Serum brain natriuretic peptide (BNP) and N-terminal brain natriuretic peptide (NT-proBNP) in heart valve disease

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ABSTRACT **Serum levels of natriuretic peptides (BNP and NT- proBNP) are known to increase in cardiac failure, and aid in the diagnosis and management of such patients. BNP and NT-proBNP also increase in patients with heart valve lesions, and may contribute to the assessment and management of these patients. There appears to be a general trend towards higher BNP values in more severe heart valve lesions, but the exact implication of a raised BNP or NT-proBNP appears to be different for each specific valve lesion. In aortic valve stenosis increased levels of BNP/NT-proBNP correlate with the degree of stenosis, symptoms and prognosis. In addition, the increased natriuretic peptide levels seem to reflect left ventricular dysfunction, as high levels predict poor long-term outcomes in conservatively treated patients as well as post-operative death and poor functional recovery in those who survive the valve replacement procedure.**

In mitral regurgitation natriuretic peptide levels correlate with the degree of valvular regurgitation, and seem to reflect subclinical left ventricular dysfunction. Serum natriuretic peptide levels are elevated in patients with mitral stenosis, and correlate with the degree of valvular stenosis and increased pulmonary pressure.

Serum levels of natriuretic peptides are elevated in other heart valve lesions, such as aortic valve regurgitation, as well as different forms of mixed valvular disease, but very little is known about the relationship between the serum levels of natriuretic peptides and the latter valve lesions.

The practical application of our knowledge concerning serum natriuretic peptides and heart valve disease is limited at this stage, and no specific cut-off values to guide patient management have been incorporated into any official guidelines as yet. This review aims to summarise current knowledge on serum BNP and NT–proBNP levels in patients with heart valve disease. The impact of this information on current clinical decision making in patients with different heart valve lesions, as well as evolving concepts concerning its potential future use, will be discussed.

INTRODUCTION

The myocardium secretes various natriuretic peptides, such as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). BNP is secreted as pro-BNP, which is broken down to BNP and N-terminal proBNP (NT-proBNP) in equimolar amounts.[1] The secretion of BNP and NT-proBNP increases in a myocardium under strain, such as in heart failure. The relationship of increased serum BNP and NT-proBNP levels to ventricular decompensation is now an established concept, and their measurement has become a valuable laboratory tool in distinguishing heart failure from pulmonary disease in patients presenting with dyspnea.[2] LV function is an important determinant of outcome in patients with heart valve lesions. The relationship between serum BNP and NT-proBNP levels and ventricular function in patients with heart valve lesions is a new and evolving topic, but clinically valuable information has already emerged.

BASIC CONCEPTS ABOUT NATRIURETIC PEPTIDES AND THE MYOCARDIUM

Brain natriuretic peptide (BNP) was first isolated from porcine brain, but was later found to be secreted mainly by the myocardium. BNP belongs to a family of peptides that also includes atrial natriuretic peptide (ANP), c-type natriuretic peptide and urodilatin.[3] These

peptides share a common structure of a 17 amino acid ring and disulfide bridge between two cysteine molecules. BNP is not stored in the myocardium, but rapid gene transcription followed by synthesis of the prehormone (proBNP) occurs in response to an increase in wall stress, mainly stretching of the myocardium. ProBNP consists of 108 amino acids, and is cleaved into equimolar amounts of the biologically active BNP (32 amino acids) containing the C-terminal fragment, and the biologically inactive N-terminal fragment, NT-proBNP, consisting of 76 amino acids.

The biological effects of BNP are mediated by cyclic GMP (cGMP), which is formed upon binding of the ligand to its receptor, and include natriuresis, diuresis, peripheral vasodilatation and inhibition of the renin-angiotensin aldosterone system. BNP has a half-life of 20 minutes, and is cleared through proteolysis by neutral endopeptidases. NT-proBNP has a half-life of 120 minutes and is cleared by renal excretion. Accordingly, the serum levels of NT-proBNP are about 6 times higher than those of BNP.

Assays for the determination of serum levels of both BNP and NT-proBNP are commercially available (AxSYM BNP, Abbott; Elecsys NT-proBNP, Roche Diagnostics). The advantage of assaying NT-proBNP is that it is more stable than BNP. In the absence of additives NT-proBNP is stable at room temperature for 72 hours, whereas BNP is stable for 24 hours in the presence of EDTA. In serum frozen at -20 or -70 degrees Celsius it is stable for several months to a year.

