Natriuretic Peptide Release during Exercise in Patients with Valvular Heart Disease:

a Systematic Review.

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Word count 2907

Statement

1. A search for studies that assessed exercise biomarkers in patients with moderate to severe valve lesions was performed.

2. We examined the relationship between rest and exercise BNP and also the endpoints of symptoms, haemodynamic or echocardiographic variables and clinical outcomes.

1. Our analysis of the published data suggests that biomarkers measured during exertion show a strong potential to offer additional clinical value, over an above resting values.

Introduction

Valvular heart disease is an important cause of morbidity and mortality and occurs in 11.3% of the total population. Its frequency is expected to double by 2050 (1). There are clear guidelines for the management of symptomatic severe valve lesions (2-3); however, the timing of intervention for asymptomatic patients remains hotly debated. It is becoming clear that some of these patients decompensate early, before reaching the thresholds currently advocated in the international guidelines. A tool to identify and risk stratify at an earlier stage in the disease process, prior to the development of complications, is therefore required. Volume or pressure overloaded states lead to myocardial stretch and elevated diastolic wall stress, resulting in exaggerated release of brain natriuretic peptide (BNP), N-terminal pro BNP and atrial natriuretic peptide (ANP) (4). Natriuretic peptides are the most widely used markers of myocardial stretch and their clinical use in the assessment of patients with valvular heart disease is emerging. Cardiac troponins indicate myocardial cell necrosis and elevated levels in patients with aortic stenosis have been associated with advanced left ventricular hypertrophy, poor prognosis and the need for aortic valve replacement.

Most of the research into biomarker valvular disease relates to the resting state. Exercise testing can unmask symptoms and latent left ventricular dysfunction in apparently asymptomatic individuals. Whether biomarkers measured during exercise provide additional information remains to be fully established.

It is established that BNP significantly increases following exercise in healthy individuals and that these exercise changes are not influenced by age, gender, body mass index, maximal workload or exercise capacity (5). In some diseases such as coronary artery disease, BNP and its rise during exercise are associated with the severity of ischaemia (6). The augmentation of natriuretic peptides and endothelin 1 levels on exercise in chronic heart failure may also be more important than resting levels as predictors of left ventricular dimensions and systolic function (7).

Natriuretic peptides also increase on exercise in patients with valvular heart disease, but to date, much of the research has come from small studies with varying study designs. The objective of this systematic review is to therefore comprehensively describe the current literature regarding the effect of exercise on biomarkers (namely BNP and NT pro-BNP), in patients with valvular heart disease. We set out to establish whether biomarkers measured during exercise might present an opportunity for better risk stratification.

Methods

Search strategy

A literature search was performed using PubMed, Embase, Ovid, Google Scholar and the Cochrane Library for studies published between 1990 and 2020. The Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines were adhered to (8). The following keywords and MeSH headings were used: "biomarker AND exercise AND valvular heart disease", "brain natriuretic peptide AND exercise AND valvular heart disease", "troponin AND exercise and valvular heart disease," "biomarker AND aortic stenosis AND exercise,

biomarker AND aortic regurgitation (incompetence) AND exercise, biomarker AND mitral stenosis AND exercise, biomarker AND exercise AND mitral regurgitation (incompetence). A medical librarian was consulted to optimize the search strategy and identify key search terms.

Figure 1 illustrates the search strategy following the PRISMA guidelines (8).

Study selection

The title and keywords of the retrieved articles were examined for relevance. The abstracts of identified publications were screened by two independent reviewers and then potentially eligible articles were then selected for full-text review. The reference lists of these articles were also reviewed.

Articles were included if they exhibited the following:

- Studies of biomarkers on exercise

- Patients with moderate or severe valve lesions

- Data or symptoms and/or clinical events

Review articles, case reports, conference abstracts and animal studies were excluded.

Outcomes

The primary outcomes were combined cardiovascular events; total mortality, valve intervention and hospitalisation.

