Natriuretic peptides in heart valve disease

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Summary

Synthesis and release of brain natriuretic peptide (BNP) are increased in heart failure and plasma levels provide important therapeutic and prognostic information. A number of recent studies have demonstrated that BNP levels are also increased with disease of the mitral and aortic valves. The extent of the increase is broadly related to the severity of the valve abnormality and the degree of consequent cardiac remodelling. BNP levels appear to relate to prognosis in these patients and might have a role in identifying suitable candidates for cardiac surgery. This paper reviews the current literature and identifies areas where further research is required if BNP is to be of practical use.
Background

The Natriuretic peptides, particularly B-type natriuretic peptide (BNP), have an emerging role in the diagnosis, treatment and prognostic assessment of patients with heart failure.[1] There are important differences in the physiology of the natriuretic peptides that underlie their potential clinical use. Atrial natriuretic peptide (ANP) is stored in granules within the atria and released rapidly in response to atrial stretch. [2] BNP on the other hand is stored in only limited amounts and increased secretion relies on increased synthesis consequent on activation of the BNP gene.[3] BNP is produced as a prohormone that is cleaved in the circulation into active BNP and the n-terminal peptide NT-proBNP.[3] Both can be assayed but NT-proBNP has a longer plasma half life and higher plasma levels.[1] In the normal heart the atria are the main source of BNP but where ventricular wall stress is chronically increased there is upregulation of ventricular BNP production, which becomes predominant.[3] Ventricular dysfunction increases plasma levels of both ANP and BNP, but the relative increase in BNP is the greater.[2]

Current management strategies for patients with valve disease rely heavily on the presence or absence of symptoms and the echocardiographic assessment of left ventricular and valvular function.[4] These assessments are not always straightforward. The onset of symptoms in patients with valve disease is often insidious and, particularly in less active subjects, may not be readily apparent. Organic mitral regurgitation is a good example. Severe mitral regurgitation makes the left ventricle look dynamic on 2D echo and may thus mask an early deterioration in pump function. Despite recent recommendations,[5] few cardiologists formally quantify the severity of mitral regurgitation and most simply eyeball ejection fraction. By the time there are obvious symptoms or a clear deterioration in ejection fraction there will also be irreversible LV impairment. Similar concerns apply in aortic valve disease. A biomarker that reflects the severity of valvular disease and the development of early ventricular dysfunction would be of great interest. Since BNP production is increased in response to increased myocardial wall stress it might potentially fulfil this role.

Natriuretic peptides in aortic valve disease.

A number of studies have found that natriuretic peptides correlate with the severity of aortic stenosis, expressed either as transvalvular gradient or valve area.[6][7][8][9][10][11][12] There are also correlations with left ventricular afterload expressed as end systolic wall stress,[6][10][13] with the degree of left ventricular hypertrophy, a consequence of increased afterload, and negatively with left ventricular ejection fraction.[10][11][12][14] Correlations are generally closer with BNP and NT-proBNP than with ANP.

Gerber and colleagues from New Zealand studied patients with aortic stenosis and a transvalvular gradient of at least 25mm Hg.[10] Log transformed levels of natriuretic peptides (BNP, NT-proBNP and ANP) correlated extensively with measures of the severity of stenosis and measures of left ventricular chamber size, wall thickness and stress, ejection fraction, left atrial size and right ventricular pressures. Overall there was a steady increase in natriuretic peptide levels with decreasing valve area and a large increase when ejection fraction fell below 50%. The closest relationships were
seen for NT-proBNP. Of seventy four individuals, forty five (61%) were symptomatic with breathlessness, angina or (pre)syncpe. As expected, symptomatic patients were older, had smaller valve areas and higher levels of all three peptides. However the relationship between log transformed peptide levels and symptoms persisted after correction for ejection fraction, valve area, age, sex and renal function. NT-proBNP was the best discriminator for symptoms with an area under the ROC curve of 0.84 with a cut off of 60pmol/l. Interestingly peptide levels correlated with breathlessness but not with angina or (pre)syncpe. Why this should be the case is not clear as chest pain in patients with aortic stenosis and normal coronary arteries is known to be related to wall stress. However pathological breathlessness is difficult to define and in practice there is often no clear demarcation between symptoms of breathlessness and chest discomfort. Lim et al obtained similar results in 70 patients with severe aortic stenosis (aortic valve area < 1cm2).[15] In their study a BNP level of 66 pg/ml identified symptoms with an area under the ROC curve of 0.86.

The results of these studies are striking as it would appear at face value that natriuretic peptide levels might discriminate between NYHA classes I and II. Attractive as it is this concept is not supported by the largest study so far published. Bergler-Klein et al studied 130 patients with severe aortic stenosis defined by a peak transvalvular velocity of >4ms-1 or valve area <1cm2.[16] Eighty seven patients were symptomatic at study entry. In contrast to the results of Gerber and Lim, levels of natriuretic peptides (in this case without log transformation) did not distinguish between patients in NYHA classes I and II, but there were significant differences between classes II and III and between class III and class III-IV.

