Peer reviewed **ORIGINAL ARTICLE**

THE PREDICTIVE VALUE OF proBNP LEVELS TO DETERMINE THE PRESENCE AND SEVERITY OF CORONARY ARTERY DISEASE IN PATIENTS WITH A POSITIVE OR INCONCLUSIVE EXERCISE STRESS TEST

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Abstract

Background Several clinical studies have shown increased levels of N Terminal-Pronatriuretic Peptide (NT-proBNP) during episodes of coronory ischaemia. Consistent with this observation, both Brain Natriuretic Peptide (BNP) and NT-proBNP correlated to severity, location, and extent of angiographic coronary artery disease (CAD). The main objective of this study was to identify the possible value of NT-proBNP level which indicates CAD.

Methods Sixty patients with signs and symptoms of CAD were recruited for this study. They were divided into two groups; Group A, consisted of thirty patients with a positive Exercise Stress Test (EST) and Group B, consisted of thirty patients with an inconclusive EST. After the EST, all patients from both groups were required to have a NT-proBNP blood test, a left and right coronary angiogram and a left ventriculogram.

Results Post EST NT-proBNP levels, in both groups, increased in the presence of CAD ($p<0.001$). For the positive EST group, the area under the ROC curve was 0.975 ($p<0.001$). A cut- off value of 120 pg/ml was identified with the highest sensitivity (95.7%) and specificity (100%). For patients in the inconclusive EST group, the area under the ROC curve was 0.912 ($p<0.001$). A cut-off value of 85 pg/ml was identified with the highest sensitivity (87.5%) and specificity (86.4%).

Conclusion EST is relatively inaccurate at predicting CAD in patients with inconclusive ESTs. The need for an additional tool, such as NT-proBNP measurements post inconclusive EST is warranted in the determination of the presence of CAD.

Keywords

BNP, NT-ProBNP, exercise stress test, coronary artery disease, angiogrphy.

INTRODUCTION

Coronary artery disease (CAD) is regarded as the most common manifestation of cardiovascular disease (CVD), which is responsible for nearly 17 million deaths per annum accounting to approximately one-third of global mortality [1].

Despite lifestyle modifications, current treatment and surgical options, CVD still remains a major problem. The need for early prevention and detection of CAD, using newer and more cost-effective user friendly tools are suggested [2].

Atheroma and vulnerable plaques are reported to be the primary causes of myocardial infarctions, however, this cannot be detected on cardiac stress tests, which are only capable of detecting medium to high-grade coronary stenosis [3]. Most "vulnerable plaques" are said to cause less than 40% lumen narrowing, a degree of stenosis too small to be detected for most stress tests methods [3]. Clinical trials conducted in the late 1990s have indicated that vulnerable plaques commonly present along various regions of the coronary arteries, and are relatively flat in structure. These plaques have a typical appearance, and usually does not protrude into the arterial lumen, to produce a substantial stenosis (usually less than 50%, average 20% by some IVUS studies) to be adequately detected by current stress testing methods. Based on the facts that current stress testing methods are limited to medium to high-grade stenosis in order to detect the risk of myocardial infarction, stress testing alone is reported as an unreliable approach of detecting CAD [3].

N-Terminal pro brain natriuretic peptide (NT-proBNP) is a cardiac neurohormone that is produced by cardiac myocytes. The main stimulus for peptide synthesis and secretion is myocyte stretch which is caused due to volume expansion and increased filling pressure of the ventricles [4]. NT-proBNP can be measured by immunoassay in human blood [5].

The natriuretic peptides and their receptors are abundantly present in atherosclerotic plaques of human coronary arteries [6], and has been borne out by several smaller clinical studies that have shown increased levels of NT-proBNP during episodes of ischaemia [7]. Consistent with this observation, both BNP and NT-proBNP correlate to severity, location, and extent of angiographic coronary disease [8]. However, it is has not yet been established if BNP levels can be used as a screening tool in identifying significant stenosis during coronary angiography in patients with stable coronary disease [4].

