Exercise Limitation in Chronic Heart Failure: Central Role of the Periphery

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The symptoms of chronic heart failure (CHF) are predominantly shortness of breath and fatigue during exercise and reduced exercise capacity. Disturbances of central hemodynamic function are no longer considered to be the major determinants of exercise capacity. The two symptoms of fatigue and breathlessness are often considered in isolation. A pulmonary abnormality is usually considered to be the cause of abnormal ventilation, and increased dead space ventilation has come to be accepted as a major cause of the increased ventilation relative to carbon dioxide production seen in CHF. Rather than decreased skeletal muscle perfusion, an intrinsic muscle abnormality is considered to be responsible for fatigue. Another abnormality seen in CHF is persistent sympathetic nervous system activation, which is difficult to explain on the basis of baroreflex activation. There is increasing evidence for the importance of skeletal muscle ergoreceptors or metaboreceptors in CHF. These receptors are sensitive to work performed, and activation results in increased ventilation and sympathetic activation. The ergoreflex appears to be greatly enhanced in CHF. We put forward the "muscle hypothesis" as an explanation for many of the pathophysiologic events in CHF. Impaired skeletal muscle function results in ergoreflex activation. In turn, this causes increased ventilation, thus linking the symptoms of breathlessness and fatigue. Furthermore, ergoreflex stimulation may be responsible for persistent sympathetic activation.

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Patients with chronic heart failure (CHF) stop exercising at lower work rates than do normal subjects. At first, the mechanism seems simple; patients with heart failure have impaired cardiac function, which results in an inability to raise cardiac output in response to exercise. "Backward failure" leads to breathlessness, and "forward failure" to fatigue. The failing left ventricle, fully utilizing the Frank-Starling mechanism, is supported by increased filling pressures, which in turn may result in pulmonary congestion or even edema. This can cause derangement to gas transfer and lung mechanics, leading to breathlessness. The failure of the heart to generate a sufficient output could cause fatigue secondary to poor skeletal muscle perfusion. However, evidence suggests that hemodynamic function is poorly related to exercise capacity and symptom generation in CHF, and points increasingly toward the periphery as an important determinant of both shortness of breath and fatigue.

In this report, we review the pathophysiology of exercise limitation in CHF and discuss possible future lines of inquiry.

Most studies addressing this subject have used incremental exercise tests with metabolic gas exchange measurement to derive peak oxygen consumption (peak VO2), an index of exercise capacity. In CHF, peak VO2 is reduced. Whether this is the most appropriate way to assess exercise function has been disputed, as different exercise protocols elicit different measurements of peak VO2 (1-3) and may not reflect everyday activity (4); nevertheless, peak VO2 is relatively reproducible and free of observer bias (5-7), and the method also allows ventilation (VE) and carbon dioxide consumption (VCO2) to be measured. The understanding of exercise limitation has increasingly involved an exploration of the possible causes of reduction of peak VO2.

Symptoms

The major symptoms of CHF are breathlessness and fatigue during exercise. Exploration of the mechanism of exercise limitation has tended to concentrate on the genesis of one or the other symptom with the tacit assumption that there are two groups of patients—one limited by some abnormality of skeletal muscle who complains of fatigue, and one in whom abnormalities of ventilation predominate and who complains of breathlessness. However, the same patients complain of different symptoms during different types of exercise (8). Cycle exercise predominantly leads to fatigue and treadmill exercise to breathlessness (9). Even using the same exercise mode, the symptom at peak exercise depends on the speed of the protocol (8), even when peak pulmonary artery pressures are the
same (10). Data from the Studies of Left Ventricular Dysfunction (SOLVD) show that breathlessness as a symptom is of little relevance in predicting outcome compared with measures of exercise capacity (11). We have shown in 202 patients that there is little difference in clinical characteristics between those stopped by breathlessness and those stopped by fatigue in terms of peak VO₂, ventilatory response to exercise or the etiology of heart failure (12). Rather than there being two groups of patients, breathlessness and fatigue may represent the same process or signal and may be generated by a similar underlying pathophysiologic mechanism.

Central Hemodynamic Function

It has been appreciated for some time that there is a weak relation between indexes of central hemodynamic function and exercise capacity (13). Although untreated patients with CHF have raised total body water and sodium (14), fluid compartments return to normal when the patients are optimally treated (15). The lack of a relation between left ventricular filling pressure and peak VO₂ (9,16) is thus not surprising. Similarly, there appears to be almost no relation between left ventricular function as measured by ejection fraction, rest cardiac output and exercise capacity (9,16–18).