Although BNP may not discriminate effectively between asymptomatic and mildly symptomatic patients with aortic stenosis there is some evidence that it might identify the transition from compensated hypertrophy to early decompensation in patients with preserved ejection fraction. In an elegant paper Vanderheyden and colleagues studied a relatively homogenous group of 40 patients with symptomatic aortic stenosis, a transvalvular velocity of at least 2.5m/s and normal ejection fraction.[14] Subjects were subdivided on the basis of an LV end diastolic pressure of 16mmHg into those with intact or impaired preload reserve. Patients with an LVEDP > 16mmHg had similar valve areas and left ventricular mass index but greater end systolic and end diastolic wall stress, larger end diastolic volumes, lower ejection fractions and demonstrated afterload mismatch. Qi et al demonstrated similar results in a group of patients subdivided by an LVEDP of 12mmHg.[9] Vanderheyden’s patients with intact preload reserve had substantially higher BNP levels than normal controls but there was a further increase in those with raised filling pressure. Unlike earlier studies there was no correlation between BNP and systolic wall stress but BNP did correlate with measures of diastolic wall stress and LV mass. The relationship with diastolic stress is in keeping with experimental observations in which diastolic stretch induces BNP gene expression.[17] Qi studied both ANP and BNP.[9] Whereas BNP related better to indices of aortic stenosis and left ventricular remodelling, ANP correlated more closely with atrial pressure. This observation raises the possibility that simultaneous measurement of both peptides might provide complementary information with the elevation of ANP indicating a rise in preload.

All patients in Vanderheyden’s study were already symptomatic and thus had an established indication for surgery.[4] However fifty percent of them had developed
symptoms despite no evidence of haemodynamic decompensation. It is not clear from the paper how many patients developed breathlessness as opposed to exertional (pre)syncope or angina but, as discussed above, the difference may be important. [15][16] It seems likely that control of BNP synthesis and release in aortic stenosis is the result of a complex interplay between systolic load, ventricular hypertrophy and diastolic stretch. Plasma levels are increased in asymptomatic patients with moderate or severe stenosis, increase further with the onset of breathlessness and further still with the onset of haemodynamic decompensation.

A striking result of Bergler-Klein’s study was the relationship of baseline peptide levels to the development of symptoms during follow up.[16] Of the 43 patients who were asymptomatic at baseline, 14 developed symptoms during follow up and in this group baseline peptide levels, especially N-BNP, were substantially higher than those who remained asymptomatic throughout. The difference was most marked in six patients who developed acute congestive heart failure. Interestingly patients who developed angina but not breathlessness had low N-BNP levels both at baseline and follow up. By multivariate analysis only N-BNP and left ventricular ejection fraction were independent predictors of remaining symptom free. Gerber et al obtained similar results in a group of 29 initially asymptomatic patients followed up with serial BNP levels for 18 months.[18] Patients with a baseline NT-proBNP above normal (>50pmol/l) were much more likely (about 10 times) to develop symptoms. However a high NT-proBNP lacked specificity as only around half of those with elevated levels at baseline actually became symptomatic within the period of observation.

Natriuretic peptides appear to discriminate well for a successful postoperative outcome in patients undergoing aortic valve replacement. In Bergler-Klein’s series N-BNP was the only independent predictor of survival and of good symptomatic status and along with preoperative ejection fraction was an independent predictor of postoperative LVEF. These findings were broadly confirmed by both Lim and Vanderheyden.[12][15]

There are variable changes in ANP and BNP in the immediate aftermath of aortic valve replacement surgery but long term follow up data is scarce.[14][19] Qi et al found a decrease in ANP levels at four and 12 months postoperatively, most marked in those patients with an elevated preoperative pulmonary wedge pressure.[14] In contrast BNP levels remained more or less unchanged, possibly because there was no regression of left ventricular hypertrophy during follow up. There is no data on whether late regression of ventricular hypertrophy is associated with down regulation of BNP production.

The New Zealand group has published a small study of natriuretic peptides in aortic regurgitation.[20] In 40 patients with moderate to severe aortic regurgitation levels of all three peptides were higher in the 27 asymptomatic individuals than in matched controls and higher again in 13 symptomatic patients. Ten of the 13 symptomatic patients were in NYHA class II. Both asymptomatic and symptomatic patients had substantially dilated left ventricles with a mean end diastolic diameter of 6.6 and 6.9cm respectively. Symptomatic patients had slightly lower ejection fractions (54% v 58%) and slightly greater end systolic wall stress but other echo parameters were very similar. This study is too small to draw any clinically useful conclusions but it is interesting that log transformed levels of all three peptides were considerably lower
than in equivalent patients with aortic stenosis despite substantial left ventricular
dilation and, by implication, elevated diastolic wall stress.[10] Another small study of
12 asymptomatic patients with aortic regurgitation and preserved left ventricular
function demonstrated a correlation between BNP and the extent of ventricular
remodelling.[21]

