Utility of N terminal pro brain natriuretic peptide in elderly patients

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ORIGINAL ARTICLE

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Objective: To evaluate the utility of N terminal pro brain natriuretic peptide (NT-proBNP) as a diagnostic marker for diastolic dysfunction or failure, systolic dysfunction, and significant valve disorders in patients over 75 years.
Design: Cohort study.
Setting: Outpatient echocardiography service in a district general hospital.
Participants: 100 consecutive patients.
Main outcome measures: Sensitivity, specificity, positive predictive values, negative predictive values, and area under receiver operating characteristic curve for NT-proBNP assay in the diagnosis of left ventricular diastolic dysfunction or failure, systolic dysfunction, and significant valve disorders.
Results: For diagnosis of systolic dysfunction NT-proBNP level of 424 pg/ml had a sensitivity of 96%, specificity of 45%, positive predictive value of 36%, and negative predictive value of 96%. The area under the curve was 0.71 (95% confidence intervals: 0.69 to 0.89). In valve heart disease, level of 227 pg/ml had sensitivity of 91%, specificity of 43%, positive predictive value of 40%, and negative predictive value of 92%. Patients with diastolic dysfunction/failure had lower plasma concentrations.
Conclusions: This study showed that NT-proBNP had excellent negative predictive value for systolic dysfunction and significant valve disorders in very elderly patients. It increased significantly in systolic dysfunction, valve heart disease, and atrial fibrillation. NT-proBNP is not useful in the diagnosis of diastolic dysfunction or diastolic heart failure using standard echocardiography criteria.

Heart failure is a clinical syndrome most commonly encountered in the very elderly,[1] but this group is least represented in clinical trials.

Heart failure could result from systolic or diastolic dysfunction. Diastolic dysfunction is defined as an abnormality of diastolic distensibility, filling, or relaxation of the left ventricle. At least one third of all patients with congestive cardiac failure have a normal or near normal ejection fraction but in over 75 years of age this may be up to three quarters of all patients.

Clinical diagnosis of heart failure is unreliable. Echocardiogram is used as the diagnostic gold standard but its availability is limited. N terminal pro brain natriuretic peptide (NT-proBNP) is emerging as a diagnostic tool in the diagnosis of heart failure. It increases with ventricular volume expansion and pressure overload. It is raised in several cardiac conditions but most studies have focused predominantly on systolic dysfunction in comparatively young patients.[2–4]

Controversies surround the diagnosis of diastolic dysfunction. Left ventricular (LV) diastolic parameters change with ageing and the echocardiographic diagnosis of diastolic dysfunction becomes complex. Hence it is imperative to determine the diagnostic role of NT-proBNP in diastolic dysfunction/failure in the elderly. However, there is only limited information regarding its use in patients over 75 years.

The aim of this study was to evaluate the utility of NT-proBNP as a diagnostic marker for diastolic dysfunction or failure, systolic dysfunction, and significant valve disorders in patients over 75 years of age.

METHODS

The study was approved by the local ethics committee. A sample of 104 consecutive patients referred for echocardiography were invited to participate. All patients had a clinical diagnosis of either cardiac failure or valve heart disease by a general practitioner or a hospital physician. Exclusion criteria included patients who could not give consent or declined to participate in the study. Information on cardiac symptoms, medical history, and drug treatment were obtained. Signs for cardiac failure were recorded. Electrocardiogram and poster-oanterior chest radiography were performed. Echocardiogram including M-mode, 2D imaging, spectral, and colour flow Doppler was performed by a single clinician or by a senior echo technician. Echocardiograms performed by the echo technician were reviewed by the same clinician. LV systolic and diastolic volumes and ejection fraction were derived from standard and modified Simpson's method. Regional wall motion abnormalities were recorded. Left atrial (LA) and LV dimensions were measured from M-mode images according to standard criteria. Transmitral pulsed Doppler velocity recordings from three consecutive cardiac cycles were used to derive measurements as follows: E and A velocities were the peak values reached in early diastole and after atrial contraction respectively. If the E/A ratio was normal, valsalva manoeuvre was performed to look for pseudonormal pattern. Deceleration time (DT) was the interval from the E wave peak to the decline of the velocity to baseline. If there was no return to baseline, extrapolation of the deceleration signal was performed. Maximum pulmonary venous systolic (S) and diastolic (D) flow velocities were obtained. Finally the isovolumetric relaxation time (IVRT), the time in milliseconds from the end of ejection to the onset of LV filling, was obtained. In patients with AF, DT, IVRT, S and D flow velocities were obtained and the average of the three readings were considered.

