More hormones spilt in heart failure: linking renal sympathetic activation to clinical outcome

Jens Peter Goetze¹* and Regitze Videbaek²

¹Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark
²Cardiac Catheterization Laboratory, Rigshospitalet, University of Copenhagen, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark

Online publish-ahead-of-print 11 March 2005

This editorial refers to 'Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure'† by M. Petersson et al., on page 906.

‘Neurohumoral activation’ is a commonly used term in papers dealing with heart failure. Although the term is short, the process is vast and complex: perhaps as complex as it gets. As heart failure affects almost all organs through reduced blood supply and compensatory regulation of auto-, para-, neuro-, and endocrine mechanisms, it seems overwhelming to rank the individual effect and regulation of one bioactive substance to the effects and regulations of others. Which substance affects which system and in what order through the course of disease progression? To make matters more complex, new substances are still being added to the long list of hormones, despite the fact that it has been over 100 years since the discovery of hormones. With this in mind, it should be recapitulated that the principal discovery of hormones was made by Ernest H. Starling, who also contributed to our present understanding of the pumping heart.¹ One cannot help but wonder how he would try to make sense of the neurohumoral puzzle in heart failure.

Scientists focused early on the heart as a target as well as a secretory organ. The sympathetic component to the heart was an important element in early cardiac physiology, which further fuelled the hypothesis of the heart as an endocrine organ.² Although this proposal was chemically identified with the discovery of natriuretic peptides, the cardiac release of noradrenalin was, at least from a diagnostic point of view, toned down.

Today, measurement of cardiac natriuretic peptides in plasma best fulfils the diagnostic criteria for a dynamic heart failure marker, as they are dominantly secreted by the heart. In addition, natriuretic peptide gene expression is induced by key events of heart disease (myocardial stretch, hypoxia, inflammation, sympathetic activation), which make them primary reporters of cardiac myocyte status rather than secondary events following the pathophysiological adaptations.

Petersson et al.³ report on the long-term outcome in relation to renal sympathetic activity in heart failure patients. By regional blood sampling during cardiac and renal catheterization, the spillover of noradrenalin from both the heart and the kidney was calculated and associated to all-cause mortality or cardiac transplantation in heart failure patients. Spillover was determined from the venous and arterial concentrations of noradrenalin combined with the organ extraction of a labelled noradrenalin. The median renal noradrenalin spillover was found to be 1.19 (0.77–1.43), whereas the cardiac spillover was much lower (0.21). Surprisingly, there was a correlation between renal noradrenalin spillover and left ventricular systolic function (LVEF) and mean pulmonary artery pressure, whereas such correlations were not found for cardiac noradrenalin spillover. Of note, cardiac sympathetic activity has been shown by others to be predictive of adverse outcome in heart failure.⁴ The relation to long-term outcome using multiple regression analyses revealed an association between renal sympathetic activity and all-cause mortality and heart transplantation. Moreover, this association proved independent of LVEF and renal function, which is perhaps the most interesting observation in the present study. The authors reasonably conclude that it may be beneficial to aim for decreasing renal sympathetic activity in heart failure patients.³

* Corresponding author. Tel: +45 3545 5509; fax: +45 3545 4640.
E-mail address: jpg@dadlnet.dk
² doi:10.1093/eurheartj/ehi184

© The European Society of Cardiology 2005. All rights reserved. For Permissions, please e-mail: journals.permissions@oupjournals.org

European Heart Journal (2005) 26, 861–862
doi:10.1093/eurheartj/ehi220
Albeit more hormones spilt in heart failure, the aim of the present study is not to introduce one more marker for heart failure. Rather, the authors suggest that renal sympathetic activation could have a pathophysiological role in parallel with renal function. This is an interesting prospect in several ways. First, the renal sympathetic activity may have an impact on the local response to beta-blockers. Patients with high renal sympathetic activity might not respond in the same way to beta-blockers when compared with patients with a low renal sympathetic activity. In partial support of this, it has been shown that renal sympathetic activity affects the haemodynamic effects of beta-blockade in the kidney.5

Secondly, increased renal sympathetic activity may cause salt and water retention, which is a clinical hallmark in heart failure. Theoretically, the increased secretion of natriuretic hormones from the failing heart should, to some extent, alleviate this condition.6 The renal response could, however, be affected by the local sympathetic activity and may separate patients with regard to their ability to respond adequately to natriuretic hormones. In turn, such an intrinsic regulation of renal resistance to natriuretic hormones could explain the link to adverse outcome.7 On the other hand, infusion of synthetic natriuretic peptide has been shown to inhibit renal noradrenalin spillover in heart failure patients.8 In accordance with this finding, renal sympathetic activity may perhaps then reflect the cardiac compensatory release of natriuretic peptides. However, the present study did not include measurements of natriuretic peptides in circulation. Finally, increased renal sympathetic activity could aggravate cardiac load either directly or via other hormonal systems such as the renin–angiotensin–aldosterone axis.9 Clinical studies, including the present one, also comprise a variable degree of medical intervention with beta-blockers and angiotensin-converting enzyme (ACE)-inhibition, which makes it less straightforward to conclude on the roles of the various hormonal axes. The underlying mechanism may be better pursued in experimental models, where medical intervention can be administered in a more uniform manner.

The link between the failing heart and the kidney continues with the report from Petersson et al.3 The renal sympathetic activity imposes and/or reports a negative impact on clinical outcome, which should be added to the long list of risk factors in heart failure. How the clinician should assess this is at present not obvious, but it seems already reasonable to appreciate the existence of such a link. The renal sympathetic activity is of relevance to the pathophysiology of heart failure and independently predicts the long-term outcome. The study also underscores the fact that renal status cannot be fully assessed by only its blood filtrating properties.

The heart secretes natriuretic hormones with renal effects and the kidneys secrete renin, which in turn imposes haemodynamic effects on the heart; and both organs are under sympathetic nervous regulation.9 Taken together, the complexity of the combined systems will most probably still offer new and useful discoveries. As these neurohormonal axes also are major targets in medical heart failure treatment, a better sequential understanding of organ-to-organ cross-talk may allow for a more patient-specific treatment regimen in the future. Some patients need more beta-blocking than others, and likewise with diuretics and ACE-inhibition. But we need to identify why and when this occurs. Moreover, new hormones and regulatory substances will certainly enter the heart failure scenario and further complicate neurohumoral activation. The newly identified inotropic hormone apelin may, for instance, prove to be a new target in heart failure treatment.10 It thus seems reasonable to contemplate that Ernest Starling would have been utterly fascinated with today’s challenges in heart failure, as it combines the principles of endocrine regulation with the laws of the heart.

References