If central hemodynamic variables are improved quickly with vasodilators (9,19,20) or with inotropic support (21), or even cardiac transplantation (22,23), there is no immediate change in exercise performance but rather a gradual improvement over weeks and sometimes months. In normal subjects, exercise capacity seems ultimately to be limited by cardiac output; increasing the exercising muscle bulk by adding arm to maximal leg exercise does not result in an increase in VO₂, suggesting that cardiac output and oxygen delivery is already maximal. In patients with CHF, the addition of arm to maximal leg exercise does produce a further increase in VO₂ (24). These findings imply that the ability of the muscle to extract oxygen, for whatever reason, rather than the heart to deliver oxygen, is the major determinant of exercise capacity. Altered cardiac function could, however, lead to secondary changes in the periphery, which in turn may determine exercise performance; these secondary changes may take months to return toward normal after hemodynamic improvement.

Pulmonary Function

A close correlate of peak VO₂ in CHF is the ventilatory response to exercise. There is an increase in ventilation at a given level of exercise (9,34–37), and this is well characterized as an increase in the slope of the relation between ventilation and carbon dioxide production (Ve/VCO₂ slope). That is, at any given level of carbon dioxide production, minute ventilation is increased (32,33). An explanation for the exercise limitation in CHF must include an explanation for the increased ventilatory response.

This raises the crucial question of what drives ventilation during exercise. The linearity of the relation between VCO₂ and Ve persuades many investigators that the primary ventilatory stimulant is carbon dioxide production. If so, then it might be anticipated that there should be a change in arterial partial pressures of blood gases as the initiating event in a feedback loop; however, arterial blood gases during exercise suggest, if anything, that hyperventilation is taking place with respect to blood gases (34,38). In those patients suspected of having CHF, abnormalities of blood gases are uncommon, and are associated with some other pathologic finding (39). The implication is that VCO₂ does not drive ventilation; rather, carbon dioxide is excreted by the lungs as a function of the mixed venous carbon dioxide tension and the minute ventilation. Anything that increases ventilation will thereby increase VCO₂. This is an important distinction; if VCO₂ follows ventilation, then there is a nonpulmonary ventilatory stimulus. It is possible that subtle changes or oscillation around the same mean level of blood gas tensions carries the ventilatory signal. There is some evidence for an increased chemosensitivity for hypoxia in CHF (40).

If VCO₂ is assumed to be the principal ventilatory stimulus, then analysis of the alveolar ventilation equation* leads to the

*Ve = VCO₂ × 863/Paco₂ × (1 – V̇E/V̇V̇̅̅), where V̇E/V̇V̇̅̅ describes dead space ventilation as a proportion of tidal ventilation; Paco₂ is the arterial partial pressure of carbon dioxide; and 863 is a constant to standardize gas measurements to body temperature, pressure and saturation.
conclusion that the increased \( \text{Ve}/\text{VCO}_2 \) slope must be caused by an increase in dead space ventilation (36,37). This has received some support (41,42) and forms an attractive theory; the failing right ventricle would result in decreased perfusion of the lung apices, with an increase in dead space ventilation. The respiratory pattern might change with an increase in rate at the same minute ventilation, causing greater ventilation of the fixed anatomic dead space (43). Davies et al. (44) reported a reduction in pulmonary capillary permeability, which related to the duration of heart failure, and Puri et al. (45) related this abnormality to increased resistance at the alveolar/capillary membrane. This potentially increases the proportion of ventilated alveoli that do not contribute to gas exchange.

Such an analysis of metabolic gas exchange has potential flaws. The alveolar ventilation equation only applies in steady state conditions, which do not exist in the rapidly incremental exercise protocols used in many studies (41,42). Indeed, during exercise with rapidly incremental stages, the \( \text{Ve}/\text{VCO}_2 \) slope is seen to increase further (46). Second, using the alveolar ventilation equation forces dead space to be the cause of the increased \( \text{Ve}/\text{VCO}_2 \) slope rather than the result of an increase in ventilation; no other factor can be invoked. Some anomalies arise in the interpretation of some studies. Wada et al. (42) found a greater \( \text{Ve}/\text{VCO}_2 \) slope in a subgroup of patients with a fall in dead space ventilation than that observed in control subjects, while at the same time concluding that dead space was a critical abnormality.