Coronary artery disease is reported to be the most common autopsy finding in cases of sudden cardiac death [9]. It now appears that NT-proBNP is not only an indicator of increased intracardiac pressure but also of ischaemic heart disease. It was first seen

in 1997 when NT-proBNP was found to be more closely related to the presence of CAD than it was to intracardiac pressure, because ischaemic or injured myocardial tissue releases extra BNP irrespective of haemodynamic factors. A previous study demonstrated that *in-vitro* ischaemic tissue expresses increased NT-proBNP [10]. Thus, increased levels of NT-proBNP may result from myocardial ischaemia, irrespective of haemodynamic considerations. This is the reason why myocardial ischaemia per se, can be identified by increased NT-proBNP levels [10]. Measurement of this cardiac biomarker (NT-proBNP) may offer superior potential of detecting silent myocardial ischaemia. In doing so, this may also prevent future possible cardiac events.

The main objective of this study was to determine the post exercise stress test (EST) predictive value of NT-proBNP to assess the presence and severity of coronary artery disease.

METHODS

This study was conducted at St Anne's private hospital in Pietermaritzburg, Kwa-Zulu Natal, South Africa. The study sample consisted of 60 male and female patients with symptoms of coronary artery disease, from all ethnic groups between the ages of 36 to 85 years. The patient sample was then divided into 2 groups: Group A – the control group, consisting of 30 patients, all of which had a positive EST and; Group B – the experimental group, consisting of a further 30 patients, all of which had an inconclusive Exercise Stress Test (EST). All patients recruited into the study were under the consultant care of the cardiologist, who confirmed the inconclusive and positive ESTs.

Only those patients that have met the inclusion criteria with: left ventricular function of >55% as measured by echocardiography, patients having symptoms, such as angina, dyspnoea and palpitations on exertion and/ or rest were selected for the study. Patients' with at least one of the following risk factors; diabetes mellitus, smoking history, obesity, hypertension, high serum cholesterol levels, family history of heart disease and/or elevated low density lipoproteins in the blood, were also taken into consideration.

Patients with abnormal renal function; myocardial infarctions over the past three months; and/or those patients on diuretics were excluded from the study.

Ethical approval was obtained from the Durban University of Technology's Ethics Committee. Written informed consent was also obtained from each patient, prior to the commencement of this study.

All patients were first consulted by the cardiologist, followed by an EST using the QRS Cardio Suite (ENU 4.05) Exercise Treadmill Stress System. The Bruce protocol was the most commonly used protocol in exercise stress testing. However, if a patient was unable to perform the EST due to some sort of debilitation, the Naughton protocol was used [11,12]. The details of the two protocols are illustrated in Table 1 and Table 2.

Patients with positive or inconclusive EST's had their NT-proBNP levels measured 10-20 minutes post peak exercise stress test. Patients with negative EST's were not sampled.

Positive EST was concluded if the patient developed hypotension (when systolic pressure decreases by more than 10 mmHg), ischaemic changes on ECG (more than 2 mm ST segment depression) or severe disabling chest pain [13].

Inconclusive EST was concluded if the patient demonstrated an inadequate heart rate response, chest pain, extreme shortness of breath or fatigue, inadequate exercise duration due to deconditioning, ECG changes that were not diagnostic of ischaemia, unifocal, premature atrial contractions or premature ventricular contractions (fewer than five per minute), right bundle branch block and left bundle branch block during exercise or when interpretation of an ECG with an intraventricular block was difficult due to obscure ischaemic changes [14]. Negative EST was concluded if the patient developed none of the above mentioned findings, was able to exercise for more than 6 minutes without any chest pain or ECG changes suggestive of ischaemia or patient reached the target heart rate [13].

The NT-proBNP levels were measured in the blood serum using the Elecsys proBNP II assay [15]. Studies support a decision threshold of 125 pg/ml for NT-proBNP [16]. A NT-proBNP value of less than 125 pg/ml excludes cardiac dysfunction and heart failure. A NT-proBNP value of greater than 125 pg/ml may indicate cardiac dysfunction and are associated with an increased risk of cardiac complications such as myocardial infarction heart failure and death [5].