The relationships between rest and exercise biomarkers were recorded, including their relationship to symptoms, haemodynamic and echocardiographic variables.

Results

Eleven studies meeting the eligibility criteria were included in the systematic review. The total number of study participants enrolled was 844 (750 patients with valvular heart lesions and 94 age and sex matched controls). 489 (61%) participants were male and the mean age was 55.2 ± 9.6 years (adult studies). Table 1 displays the relevant patient and study characteristics.

The predominant valve lesion was aortic stenosis in five studies, co-existing aortic stenosis and regurgitation in one study, mitral regurgitation in two and mitral stenosis in three studies. The majority of patients were asymptomatic at baseline.

The majority of studies evaluated BNP and NT pro-BNP on exercise, although two of the early publications examined the effects of atrial natriuretic peptide.

There was a variation in the number of blood samples taken and the timing of venous blood sampling post exercise. The resting blood samples were taken after 20-30 minutes after supine rest and the post exercise sample was taken 2-3 minutes after the cessation of exercise. There were only three studies where blood samples were taken at serial intervals post exercise (12-14).

3 studies described the effect of exercise BNP on cardiovascular outcomes (10, 15-16). Tertiles of exercise BNP were used (Table 2).

Aortic stenosis (AS)

Three studies examined the role of exercise BNP in patients with asymptomatic severe AS
(9-11,13).

The largest of these by Capoulade *et al* showed that BNP level increased significantly from
rest to peak exercise (p<0.0001) and both while resting and peak exercise BNP levels were
strongly correlated (r=0.89, p<0.0001), peak exercise BNP was associated with mean
gradient, left atrial area and valvulo-arterial impedance (Zva). Furthermore, during a mean
follow up of 1.8 ± 1.3 years, BNP levels during exercise were significantly associated with an
increased risk of death or aortic valve replacement after adjusting for clinical,
echocardiographic and exercise variables. There was a significant graded relationship
between each tertile of peak exercise BNP level and events (p<0.0001). At both time points
tertiles 2 and 3 of peak exercise BNP remained associated with a significant increase in the
risk of events; resting BNP was not (10).

In the ROC curve analysis, the area under the curve to predict 1-year events was higher with
peak exercise BNP compared with resting BNP. The best cut point value was 86pg/ml for
peak exercise BNP and 58pg/ml for resting BNP. In multivariate COX analysis, peak exercise
BNP>86pg/ml was significantly associated with increased risk of events, whereas resting
BNP>58pg/ml was not (10).

The study of Van Pelt *et al* showed that both the rest and exercise levels of BNP were
elevated in AS patients compared to controls (BNP at rest 11.4 ± 6.5 vs. 7.4 ± 4.0 pmol/l and
BNP on exercise 14.5 ± 8.0 vs. 10.5 ± 6.0pmol/l). The association between BNP and

echocardiographic and exercise measures were similar but slightly stronger for BNP measured at rest. The study did not evaluate prognosis or events, but did demonstrate a relationship between higher exercise BNP and blunted exercise blood pressure response, itself a marker of higher morbidity (9).

In contrast, a more recent study by Dobrolowski *et al* demonstrated that NT pro-BNP measurements during exercise did not provide any incremental value to NT pro-BNP measured at rest, in patients with aortic stenosis. NT pro-BNP did however track to left ventricular mass index, mean gradient and aortic valve area (11).

Mitral regurgitation (MR)

Magne *et al* sought to identify the determinants of BNP measured on exercise and to evaluate its prognostic importance over resting BNP, in patients with asymptomatic moderate to severe mitral regurgitation and preserved left ventricular ejection fraction (LVEF). In the group of patients where MR was or became severe during exercise, significantly higher exercise (but not resting) BNP levels were observed, compared to those with moderate exercise MR (15).