Rajfer et al. (47) used different methods to determine dead space fraction and found a fall in dead space in patients with heart failure during exercise. They also found hyperventilation relative to arterial blood gas tensions. We found no relation between right ventricular function and ventilation (29). In other experiments, we found that altering the respiratory rate at the same minute volume causes no change in the \( \text{Ve}/\text{VCO}_2 \) slope, at least in normal subjects (48), so that an alteration in respiratory pattern cannot explain the change in CHF.

The other possible component to ventilation-perfusion mismatch is an increase in perfused but underventilated areas of lung. If present, this shunt would result in an increase in the alveolar arterial oxygen difference and arterial desaturation. Small increases in alveolar arterial oxygen difference have been reported (38,47). Other workers have suggested that exercise capacity is increased in patients with heart failure by supplemental oxygen (49). However, in the absence of any significant abnormality of arterial oxygenation in the majority of patients with CHF (39), ventilation-perfusion matching is unlikely to be as important as is often concluded.

### Evidence for Role of the Periphery

If ventilation-perfusion mismatch is not the major cause of increased ventilation, then there must be a non-carbon dioxide signal to ventilation to explain the hyperventilation with respect to \( \text{VCO}_2 \). This certainly fits the observed behavior of arterial blood gases where \( \text{Paco}_2 \) is observed to fall during exercise. Further support comes from a closer analysis of the \( \text{Ve}/\text{VCO}_2 \) relation. The work of Metra et al. (41) showed that the \( \text{Ve}/\text{VCO}_2 \) slope calculated from the data acquired early in exercise is a remarkably poor predictor of the slope calculated from the exercise data as a whole (50). We have shown that in patients with CHF, the instantaneous \( \text{Ve}/\text{VCO}_2 \) ("ventilatory equivalent for carbon dioxide") rises toward the end of exercise, and that the more severe the heart failure, the more the \( \text{Ve}/\text{VCO}_2 \) deviates from a straight line relation (51). These observations suggest that there is a non-carbon dioxide stimulus to ventilation of increasing importance as the severity of CHF increases, causing progressively greater ventilatory response to exercise.

What is the origin of such an abnormal ventilatory stimulus and could it also explain the sensation of breathlessness? Increasingly, the evidence points toward abnormalities of skeletal muscle as being the source of both the symptoms of exercise intolerance and the excessive ventilatory response in patients with CHF.

### Skeletal Muscle in CHF

**Structure.** The histologic appearance of skeletal muscle in chronic heart failure has been reported to be abnormal in many studies (Table 1). An early study examining forelimb biopsies found increased lipid deposits and endomysial fibrosis (52). Lipkin et al. (53) reported on patients with severe CHF and described an increase in muscle fiber size variance, with a shift toward type II fibers. There were atrophic fibers and intracellular lipid droplets. Mancini et al. (54) reported a shift toward type IIb fibers in CHF and atrophy of type IIa fibers, and the presence of type Ic fibers in a study of 22 patients and 8 control subjects (54). In this study, type I fibers were not found to be significantly reduced. Capillary density per fiber was unchanged in patients with CHF compared with control subjects but was increased when expressed per square millimeter.

Sullivan et al. (55) found a reduction in type I fibers and a shift toward type IIb fibers. Type Ic fibers were seen in one control subject only. The type IIb fibers were smaller in patients with CHF than in control subjects. The ratio of capillaries to fiber cross-sectional area was unchanged; as the fibers were smaller than normal, the number of capillaries per fiber was reduced. Drexlert et al. (56) examined biopsies in 57 patients and 18 control subjects to assess mitochondrial structure. Type I fibers were reduced and type II fibers relatively increased (subtypes of type II fibers 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 a subset of patients, capillary length density (a measure of the length of blood capillaries per unit volume of muscle tissue) was reduced.

