heart transplant recipients without evidence of cardiac reinnervation is another reason to challenge the ventricular baroreceptor hypothesis in vasovagal syncope. Finally, the group of Morita et al. made the interesting observation that during hypotensive haemorrhage in unanaesthetized animals, there was a decrease in afferent renal nerve activity. This decrease was not prevented by vagal denervation which seems to indicate that it does not depend on stimulation of cardiac receptors. On the other hand, the decrease in afferent renal nerve activity was prevented by blockade of opiate receptors by naloxone. The latter observation, among others, raised the question of a possible role of endogenous opioid mechanisms in vasovagal attacks.

In 1994, Wallbridge and colleagues demonstrated an increase in plasma beta-endorphin levels prior to the onset of syncope in subjects with vasovagal attacks induced by tilt-testing. In a follow-up to these preliminary results, the same group reports in this issue on the failure of naloxone to modify the vasovagal response in well characterized subjects with frequent spontaneous syncope and a reproducible vasovagal response to tilt-testing. Their observation leads to the conclusion that endogenous opioid mechanisms are not an important trigger for vasovagal events in humans, but probably relate to co-release with adrenocorticotrophic hormone from the pituitary in response to stimulation of low-pressure atrial baroreceptors by relative central hypovolamia.

I found this paper interesting for three different reasons: (1) In spite of its frequency and of its easier diagnosis since the introduction of head-up tilt-testing, vasovagal syncope remains a condition which is poorly understood. The hypothesis implying that the mechanism of syncope may be similar to the Bezold-Jarich reflex is undoubtedly attractive but is contradicted by several experimental or clinical observations. Further research is justified in that area. (2) Opioids may play an important role in modifying baroreceptor physiology and substantial experimental literature supports the concept of a sympathoinhibitory action of these agents. Their effects, however, are not easy to investigate since opioids do not act in isolation but rather as neuromodulators. They surely deserve further attention (3) The discussion on the mechanisms of the vasovagal syncope raises renewed interest in the fascinating and broad discipline of 'neurocardiology'. The complexity of the numerous electrophysiological mechanisms and neuroendocrine systems involved in cardiovascular regulation also constitutes an attractive area for future research.

H. E. KULBERTUS
Cardiology,
CHU Sart Tilman,
Liege, Belgium

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Heart failure patients: why do they fatigue, how do they get better?

See page 1678 for the article to which this Editorial refers

The study of heart failure has changed. First we assumed that poor myocardial contractility causes all the symptoms, and that treatments that increased contractility would both make patients feel better and live longer. This was a mistake. Later the importance of the body's reflex responses to the ventricular dysfunction were appreciated and their importance
in the progression of the condition was noted. Treatments that inhibited this excessive vasoconstriction and neuro-hormonal activation were shown to be the most effective at improving prognosis and symptoms. Only very much more recently was it realized that we did not even know what caused the symptoms limiting exercise in most of our stable well-diuresed patients. The theories of backward heart failure causing dyspnoea by congestion of the lungs and poor cardiac output explaining muscular fatigue have been disproved.

Chronic heart failure is a multi-organ disorder in which the left ventricular dysfunction itself, although of paramount importance in setting things in motion, becomes accompanied by a panoply of reflex, hormonal and metabolic disturbances which can dominate the clinical picture, and profoundly influence the symptoms of the patient. So much so that in some regards it has much in common with apparently unrelated conditions such as cancer cachexia, the 'slim disease' of AIDS or end-stage liver disease. All are associated by neuro-hormonal activation, skeletal muscle wasting and severe exercise intolerance. Could there be a common final wasting syndrome in all these conditions?

In the search for the pathophysiology explaining exercise intolerance in heart failure much attention has focused on the cause of muscular fatigue. Many studies attest to abnormal bulk, strength, fatiguability, histology, enzymic content, and in vivo metabolism of chronic heart failure. In a severe form these muscle changes, as in cardiac cachexia, are associated with a very poor prognosis. We know little of the genesis of these changes. Perhaps inactivity plays a role; in cachexia cytokine activation and loss of normal anabolic function are probably important as well. There is also almost certainly an impact of impaired nutritive blood flow, due to reflex vasoconstriction, capillary rarefaction and deficient endothelial vasodilator function. What then do we know about therapeutic interventions to correct these abnormalities, thereby hopefully correcting the enigmatic fatigue of these patients?

