Natriuretic peptides to probe haemodynamic overload in hypertrophic cardiomyopathy

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Plasma levels of natriuretic peptides have gained widespread acceptance as markers of myocardial stretch, resulting from mechanical overload or contractile dysfunction\[1\]. In patients with heart failure, plasma levels of both atrial natriuretic peptide and brain natriuretic peptide have been proposed as diagnostic markers and prognostic indicators\[2\]. In patients with systolic left ventricular dysfunction and depressed ejection fraction, increased production and release of both peptides is thought to result from diastolic stretch on atrial or ventricular myocardium because of an increase in transmural diastolic left ventricular pressure necessary to recruit left ventricular preload reserve. In this issue Briguori et al\[3\] investigated determinants of natriuretic peptide plasma levels in hypertrophic cardiomyopathy, a disease mainly characterized by diastolic left ventricular dysfunction and elevated ejection fraction. Their elegant and meticulous study touches upon several important issues pertaining to the clinical management of hypertrophic cardiomyopathy and to the mechanisms involved in natriuretic peptide release: (1) Does the outflow tract gradient in hypertrophic cardiomyopathy substantially contribute to left ventricular systolic load?; (2) What is the relative importance of diastolic left ventricular dysfunction and of the outflow tract gradient in the reduction of exercise tolerance frequently observed in hypertrophic obstructive cardiomyopathy?; (3) Using atrial natriuretic peptide as a measure of chronically elevated left atrial pressure, should we rely on complex Doppler echocardiographic measurements of mitral and pulmonary vein flow velocity, or have a simple look at left atrial size and function to estimate diastolic left ventricular dysfunction?; (4) Is the observed increase in plasma levels of natriuretic peptides deleterious because of the potential of a vasodilation-induced increase in the outflow tract gradient?; (5) Are the mechanisms underlying the increase in plasma levels of atrial and brain natriuretic peptide similar?

The functional significance of the outflow tract gradient in patients with hypertrophic obstructive cardiomyopathy used to be a hotly debated topic\[4\]. Although the outflow tract gradient elevates mid-to-end-systolic pressures, this elevation does not necessarily induce a large increase in left ventricular wall stress because of the obliterated left ventricular cavity in mid- to late systole as a result of hyperdynamic ejection. This reasoning was supported by micromanometer left ventricular and aortic pressure and flow measurements, but challenged by the outcome of myectomy surgery which resulted in significant improvement in symptoms and in radionuclide perfusion defects\[5\]. Using plasma levels of natriuretic peptides to probe the mechanical overload in hypertrophic obstructive cardiomyopathy, the present study confirms the result of a previous study showing elevated levels, especially of brain natriuretic peptide, in patients with hypertrophic obstructive cardiomyopathy\[6\]. The most straightforward interpretation of this finding is that the outflow tract gradient indeed contributes to systolic left ventricular overload. A confounding finding, however, is the significant correlation between brain natriuretic peptide and the extent of left ventricular hypertrophy. This correlation raises suspicions that the rise in brain natriuretic peptide was only a marker of hypertrophy-induced re-expression of the fetal gene programme and not necessarily of mechanical systolic overload. This suspicion is corroborated by a previous study\[6\] which established a nice correlation between plasma brain natriuretic peptide levels and aortic valve gradients in patients with aortic stenosis, but failed to demonstrate a correlation between plasma brain natriuretic peptide levels and the outflow tract gradient in hypertrophic obstructive cardiomyopathy. It therefore seems prudent to await further studies, which should eventually establish a drop in brain natriuretic peptide following surgical myectomy or alcohol septal ablation, before interpreting the high brain natriuretic peptide levels in hypertrophic obstructive cardiomyopathy as an outflow tract gradient induced elevation in systolic wall stress.

In patients with hypertrophic obstructive cardiomyopathy, it is often difficult to attribute a reduction in exercise tolerance to diastolic left ventricular dysfunction or to the outflow tract gradient. The study by Briguori et al\[3\] established an inverse relationship between peak exercise oxygen consumption and atrial natriuretic peptide plasma levels but not brain natriuretic peptide plasma levels. Since atrial natriuretic peptide plasma levels were closely related to diastolic left ventricular function and brain

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natriuretic peptide plasma levels to the outflow tract gradient, the presence of an outflow tract gradient did not therefore appear to be a major contributor to the reduction in exercise tolerance. These considerations should dampen the current surge of enthusiasm for alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy suffering from reduced exercise tolerance.