**Natriuretic peptides in mitral valve disease**

A few small studies have examined natriuretic peptide levels in mitral
stenosis.[22][23][24] Plasma levels of both ANP and BNP are elevated and decline
with successful balloon valvotomy. There is more published data on natriuretic
peptides in patients with mitral regurgitation. Several early studies found elevated
peptide concentrations in patients with mitral regurgitation but none of these
distinguished patients with ischaemic regurgitation from those with non-ischaemic
regurgitation.[25][26][27] In a population-based study of elderly people living in
Finland, N-terminal ANP was significantly elevated in those with moderate or severe
mitral regurgitation.[25] A study in patients with suspected left ventricular
dysfunction also found an association between N-terminal pro-BNP and the severity
of mitral regurgitation.[26] Another small study found elevated plasma BNP
concentrations in patients with moderate or severe mitral regurgitation of mixed
aetiology.[27] None of these studies excluded or satisfactorily-controlled for patients
with angina pectoris, left ventricular dysfunction secondary to myocardial infarction,
or concomitant valve disease, and all used qualitative methods for assessing mitral
regurgitation.

More recently Sutton et al studied 49 patients with varying degrees of isolated mitral
regurgitation due to degenerative or rheumatic pathology and an ejection fraction of
greater than 55%.[28] Levels of ANP, BNP and NT-proBNP were elevated as
compared with controls. Of all the peptides NT-proBNP correlated most closely with
clinical and echocardiographic variables and was related to the severity of mitral
regurgitation and left atrial dimension as well as age and sex. There was no relation
to left ventricular dimensions or ejection fraction but this may reflect the relatively
narrow range of left ventricular function and the use of dimensions rather than
volumes to assess left ventricular size.

By far the largest study yet published is that of Detaint et al from the Mayo clinic who
followed a relatively unselected group of 124 patients with greater than mild organic
mitral regurgitation.[29] Just over a third of their patients had severe MR. They found
that symptoms, the presence of atrial fibrillation and the extent of both atrial and
ventricular remodelling were independently associated with higher BNP levels. The
severity of MR, although univariately associated with BNP levels, was not an
independent predictor. Uniquely, this study also examined outcome over a mean of
4.4 years. After controlling for age, sex, functional status, LV function and severity of
regurgitation, BNP was independently predictive both of death and the combined end
point of heart failure or death. The implication of these findings is that BNP is not
just a marker for the severity of MR or a surrogate for symptoms. Rather it seems to
reflect the consequences of mitral regurgitation for the heart, including adverse
clinical outcome.

**Potential clinical use and limitations.**
The test of whether BNP is clinical useful in valve disease is whether it simplifies patient management and ultimately contributes to improved outcomes. In symptomatic patients with an established indication for operation a high BNP predicts a worse late outcome and might be useful in risk stratification.[16][28] There is, however, no justification for withholding surgery on the basis of a high BNP. If BNP is to have a specific role in valve disease it is likely to be in the optimal management of those patients with asymptomatic severe aortic stenosis or degenerative mitral regurgitation who do not fit standard indications for surgery. An elevated BNP in these patients could in principle be used to select individuals at high risk of developing symptoms or ventricular impairment over a relatively short time frame and prompt earlier operation. Similarly BNP might also be useful in those patients with non-specific symptoms, such as fatigue, not clearly related to the valve pathology where a high level might again prompt early surgical referral. The relationship between BNP and exercise testing needs to be further investigated. In apparently asymptomatic patients with aortic stenosis the development of symptoms during exercise testing is a strong predictor of the development of spontaneous symptoms and the need for valve replacement.[30] It is possible that BNP might provide additional predictive information but no data are yet available. Levels of natriuretic peptides are influenced by factors other than valve disease. Plasma BNP is increased by, amongst other conditions, coronary disease, atrial fibrillation and renal failure. Patients with aortic stenosis often have aortic regurgitation or mitral regurgitation. Mild regurgitation is unlikely to influence BNP levels to any great extent but moderate or worse insufficiency will have an impact. The presence of potential confounding factors is not unique to natriuretic peptides but it does raise questions about the wider applicability of BNP measurement in valve patients. Studies performed to date have generally selected patient populations with ‘pure’ valve disease free of most confounding variables and have been relatively small, cross sectional or both. There is a need for larger longitudinal studies in a broader range of asymptomatic patients with aortic valve disease and degenerative mitral regurgitation to better define the relationship between BNP levels and the onset of symptoms or the first signs of left ventricular dysfunction.

**Conclusions**

Numerous studies have looked at the relationship of natriuretic peptides to the severity of valvular heart disease. In general peptide levels are greater with increasingly severe valvular abnormality, the presence of symptoms and with pronounced ventricular remodelling. Both in aortic stenosis and degenerative mitral regurgitation there is evidence that BNP might identify those asymptomatic patients on the verge of developing symptoms or haemodynamic compromise. Larger scale longitudinal studies are required to determine whether BNP might have a clinically useful role.

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