguchi K, Koike A, Doi M: Evaluation of severity of heart failure using ventilatory gas analysis. *Circulation* 1990; 81 (1 suppl 2): II31-II37.

[35] Holloszy JO, Coyle EF: Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *J Appl Physiol* 1984; 56: 831-838.

[36] Holloszy JO: Adaptations of muscular tissue to training. *Prog Cardiovasc Dis* 1976;18: 445-458.

[37] Hultman E, Sjöholm H: Blood pressure and heart rate response to voluntary and non-voluntary static exercise in man. *Acta Physiol Scand* 1982; 115: 499-501.

[38] Iaria CT, Jalar UH, Kao FF: The peripheral neural mechanism of exercise hyperpnoea. *J Physiol* 1959;148: 49P-50P.

[39] Jette M, Heller R, Landry F, Blumchen G: Randomised 4-week exercise program in patients with

[89] Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR: Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. Muscle blood flow is reduced with maintenance of arterial perfusion pressure. *Circulation* 1989; 80: 769-781.

[90] Swan JW, Walton C, Godsland IF, Clark AL, Coats AJS: Insulin resistance in chronic heart failure. *Eur Heart J* 1994: 15: 1528-1532.

[91] Sylven C, Jansson E, Cederholm T, Hildebrand IL, Beermann B: Skeletal muscle depressed calcium and phosphofructokinase in chronic heart failure are upregulated by captopril-a double-blind, placebo-controlled study. *J Int Med* 1991; 229: 171-174.

[92] The Xamoterol in Severe Heart Failure Study Group: Xamoterol in severe heart failure. *Lancet* 1990; 336: 1-6.

[93] Volterrani M, Clark AL, Ludman PF, Swan JW, Adamopoulos S, Piepoli M, Coats AJS: Determinants of exercise capacity in chronic heart failure. *Eur Heart J* 1994; 15: 801-809.

[94] Weber KT, Janicki JS: Lactate production during maximal and submaximal exercise in patients with chronic heart failure. *J Am Coll Cardiol* 1985; 6: 717-724.

[95] Weber KT, Kinasewitz GT, Janicki JS, Fishman AP: Oxygen utilisation and ventilation during exercise in patients with chronic cardiac failure. *Circulation* 1982; 65: 1213-1223.

[96] Weber KT, Wilson JR, Janicki J, Likoff MT: Exercise testing in the evaluation of the patient with chronic cardiac failure. *Am Rev Respir Dis* 1984; 129 (Suppl): S60-62.

[97] Wiener DH, Fink LI, Maris J, Jones RA, Chance B, Wilson JR: Abnormal skeletal muscle bioenergetics during exercise in patients with heart failure: role of reduced muscle blood flow. *Circulation* 1986; 73: 1127-1136.

[98] Wilson JR, Mancini DM, Dunkman WB: Exertional fatigue due to skeletal muscle dysfunction in patients with heart failure. *Circulation* 1993; 87: 470-475.

[99] Wilson JR, Mancini DM, Ferraro N, Egler J: Effect of dichloroacetate on the exercise performance of patients with heart failure. *J Am Coll Cardiol* 1988; 12: 1464-1469.

[100] Wilson JR, Mancini DM, Simson M: Detection of skeletal muscle fatigue in patients with heart failure using electromyography. *Am J Cardiol* 1992; 70: 488-493.

[101] Wilson JR, Martin JL, Ferraro N: Impaired skeletal muscle nutritive flow during exercise in patients with congestive heart failure: role of cardiac pump dysfunction as determined by the effect of dobutamine. *Am J Cardiol* 1984; 53: 1308-1315.

[102] Wilson JR, Martin JL, Schwartz D, Ferraro N: Exercise intolerance in patients with chronic heart failure: role of impaired nutritive flow to skeletal muscle. *Circulation* 1984; 69: 1079-1087.

[103] Yancy CW Jr, Parsons D, Lane L, Carry M, Firth BG, Blomqvist CG: Capillary density, fiber type and enzyme composition of skeletal muscle in congestive heart failure. *J Am Coll Cardiol* 1989; 13 (suppl): 38A.

[104] Zelis R, Delea CS, Coleman H, Mason DT: Arterial sodium content in experimental congestive heart failure. *Circulation* 1970; 41: 213-216.

[105] Zelis R, Flaim SF: Alterations in vasomotor tone in congestive heart failure. *Prog Cardiovasc Dis* 1982; 24: 437-459.