Furthermore, there was a significant relationship between increasing exercise BNP and an increased incidence of cardiac events. Patients in tertiles 2 and 3 had a 2.9 and 5.8 fold increase in risk during follow up. The authors were able to construct ROC curves demonstrating the best cut off value of exercise BNP level to predict cardiac events was 64pg/dl (sensitivity 86%, specificity 61%) (15).

Similar results were obtained in a subsequent study carried out in 223 patients with severe primary mitral regurgitation and good left ventricular function, undergoing exercise treadmill testing. During a 15-month follow up period, pre-defined cardiac events (mitral valve replacement or cardiac hospitalisation) occurred in 83 patients (37.2%) and these patients had a significantly higher exercise BNP level than those without any events (165 ± 119 pg/ml vs. 57 ± 48 pg/ml; p < 0.001). The best cut-off value of exercise BNP level to predict cardiac events was 90pg/ml. In patients with mitral regurgitation, 66 patients (29.5%) stopped exercise due to dyspnoea. These patients had similar resting BNP levels (66.13 ± 43.84 pg/mL vs. 64.85 ± 44.58 pg/mL; p = 0.23) but significantly higher exercise BNP levels (136 ± 109.7 pg/mL vs. 84.88 ± 90.2 pg/mL; p < 0.001 (16).

A funnel plot in an attempt to detect publication bias in the studies of cardiovascular outcome in aortic stenosis and mitral regurgitation (10, 15-16) is displayed in Appendix 1.

Mitral stenosis (MS)

Several small studies in patients with mitral stenosis showed that exercise increased the levels of ANP and BNP. Atrial natriuretic peptide (ANP) levels increased from 107 ± 70 to 183 ± 96 pg/ml (p < 0.01) during exercise testing, in Ishikura's study. The change in ANP during exercise reflected the increment in mean transmitral gradient, heart rate and systolic blood pressure. There was a significant relationship only between the change in ANP and mean transmitral pressure gradient (r= 0.70, p<0.01) (17).

Serial biomarker measurements

3 out of the 10 study investigators sought to determine the optimal timing of biomarker response, by blood sampling at different timepoints after exercise (12-14)

Mawad et al carried out a study to determine the optimal timing of biochemical response of NT pro-BNP and highly sensitive cardiac troponin (hs-cTNT) in children with asymptomatic moderate AS, moderate AR and healthy controls. Following treadmill exercise, NT-proBNP increased significantly at 40 minutes (99.2 ± 48.6 ng/L; p = 0.04) into recovery and remained elevated at 60 minutes (100.0 ± 53.7 ng/L; p = 0.01) into recovery, in the AR group. In moderate AS, these levels did not vary significantly after exercise challenge. Troponin was significantly higher at rest in both disease groups compared to control. The increase in hs-cTnT was significant only at 60 min into recovery for moderate AS and AR (14).

The study looking at CT-ADP and HMWM during exercise showed that these levels did not change significantly between rest and exercise (p=0.45 and p=0.65, respectively). In 4 out of the 10 subjects, no valid aortic valve velocity could be recorded on exercise; however in the remaining 6 patients, CT-ADP during exercise correlated well with aortic valve peak velocity (rho 0.82, p=0.04) (12).

Discussion

We were able to draw the following conclusions based on the available literature regarding exercise biomarkers, in patients with heart valve disease. Firstly, variability in the

methodology and the timing of biomarker measurement limits the comparability of the existing literature. Secondly, biomarkers clearly increase during exercise in both stenotic and regurgitant valve lesions, but whether this provides incremental value over resting measurements is less clear, especially in aortic stenosis. Finally, there is a strong signal that exercise biomarkers track to adverse clinical outcomes, and the evidence is stronger in mitral regurgitation than in aortic stenosis.

Our data demonstrates that elevated exercise BNP is independently associated with a higher risk of cardiac events, in patients with aortic stenosis and mitral regurgitation. Furthermore, the results show that exercise BNP may improve risk stratification beyond what is obtained from patient demographics, echocardiographic parameters, and resting BNP. The peak exercise BNP outperformed the resting BNP in several different analyses and was able to further risk stratify both those with a lower and higher resting BNP level. These data provide some important insights into novel strategies for the risk stratification of asymptomatic patients.

