Summary

Background: Amino terminal pro-B-type natriuretic peptide (NT-proBNP) is a sensitive marker of ventricular dysfunction. Exercise causes an increase in the secretion of NT-proBNP, and with myocardial ischaemia the increase is more pronounced. This increase has been found to improve the diagnostic sensitivity of the stress ECG in diagnosing myocardial ischaemia in subjects with normal ventricular function.

Objective: To assess whether the change in NT-proBNP can be used to diagnose effort-induced myocardial ischaemia in an unselected population.

Methods: We enrolled a total of 51 consecutive patients, referred for exercise stress 99mTc-sestamibi SPECT MPI (single-photon emission computed tomography myocardial perfusion imaging) to diagnose inducible myocardial ischaemia. NT-proBNP was determined at rest and 30 minutes after cessation of exercise.

Results: Of the 51 patients, 28 had normal perfusion scans, seven had scans with fixed perfusion defects (previous myocardial infarction with no inducible ischaemia) and 16 had reversible perfusion defects (inducible ischaemia). There was no correlation between ischaemia and resting NT-proBNP, post-stress NT-proBNP or the change in NT-proBNP (delta-NT-proBNP).

Conclusion: In an unselected population the change in NT-proBNP cannot be used to diagnose effort-induced myocardial ischaemia.

Materials and methods

In the study, we enrolled 51 consecutive patients referred for exercise-stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) to exclude reversible myocardial ischaemia. The studies were performed at the Nuclear Medicine Department of the Johannesburg and Chris Hani-Baragwanath Hospitals. The study had institutional ethics approval and informed consent was obtained from the subjects prior to enrolment into the study.

The study period was between January and October 2006. The median age of the study population was 58 years (32–82 years) and the male-to-female ratio was 32:19. The exclusion
criteria were: asthma or severe chronic obstructive pulmonary disease, beta-blocker use, the inability to reach a target heart rate (these patients were assessed as performing an inadequate stress test and were tested using a dipyridamole stress), and refusal of consent. There were no adverse outcomes during the time of the study.

SPECT MPI protocol
A two-day 99mTc-methoxyisobutyl isonitrile (Sestamibi) SPECT MPI protocol was used. On the first day the stress test was carried out, with the rest study done on day two. Exercise was performed on a treadmill, using a Bruce protocol; 99mTc sestamibi (740 MBq) was given at peak stress while the subject continued to exercise for one minute after the injection of the radiotracer. The patient was allowed to rest and images were acquired between 30 and 60 minutes after the injection of the radiotracer. Imaging was performed using a double-head rotating field-of-view gamma camera (Infinia Hawkeye, GE Medical Systems) equipped with low-energy, high-resolution, parallel-hole collimators. SPECT images were acquired on a 64 × 64 matrix using the step-and-shoot mode with a total angular range of 180 degrees and 20 seconds per image.

MPI assessment
Myocardial ischaemia was assessed visually and by means of semi-quantitative scoring of the extent of disease (summed difference score = SDS). This is calculated by subtracting the summed resting score (SRS) from the summed stress score (SSS), using the Xeleris multisync fitted with the QGS/QPS, which uses a 20-segment model to quantify myocardial perfusion on an arbitrary scale. The sensitivity of the SPECT MPI technique in diagnosing ischaemic heart disease is 91% and the specificity is 81%, compared to exercise-stress ECG with a sensitivity ranging from 37 to 100% and a specificity of 83%.

Three trained nuclear physicians performed the MPI assessments; they were blinded to the NT-proBNP results. An SDS of more than 4 indicates the presence of myocardial ischaemia. This can be graded: an SDS of 4–8 is mild, 9–12 is moderate and greater than 13 is severe myocardial ischaemia. A visual inspection of the MPI scan was carried out to assess the perfusion defect when there was any doubt about the diagnosis or the extent of the myocardial ischaemia.

Blood sampling
In the literature, blood sampling of BNP and NT-proBNP was done within minutes of completing exercise. These studies assessed BNP and NT-proBNP, or only BNP, or only NT-proBNP. Due to the differing half-lives of BNP and NT-proBNP, we performed a limited trial to assess the optimal timing of blood sampling for NT-proBNP and found the ideal time to be 30 minutes after the cessation of exercise, however there is no clear evidence as to the optimal timing of blood sampling.

A resting blood sample was obtained before exercise and the post-stress blood sample was obtained 30 minutes after the cessation of exercise. The sample was allowed to clot and then centrifuged at 3 000 rpm for 10 minutes. The serum was stored at −70°C and analysed in batches.

