Blood Flow and Skeletal Muscle in Patients with Heart Failure*

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The factors that contribute to the symptoms of breathlessness and fatigue, and that limit exercise capacity in patients with chronic heart failure are poorly understood. Recent evidence suggests that the major mechanism is not related to central hemodynamics but to a reduction of skeletal muscle mass and diminished blood flow to skeletal muscle on exercise.

The judicious use of diuretics, angiotensin-converting enzyme (ACE) inhibitors, vasodilators, and occasionally digoxin has greatly improved the treatment of patients with chronic heart failure in the last 20 years. The major advance has been in the elimination of excess salt and water and the reestablishment of normal fluid volumes. Exercise time is increased by diuretics and ACE inhibitors. Two trials of drug therapy have shown mortality to be reduced; in the first, an ACE inhibitor was used in patients with severe heart failure and in the second, vasodilators were studied in patients with moderate heart failure.

Despite these encouraging results, supported by several completed but unpublished further studies, patients still return to the physician complaining of shortness of breath or fatigue. Shortness of breath is not easy for the physician to assess, as patients may confuse shortness of breath with angina or exhaustion, and formal exercise testing with measurement of gas exchange is often expensive. Fatigue is also a difficult symptom to quantify, as tiredness, fatigue, exhaustion, and lethargy may be synonymous. The logical treatment of patients with chronic heart failure requires an understanding of the nature of these symptoms and their cause.

CAUSE OF SYMPTOMS

In acute heart failure, the patient is short of breath and this is attributable to an elevated left ventricular pressure. Lowering of this pressure by short-term interventions reduces the pressure and alleviates symptoms. This observation has been incorrectly applied to patients with chronic heart failure in whom fluid overload has been treated. A considerable amount of evidence now shows that symptoms are not related to central hemodynamics. Abnormal hemodynamics identify patients with heart failure but not the mechanism of the symptoms. If the left ventricular pressure were the limiting factor, then all patients should stop exercising when that pressure reaches a given high value. That is not observed. Furthermore, drugs can be used short term that alter the hemodynamics in what should be a favorable direction but are not associated with an increase of exercise capacity.

The reasons for the limitation of exercise capacity (Fig 1) are not fully understood both in patients with heart failure and in normal subjects. In athletes occasionally it is possible to demonstrate that oxygen capacity has reached a maximum, at which stage there may be an increase in work load or carbon dioxide production without any increase of oxygen consumption. When a true maximum oxygen consumption is observed, then this provides strong evidence that the circulation is the limiting factor. In most normal subjects, a plateau of oxygen consumption is not reached and thus it is not known whether oxygen delivery or the circulation is the limiting factor. The alternative explanation is that some sensation of loss of power in the muscles prevents the person from continuing to exercise. Acidosis, accumulation of phosphate, and an increase of intracellular magnesium concentration may be factors that contribute to a reduction of muscle function. In patients with heart failure, a true maximal oxygen consumption is rarely if ever seen. This is surprising since the expectation would be that in heart failure, the circulation would limit exercise.

EXERCISE IN HEART FAILURE

Exercise testing with measurement of gas exchange has justifiably become popular for the assessment of patients with heart failure. The increments of oxygen consumption with increased work load are shown in Figure 2. It is noticeable that at least 2 min are necessary for a new steady state to be reached, and even longer stages may be needed in patients with heart failure. Figure 3 shows the plot of oxygen consumption against carbon dioxide production in a normal person, a patient with moderate heart failure, and a patient with severe heart failure. In no person is a maximum

Reasons for limitation of exercise

<table>
<thead>
<tr>
<th>Failure of oxygen delivery</th>
<th>Failure of muscle function</th>
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<td>Plateau in O₂ consumption</td>
<td>No plateau in O₂ consumption</td>
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<td>Fall in tissue O₂ content</td>
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oxygen consumption reached. The relation between the 2 variables is not well-represented by 2 straight lines but fits closely to a hyperbolic relation. At low levels of exercise, the oxygen consumption for a given carbon dioxide production is the same in a normal person and the patients. The ability to exercise without oxygen is small and represents a minor percentage of the total oxygen consumption except in very severe heart failure. These findings suggest that the limiting factor is the blood flow to the skeletal muscle.