The guideline recommended indications for surgery in asymptomatic severe valve lesions include the presence of left ventricular dilatation (mitral and aortic regurgitation) or impairment (LVEF<50% in aortic stenosis and aortic regurgitation, LVEF < 60% in mitral regurgitation) (2-3). However, we know there is a strong signal/ residual risk with myocardial fibrosis (demonstrated by MRI); leading to subclinical left ventricular dysfunction, suggesting that earlier intervention may be required in a proportion of patients (20).

Assessment of heart valve disease in a resting state does not provide a complete evaluation of valve haemodynamics as the severity of valve obstruction and regurgitation is dynamic. Whilst an abnormal left ventricular response to exercise (manifest by a lack of increment or a decrease in LVEF/ global longitudinal strain on exercise) is associated with increased likelihood of developing symptoms and cardiac events, there is a growing need for other objective measures to help identify patients with subtle LV dysfunction (21-24), that will benefit from early intervention. Plasma BNP and NT pro-BNP levels have been shown to correlate positively with lesion severity and symptomatic status (25-28). However, the main value of using these biomarkers is their potential to predict adverse events in asymptomatic patients (29-30). BNP is released by the ventricular myocytes in response to stretch and in patients with valvular heart disease is influenced by volume and pressure overload. A higher exercise BNP may help integrate the various stresses on the heart and identifies the point where the heart is closer to the point of decompensation. The results suggest that patients with a high exercise BNP may potentially benefit from early referral to surgery; whereas patients with a low exercise BNP had a lower incidence of cardiovascular events, suggesting that conservative management and watchful waiting may be acceptable in this cohort.

The tertiles of exercise BNP were variable, did not have the same cut off values, and their use was post hoc. The cut off values of 64 and 90pg/ml were also data driven.

These studies are limited by the lack of serial measurements to determine the optimal timing of the biochemical response. The study by Mawad *et al* specifically aimed to determine the timing at which the maximal values of NT-proBNP and hs-cTnT occurred after exercise. Following treadmill exercise, NT- proBNP increased significantly in moderate AR at 40 minutes into recovery and remained elevated at 60 minutes. In the patients with

moderate AS, the levels did not change significantly after exercise challenge. Highly sensitive troponin however was significantly higher at rest in both disease groups and the levels remained similar at 20 and 40 minutes into recovery (14). The results suggest a novel way to assess valvular heart disease

Although BNP measured on exercise has demonstrated a superior predictive capacity to the resting concentration, the presence of confounding factors such as renal impairment and atrial fibrillation may lead to falsely elevated levels. The role of more diverse biomarkers such as soluble ST2 (sST2), a member of the interleukin-1 receptor family, is a new biomarker for myocardial distress and avoids these confounders. sST2 distinguishes and identifies the symptomatic from the non-symptomatic patient with aortic stenosis and elevated levels are associated with heart failure (31). It is physiologically linked to not just to heart muscle stretch (like the more established BNP) but also cardiac hypertrophy, fibrosis, and ventricular dysfunction. All these processes are implicated in the development of less optimal outcomes after surgery / intervention.

Von Willebrand factor is another biomarker, which is known, in aortic stenosis for its role in Heyde's syndrome. In a recently published study by Zelis *et al*, blood samples for HMWM and CT-ADPs were taken at baseline, 4 minutes after the start of exercise, during peak exercise and at 5, 10 and 30 minutes after exercise. The biomarkers did not change significantly with exercise in patients with symptomatic moderate or severe AS. Peak CT-ADP showed a good correlation with peak AV velocity suggesting that this may be an easily available surrogate for peak transaortic pressure gradient on exercise. Long-term outcomes, however, were not evaluated (13). These biomarkers remain almost wholly unexamined.