NT-proBNP assay
NT-proBNP was measured using kits supplied by Roche Diagnostics, SA. The assay is an electrochemiluminescence immunoassay that uses a sandwich technique. The analytical range is 5–35 000 pg/ml. The reference cut-off value based on the manufacturer’s data is 125 pg/ml. Patients with values below this can exclude cardiac dysfunction with a high level of certainty and levels above 125 pg/ml may indicate cardiac dysfunction, and are associated with an increased risk of cardiac complications (myocardial infarction, heart failure, death). This value was not corrected for age or gender (women tend to have higher values than men and values increase with age). The analytical coefficient of variation for the assay was 1.8–2.7%.

Statistical analysis
The statistical analysis was done using SAS Software V9.1 (SAS Institute Inc, Cary, NC, USA). The Spearman correlation coefficient was used to calculate correlations, and the Kruskal-Wallis test was used to assess differences in NT-proBNP between the three groups: subjects with no perfusion defects, fixed perfusion defects and inducible perfusion defects. The Wilcoxon test was used to determine differences at rest and post stress for NT-proBNP.

Results
Of the 51 subjects, 28 had normal perfusion scans (no perfusion defects), seven had fixed perfusion defects (previous infarct, no ischaemia) and 16 subjects had reversible perfusion defects (inducible ischaemia).

The median resting NT-proBNP of all the subjects was 296 pg/ml, with a range of 5–4 463 pg/ml. The highest median resting NT-proBNP result was in the subjects with reversible perfusion defects, followed by those with fixed perfusion defects, and the lowest was seen in the patients with normal MPI scans. These differences were not statistically significant. The characteristics of the study group are summarised in Table 1 and Fig. 1.

There was no correlation between the index of ischaemia (SDS) and resting, post-effort, or delta-NT-proBNP (post-effort – resting NT-proBNP) (Fig. 2). However, there was a correlation between resting NT-proBNP and ventricular function as reflected by end-diastolic volume (r = 0.34, p = 0.01) (Fig. 3), and ejection fraction (r = −0.43, p = 0.0014), as well as end-systolic volume (r = 0.38, p = 0.006).

| TABLE 1. STUDY GROUP'S CHARACTERISTICS |
|--------------------------------------|
| Normal | Fixed defect | Reversible defect |
|---|---|---|
| Number of subjects | 28 | 7 | 16 |
| Age (years)* | 59.5 (32–79) | 59 (33–74) | 55.5 (36–82) |
| Male:female | 15:13 | 5:2 | 12:4 |
| Resting end-diastolic volume (ml)* | 86 (34–331) | 114 (64–174) | 116.5 (64–381)** |
| Resting NT-proBNP (pg/ml)* | 147.5 (5–3165) | 281 (157–1594) | 416 (8–4463) |
| Resting ejection fraction (%)* | 56 (22–83) | 45 (25–61) | 38.5 (9–61)*** |

*Median values (range); **p < 0.05; ***p < 0.01 between the three groups.
Discussion

The utility of NT-proBNP lies in the fact that it is a sensitive marker of ventricular dysfunction. Myocardial ischaemia, chronic or acute, induces ventricular dysfunction and causes an elevation of NT-proBNP. This elevation can be used as part of risk stratification and prognosis.5,25,26

The relationship between B-type natriuretic peptides and exercise has been extensively studied. Exercise has been shown to increase the secretion of B-type natriuretic peptides in normal individuals, as well as in individuals with myocardial ischaemia. Exercise-induced myocardial ischaemia causes a more significant increase, and in individuals with normal ventricular function it can be diagnostic of myocardial ischaemia (SDS). The median NT-proBNP was highest in subjects with reversible ischaemia, however there was a large overlap in values.

The secretion of BNP is a dynamic process, which is dependent on mechanical (ventricular stretch) as well as endocrine factors.34 Ventricular function is also important; the dysfunctional ventricle can secrete BNP more readily than the normal ventricle. The individual with good LV function is able to perform a more adequate stress test, with a longer duration of exercise, a higher heart rate and higher sympathetic tone, potentially causing a greater stimulus for the release of BNP. These different factors (ventricular function, volume status, sympathetic tone) form a complex interaction when considering the secretion of NT-proBNP and its ability to diagnose inducible myocardial ischaemia.

This is the most likely reason for the differing responses seen in the literature. In subjects with a normal ejection fraction, exercise-induced ischaemia causes a rise in NT-proBNP; in unselected individuals there is no correlation. This lack of correlation is also observed in individuals undergoing pharmacological stress testing.35-37

Possible limitations of the study are the small number of subjects in the study and the optimal timing of blood sampling for NT-proBNP after exercise. This may have influenced the results.

