Coronary artery disease, heart failure, and cardiac natriuretic peptides in the middle

Jens Peter Goetze*

Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark

Online publish-ahead-of-print 24 October 2005

This editorial refers to 'Plasma N-terminal pro-brain natriuretic peptide concentration predicts coronary events in men at work: a report from the BELSTRESS study'† by J. De Sutter et al., on page 2644

An experienced cardiologist recently reminded me that most heart failure patients have a medical history of arteriosclerosis and coronary artery disease (CAD) (Figure 1). With or without myocardial infarction, the ventricular myocardium becomes hypoxic during increased workload, which, in turn, strandAPes cardiac performance and initiates pathological remodelling of the myocardium. In the course of reduced left ventricular systolic function, the endocrine heart compensates with increased production and secretion of natriuretic hormones, that is, the cardiac natriuretic peptides. In fact, the association between cardiac disease and increased concentrations of natriuretic peptides was reported more than 20 years ago. Since then, numerous clinical studies have established that the plasma concentrations of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) reflect left ventricular systolic function and accordingly are helpful markers in heart failure diagnostics. However, the most feasible clinical application today seems to be as rule-out markers, which means that low plasma concentrations efficiently can exclude left ventricular systolic dysfunction. In contrast, the relatively low diagnostic specificity in heart failure diagnosis suggests that also other pathophysiological stimuli besides left ventricular systolic dysfunction can trigger increased production and secretion of natriuretic peptides from the cardiac myocytes.

In the last decade, there has been an increasing focus on the association between ischaemic heart disease and the cardiac natriuretic peptides. Several studies have shown that the plasma concentrations of pro-BNP-derived peptides (both the N-terminal pro-BNP fragment and the C-terminal BNP-32 hormone) are increased in patients presenting with acute myocardial infarction with or without ST-elevation. Notably, increased concentrations are associated with later development of heart failure and death, which clearly provides critical information for identifying high- and low-risk patients. Most of the information so far comes from clinical studies on hospital patients with symptoms or signs of CAD. De Sutter et al.† take one step back and examine men at work. In this case-control study, they are able to show that the plasma concentration of N-terminal pro-BNP (sometimes abbreviated as NT-pro-BNP or N-BNP) provides predictive information on later development of coronary events defined as myocardial infarction, unstable angina, or coronary revascularization. Moreover, this prognostic information was established after a relatively short follow-up period. The work therefore seems to support the conception that measurement of cardiac natriuretic peptides may provide new information on CAD risk assessment. In support of this, a recent study on CAD risk assessment. In support of this, a recent study from Kragelund et al.4 assessed the long-term prognostic value of N-terminal pro-BNP measurement in connection to coronary angiography in symptomatic, stable CAD patients. This study disclosed that N-terminal pro-BNP measurement is a marker of long-term mortality and provides prognostic information beyond that of conventional risk factors and the degree of left ventricular dysfunction. Other reports seem to point in the same direction (for reviews, see Costello-Boerrigter and Burnett5 and Struthers and Davies6).

Some speculation on what increased concentrations of cardiac natriuretic peptides actually reflect in a biological context seems appropriate. Although it is sometimes stated that the endocrine heart responds to ‘cardiac strain’, this is not a clear and well-defined pathophysiological mechanism. Cardiac strain neither has a uniform treatment strategy. Rather, the likely pathophysiological stimuli should be narrowed down to preferably measurable entities. For instance, some experimental data suggest that the BNP gene expression, in fact, is stimulated directly by myocardial hypoxia, which could well explain most of the new clinical results. In simple terms, that would mean that plasma concentrations of cardiac natriuretic peptides reflect the ischaemic burden, which in itself is predictive of later clinical outcome. We recently established that the myocardial BNP gene expression can be stimulated both in vivo and in vitro by reduced oxygen delivery.7 Others have shown that the related ANP gene promoter is directly activated by the hypoxia inducible transcription

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

*Corresponding author. Tel: +45 3545 5509; fax: +45 3545 4640.
E-mail address: jpg@dadlnet.dk

© The European Society of Cardiology 2005. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org
factor HIF 1α, which is activated by low oxygen tension. In addition to myocardial hypoxia, another feasible mechanism may relate to the inflammatory process underlying arteriosclerosis. According to this suggestion, the inflammatory reaction in the coronary vasculature may stimulate local BNP gene expression by cytokines or other substances. De Bold and co-workers recently reported that cardiac myocytes in vitro respond to several pro-inflammatory cytokines by increased BNP gene expression. Whether such processes are also relevant in human CAD is by no means yet established, but this could potentially be worth exploring as the cardiac natriuretic peptides may be markers of diffuse coronary arteriosclerosis without significant luminal occlusion. Whether increased cardiac BNP secretion reflects myocardial hypoxia, vascular inflammation, or both, has been reported that the increase in plasma concentrations is associated with the number of affected coronary arteries.

Finally, it is reasonable to recapitulate that most of the earlier clinical studies on heart failure patients may be strongly related to CAD. In particular, the reports on so-called asymptomatic heart failure (an unfortunate term) often included patients with CAD, and the results are thus not necessarily that different from the new data. Heart failure patients have not been clearly divided into groups with or without CAD, which may be due to the fact that the prevailing focus has been on haemodynamic alterations and myocyte stretch as the principal BNP stimulus. However, if one applies the new paradigm of cardiac natriuretic peptides in CAD, it is sometimes almost impossible to differentiate between increased plasma concentrations elicited by either CAD (cause) or heart failure (consequence). In everyday life, this should probably remind us that increased plasma concentrations of cardiac natriuretic peptides should not only be pursued with echocardiography. Rather, it seems plausible that coronary angiography or some other test for ischaemic heart disease is in order. In most subjects without obvious cardiac disease signs and symptoms, these examinations may even be undertaken in the reverse order, as CAD precedes left ventricular systolic dysfunction.

After 20 years of clinical research on the diagnostic performance of cardiac natriuretic peptides in heart failure diagnostics, we are still somewhat restricted by the troublesome low specificity. The appreciation of increased concentrations in persons and patients with stable ischaemic heart disease may bring the future for clinical BNP measurement forward. If the plasma concentration is elevated but echocardiography does not reveal left ventricular systolic dysfunction, it should not be disregarded as a ‘mistake’ or perhaps raise suspicion of some less defined cardiac disorder such as diastolic dysfunction. Rather, it seems more likely that it may reflect the most common cardiac disease of them all. Surely, many experienced cardiologists already would have guessed this without ever having worked with cardiac natriuretic peptides. In addition, the new era for the cardiac natriuretic peptides could somewhat ironically evolve from ‘markers of heart failure’ to markers that may be useful in avoiding heart failure.

Conflict of interest: none declared.

References

5. Ma KK, Ogawa T, De Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. J Mol Cell Cardiol 2004;36:505–513.