The origin of symptoms in chronic heart failure

A popular view of how the syndrome of chronic heart failure (CHF) develops is that initial myocardial damage causes a low output state and fluid retention; the fluid retention results in breathlessness as fluid “leaks” into the lungs, and the low output state results in fatigue due to failure of muscle perfusion. This model of CHF gives a central role to the baroreceptors; reduced cardiac performance results in baroreceptor activation and subsequent sympathetic activation and fluid retention in an attempt to maintain tissue perfusion pressure. The resultant vasoconstriction in turn leads to further demands on the failing myocardium, completing the vicious circle of CHF. This might be termed the “wet lung” hypothesis.

This theory has been added to in recent times by the emerging concept of heart failure as a multisystem neuroendocrine disease; the principal focus is that the reduction in cardiac output leads to intense stimulation of the renin-angiotensin-aldosterone system leading to fluid retention and vasoconstriction secondary to the action of angiotensin II. Much of the interest in these hypotheses is driven by the potential for therapeutic modulation. This has perhaps diverted our attention from the more basic question of the factors responsible for the symptoms of CHF. One of our principal aims must be the reduction of the distressing sensations of breathlessness and fatigue that result in greater impairment of quality of life than caused by any other chronic medical condition.

A number of observations suggests that this model may be inaccurate. Baroreceptors appear to be inactivated in both animal models and human heart failure, suggesting that some other factor is responsible for sympathetic activation. There is little evidence in favour of central haemodynamics as predictors of exercise performance, and there is no evidence for increased body water in treated heart failure. A possible unifying hypothesis for the origin of symptoms is the “muscle hypothesis”, which proposes the possibility that abnormal skeletal muscle in CHF results in activation of muscle ergoreceptors, which in turn leads to an enhanced signal to ventilation, and results in sympathetic activation.

Haemodynamics
Were the wet lung model of heart failure correct, there should be some relation between left ventricular function and symptoms. While there is little relation between resting left ventricular function and either exercise capacity or the ventilatory response to exercise, the situation during exercise is more complex. Cardiac output at submaximal levels of exertion is close to normal and rises during exercise as a function of exercise load. Peak cardiac output will necessarily correlate with exercise capacity. In normal subjects, the rise in cardiac output appears to be one of the principal determinants of exercise capacity; however, for patients with CHF at peak treadmill exercise, if an additional load in the form of arm exercise is added, then cardiac output and oxygen consumption further increase. These observations suggest that left ventricular function is not limiting exercise.

Breathlessness and the lungs
The cardinal symptom of chronic heart failure is exercise intolerance, usually ascribed to breathlessness or fatigue. The breathlessness might be thought to be due to pulmonary oedema or deranged metabolic gas exchange. A number of abnormalities of ventilation has been discovered in CHF. There is an objective increase in ventilation with respect to carbon dioxide production, and this increase correlates with the severity of exercise limitation. Spirometric variables correlate with exercise capacity, although FEV₁ and FVC are compound measures dependent on skeletal muscle strength as well as any pulmonary abnormality. Bronchial hyperresponsiveness has been reported by some investigators, although other investigators have found no evidence for increased bronchial sensitivity. Abnormalities of diffusion capacity have also been reported, which correlate with some indices of disease severity.

An increase in dead space ventilation has also been described in heart failure, which correlates with the ventilatory response to exercise. Where might the extra dead space come from? An altered respiratory pattern with increased respiratory rates at a given minute volume will result in an increase in fixed anatomical dead space ventilation in the form of the oropharynx, trachea, and bronchi. Another possibility is that impaired right ventricular function might result in failure to perfuse the lung apices resulting in an increase in physiological dead space (alveoli will be ventilated but not perfused).