FACTORS THAT INCREASE SERUM LEVELS OF BNP AND NT–proBNP

The main interest in serum BNP and NT-proBNP stems from the observation that their levels are increased significantly in patients with heart failure, where they can be used to distinguish dyspnea due to heart failure from dyspnea secondary to pulmonary pathology, with a high sensitivity in both the acute as well as in the community settings.[1, 2] For BNP a value above 100 pg/mL is indicitave of heart failure, whereas there are age-specific cut-offs for NT-proBNP - 125 pg/mL for patients less than 75 years and 450 pg/mL for patients 75 years and older. Serum levels of BNP and NT-proBNP are higher in females, the elderly and patients with impaired renal function, even in the absence of myocardial disease. Elevated levels are also seen in atrial fibrillation, pulmonary embolism, hypertension and hypertrophic cardiomyopathy[3] It is, therefore, not surprising that increased levels have been described in patients with heart valve lesions. Although it is now well established that raised levels of BNP and NT-proBNP can be used to predict prognosis in patients with heart failure[4] and even in patients with stable coronary artery disease without heart failure,[5] knowledge on the exact meaning of increased levels in patients with heart valve lesions is still evolving.

FINDINGS REGARDING BNP/NT-proBNP AND VARIOUS HEART VALVE LESIONS

AORTIC VALVE STENOSIS (AS)

The main indication for aortic valve replacement (AVR) in patients with severe AS is the onset of symptoms, notably dyspnea, syncope and angina. AVR performed at this stage interrupts the natural course of the disease and prevents death. Can BNP and NT-proBNP determination add to the management of patients with AS? BNP and NT-proBNP levels in patients with aortic valve stenosis have been shown to relate to (i) symptoms, (ii) severity of aortic valve stenosis and clinical prognosis, and (iii) surgical outcome. In addition, recent data suggest that (iv) BNP and NT-proBNP levels may be helpful in distinguishing true severe AS from pseudosevere AS, and may predict outcomes in this subgroup of patients.

(i) BNP/NT-proBNP and correlation with symptoms in AS

It is well known that some patients adapt to their functional impairment by limiting their activity and, when asked, often deny symptoms such as dyspnea or functional impairment. It would, therefore, be useful if a biomarker such as BNP or NT-proBNP could distinguish symptomatic from asymptomatic patients. In general, higher serum levels of BNP and NT-proBNP reflect symptoms. Two groups found that a normal BNP predicted an asymptomatic state, and thus by implication, patients who were not at risk.[6, 7] An NT-proBNP value of 190 pg/mL had a 79% sensitivity and 88% specificity for being symptomatic (i.e. Class II dyspnea) in the study by Nessmith et al.,[6] whereas in the study by Lim et al.[7] a BNP level of > 66 pg/ml had a similar sensitivity for being symptomatic, namely 84% . However, in an excellent prospective study by Bergler-Klein et al.,[8] it was found that BNP levels did not differ significantly between patients with Class I and Class II dyspnea – only at

increasing levels of dyspnea did the differences become significant. Differences in the results seen in these studies may be due to the fact that, in the study by Bergler-Klein, all patients had significant aortic valve stenosis, whereas in the other studies there was a wide range in the severity of stenosis amongst patients. Another explanation for the differences between the cited studies may be that some patients with severe AS decrease their functional activity without noticing it, thus denying the symptom of dyspnea on clinical evaluation. However, Bergler-Klein et al. did find that a BNP level of < 449 pg/ml and an NT-proBNP level of < 677 pg/ml predicted the absence of development of symptoms over the subsequent 6 to 9 months and, even more importantly, BNP or NT-proBNP levels higher than the latter cut-offs predicted the occurrence of symptoms within the following 6 to 12 months.[8] The fact that no functional tests were performed in any of the cited studies makes it difficult to come to a final conclusion regarding the relationship between serum natriuretic levels and symptoms in patients with aortic valve stenosis.