Abbreviations: NT-proBNP, N terminal pro brain natriuretic peptide; AUC, area under curve; LV, left ventricular; LA, left atrial; DT, deceleration time; IVRT, isovolumetric relaxation time; ROC, receiver operating characteristic curve

Table 1 Characteristics of all patients

Demographic data:	
Sex	
Male/female (n)	40/60
Age (y)	
Mean	82.4
Range	75–94
Symptoms and signs (%)	
Shortness of breath	77
Paroxysmal nocturnal dyspnoea	6
Orthopnoea	21
Pedal oedema	58
Raised JVP	16
Lung crepitations	34
Comorbidity (%)	
Hypertension	35
Diabetes mellitus	10
Ischaemic heart disease	38
Atrial fibrillation	35
Drug treatment (%)	
Loop and thiazide diuretics	58
β blockers	33
ACE inhibitors/angiotensin II blockers	42
Spironolactone	4
Digoxin	22
Echocardiographic diagnosis (n)	
Systolic dysfunction	25
Diastolic dysfunction*	26
Diastolic dysfunction with LAE and LVH*	8
Diastolic failure*	13
Valve heart disease*	22

*In the absence of systolic dysfunction.

Systolic dysfunction was defined as left ventricular ejection fraction (LVEF) <50%. Diastolic dysfunction was defined as normal LVEF >50% and evidence of abnormal left ventricular relaxation (IVRT >105 ms) and/or slow early left ventricular filling (E/A ratio<0.5 and DT>280 ms) and/or S/D>2.5. Diastolic heart failure was defined as the presence of symptoms and signs of congestive cardiac failure and diastolic dysfunction on echocardiogram. Patients were categorised as having significant valve disease if there was evidence of valve stenosis or more than mild regurgitation.

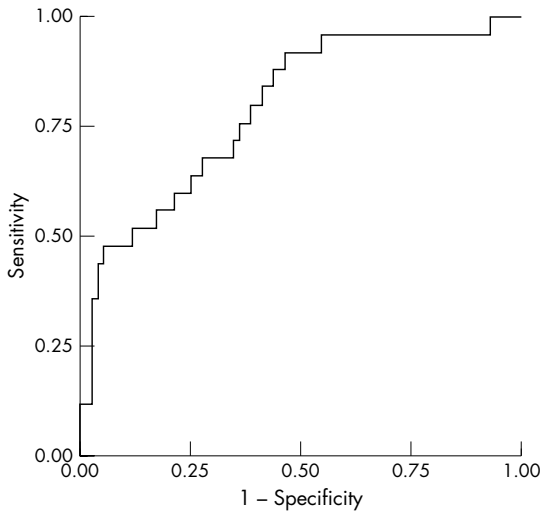
Plasma concentration of NT-proBNP was measured (Roche Diagnostics) after echocardiography. This assay has a wide range, is free from common interferences, is stable at room temperature, and does not cross react with BNP. The test is fully automated and accommodates testing of large numbers of samples.[5]

Statistical analysis

The usefulness of the NT-proBNP in various groups was assessed by plotting receiver operating characteristic curves (ROC) with sensitivity on the y axis and 1−specificity on the x axis for various cut off values. The characteristics of the ROC curves were used to determine cut off points for NT-proBNP permitting examination of the sensitivity, specificity, negative, and positive predictive values of NT-proBNP in each case. ROC curves were used to examine the diagnostic utility of NT-proBNP for several conditions including systolic dysfunction, diastolic dysfunction, diastolic dysfunction with LA enlargement, and left ventricular hypertrophy (LVH), diastolic failure, significant valve heart disease, and atrial fibrillation. NT-proBNP values were compared for each group with and without the respective diagnosis. As the distribution of NT-proBNP values was highly positively skewed, they were log transformed and the geometric mean with 95% confidence intervals was reported. Similarly comparisons between groups using *t* tests were conducted on the log transformed values of NT-proBNP.