All patients selected for the study were referred to for a coronary angiogram to assess the presence and severity of CAD. The procedure was performed by the cardiologist and the principle investigator, in the cardiac catheterization laboratory. The duration of the procedure lasted about 30 minutes.

The results of the coronary angiogram were then compared to the NT-proBNP levels in order to assess the strength of the correlations.

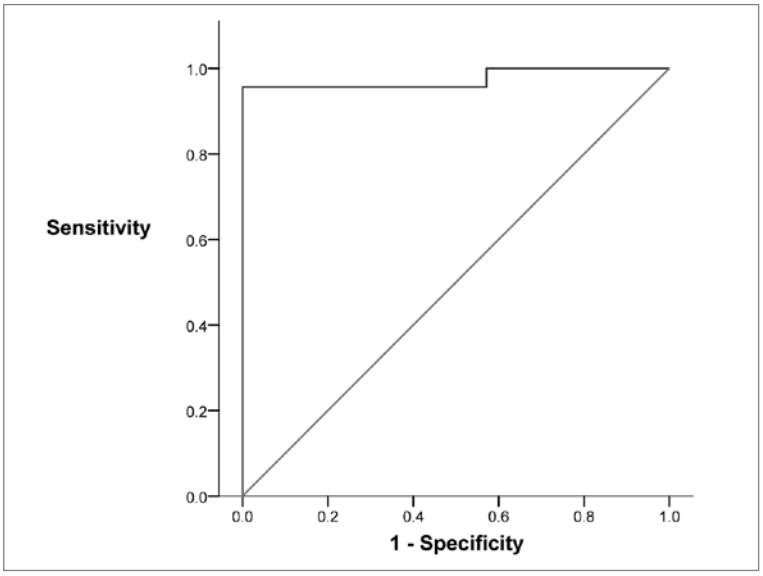
SPSS version 15.0 (SPSS Inc., Chicago, Illinois) was used to analyse the data. A p value of <0.05 was considered as statistically

Table 1: Bruce Protocol [13]

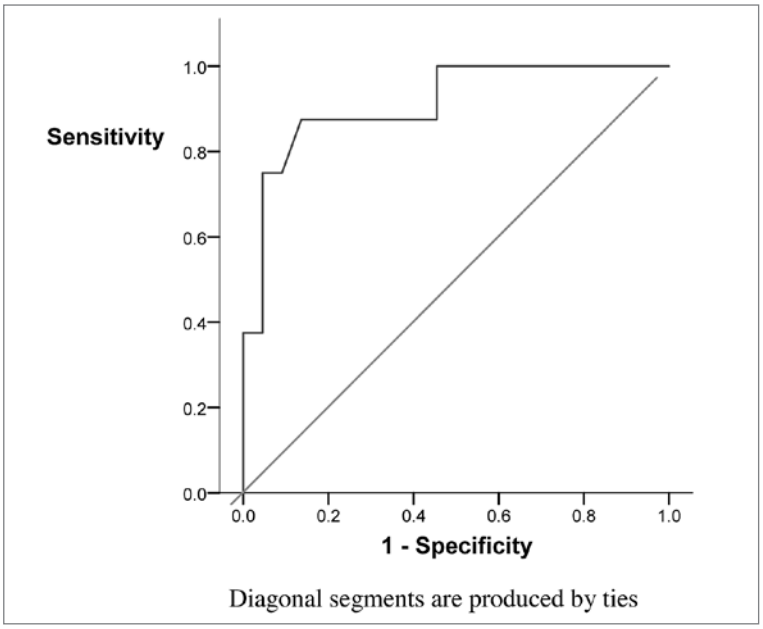
Stage	Speed (km/hr)	Speed (mph)	Gradient %
1	2.74	1.7	10
2	4.02	2.5	12
3	5.47	3.4	14
4	6.76	4.2	16
5	8.05	5.0	18
6	8.85	5.5	20
7	9.65	6.0	22
8	10.46	6.5	24
9	11.26	7.0	26
10	12.07	7.5	28