Conclusion

No relationship could be demonstrated between exercise-induced myocardial ischaemia and a change in NT-proBNP. This suggests that the serial measurement of NT-proBNP in the routine assessment of exercise-induced myocardial ischaemia is not indicated.

Elena Libbaber performed the statistical analysis, Roche Diagnostics South Africa provided proBNP test kits and the NHLS Core Laboratory, Tswane Academic Division performed the analyses.
References
1. Costello-Boerrigter LC, Burnett JC (jun). The prognostic value of N-terminal pro-B-type natriuretic peptide. Nat Clin Pract Cardiovasc 2005; 2: 194–201.
2. Anand IS, Fisher LD, Chiang Y, Latini R, Masson S, Maggioni AP, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2003; 107: 1278–1283.
3. Schnabel R,ribi, Lubos E, Rupprecht H, Espinola-Klein C, Bickel C, Lackner KJ, et al. B-type natriuretic peptide and the risk of cardiovascular events and death in patients with stable angina. J Am Coll Cardiol 2006; 47: 552–558.
4. Pegoraro NR, Naidoo DP, Esterhuizen TM. Prognostic value of N-terminal-pro-brain natriuretic peptide measurement in patients with acute coronary syndromes. Cardiovasc J S Afri 2006; 17: 60–66.
5. Morrow DA, De Lemos JA, Blazing MA, Sabatine MC, Murphy SA, JaroHim P, et al. Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease. J Am Med Assoc 2005; 294: 2866–2871.
6. Huang W, Lee M, Perg H, Yang S, Kuo S, Chang H. Circulating brain natriuretic peptide values in healthy men before and after exercise. Metabolism 2002; 51: 1423–1426.
7. Foote RS, Pearlman JD, Siegel AH, Yeo KJ. Detection of exercise-induced ischaemia by changes in B-type natriuretic peptides. J Am Coll Cardiol 2004; 44: 1980–1987.
8. Yeo K, Lee h, Wong K, Foote R. Can exercise-induced changes in B-type natriuretic peptide be used to detect cardiac ischaemia? J Card Fail 2005; 11: S59–S64.
9. Hall C. Essential biochemistry and physiology of (NT-pro) BNP. Eur J Heart Fail 2004; 6: 257–260.
10. Hall C. NT-proBNP: The mechanism behind the marker. J Card Fail 2005; 11: S81–S83.
11. Goetze JP. Biochemistry of pro-B-type natriuretic peptides: The endocrine heart revisited. Clin Chem 2004; 50: 1503–1510.
12. De Bruyne B, Bronzwaer JGF, Heyndrickx GR, Paulus WJ. Comparative effects of ischemia and hypoxemia on left ventricular systolic and diastolic function in humans. Circulation 1993; 88: 461–471.
13. Masson S, Latini R, Anand IS, Vago T, Angelici L, Barlera S, et a. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: The Valsartan Heart Failure (Val-HeFT) data. Clin Chem 2006; 52: 1528–1536.
14. Hamman-Lercher A, Neubauer E, Muller S, Pachinge O, Puschendorf B, Mair J. Head-to-head comparison of N-terminal pro-brain natriuretic peptide, brain natriuretic peptide and N-terminal pro-atrial natriuretic peptide in diagnosing left ventricular dysfunction. Clin Chim Acta 2001; 310: 193–197.
15. Mueller T, Gegenhuber A, Poelz W, Halmayer M. Head-to-head comparison of the diagnostic utility of BNP and NT-proBNP in symptomatic and asymptomatic structural heart disease. Clin Chim Acta 2004; 341: 41–48.
16. Richards M, Nichols G, Espiner EA, Lanchbury JG, Troughton RW, Elliot J, et al. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischemic heart disease. J Am Coll Cardiol 2006; 47: 52–60.
17. Pfister R, Schneider CA. Natriuretic peptides BNP and NT-pro-BNP: established laboratory markers in clinical practice or just perspectives? Clin Chim Acta 2004; 349: 25–38.
18. Luchner A, Hengstenberg C, Lowel H, Rieger GAI, Schunkert H, Holmer S. Effect of compensated renal dysfunction on approved heart failure markers: Direct comparison of brain natriuretic peptide (BNP) and N-terminal pro-BNP. Hypertension 2005; 46: 118–123.
19. Underwood SR, Anostopoulos C, Cercequira M, Ell PJ, Flint EJ, Harbinson M, et al. Myocardial perfusion scintigraphy: The evidence. Eur J Nuclear Med Molec Imag 2004; 31: 261–291.