Table 2 Characteristic NT-proBNP (pg/ml) concentrations for patients with and without systolic dysfunction

Systolic dysfunction	Yes	No
Number	25	75
Geometric mean	3227.8	507.6
95% CI	1642.1 to 6344.5	335.0 to 749.2



NT proBNP cut off (pg/ml)	Sensitivity	Specificity	PPV	NPV
424	96	45	36	97
1226	68	68	41	86
1689	60	76	45	85
6180	44	96	79	84

Figure 1 The predictive utility of NT-proBNP for systolic dysfunction evaluated using an ROC analysis comparing sensitivity to specificity (above). Below the curve sensitivity, specificity, positive, and negative predictive value (PPV and NPV) of NT-proBNP (pg/ml) at four cut off values.

NT-proBNP values are known to be raised in patients with systolic failure and with valve heart disease.[6 7] Hence to evaluate the utility of NT-proBNP in diastolic dysfunction and diastolic failure, patients with systolic dysfunction and valve heart disease were excluded from analysis. Thereafter, patients were divided into groups with either (a) presence or absence of diastolic dysfunction (b) presence or absence of diastolic failure (c) presence or absence of diastolic dysfunction with LA enlargement and LVH. To evaluate patients with valve heart disease, patients with systolic dysfunction were excluded and the remaining patients were categorised into those with and without significant valve heart disease.

RESULTS

In total 100 patients were included in the study and their characteristics are shown in table 1. Four patients were excluded in line with the exclusion criteria.

Systolic dysfunction

Table 2 gives the NT-proBNP for the groups of patients with and without systolic dysfunction. The geometric mean for the

Table 3 Characteristic NT-proBNP (pg/ml) concentrations for patients with and without diastolic dysfunction diastolic dysfunction with LA enlargement and LVH, and diastolic failure

	Diastolic dysfunction		Diastolic dysfunction and LAE and LVH		Diastolic failure	
	Yes	No	Yes	No	Yes	No
Number	26	27	8	45	13	40
Geometric mean	193.2	636.1	190.7	395.9	244.6	399.5
95% CI	115.0 to 324.6	294.3 to 1374.4	105.0 to 346.4	226.7 to 691.2	129.7 to 461.2	216.6 to 736.7

group with systolic dysfunction was higher and the difference was significant (t (98) = 4.8, p<0.001).

The diagnostic utility of NT-proBNP for systolic dysfunction was evaluated using an ROC analysis (fig 1). The AUC was 0.71 (95% confidence limits from 0.69 to 0.89). The sensitivity, specificity, positive, and negative predictive values at four cut off levels for NT-proBNP are also shown.

Diastolic dysfunction

Table 3 compares the geometric mean values of NT-proBNP (pg/ml) for patients with and without diastolic dysfunction, diastolic dysfunction with LA enlargement (LAE) and LVH, and diastolic failure. The group diagnosed with diastolic dysfunction had lower plasma NT-proBNP than the group without diastolic dysfunction. The difference between the two groups was significant (t (51) = 2.6, p = 0.01). Despite the stricter diagnostic criterion in the other categories patients without abnormal heart function had high NT-proBNP (pg/ml) and hence the ROC analyses for these diagnostic groups were not presented.

Atrial fibrillation

After excluding patients with systolic dysfunction, patients with atrial fibrillation showed higher concentrations of NT-proBNP (pg/ml) (t (51) = 3.2, p = 0.01) (table 4).

Valve heart disease

After excluding patients with systolic dysfunction, patients with significant valve heart disease showed higher concentrations of NT-proBNP (pg/ml) and the difference was significant (t (73) = 3.0, p = 0.004) (table 5).

The sensitivity, specificity, positive, and negative predictive values at three cut off levels for NT-proBNP are also shown (table 6).

In the case of left ventricular hypertrophy, the difference in NT-pro BNP for those with and without LVH was not significant (t (41)<1).

The expected 97.5 centile values quoted by manufacturers of the assay for subjects aged between 50 and 65 years are <334 pg/ml for women and <227 pg/ml for men. NT pro BNP and BNP are known to increase with age but normal values are yet to be determined. Extrapolating the values to the over 75 age group, only 18 of 60 women and 10 of 40 men had values less than 334 and 227 respectively. Of 28 patients, one had evidence of systolic dysfunction, two had significant valve disorders. McDonagh *et al*[8] has quoted 123 pg/ml and 67 pg/ml as 95th centile values for this age group in normal women and men respectively. Eleven women and four men had values less these values; of 15, one had systolic dysfunction and none had significant valve disorder.

DISCUSSION

This study investigated the utility of NT-proBNP in a cohort of very elderly patients with suspected cardiac disorders referred for echocardiography. Hence, NT-proBNP values were generally high.