Using atrial natriuretic peptide plasma levels as a measure of chronically elevated left atrial pressure, the study by Briguori et al.[3] also provides intriguing data on the adequacy of different Doppler echocardiographic indices to establish diastolic left ventricular dysfunction. In their study, the closest correlation was observed between plasma atrial natriuretic peptide levels and left atrial fractional shortening, which was derived from 2D-echo left atrial maximal and minimal dimensions. No correlation was observed between plasma atrial or brain natriuretic peptide levels and an elaborate set of Doppler mitral and pulmonary venous flow velocity indices. In patients with systolic heart failure[7], a restrictive Doppler mitral flow velocity pattern has previously been shown to be an independent predictor of plasma atrial natriuretic peptide levels in addition to left ventricular ejection fraction. Failure to observe a similar predictive value of Doppler mitral flow velocity patterns in patients with diastolic heart failure of hypertrophic cardiomyopathy, leaves us with the frustrating conclusion that Doppler indices of left ventricular filling dynamics fall short of identifying chronic elevation of left atrial pressure in a group of patients in whom we need it most, namely patients with primary diastolic heart failure!

Vasodilator effects of natriuretic peptides could potentially augment the left ventricular outflow gradient in obstructive hypertrophic cardiomyopathy, and their elevated plasma levels could therefore be deleterious. Through activation of myocardial particulate guanylate cyclase, natriuretic peptides have, however, also been shown to exert beneficial effects on left ventricular relaxation[8] and their intravenous administration increases exercise tolerance in patients with diastolic heart failure[9]. Similar left ventricular relaxation-hastening and distensibility-increasing effects have been observed for nitric oxide, which stimulates myocardial soluble guanylate cyclase, and cyclic GMP itself[10]. By increasing left ventricular distensibility, natriuretic peptides would enlarge left ventricular operating volumes. Such a distensibility-related increase in left ventricular end-diastolic volumes could well counterbalance a vasodilation-related reduction in left ventricular volume and leave the left ventricular outflow tract gradient unaltered. Comparison of the left ventricular outflow tract gradient during intravenous and intra-coronary administration of nesiritide, a recombinant human brain natriuretic peptide, could clarify this issue[11].

In left ventricular hypertrophy related to systolic left ventricular overload, the mechanism of production and release of atrial natriuretic peptide and brain natriuretic peptide appears to be similar, namely inappropriate myocardial stretch related to elevated distending pressure. In conditions such as hypertensive heart disease and aortic stenosis, parallel increases in both natriuretic peptides are therefore observed[6]. In hypertrophic cardiomyopathy, however, the stimulus for myocardial hypertrophy is not mechanically but genetically determined and the study of Briguori et al.[3] confirms this difference in stimulus for left ventricular hypertrophy, by observing a correlation only between the extent of left ventricular hypertrophy and plasma brain natriuretic peptide but not plasma atrial natriuretic peptide. This finding raises the possibility of two different mechanisms for the production of natriuretic peptides in hypertrophic cardiomyopathy: brain natriuretic peptide production as part of the hypertrophy-related re-expression of the fetal gene programme and atrial natriuretic peptide production as a result of the hypertrophy-related reduction in diastolic left ventricular distensibility.

In conclusion, plasma levels of natriuretic peptides are elevated in hypertrophic cardiomyopathy[3]. Atrial natriuretic peptide levels correlate closely with left atrial performance and elevated atrial natriuretic peptide levels therefore indicate diastolic left ventricular overload because of diastolic left ventricular dysfunction. Brain natriuretic peptide levels correlate with left ventricular outflow tract gradient and the extent of left ventricular hypertrophy. Elevated brain natriuretic peptide levels could therefore be consistent with outflow tract gradient-induced systolic left ventricular overload, but because of the correlation with the extent of left ventricular hypertrophy they could equally well indicate hypertrophy-related myocardial fetal gene re-expression. Repeat brain natriuretic peptide determinations following myectomy or transcatheter septal ablation could further clarify this issue.

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References
Digital cellular telephones and ICDs

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For several years, various sources of electromagnetic interference have been described, stimulating engineers and physicians to investigate this field, but also inducing a significant amount of concern in the population of pacemaker patients.

Many studies\cite{1-9} clearly demonstrated the possibility that an implanted pulse generator may be triggered to its programmed upper rate limit or temporarily inhibited by external electromagnetic interference. The clinical impact of this negative interaction is clearly dependent on the type of interference. The type of pulse generator (different brands), the type of excitation or conduction interference episodes during ringing vs 26 during the off/on phase; (P<0·0001); 106 at the maximum sensitivity level vs 51 at the ‘base’ value; (P<0·0001). Prolonged pacing inhibition (>4 s) was seen at the pacemaker ‘base’ sensing value in six patients using the GSM, but in only one patient using the TACS telephonic system.

No permanent malfunctioning or changes in the programmed parameters were detected. No interference was observed using the mobile phone at a distance longer than 10 cm from the pacemaker site. Similar results were shown in vivo by other research, while a higher incidence of interference was observed

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