Muscle metabolic abnormalities in developing heart failure can be avoided by appropriately timed exercise training in a rat post-infarction model[1]. In established heart failure training can improve single-limb metabolism[2], large muscle bulk function[3] and mitochondrial pathophysiology[4]. Even low intensity training of individual muscle groups can 'add up' to improved whole body exercise performance[5]. What is even more interesting is what does not reliably improve the muscle function, e.g. cardiac transplantation[6], perhaps in part explaining why exercise tolerance and symptoms often remain extremely poor after this procedure[7]. The paper by Schaufelberger and colleagues from Göteborg in this issue[8], sheds interesting light on this issue. They have confirmed some previously described histological and enzymic abnormalities in chronic heart failure, and demonstrated that some of these can be improved by 3 months enalapril treatment. Muscle fibre size areas were increased, and there was an increase in the glycolytic enzyme lactate dehydrogenase, but there was no increase in capillarization of the muscle or in oxidative enzyme activities. A type II statistical error in these negative finding is possible, given the inevitably small sample size of this double biopsy study, but it also raises the spectre that we still do not know how the angiotensin-converting enzyme inhibitors do their work. It may not be haemodynamic, it may not be specific to a reduction in circulating angiotensin II, and it may depend more on local autocrine systems within many organs including skeletal muscle. Although Drexler has shown a long-term benefit of angiotensin-converting enzyme inhibition on increasing muscle blood flow[9], the results of Schaufelberger's study suggest no increase in capillary density and an increase only in a glycolytic enzyme, raising the fascinating possibility that in these patients the muscle is being driven harder and hence is dependent on increasing its anaerobic capacity, suggesting the possibility of further improvement with specific blood flow enhancing agents, such as those correcting endothelial dysfunction. Whilst this study cannot answer all the myriad questions that remain about the genesis, implications and therapeutic targets revealed by an appreciation of the importance of muscle pathophysiology in heart failure, it does encourage us to delve deeper into the mechanisms of action of agents that do improve symptoms, and to test out strategies that might augment these improvements yet further. We will find only what we seek, and in heart failure, that means looking at the complexity of the pathophysiology of the condition in the intact human patient. It is often how systems interact with each other that generates understanding and novel treatment strategies. Heart disease is at the centre of internal medicine and for heart failure this means we will hear more of autonomic, endocrine, metabolic and cytokine abnormalities, which by detailed clinical investigation will lead to previously undreamt of opportunities to intervene for the benefit of to our patients.

A. J. S. COATS

National Heart and Lung Institute,
Dovehouse Street,
London SW3 6LY, U.K.
Diastolic dysfunction and ANP/BNP levels

See page 1694 for the article to which this Editorial refers

Doctors who work in diabetes or in hypertension have the luxury of one parameter (blood sugar or blood pressure) against which the diagnosis can be made and the treatment monitored. Sadly, in cardiology and especially in heart failure, we have no such single parameter to guide us.

Even if we restrict ourselves to systolic heart failure, there is not one single parameter. Traditionally most large studies have used the left ventricular ejection fraction as their principal entry criteria, despite recognised limitations, such as a low left ventricular ejection fraction did not even predict the development of heart failure in the SAVE study and it is not as good a prognostic predictor as left ventricular end systolic volume. Cardiac output per se might be the ideal parameter but is seldom measured.

This situation becomes even more complex when we recognise that heart failure may not simply be systolic dysfunction but that diastolic abnormalities may also be relevant. If defining and measuring systolic dysfunction was tricky, defining and measuring diastolic dysfunction has been even more complex. Nevertheless, admirable progress has been made in this difficult area. Abnormal diastolic mitral flow patterns have been characterized on the basis of the E/A ratio and the deceleration time of the E wave into either non-restrictive or restrictive patterns. A recent important publication suggests that in patients with systolic failure, a shortened E deceleration time (a restrictive pattern) is the most powerful indicator of cardiac death or transplantation.

A different but related notion among heart failure investigators is the idea that measuring natriuretic peptide levels might give added useful information. This information might be valuable in two ways. Firstly, natriuretic peptide levels may be of value to help diagnose heart failure or even select patients for echocardiography where echocardiographic resources are scarce. Secondly, natriuretic peptide levels may give added information on prognosis over and above traditional measures of disease severity. For example, Hall et al. showed clearly that N-terminal pro atrial natriuretic factor values were predictive of a poor outcome over and above other predictors such as left ventricular ejection fraction. We recently found the same for BNP.

In this issue Yu et al. bring these two ideas together. In this paper, they studied 68 patients who had definite systolic heart failure. It is firstly important to realise that this paper is about diastolic function in patients with known systolic dysfunction. It tells us nothing about the entity of diastolic dysfunction in the presence of normal systolic function. In this paper they found that all but 7% of their patients with systolic dysfunction had diastolic abnormalities of some kind. The restrictive filling pattern described above was found in 62% of these patients. When they compared those with versus those without the restrictive pattern, plasma levels of ANP and BNP were much higher in those with the restrictive pattern.

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