20. Froelicher VF, Lehmann KG, Thomas R, Goldman S, Morrison D, Eidson R, et al. The electrocardiographic exercise test in a population with reduced workup bias: diagnostic performance, computerized inter- pretation, and multivariable prediction. Veterans Affairs Cooperative Study in Health Services #016 (QUESTA) study group. Quantitative exercise testing and angiography. Ann Intern Med 1998; 128: 965–974.
21. Sandler MP, Coleman RE, Patton JA, et al. Diagnostic Nuclear Medicine, 4th ed, Philadelphia: Lippincott Williams & Wilkins, 2003.
22. Sabatine MS, Morrow DA, de Lemos JA, Omland T, Desai MY, Tanasijevic, et al. Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. J Am Coll Cardiol 2004; 44: 1985–1995.
23. Staub D, Jonas N, Zellweger MJ, Nusbaumer C, Wild D, Pfisterer ME, et al. Use of N-terminal pro-B-type natriuretic peptide to detect myocardial ischemia. Am J Med 2005; 118: e9–e16.
24. Weber M, Dill T, Arnold R, Rau M, Eknici O, Muller KD, et al. N-terminal B-type natriuretic peptide predicts extent of coronary artery disease and ischemia in patients with stable angina pectoris. Am Heart J 2004; 148: 612–620.
25. Wolfer T, Maeder M, Weilenmann D, Furu F, Bluzaite I, Riesen W, et al. Integration of B-type natriuretic levels with clinical data and exercise testing for predicting coronary artery disease. Am J Cardiol 2006; 98: 764–767.
26. Apple FS, Panteghini M, Ravikilde J, Mair J, Wu AHB, Tate J, et al. Quality specification for B-type natriuretic peptide assays. Clin Chem 2005; 51: 486–493.
27. Win HK, Chang S, Raizner M, Shah G, Al Basyk F, Desai U, et al. Percent change in B-type natriuretic levels during treadmill exercise as a screening test for exercise-induced myocardial ischemia. Am Heart J 2005; 150: 695–700.
28. Palumbo B, Siepi D, Lupatelli G, Sinzinger H, Finucci G, Annibletti PF, et al. Usefulness of brain natriuretic peptide levels to discriminate patients with stable angina pectoris without and with electrocardiographic myocardial ischemia and patients with healed myocardial infarction. Am J Cardiol 2004; 94: 780–783.
29. Bibbins-Domingo K, Ansari M, Schiller NB, Massie B, Whooley MA. B-type natriuretic peptide and ischemia in patients with stable coronary disease. Circulation 2003; 108: 2987–2992.
30. Bergeren S, Moller E, Baiy KR, Chen HH, Burnett JC, Pellika PA. Exertional changes in circulating cardiac natriuretic peptides in patients with suggested coronary artery disease. J Am Soc Echocardiogr 2006; 19: 772–776.
31. Marumoto K, Hamada M, Hiwada K. Increased secretion of atrial and brain natriuretic peptides during acute myocardial ischemia induced by dynamic exercise in patients with angina pectoris. Clin Sci (Lond) 1995; 88: 551–556.
32. Zaid GH, Tanchilevitch A, Rivlin E, Gropper R, Rosenschein U, Lanir A, Goldhammer E. Diagnostic accuracy of serum B-type natriuretic peptide for myocardial ischemia detection during exercise testing with Spet perfusion imaging. Int J Cardiol 2007; 117: 157–164.
33. Staub D, Nusbaumer C, Zellweger MJ, Jonas N, Wild D, Pfisterer ME, et al. Use of B-type natriuretic peptide in the detection of myocardial ischemia. Am Heart J 2006; 151: 1223–1230.
34. Suttner SW, Boldt J. Natriuretic peptide system: Physiology and clinical utility. Curr Opin Crit Care 2004; 10: 336–341.
35. Salinas G, Daher IN, Okorodudu AO, Ahmad M. B-type natriuretic peptide is not a marker of ischemia during dobutamine stress echocardiography. J Am Soc Echocardiogr 2007; 20: 23–26.
36. Asada J, Tsuji H, Iwasaka T, Thomas J, Lauer MS. Usefulness of plasma brain natriuretic peptide levels in predicting dobutamine-induced myocardial ischemia. Am J Cardiol 2004; 93: 702–704.
37. Karabios I, Kavrouvi E, Chiotinis N, Papadopoulos A, Simeonidis P, Tsolias O, Katrisitis D. Acute changes in N-terminal pro-brain natriuretic peptide induced by dobutamine stress echocardiography. Eur J Echocardiogr 2007; 4: 265–274.