**Biochemistry.** Associated with the histologic abnormalities, there is a reduction in the oxidative enzymatic capacity of the muscles. There is a reduction in beta-hydroxyacyl coenzyme A dehydrogenase activity (an enzyme mediating fatty acid oxidation), but levels of citrate synthase, lactate dehydro-
Table 1. Summary of Skeletal Muscle Changes in Chronic Heart Failure

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<th>Investigators (ref no.)</th>
<th>Fiber type</th>
<th>Glycolytic pathway</th>
<th>Krebs' cycle</th>
<th>Lipid oxidation</th>
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<th>ATP/CrP</th>
<th>Mitochondria</th>
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There is a generalized shift away from type I (slow twitch, aerobic) toward type II (fast twitch, anaerobic) fibers. Although the glycolytic pathway appears to be unaffected, there is a reduction in oxidative capacity, including that for beta-oxidation of fatty acids. There is a generalized reduction in capillary density, although whether there is a reduction per muscle fiber remains unclear. ATP = adenosine triphosphate; CrP = creatine phosphate; Lipid oxidation = hydroxyacyl coenzyme A dehydrogenase activity; Ox phos = oxidative phosphorylation enzymes; ref = reference; ↓ = decreased; ↑ = unchanged; † = increased; (1") fiber subtypes not reported.

Skeletal muscle is functionally abnormal in CHF. We have found a reduction in quadriceps muscle strength (53) and an association between quadriceps strength and exercise performance (63). Other workers have not found a reduction in skeletal muscle strength (64,65), possibly because loss of skeletal muscle bulk may be an important determinant of strength (52)—mean force per unit area was within the normal range, implying that myofibril force production was normal. From the patient's point of view, the ability to perform repeated submaximal exercise is more important than peak force generation, and early quadriceps fatigability has been reported (52,65). This reduction in endurance correlates with exercise performance, as has been found by other investigators (66).

Fatigue appears to be independent of acute changes in blood flow (64,65) and of central factors (66). Fatigability has been shown in a very small muscle group in which blood flow is unlikely to be limited by cardiac reserve (63), suggesting that intrinsic muscle factors mediate fatigability of muscle.

Muscle bulk. Muscle wasting in CHF has been recognized since ancient times (67). Decreased muscle bulk could potentially explain many of the observed lower limb abnormalities seen in CHF, such as an increase in fatigue and a decrease in exercise tolerance as a result of increased load per unit myofibril and a proportionate reduction in leg blood flow. The increased vascular resistance might result partly from the decreased vascular conductance purely on anatomic grounds. Mancini et al. (68) showed that muscle wasting occurred even in mild heart failure. Further, they showed that peak exercise capacity correlated with calf muscle volume. We found that exercise capacity correlated with both strength and muscle mass, and that reduced leg blood flow may be a consequence of muscle wasting (69).

Minotti et al. (70) found a reduction in muscle size 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 while maximal force per unit muscle is not impaired, at least in mild to moderate heart failure. Nevertheless, there also appears to be a qualitative difference between normal and heart failure muscle, as fatigue was not fully explained by the reduction in muscle size. This may be related to muscle quality or to alterations in gross structure, such as intramuscular fat content.

Muscle metabolism. In CHF, there is early onset of intramuscular acidosis and excessive lactate production, often measured as an increase in arterial and venous lactates at a given work load (71,72), and a lower ventilatory anaerobic threshold (46,73). Katz et al. (74) found that during 30 min of submaximal exercise (at two thirds of the previously determined peak VO₂), femoral venous and arterial lactate levels were unchanged, although lactate turnover was twice that at rest. Simple measures of arterial or venous lactate are only poorly related to the metabolic state of the exercising muscle.

The metabolic consequences of exercise can be explored using phosphorus-31 (31P) nuclear magnetic resonance spectroscopy. The relative concentrations of inorganic phosphate (Pi), PCr and ATP can be determined from analysis of phosphorus spectra. Arm muscle demonstrates more rapid depletion of PCr in patients with CHF than in control subjects (75–77), and these findings have been extended to the lower limb. Mancini et al. (78) used circulatory occlusion to "freeze" the metabolic state of the muscle at peak exercise (79). Mancini et al. showed that the slope of the increase in Pi/PCr relative to VO₂ was increased in the calf muscle in patients with CHF; that is, at any given work load there was greater depletion of PCr. The rate at which PCr was resynthesized was slower in the patients.

Using a larger coil to allow leg exercise inside the magnet, Arnolda et al. (80) showed a seven times greater fall in the PCr/(PCr + Pi) ratio in patients with heart failure during the early stages of plantar flexion exercise. At peak exercise, the PCr/(PCr + Pi) ratio and pH were lower than in control subjects. In this small study of seven patients, recovery of PCr after exercise was not significantly slower in patients with CHF. Simultaneous leg blood flow measurements showed that blood flows at a given level of exercise were the same in both patients and control subjects, a further indication that blood flow itself is not a determinant of muscle metabolism, at least acutely.