Table 2: Naughton Protocol [13]

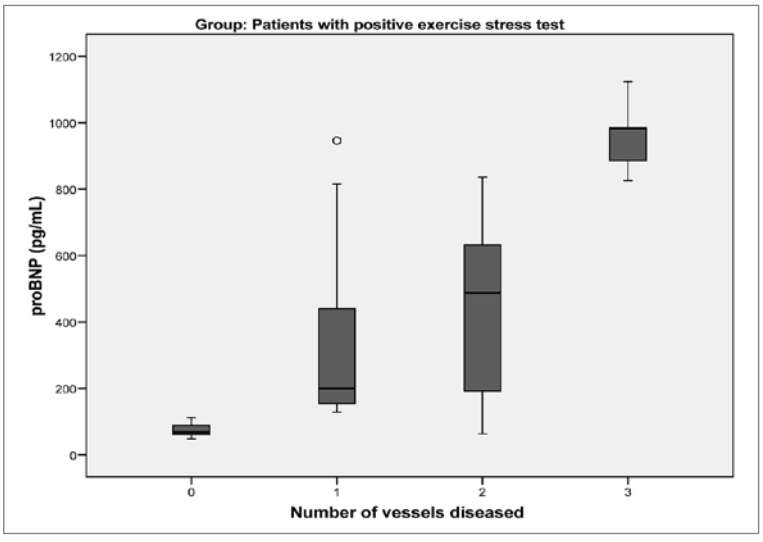
Stage	Speed (mph)	Gradient %
1	1.2	10
2	1.5	12
3	1.5	14
4	1.5	16
5	1.5	18
6	2.0	20



Graph 1: ROC curve for NT-proBNP vs. CAD in patients with a positive EST.



Graph 2 : ROC curve for NT-proBNP vs. CAD in patients with an inconclusive EST.



Graph 3: Boxplot of NT-proBNP levels by number of diseased vessels in positive EST group.

significant. In order to identify the optimum cut-off point of NT-proBNP to indicate the presence of CAD (one or more vessels involved), receiver operator curves (ROC) were constructed in each group separately. The area under the curve was computed and tested for significance. A non parametric distribution was assumed. Cut-off points were decided, by examining the sensitivity and specificity of each value in the results and choosing a value which optimised these parameters.

RESULTS

Thirty patients comprised the group of positive EST (Group A) and thirty in the group of inconclusive EST (Group B). In each group there were fifteen males and fifteen females with age-group ranging from 36 to 85 years old. There was, however, a significant difference in mean age between the two groups (p=0.004). The mean age of the positive EST group was higher than that of the inconclusive group.

The composition of patients in Group A, were predominantly White (43.3%) followed by Indian (26.7%), Coloured (16.7%) and Black (13.3%). Similarly in Group B there were predominantly Indian (43.3%) followed by White (36.7%), Coloured (10%) and Black (10%). All patients presented with at least one of the cardiac risk factors.

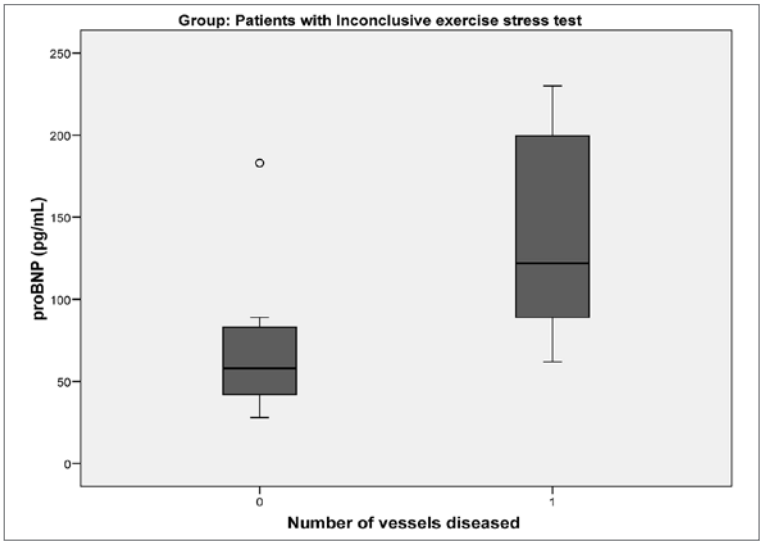
There was no significant difference between the two groups in terms of ethnicity (p=0.572). However, there were more Whites in the positive EST group and more Indians in the inconclusive EST group. Therefore, correlations could not be done among ethnic groups due the small sample size which was also a limiting factor.