**Blood Flow in Skeletal Muscle**

In heart failure, there is an altered distribution of blood flow in the body. The blood pressure at peak exercise in patients with heart failure may be slightly reduced compared with normal subjects. However, measurements of exercising skeletal muscle blood flow show the flow to be reduced up to 5-fold, thereby suggesting that the resistance in the vascular bed is increased approximately 5-fold. This resistance to blood flow is a long-term consequence of heart failure but is not directly related to the ability of the heart to generate a cardiac output, since flow is determined by the resistance and perfusion pressure and not by the cardiac output per se. The failure of oxygen delivery to the exercising skeletal muscle is not due to arteriovenous shunting, as the oxygen saturation in the femoral vein is almost zero at peak exercise, suggesting that all the available oxygen is being used by the limb.

The cause of the increased resistance in the vessels supplying the limbs is unknown. Structural changes in the arterioles and endothelial cell swelling have not been demonstrated. The effect is not due to activation of the sympathetic system or the renin-angiotensin system since it cannot be reversed acutely by inhibitors of these systems. Endothelial cell function is being widely investigated but no clear abnormality has yet been shown in man. Another possibility is that those mechanisms that normally cause vasodilatation on exercise are abnormal. Receptors such as adenosine receptors might be deficient or the response of ion channels to the ischemic environment occurring on exercise may be abnormal.

Recent work has shown that these concepts have clinical application. Following heart transplantation, the forearm resistance does not return to normal for at least 4 weeks. This finding strongly suggests that the changes are not directly linked to central hemodynamics. In a trial of an ACE inhibitor, the increase in exercise capacity was accompanied by an increased blood flow to the legs.

**Skeletal Muscle—Role of Muscle Atrophy**

Two groups have shown that the biochemical response to exercise in skeletal muscle is abnormal in patients with heart failure. The maximum force generated by the quadriceps is reduced and relates to the reduction in exercise capacity. Histologic changes in muscle have been reported. The function of small muscle groups is also abnormal. These observations have been interpreted as indicating that in heart failure there exists a metabolic defect in skeletal muscle. That would not be surprising since heart failure is accompanied by such an extensive activation of hormone systems, including tumor necrosis factor.

In patients with heart failure, there is increased exposure of muscles to exercise-induced ischemia. There are also more prolonged periods of muscular inactivity, although the histologic features of skeletal muscle from patients with heart failure are not typical either of rest atrophy or ischemia.

A major issue at the present time is whether all, or at least the great majority, of the changes in skeletal muscle observed in heart failure can be explained by atrophy. A reduction of muscle mass diminishes the maximum strength of the muscle group, and may give rise to changes of gas exchange on exercise similar to those seen in heart failure (Fig 4). Because the smaller mass of muscle is undertaking a similar work load, the biochemical changes in the muscle will be different from normal for that given work load. If
atrophy is selective for particular muscle groups or fiber types, changes in the use of substrates on exercise will be altered, and there may be alterations of the mechanical efficiency of the muscle. A reduction in muscle mass will also result in an increase in vascular resistance if a comparison is made with a normal person with a normal muscle mass, although the increase of resistance attributable to this alteration in organ size is unlikely to be as great as that actually observed.

CONCLUSION
The cause of symptoms in heart failure is still unknown. A major issue at the present time is whether the reduction in skeletal muscle mass that accompanies heart failure is the cause of an altered response to exercise and whether the patient perceives the changed pattern of signals in such a way as to give rise to the symptoms described as breathlessness and fatigue.

REFERENCES

FIGURE 4. Oxygen consumption is plotted against carbon dioxide production in the same person using different amounts of muscle to exercise. Note the similarity of the record with that of severe heart failure shown in Figure 3. The lines have been fitted to the points, and EMO represents the estimated maximal oxygen consumption. 4

Skeletal Muscle in Congestive Heart Failure (Minotti, Christoph, Massie)