(ii) BNP/NT-proBNP, severity of aortic valve stenosis and outcomes

Increased serum BNP and NT-proBNP values reflect the severity of valve stenosis as well as the functional consequences, as NT-proBNP levels correlate with mean transvalvular gradients as well as left ventricular hypertrophy (as reflected by mass), LV end-systolic wall stress and end-diastolic pressure.[7, 9, 10] An NT-proBNP value of 550 pg/ml has been shown to predict conventional indications for AVR with a sensitivity of 71% and specificity of 68%.[10]

Serum BNP and NT-proBNP serum levels not only correlate with stenosis severity, but also provide information about clinical prognosis. In general, the higher the serum levels of BNP and NT-proBNP, the worse the outcome. In the study by Lim et al.,[7] a BNP level of 97 pg/mL separated the survivors from the non-survivors after one year follow-up, irrespective of symptomatic status. These findings are supported by Nessmith et al.,[6] who found that no patient with an NT-proBNP value < 100 pg/mL died during one-year follow-up, whereas the one-year mortality rate of patients with values between 100 and 296 pg/ml, between 296 pg/ml and 819 pg/ml and > 819 pg/ml was 6%, 34% and 60% respectively. In a study in which patients were followed up for a median of 902 days a serum level of NT-proBNP of 640 pg/ml predicted an adverse outcome in conservatively treated patients with severe AS.[11]

(iii) BNP in predicting surgical outcomes post aortic valve replacement

Evidence is accumulating that pre-operative BNP and NT-proBNP levels may predict post-operative outcomes, with higher levels predicting poorer outcome. In the study by Vanderheyden et al.,[12] those patients who underwent aortic valve replacement based on conventional criteria and experienced clinical deterioration post-operatively had a significantly higher pre-operative BNP level than those who had no complications (399 ± 82 vs. 124 ± 41 pg/ml). These data are supported by Bergler-Klein et al.,[8] who found that pre-operative NT-proBNP was the only independent predictor of both survival and post-operative symptomatic status on multivariate analysis - BNP higher than 369 pg/ml and NT-proBNP higher than 2745 pg/ml predicted death.

These findings prompt the question whether BNP or NT-proBNP levels should be considered when deciding on valve replacement for aortic valve stenosis and, more specifically, whether valve replacement should be advised on the basis of high circulating levels of natriuretic hormones even in the absence of symptoms. The basic pathophysiological correlate suggested by these studies is that markedly increased BNP and NT-proBNP levels reflect a lack of left ventricular reserve. Data are still lacking, however, and the results of larger studies are awaited before such management can be advocated.

(iv) BNP levels and low flow, low gradient AS

It is currently accepted that patients with severe AS but reduced ejection fraction (EF) have good outcomes after aorta valve replacement if the low EF is caused by a high afterload in the absence of true left ventricular dysfunction (afterload mismatch). However, patients with pseudo AS, as reflected in low flow gradients (<30 mmHg) in the presence of low EF (<40%), are not expected to benefit from AVR to the same extent. In contrast, patients with severe true AS and impaired left ventricle function (i.e. low EF and low gradients) may benefit from aortic valve replacement if inotropic reserve (increase of 20% in stroke volume at peak dobutamine infusion rate) is demonstrated.[13] In a recent study by Bergler-Klein et al.,[14] the ability of BNP levels to

distinguish between patients with true severe AS and pseudo AS, and the predictive value for post-operative outcome in these patients were investigated. The authors found that BNP levels were significantly higher in true AS than in pseudo AS, yet overlap between the values in the two groups precluded using BNP values as an accurate discriminator. The most important findings of this study were that a serum BNP value of > 550 pg/ml identified patients who had a poor prognosis, whether they had true or pseudo AS, no matter whether they were treated surgically or medically. Furthermore, even patients with poor contractile reserve and true severe AS had a good outcome if the BNP levels were < 550 pg/ml. However, the number of patients studied was too small to justify a change in current management and more data are needed to verify these findings.

In summary, BNP and NT-proBNP serum levels reflect aortic valve stenosis severity, symptomatology and outcome in patients with AS (Table I). In general, the higher the serum levels, the more symptomatic the patients, the more severe the aortic valve stenosis and the worse the outcome after aortic valve replacement.

TABLE 1: Relationship between serum natriuretic peptide levels and aortic valve stenosis*

	BNP (pg/ml)	NT-proBNP (pg/ml)
Symptoms	>66 pg/ml[7] >449 pg/ml[8]	>190 pg/ml[6] > 677 pg/ml[8]
Poorer prognosis	>97 pg/ml[7]	>296 pg/ml[6] >640 pg/ml[11]
Poor post-operative outcome	369 pg/ml predicts post-op death[8]	2745 pg/ml predicts post-op death[8]
Irreversible LV deterioration	>550 pg/ml[14]	

** Discrepancies between reference values may relate to patient populations studied.*

MITRAL REGURGITATION (MR)