In normal subjects, voluntary alteration of respiratory pattern does not result in any change in ventilation relative to carbon dioxide production. Altered ventilatory pattern is seen in heart failure, but patients invariably stop exercising before reaching maximal voluntary ventilation and at peak exercise they have a ventilation in the order of 50 l/min compared with controls of approximately 100 l/min. Patients who have had Fontan’s procedure for congenital heart disease, and have no functioning right ventricle in the circulation, may have normal exercise capacity and ventilatory response to exercise. A further possible link between the lungs and ventilatory response to exercise might be via arterial chemoreceptors. The chemoreceptors have increased sensitivity in heart failure. Although their sensitivity correlates with ventilatory response, the proportionate contribution of the chemoreceptors to ventilation appears unchanged in heart failure.

Another consideration is that if pulmonary pathology were a determinant of ventilatory abnormalities, some derangement of blood gases might be anticipated as the signal to increase ventilation. Arterial blood gas analysis suggests that hyperventilation is occurring with respect to PâžCO₂ and PâžO₂, and the arterial content of oxygen appears to be raised in chronic heart failure.

Skeletal muscle
The fatigue of CHF could be related to decreased perfusion of skeletal muscle, but there is a group of patients in whom skeletal muscle is demonstrably abnormal who nevertheless have relatively normal blood flow. Skeletal muscle in CHF patients is histologically and biochemically abnormal. These changes are associated with decreased muscle bulk from an early stage in the progression of CHF, decreased strength, and decreased endurance.
Symptoms and the termination of exercise

There appears to be little difference in exercise responses between patients who complain of breathlessness and those complaining of fatigue. Indeed, these responses may occur on different occasions in the same patient depending on the type of exercise undertaken. Breathlessness and fatigue may reflect a single underlying pathophysiological process. How might the abnormal skeletal muscle be related to breathlessness?

The muscle hypothesis proposes that a neural link, termed the ergoreflex, exists between exercising muscle and the ventilatory response to that exercise; ventilation is abnormally increased in CHF as a result of abnormal skeletal muscle. Evidence for this link comes from studies in normal subjects, in whom the ventilatory response appears to be related to the muscle bulk used to perform a given level of exercise, and in whom the ventilatory response is enhanced by circulatory occlusion of the exercising limb.

The ergoreflex can be quantified in cuff occlusion experiments. At peak exercise, a cuff is inflated around the exercising limb to “freeze” the metabolic state of the muscle. The difference in ventilation between cuff and non-cuff runs during recovery is presumed to be due to continued stimulation of the muscle ergoreceptors. The ergoreflex has been shown to be enhanced in CHF, and to be partially stimulated by sympathetically released norepinephrine. The ergoreflex has been proposed as a potential mechanism for the increased ventilatory response to exercise in CHF. However, it is not clear to what extent this reflex is activated by other stimuli, such as hypoxia and acidosis, which may also contribute to the increased ventilatory response to exercise in CHF.

A unitary hypothesis for the origin of symptoms in chronic heart failure can now be proposed. Abnormal cardiac function results in a skeletal myopathy and consequent abnormal muscle responses to exercise. The abnormal muscle responses are present throughout exercise, and do not simply limit peak exercise. The result is enhanced ergoreflex activity. Abnormal muscle generates the symptoms of fatigue, and the enhanced ergoreflex activity may explain the increased ventilatory response to exercise and the sensation of breathlessness. An additional feature of this hypothesis is that the sympathetic activation of heart failure can also be explained by enhanced ergoreflex activity.

How reduced cardiac function causes the myopathy at the outset of chronic heart failure is not yet clear, and may involve activation of catabolic factors as well as simple disuse atrophy. However it arises, it opens up new treatment possibilities in the form of exercise training, which not only improves exercise capacity but decreases sympathetic activity and may improve cardiac function, factors associated with poor prognosis. Following the failure of treatment directed at stimulating the myocardium, training seems a simple way to relieve symptoms. The muscle hypothesis supplies a rationale to this approach.

Dr McDonagh is supported by the Medical Research Council (GB).

A L CLARK

Department of Cardiology,
Western Infirmary,
Glasgow G11 6NT, UK