Mancini et al. (54) also showed no relation between histologic and biochemical abnormalities and magnetic resonance spectroscopic variables. This later finding suggests that the observed histologic and biochemical changes do not closely predict the abnormal metabolic response. Marie et al. (81) found that the load taken to achieve a given level of PCr depletion during calf exercise was about one third of that in normal subjects. Mancini et al. (68) also analyzed the time constant of recovery for PCr. This variable is said to be independent of work load and muscle mass used. The constant correlated better with work slope than did measures of muscle mass, which has been interpreted as suggesting that intrinsic alterations of muscle fibers rather than atrophy (at least as far as external muscle size is concerned) are the dominant mechanisms for reduced exercise tolerance (82).

Some of these findings apparently contradict the findings of Sullivan et al. (57) of less lactate generation and less PCr decline at peak exercise on muscle biopsy studies. This may be because in their study maximal exercise was used, whereas in the magnetic resonance spectroscopy studies, smaller muscle groups were used. With a small muscle group, exercise capacity 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 ventilatory response, may become more important determinants of exercise capacity.

Origins of Muscle Changes

Peripheral hemodynamic variables. The origin of the histologic and biochemical abnormalities must ultimately be due to heart failure, although there is no consensus on how this comes about. A reduction in blood flow to the exercising muscle seems a likely possibility. Wilson et al. (83) found a reduction in blood flow to exercising leg muscle in patients with CHF compared with control subjects. The delayed improvement in exercise capacity seen after treatment with angiotensin-converting enzyme inhibitors is correlated closely with the increase in leg blood flow (20). There is near maximal oxygen extraction by exercising muscle, and the widened arteriovenous oxygen difference (20,84) suggests 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 (85). There is a reduced response to endogenous vasodilatory stimuli (86,87), to infused hyperosmolar solutions (88) and to pharmacologic agents (89). Alternatively, an increase in levels of endothelin or a reduction in response to endothelial vasodilatory capacity may contribute (90). LeJemtel et al. (91) showed that the peripheral resistance is greatly elevated in CHF. The site of the increased peripheral resistance is not yet understood. An increase in the arterial wall sodium has been reported in an experimental model (92); this could result in smooth muscle contraction within the arterial walls. The muscle capillary structure appears normal, and although the capillary basement membrane appears thickened in CHF, the difference between patients and control subjects is small (93). Arterioles are more difficult to examine, but recent studies have suggested that hyalinosis within terminal arterioles correlated with an increased minimal vascular resistance in patients with dilated cardiomyopathy (94). Large artery abnormalities have also been observed (95).

The relation between leg blood flow and exercise capacity is more complex than these findings suggest. Wilson et al. (96) used dobutamine to cause an immediate improvement in leg blood flow. At any given work load, the lactate response to exercise was unchanged, drawing attention to the possible
distinction between blood flow and “nutritive flow.” Further, Wilson et al. (97) reported a subset of patients with normal femoral blood flow on exercise, who had abnormal leg muscle as lactate production was increased, compared with normal subjects. There appear to be abnormalities of leg muscle that are independent of changes in blood flow. There seems to be no relation between leg blood flow and exercise capacity (69). Alterations in muscle biochemistry thus appear to be intrinsic, and do not depend, at least acutely, on alterations in blood flow.

The changes seen in patients with CHF are similar to those seen in normal subjects undergoing “detraining,” with skeletal muscle wasting and depletion of oxidative enzymes (98,99) and activation of the sympathetic (100) and renin-angiotensin (101) systems. Possible mechanisms for muscle wasting include malnutrition and malabsorption (102,103) and an increase in myofibrillar breakdown (104). In patients with ischemic heart disease, skeletal muscle ischemia may be another factor (105). Chronic hypoxia in normal subjects causes a reduction in fiber size and a decrease in aerobic enzymes (106). However, studies of detraining have shown generalized fiber wasting and no change in the distribution of muscle fiber types (107,108), although training can result in a shift toward type I and IIa fibers (109). The fact that changes are seen in small arm muscles suggests that simple disuse is unlikely to be the only contributor to the muscle changes.