Currently the decision to perform valve replacement for severe mitral regurgitation (MR) primarily relies on the presence of symptoms and/or evidence of left ventricular dysfunction, as indicated by echo-cardiographic parameters such as an ejection fraction below 60% and a left ventricular end-systolic (LVES) measurement of > 45 mm. Quantitative evaluation of MR adds significantly to outcome prediction, but requires additional training and can be cumbersome to perform in the busy outpatient setting. Furthermore, measurement of LV systolic function (muscle function) can be difficult to accurately assess in MR due to the load dependency of commonly used parameters such as ejection fraction. In severe MR there is significant offloading of the LV into the LA, a low pressure system compared to the aorta, and thus early dysfunction of the LV may not be apparent when using these parameters. This raises the question whether BNP or NT-proBNP could serve as a biochemical parameter to assist the clinician in assessing the severity of mitral valve regurgitation and to time valve replacement more appropriately.

Studies on the relationship between BNP and NT-proBNP in mitral regurgitation suggest that increased serum levels of BNP and NT-proBNP in patients with MR may indeed be helpful, as increased serum levels (i) reflect the severity of mitral regurgitation, and reflect the deleterious structural consequences such as left ventricular remodelling and increase in left atrium size, (ii) reflect functional impairment of the left ventricle and (iii) predict survival and the occurrence of heart failure. In addition, (iv) the change in BNP and NT-proBNP serum levels in operated patients identifies patients who have benefited from surgery, and separates them from the group in whom no improvement is expected to occur, thus suggesting a relationship between serum natriuretic peptide levels and LV dysfunction, separate from their relationship to degree of regurgitation.

(i) BNP and NT-proBNP and the severity of mitral regurgitation

BNP and NT-proBNP are increased in patients with MR, being higher in symptomatic patients than in asymptomatic ones.[15, 16] In the study by Sutton et al.[16] a BNP cut-off point of >424 pg/ml had a sensitivity of 88% in predicting symptoms, compared to a sensitivity of 13% if a left ventricular end-systolic diameter (LVES) cut-off of >45 mm was used. Strong correlations were shown for BNP and NT-proBNP levels with both increased left atrial size or volume, and peak systolic pulmonary artery pressure,[16, 17] but they differed with regard to correlations with left ventricular dimensions (see below). Serum natriuretric peptides were significantly more predictive for identifying symptomatic patients than identifying a big LA, the degree of mitral regurgitation (as formally quantified using effective regurgitant orifice area, regurgitant fraction and regurgitant volume) or end-systolic dimensions.

In a follow-up study to evaluate the relationship between increased BNP values in MR, and systolic parameters, Detaint et al.[18] studied BNP levels in patients with organic and functional MR, and found that BNP levels were higher in functional than in organic MR, and that the best indicator of BNP levels was end-systolic volume index (ESVI), irrespective of the etiology of the valve disease. A BNP level of > 90pg/ml predicted an end-systolic volume index (ESVI) of >60ml/m^2 with an odds ratio of 16. Thus, increased BNP levels in patients with both organic and functional MR are a marker of a high LV ESVI, and thus of LV remodelling, and should raise the concern of undetected alterations in LV function.

These findings suggest that increased serum levels of BNP and NT-proBNP in a patient with MR should raise the suspicion of severe disease and prompt careful assessment of the grade of regurgitation. The reverse is also true - if levels are not increased, it is unlikely that MR is severe.

(ii) BNP and NT-proBNP as indicators of functional impairment of the left ventricle in mitral regurgitation

The next question is whether serum BNP and NT-proBNP levels provide any information about left ventricular dysfunction. Some relationship between BNP and NT-proBNP levels and LV dimension is expected, as its secretion is activated by stretch of the myocardium. In the study by Detaint et al.,[17] serum levels weakly correlated with ESVI ($r = 0.26$), and there was a trend for correlation with LV end-diastolic volume index (EDVI). However, in the study by Sutton et al.,[16] no correlation was found between BNP and NT-proBNP levels and either LV end systolic or end-diastolic dimensions. Because LV dilatation in the context of severe MR is indicative of LV dysfunction, the absence of a strong correlation between BNP and NT-proBNP levels and both end-diastolic and end-systolic dimensions raises the question whether the natriuretic peptide levels are markers only of severity of MR, rather than the functional impairment secondary to the mitral valve lesion.