The results reinforced the usefulness of NT-proBNP in patients with systolic dysfunction. Utility of NT-proBNP in the diagnosis of systolic heart failure is well established in community based studies. This study confirms its negative predictive value in systolic dysfunction in secondary care setting in the very elderly. Although values of NT-proBNP were significantly higher in the systolic dysfunction group, many subjects without systolic dysfunction had high NT-proBNP thus reducing its specificity.

In our study, NT-proBNP values were significantly lower in patients with diastolic dysfunction and diastolic failure when compared with patients without these disorders. Our results are similar to the results obtained by Dahlstrom *et al* in their study of diastolic heart failure or dysfunction in the elderly.[9] Besides the hypothesis postulated by Dahlstorm *et al*, this finding may also be attributable to the pitfalls in the diagnostic criteria for diastolic dysfunction/failure in the elderly that remains controversial. The European Study Group on diastolic heart failure requires signs or symptoms of congestive cardiac failure, normal or only mildly reduced left ventricular systolic function and abnormal left ventricular relaxation, filling, and diastolic stiffness.[10] A single set of values are applied to subjects aged 50 and above. However, diastolic parameters change with increasing age[11 12] and in the very elderly, precise parameters required to make the diagnosis remains unclear. A single set of values for over 50 years of age may not differentiate abnormal dysfunction from normal ageing.

Obtaining high quality Doppler signals are difficult in the elderly,[13] which makes it even more difficult to diagnose diastolic dysfunction in this group. It has been suggested that there is no concordance in diastolic parameters used in the diagnosis of diastolic dysfunction.[14] Presence of atrial fibrillation makes these parameters even less reliable and

Table 4 Characteristic NT-proBNP concentrations for patients with and without atrial fibrillation in the absence of systolic dysfunction and valve heart disease

Atrial fibrillation	Yes	No
Number	13	40
Geometric mean	1242.5	239.5
95% CI	481.7 to 3434.8	142.2 to 391.2

Table 5 Characteristic NT-proBNP concentrations for patients with and without valve heart disease in the absence of systolic dysfunction

Valve heart disease	Yes	No
Number	22	53
Geometric mean	1205.0	354.6
95% CI	709.9 to 2045.5	219.1 to 573.9

Table 6 Sensitivity, specificity, and predictive values in valve heart disease for different cut off values of NT-proBNP

NTproBNP cut off (pg/ml)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
227	91	43	40	92
334	91	53	44	93
424	82	55	43	88

hence highlighting the difficulties in interpreting abnormal diastolic values in the elderly. Hence our findings need to be interpreted in the context of pitfalls in the diagnosis of diastolic dysfunction.

Our study has proved that NT-proBNP can be used reliably to exclude significant valve heart disease with negative predictive values exceeding 90%. Noticeably 28% of patients referred for echocardiography had normal NT-proBNP values with good negative predictive values for systolic dysfunction and significant valve disorders. This has significant implications for service provision. This may have a role in rationalising the utility of echocardiography in secondary care. Confronted with a normal NT proBNP, it is down to the clinician to weigh the clinical suspicion and the high negative predictive value while requesting an echocardiogram. In patients with increased NT-proBNP, raised levels are non-specific and the need for further investigations such as an echocardiogram will not be significantly reduced.

There are limitations in this study, including its small sample size and the small number of patients in each cohort, which made it difficult to further categorise diastolic dysfunction. The concentrations of NT proBNP in this study could have been influenced by renal and thyroid function and heart rate that were not analysed and correlated as there is emerging evidence that values of natriuretic peptides are affected by these variables.

Key points

- NT-proBNP is a reliable test in ruling out systolic dysfunction and significant valve disorder in patients aged 75 and over.
- NT-proBNP is not useful in the diagnosis of diastolic dysfunction or failure in patients aged 75 and above using standard echocardiographic criteria.

CONCLUSIONS

This study showed that NT-proBNP has excellent negative predictive value for systolic dysfunction and significant valve disorders in very elderly patients. It increases significantly in systolic dysfunction, significant valve heart disease and atrial fibrillation in patients aged 75 years and over. NT-proBNP is not useful in the diagnosis of diastolic dysfunction or diastolic failure using standard echocardiography criteria.

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CONTRIBUTORS

RS, KP, ML, PG, and SAK contributed to the design of the study and the writing of manuscript and DW contributed to the statistical aspects.

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Conflicts of interest: none declared.

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