The generalized activation of the sympathetic system seen in CHF could act as a further mediator of skeletal muscle change, together with possible contribution from catabolic factors and loss of anabolic function. Increased sympathetic efferent activity is seen early in the clinical course of the disease (110). Tumor necrosis factor has been found to be elevated (111,112). Insulin resistance is also present in patients with CHF (113), and the insulin resistance found may contribute to muscle catabolism. The persistent sympathetic activation seen in CHF is not well explained. It is often thought to be due to chronic withdrawal of baroreflex inhibition by reduced perfusion pressure. However, the baroreflex gain is greatly reduced in CHF (114–116), and ultrafiltration to remove over 31 body fluids, while resulting in a fall in blood pressure, results in suppression of the neurohormonal axis (117).

The existence of ergoreceptors (118) or metaboreceptors (119) sensitive to muscle work and transmitting to the central nervous system through small unmyelinated nerve fibers (120) and enhanced by accumulation of metabolites (121,122) suggests a different “vicious cycle.” These chemically sensitive afferent fibers from muscle drive blood pressure responses and increase sympathetic activity in normal subjects (123–125), and the presence of increased ergoreceptor activity in CHF (126) might maintain the increased sympathetic outflow, increasing peripheral resistance and decreasing skeletal muscle perfusion (85–92). In turn, the skeletal muscle may deteriorate further. These receptors and their afferent fibers may mediate the sensation of fatigue and possibly breathlessness.

**Evidence From Exercise Training**

Early corrective changes in hemodynamic variables in CHF are not accompanied by early increases in exercise capacity (19–23). Exercise training regimens have been shown to have beneficial effects on exercise capacity (127–130). There may be an improvement in cardiac performance with training (131), but the majority of the training effect is seen in the periphery. There are improvements in forearm metabolic capacity with training (132) and increased leg blood flow secondary to a reduction in leg vascular resistance (127). There is a decrease in the lactate rise during exercise, associated with an increase in the ventilatory anaerobic threshold (133). Adamopoulos et al. (134) have shown improvements in the leg metabolic abnormalities measured by 31P magnetic resonance spectroscopy with training, and the arm abnormalities are at least partially reversed (135). The improvements in exercise capacity appear to occur largely in the absence of improvements in central hemodynamic function (136,137). Training also causes a decrease in the ventilatory response to exercise (138).

**Skeletal Muscle and Ventilation in CHF**

What is the relation between exercise limitation, increased ventilation, skeletal muscle changes and symptoms of chronic heart failure? Kraemer et al. (139) found a relation between spirometric variables and peak VO2, but this could simply reflect a general relation between muscle strength and exercise capacity. Dyspnea can result from respiratory muscle changes, such as increased diaphragmatic work and accessory muscle deoxygenation (140,141), and reduced respiratory muscle strength (142,143). This hypothesis does not explain the increase in VE/VO2 slope. It may be that there is a specific ventilatory signal arising from exercising muscle (possibly including respiratory muscle), which is abnormally enhanced in CHF.

Circulating metabolites have been proposed as ventilatory stimuli. Lactic acid production has been considered, but the time course of the rise in lactate does not closely follow that of the rise in ventilation (144,145). Patients with McArdle’s syndrome are unable to generate lactate and yet still show an increase in ventilation with exercise (146). Further, dichloroacetate administration in patients with CHF prevents the exercise-induced rise in lactate but does not alter peak exercise capacity or ventilation (147).

Arterial potassium rises during exercise and closely follows the time course of the ventilatory response (145,148). The rise in potassium may be greater at matched work loads in patients with CHF (149). 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 (150). We found no relation between the rise in arterial and venous potassium and the rise in ventilation in patients with CHF. The potassium rise paralleled the rise in VO2 rather than that in
VE. The implication of this experiment is that both potassium and carbon dioxide are independent of the cause of the increase in ventilation (151), both reflecting the amount of exercise performed. Moreover, in patients undergoing treatment with erythropoietin for the anemia of chronic renal failure, the ventilatory response to exercise fell, while there was an increase in circulating potassium concentrations (152). Nevertheless, as a local intramuscular mediator, potassium may be important—perhaps being a natural stimulant of the muscle ergoreceptor.

There may be alternative humoral ventilatory stimuli. Tibes et al. (144) found no evidence for a range of possible metabolites in normal subjects. There could be an alteration in chemoreceptor responsiveness at the onset of exercise so that those with a greater ventilatory response develop an increase in chemoreceptor sensitivity. In preliminary studies of normal subjects, we found no evidence for this possible effect—exercising with cuffs inflated around the thighs to suprasystolic pressure results in an increase in VE:VCO₂ slope, which could not be of humoral origin (153), although a neural link to increased chemoreceptor sensitivity is possible.