Yusoff et al.[19] assessed NT-proBNP as a marker of functional capacity, symptoms and cardiac remodelling in patients with severe mitral regurgitation and preserved ejection fraction. These authors showed that NT-proBNP was an independent marker of functional capacity – it showed a very strong negative correlation with VO_2max ($r = - 0.6$) and exercise time ($r = - 0.52$), and only weakly correlated with conventional echocardiographic parameters. These data strongly suggest that NT-proBNP levels reflect the impact of MR on cardiac structure and function, and are not simply a reflection of disease severity, degree of regurgitation or symptoms. This illustrates an extremely important principle – resting measurements did not reflect LV dysfunction, but the failure of contractile reserve only became manifest upon exercise, and was predicted by high NT-proBNP levels.

It seems that increased BNP and NT-proBNP levels do reflect LV dysfunction, which is unmasked by dynamic testing.

(iii) BNP and NT-proBNP predict survival and occurrence of heart failure in mitral regurgitation

The strongest argument for the ability of natriuretic peptides to predict LV dysfunction in MR comes from outcomes data, however limited it may be at this stage. In a study involving 124 patients it was found that a BNP level > 31 pg/ml predicted mortality – 95 ± 5% patients below this cut-off were alive after 5 years versus 73 ± 10% above this cut-off.[17] Using death and new heart failure as end-point, they showed an incidence of 42 ± 10% versus 16 ± 7% for the higher versus the lower group. The importance of this observation is highlighted by the fact that the only clinical predictors of outcome, namely symptoms and LV dysfunction, are present only in a minority of patients, and occur late in the disease. Data are currently lacking, but measurement of BNP and NT-proBNP may become an independent additional tool in the decision making process concerning mitral valve replacement.

(iv) The change in BNP separated responders from non-responders following surgery

The emerging concept with regard to the relationship of BNP to mitral regurgitation is thus that it reflects disease severity to some extent, certainly reflects structural remodelling (LA increase) and increased pulmonary artery pressures, and may be a marker of subclinical left ventricular dysfunction. More support for the latter comes from observations on changes in BNP levels after surgery. In 22 patients undergoing mitral valve repair, patients who had a decrease in BNP also had a decrease in symptoms and left atrial size, as well as a reversal of left ventricular remodelling.[20] Those in whom BNP did not decrease

had no decrease in left atrial size, no reversal (and even progression) of left ventricular remodelling and had no improvement in symptoms. Obviously this is of little practical consequence, and the more important question is whether pre-operative BNP values were of assistance in identifying the patients that did improve. Unfortunately there were no distinguishing features setting the responders apart from the non-responders.

In summary, increased BNP and NT-proBNP levels in patients with MR suggest a more severe degree of regurgitation, larger left atrial volumes and higher pulmonary artery pressures and perhaps larger end-systolic volumes. The most impressive data, however, is the correlation of high NT-proBNP levels with impaired functional ability, indicating that left ventricular dysfunction could be unmasked by exercise. These data, together with the poor survival outcome associated with high BNP levels, suggest that BNP and NT-proBNP levels are valuable tools that can alert the clinician to a more severe underlying degree of disease and probable left ventricular dysfunction, and may in the future become an independent parameter to utilize in the assessment of patients for timing of surgery.

MITRAL STENOSIS (MS)

All studies concerning serum levels of BNP and NT-proBNP in mitral stenosis (MS) report a marked increase in the levels of these peptides in MS.[21-23] There are different reasons for this increase. Many of these patients are in atrial fibrillation (AF), which is known to be associated with increased levels. In one study, levels in patients with MS and AF were nearly twice as high as when patients were in sinus rhythm,[22] whereas there was no difference between patients with MS in sinus rhythm and AF in the study by Shang et al.[24] In the latter study BNP levels remained unchanged 24 hours after mitral valvuloplasty in patients who were in AF, whereas they significantly decreased in patients who were in sinus rhythm – thus showing the triggering effect of AF on BNP secretion. BNP is secreted from the atria, albeit less so than ANP, and there is some speculation that left atrial stretch may contribute to serum BNP levels. In view of the pulmonary hypertension caused by MS, hypertrophy and dilatation of the right ventricle could conceivably be a source of BNP, and the correlation with peak pulmonary artery pressure (PAP) is very strong in most studies.[21, 22]

Whatever the source of BNP in MS, BNP levels seem to reflect the severity of the valve lesion, as they strongly correlate with symptoms as reflected in NYHA functional class ($r = 0.6$) and left atrial size ($r = 0.7$), mitral valve area ($r = -0.45$) and mean mitral gradient ($r = 0.57$).[22] In the latter study, serum BNP levels also correlated with right ventricular diameter ($r = 0.4$) and peak pulmonary pressure ($r = 0.7$), reflecting pulmonary hypertension. It has therefore been suggested that serum BNP levels be used for the follow-up of patients with MS as a surrogate for echocardiography to monitor the development of pulmonary hypertension where echocardiography is not available.[22] However, no cut-off value for either BNP or NT-proBNP has been established to guide clinical decision making regarding the timing of mitral valve replacement or mitral valve balloon valvuloplasty.