In patients with a positive EST, the area under the curve was 0.975 (p<0.001), which was an indication that NT-proBNP was fairly accurate in the predicting the presence of CAD. The cut-off value of 120 pg/ml was identified with the highest sensitivity (95.7%) and specificity (100%) (Graph 1).

In patients with inconclusive EST, the area under the curve was 0.912 (p<0.001), which was also an indication that NT-proBNP could also predict the presence of CAD. The cut-off value of 85 pg/ml was identified with the highest sensitivity (87.5%) and specificity (86.4%) (Graph 2).

The median NT-proBNP level was compared between the groups with different numbers of diseased vessels using Kruskal-Wallis tests. In patients with a positive EST, the median NT-proBNP value showed an increase as the number of diseased vessels increased (p<0.001). Refer to the trend as shown on Graph 3.

Patients with an inconclusive EST presented with either 0 or 1 diseased vessel. Predictably, the median NT-proBNP value was higher in those with one vessel diseased, as compared to those with none (p=0.001). Graph 4 shows this trend graphically. There was also



Graph 4: Boxplot of NT- proBNP levels by number of diseased vessels in inconclusive EST group.

a highly significant difference in median NT-proBNP between the groups (p<0.001).

There was a significant difference between the median NT-proBNP values for males and females with positive EST (p=0.048). The values of males were higher than females in this group. There was however, no significant difference between the genders in the group with an inconclusive EST.

In patients with a positive EST a cut-off of 120 pg/ml (identified with the highest sensitivity and specificity in Graph 1) was used to determine the presence or absence of CAD, and showed zero false positive NT-proBNP values. These results suggest the probability of a low false positive elevated NT-proBNP values in the presence of CAD. Therefore the sensitivity of NT-proBNP was 95.7% and the specificity was 100%. The probability of false negative NT-proBNP value is 12.5% (1/8 at a value of 120 pg/ml in the presence of CAD).

In patients with an inconclusive EST a cut-off of 85 pg/ml (identified with the highest sensitivity and specificity in Graph 2) was used to determine the presence or absence of CAD, and showed 3 false positive NT-proBNP values. These results suggest that the probability of false positive elevated NT-proBNP values in the presence of CAD to be 30%. Therefore the sensitivity of NT-proBNP was 87.5% and the specificity was 86.4%. The probability of a false negative NT-proBNP value is 5% (1/20 at a value of 85 pg/ml in the presence of CAD).

DISCUSSION

In this study, 60 patients underwent coronary angiography to determine the presence of CAD. Of the sixty patients, 74.2% in the positive EST group and 25.8% in the inconclusive EST group had CAD.

Brain natriuretic peptide is currently being used as a marker of left ventricular dysfunction. In addition to popular belief that the main pathophysiological process underlying increased BNP and NT-pro-BNP levels, is not only as a result of increased left ventricular wall stress, but also as a direct result of cardiac ischaemia [3]. This was demonstrated in the present study by the relationship between NT-proBNP and the presence of CAD using Kruskal-Wallis tests. In patients with a positive EST, the median NT-proBNP value increased significantly as the number of diseased vessels increased (p<0.001). This increase is shown graphically in Graph 3. In patients with an inconclusive EST, there were only patients with either 0 or single vessel disease. Predictably, the median NT-proBNP value was significantly higher (p=0.001) in those with single vessel disease compared to those with none. This increase is shown graphically in Graph 4. The positive EST group had a significantly higher median NT-proBNP level than the inconclusive EST group (p<0.001) as well as a significantly higher number of diseased vessels. This suggests that NT-proBNP levels will increase in the presence of CAD.