The ergoreceptors postulated earlier to have a role in the vicious cycle of sympathetic activation and muscle wasting may also be related to the ventilatory response to exercise; during exercise in normal subjects, there is a signal arising from exercising muscle that stimulates ventilation, and is enhanced by circulatory occlusion (154). Data from our laboratory suggest that the ventilatory stimulus in normal subjects is related to the muscle bulk being used rather than the external work load being performed, and that the response is enhanced by circulatory occlusion to the exercising muscles (153) and is more marked if a smaller muscle group performs the same work load during exercise.

Fatigue and 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 United States, and cycle exercise is usually terminated by fatigue (5). Treadmill exercise, more common in the United Kingdom, is more frequently terminated by shortness of breath (12). The same patient may complain of different symptoms depending on the type of exercise undertaken (8). There is no difference in cardiac function and ventilatory responses between those patients stopping owing to breathlessness and those stopping owing to fatigue (12). It is not clear that fatigue and this form of dyspnea are discrete phenomena.

It might be thought that fatigue should be related to the metabolic state of the muscles, particularly to lactate accumulation. 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 (155). In CHF, lactate reduction causes no change in leg blood flow or exercise capacity (147), 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 (156). Other possible sites for the generation of fatigue have been identified, including intramuscular potassium (150). The possibility that the sensation of fatigue is generated as a central mechanism to protect against hypoxic damage to essential organs (157,158) is attractive.

Nevertheless, muscle factors appear to be important as determinants of exercise. In contrast to hemodynamic variables, muscle bulk is a good predictor of peak VO₂ (68–70). This again raises the possibility that the ergoreceptors may be important; the same receptors may be responsible for mediating both dyspnea and the sensation of fatigue.

Implications. The therapeutic response in CHF to inotropic agents has been disappointing, with an increase in mortality after therapy with, for example, milrinone (159), fosinopril (160) and xamoterol (161); although some of these agents have proved to have symptomatic benefit (162). Vasodilators appear to result in a decrease in mortality in heart failure (163–165), but the effect does not depend only on vasodilation; angiotensin-converting enzyme inhibitors are more effective at reducing mortality than other vasodilators, despite similar degrees of vasodilation (166,167). Indeed, the evidence that vasodilators other than angiotensin-converting enzyme inhibitors benefit mortality is doubtful (168,169). Improvements in mortality may depend on effects on the neurohormonal abnormalities of heart failure (170).

The muscle hypothesis (171) (Fig. 1) suggests new strategies for intervention. The major determinant of symptoms in chronic heart failure may be the abnormalities of skeletal muscle, resulting in early fatigue and an increase in the ventilatory stimulus and thus an increased ventilatory response to exercise. The key abnormalities are bulk, blood flow and function. The abnormal muscle results in persistent activation of the sympathetic nervous system, with increased afterload and reduced peripheral blood flow. In turn, cardiac function deteriorates with further patient inactivity, causing further deterioration in skeletal muscle. In addition, a catabolic state exists, further causing muscle wasting, perhaps related to cytokine activation and insulin resistance. Rather than treating the consequences of this proposed cycle of deterioration, ACE inhibitors and exercise training interrupt it, at least partially.

Conclusions

The evidence presented in this report suggests that new forms of treatment focused on skeletal muscle may improve the patient’s quality of life. If exercise training can prevent a deleterious cycle, it may even slow or arrest progression of the disorder. Exercise training has been shown to modify some of the predictors of mortality in chronic heart failure (128). It may prove possible in the future to improve skeletal muscle function pharmaceutically, perhaps with anabolic steroids or beta₂-adrenoceptor agonists (172), or even with pharmacologic “training” (173).

The evidence presented here does not prove that central
hemodynamic variables are unimportant. In the genesis of the heart failure syndrome, an initial cardiac abnormality is essential. Similarly, abnormalities of pulmonary function have been found by many investigators and may contribute to breathlessness and exercise limitation. The syndrome of chronic heart failure causes changes in many body systems and may represent a heterogeneous condition with some patients limited by pulmonary abnormalities, some by blood flow and some by skeletal muscle changes. Treatment aimed at the heart alone may not be the most successful approach. The potential importance of skeletal muscle abnormalities offers new possibilities for treatment of a common and debilitating condition.

References


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