Study limitations

A limitation of our analysis is that all the studies analysed were observational and are subject to possible selection bias. There was significant heterogeneity between studies with different patient demographics, time periods and follow up duration. The inclusion criteria of the studies were not standardised and the definitions of each biomarker tertile range was determined by the individual investigator. The outcome data were also not uniform between studies.

All but one of the studies was not blinded so events may have been influenced by the physician's perception and interpretation of disease severity and symptomatic status.

Conclusions

Resting echocardiography and clinical factors insufficiently describe heart function in patients with severe valve lesions and no symptoms. Exercise testing to document either symptomatic limitation or latent left ventricular dysfunction is now widely used in clinical practice and is represented in contemporary guidance, in the case of aortic stenosis. The same is true of a variety of biomarkers, especially BNP and NT proBNP; these provide both clinical but also pathological insights into the effect of a valve lesion.

Our analysis of the published data suggests that biomarkers measured during exertion show a strong potential to offer additional clinical value. The literature at present however, is too small, too various in methodologies, and of insufficient methodological rigour to advocate current use. The next step is therefore to develop a methodological consensus that can then be applied to well described specific populations, especially patients with asymptomatic

moderate and severe valve lesions, in order to potentially refine recommendations about

the timing of intervention.

References

1. d'Arcy J, Coffey S, Loudon M, et al. Large scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: The OxVALVE Population Cohort Study. Eur H Journal 2016; 37(47): 3515-3522
2. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of patients with valvular heart disease. Eur H Journal; 38(36): 2739-2791
3. Nishimura R, Otto CM, Bonow RO, et al. AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American college of cardiology/American heart association task force on practice guidelines. Journal of the American College of Cardiology, 63(22).
4. Hystad ME, Geiran OR, Attramadal H, et al. Regional cardiac expression and concentration of natriuretic peptides in patients with severe chronic heart failure. Acta Physiol Scand. 2001. 171:395–403.
5. Scharhag J, Hermann M, Urhausen A, et al. Independent elevations of N-terminal pro-brain natriuretic peptide and cardiac troponins in endurance athletes after prolonged strenuous exercise. Am Heart J. 2005 150(6):1128-34
6. Sabatine MS, Morrow DA, De Lemos JA, et al. Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. J Am Coll Cardiol 44: 1988-1995, 2004.
7. Yousufuddin M, Shamim W, Henein M, et al. Neurohumoral response during exercise in healthy controls and patients with chronic heart failure. *J Am Coll Cardiol* 2000;35(2 suppl A):175A.1–2
8. Moher D, Liberati A, Tetzlaff J, Altman DG. & The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLOS Medicine 2009. 6 e1000097 (10.1371/journal.pmed.1000097
9. Van Pelt NC, Kerr AJ, Legget ME, et al. Increased B-type natriuretic peptide is associated with an abnormal blood pressure response to exercise in asymptomatic aortic stenosis. Int J Cardiol 2008 127(3): 313-320
10. Capoulade R, Magne J, Dulgheru R, et al. Prognostic value of plasma B-type natriuretic peptide levels after exercise in patients with severe asymptomatic aortic stenosis. Heart. 2014; 100: 1606-1612.
11. Dobrowolski P, Lech A, Klisiewicz A, et al. Evaluation of NT-proBNP concentrations during exercise in asymptomatic patients with high gradient severe aortic stenosis. Pol Arch Med Wewn 2016; 126(9): 635-641.
12. Zelis JM, Zimmerman FM, Andriessen FPJ, et al. Assessment of exercise induced changes in von Willebrand factor as a marker of severity of aortic stenosis. Heart 2020 7(1)
13. Riecansky I, Liska B, Vransky M, et al. Natriuretic peptides in patients with aortic stenosis. Vnitr Lek 2010. 56(7): 715-20
14. Mawad W, Abadir S, Fournier A, et al. Timing of Dynamic NT-proBNP and hs-cTnT Response to Exercise Challenge in Asymptomatic Children with Moderate Aortic Valve Regurgitation or Moderate Aortic Valve Stenosis. Pediatr Cardiol 2015 36(8) 1735-41
15. Magne J, Mahjoub H, Pibarot P, et al. Prognostic importance of exercise brain natriuretic peptide in asymptomatic degenerative mitral regurgitation. Eur J Heart Fail 2012;14(1): 293–302.