The main objective of the study was assessed by constructing a receiver operator curve (ROC) to assess the ability of NT-pro-BNP to detect the presence and severity of coronary artery disease. This analysis was done separately for the two groups of participants (Group A and B). This is because we hypothesized that the cut-off points found in the two groups were very different, indicating that separate cut-off points should be used in the clinical situation depending on whether the patient has a positive or inconclusive stress test. For the positive EST group, the area under the curve was 0.975 and was statistically significantly different from the null hypothesis value of 0.5 (p<0.001) (Graph 1), indicating that NT-proBNP could very accurately predict the presence of CAD. The cut-off value of 120 pg/ml was identified with the highest sensitivity (95.7%) and specificity (100%).

For patients in the inconclusive EST group, the area under the curve was 0.912 and was statistically regarded as highly significantly different from the null hypothesis value of 0.5 (p<0.001) (Graph 2), indicating that NT-proBNP could very accurately predict the presence of CAD. The cut-off of 85 pg/ml was identified with the highest sensitivity (87.5%) and specificity (86.4%) (Graph 2).

In a similar study, NT-proBNP levels were measured in 781 consecutive patients with normal left ventricular function referred for coronary angiography owing to symptoms or signs of CAD. Results showed that elevated NT-proBNP levels were significantly associated with the extent of CAD and with the female

gender. The ability of NT-proBNP to predict significant coronary disease at angiography was assessed separately for males using a cut-off point of 85 pg/ml and 165pg/l for females. The area under the receiver operating characteristic (ROC) curve was 0.72 for males and 0.71 for females [17]. In the present study no adjustments were made for age and gender as there was no significant difference between age and gender in both EST groups. Instead, ROC curves were constructed for each group separately since this study is mainly concerned with the large number of inconclusive ESTs produced in this practice.

Another study assessed the relationship between NT-pro-BNP and the extent of ischaemia on stress myocardial perfusion imaging in stable patients with a normal left ventricular ejection fraction. The study suggested that the post-stress increase in NT-pro-BNP is related to myocardial ischemia and accurately predicts the presence or absence of myocardial perfusion defects. It further established an optimal NT-proBNP cut-off value of 214 pg/ml for predicting CAD [18]. Our study differs considerably as the cut-off value for the positive EST group was 120pg/ml and 85pg/ml for the inconclusive group.

Other causes of increased NT-proBNP levels are; abnormal renal function, emphysema or chronic obstructive pulmonary disease (COPD). Increased levels of proBNP have also been observed in patients on diuretics, patients with atrial fibrillation, congestive heart failure and patients who had a recent MI [19]. However, all these patients were excluded from this study. The probability of a false negative NT-proBNP value was 12.5% (1/8 at a value of 120 pg/ml in the presence of CAD).

A cut-off value of 85 pg/ml was used to determine the presence or absence of CAD, and showed 3 false positive NT-proBNP values in the inconclusive EST group. These results suggest that the probability of having false positive elevated NT-proBNP values in the presence of CAD is 30%. Therefore, the sensitivity of NT-proBNP was 87.5% and the specificity was 86.4%. The probability of a false negative NT-proBNP value is 5% (1/20 at a value of 85 pg/ml in the presence of CAD).

The probability of a false positive result for EST (i.e. positive EST but no CAD) was 24.1% . The probability of a false negative result (i.e. inconclusive EST but presence of CAD) was 25.8%. The positive EST was therefore, relatively accurate at predicting CAD. However, only 25.8% of patients with an inconclusive EST had CAD, suggesting that 75.9% of patients with an inconclusive EST had to undergo coronary angiography, unnecessarily. Exercise stress testing in this regard, is therefore useful in providing additional information in the prediction of CAD, in patients with inconclusive ESTs.

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