In summary, BNP and NT-proBNP therefore seem to reflect pulmonary hypertension in MS, and may have a role in assessing the development of pulmonary hypertension during follow-up where echocardiography is not available.

AORTIC VALVE REGURGITATION (AR)

Information about serum BNP and NT-proBNP levels in isolated aortic valve regurgitation (AR) is scant.[25-27] BNP and NT-proBNP levels are significantly increased in subjects with AR, even in those who are asymptomatic. The correlation between serum levels and valve lesion severity and left ventricular dysfunction is, however, less clear. In a group of 60 patients with a mean age of 22 years, it was found that levels increased with an increase in valvular regurgitant severity as defined by the diameter of the vena contracta[27] – levels increased even in mild AR (despite no difference in LV end-diastolic diameter compared to control), and were highest in severe AR. These results suggest that serum levels do reflect valve lesion severity. If that were true, serum levels would be expected to correlate with conventional parameters of LV remodelling such as LVED and LVES. This was indeed observed by Eimer et al.,[26] but could not be corroborated in the larger study by Gerber et al.[25] However, the latter authors also clearly demonstrated that serum levels were significantly higher in symptomatic patients when compared to asymptomatic patients, and it was deduced that serum levels could not be explained by LV remodelling. The observation that serum levels were increased in these patients, who all

had an ejection fraction above 50%, was interpreted as probably reflecting early LV dysfunction. Currently there is no information regarding the relationship between BNP/NT-proBNP and prognosis.

There is evidence that serum levels (of BNP) in AR may reflect valve lesion severity and, to some extent, LV dysfunction, but no data exist on the relationship between BNP or NT-proBNP and mortality outcomes in AR.

MIXED VALVE LESIONS

There are very little data about BNP and NT-proBNP levels in mixed valvular disease, but natriuretic peptide levels are usually even higher than in isolated heart valve lesions.[28] No information is currently available on the relationship between natriuretic hormone levels, prognosis and outcomes in mixed heart valve disease.

SUMMARY

- Serum levels of BNP and NT-proBNP are increased in patients with various forms of heart valve lesions. Most information is available for AS and MR and, in both valve diseases, increased serum levels predict valve lesion severity to some extent. The meaning of increased BNP and NT-proBNP levels in other valve disease such as MS, AR and mixed valvular disease is currently not clear.

- Serum levels of BNP and NT-proBNP seem to provide information about underlying left ventricular function. High levels predict poorer survival in patients with AS and MR who are not operated on, and in the case of AS, predict poor post-operative outcomes.

- Currently no definite statement can be made regarding the use of natriuretic peptide levels to guide decision making in aortic valve replacement. In patients with AS, high levels (BNP > 90 pg/ml and NT-proBNP levels of > 190 pg/ml) should at least prompt the managing physician to re-evaluate the patient carefully for valve stenosis severity, regular review and meticulously search for the presence of any conventional indication for aorta valve replacement, mindful that some patients may give a poor history about exercise capability, masking the symptoms of left ventricular dysfunction.

- Similarly, high natriuretic peptide levels in patients with MR (BNP level of more than 30 – 50 pg/ml) should prompt careful assessment and quantification of the degree of mitral regurgitation (the PISA method, for example, may be used to calculate the effective regurgitation orifice area and regurgitant volume) as well as presence of symptoms.

- In MS, increased BNP and NT-proBNP levels reflect increased pulmonary artery pressure, and may be useful to follow patients with known MS to detect increased pulmonary pressure if echocardiography is not available.

- In AR, BNP and NT-proBNP levels increase with regurgitation severity.

- Future studies will clarify whether serum levels of BNP and NT-proBNP should be used routinely to guide clinical decision making when deciding on the timing of AVR and MVR in patients with AS and MR, and will define its role in the evaluation and management of patients with other valve diseases.

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