16. Sinha SK, Garg S, Thakur R, et al. Prognostic importance of Brain Natriuretic Peptide in Asymptomatic Chronic organic mitral regurgitation: an observational study. J Clini Med Res 2016; 8(11): 797-804
17. Ishikura F, Nagata S, Akaike M, et al. Effects of percutaneous transvenous mitral commissurotomy on levels of plasma atrial natriuretic peptide during exercise.1991; 67(1): 74-78
18. Matsumoto A, Hirata Y, Monomura S, et al. Effects of exercise on plasma level of brain natriuretic peptide in congestive heart failure with and without left ventricular dysfunction. Am Heart Journal 1995
19. Kilickesmez KO, Ozkan AA, Abaci O, et al. Serum N-terminal brain natriuretic peptide indicates exercise induced augmentation of pulmonary artery pressure in patients with mitral stenosis. Echocardiography 2011; 28(1): 8-14
20. Treibel TA, Kozor R, Schofield R, et al. Reverse Myocardial Remodelling Following Valve Replacement in Patients with Aortic Stenosis. J Am Coll Cardiol 2018 71(8): 860-871
21. Lancellotti P, Lebois F, Simon M, et al. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. Circulation 2005; 112 9 Suppl: I377-I382.
22. Donal E, Thebault C, O'Connor K, et al. Impact of aortic stenosis on myocardial deformation during exercise. Eur J Echocardiogr. 2011; 12: 235-241
23. Wahi S, Halsuka B, Pasquet A, et al. Exercise echocardiography predicts development of left ventricular dysfunction in medically and surgically treated patients with asymptomatic severe aortic regurgitation. Heart 2000; 84: 606-614
24. Magne J, Lancellotti P, Pierard LA. Exercise-induced changes in degenerative mitral regurgitation. J Am Coll Cardiol. 2010; 56:300–309
25. Weber M, Arnold R, Rau M et al. Relation of N-terminal pro-B-type natriuretic peptide to severity of valvular aortic stenosis. Am J Cardiol 2004; 94:740–5.
26. Rajani R, Rimington H, Chambers J. B-type natriuretic peptide and tissue doppler for predicting symptoms on treadmill exercise in apparently asymptomatic aortic stenosis. J Heart valve disease 2009
27. Gerber IL, Stewart RA, French JK, et al. Associations between plasma natriuretic peptide levels, symptoms, and left ventricular function in patients with chronic aortic regurgitation. Am J Cardiol 2003; 92:755–8
28. Arat-Ozkan A, Kaya A, Yigit Z, et al. Serum N-terminal pro BNP levels correlate with symptoms and echocardiographic findings in patients with mitral stenosis. Echocardiography 2005; 22(6): 473-8
29. Lim P, Monin JL, Monchi M, et al. Predictors of outcome in patients with severe aortic stenosis and normal left ventricular function: role of B-type natriuretic peptide. Eur Heart J 2004. 25:2048–53.
30. Pizarro R, Bazzino OO, Oberti PF, et al. Prospective validation of the prognostic usefulness of B-type natriuretic peptide in asymptomatic patients with chronic severe aortic regurgitation. JACC 2011. 58(16); 1705-1714
31. Lancellotti P, Dulgheru R, Magne J, et al. Elevated Plasma Soluble ST2 is associated with Heart failure Symptoms and Outcome in Aortic Stenosis. PLoS One 2015; 10(9)