SHORT REPORT

NT-proBNP and the diagnosis of left ventricular systolic dysfunction within two acute NHS trust catchment areas: the initial Teesside experience

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Purpose: To evaluate the predictive value of N-terminal pro B-type natriuretic peptide (NT-proBNP) reference cut-off values as diagnostic markers for left ventricular systolic dysfunction (LVSD).

Study design: A retrospective study assessing the use of NT-proBNP in the diagnostic algorithm for the investigation of patients with suspected signs and symptoms of LVSD presenting to primary care.

Results: A generic NT-proBNP cut-off (150 ng/l) value has similar negative and positive predictive values, specificity and sensitivity compared to age and sex specific cut-off values.

Conclusion: When using NT-proBNP as a triage tool for screening patients with signs and symptoms suggestive of LVSD, a simple generic cut-off level is as effective as more complex age sex specific cut-off values.

Left ventricular systolic dysfunction (LVSD) is a common condition that is expensive to treat, has high morbidity and mortality rates, can be difficult to diagnose clinically and has a 5 year survival rate equivalent to many malignancies.¹ The diagnosis relies on a collection of non-specific clinical symptoms and signs supported by objective evidence of systolic dysfunction.² Within the primary care setting, obesity and respiratory disease are common co-morbidities whose non-specific features are intermingled with those of LVSD, making the diagnosis difficult and inaccurate in many patients. Correct diagnosis is vital if evidence based, disease modifying interventions are to be used effectively.^{2–4}

A paradox exists. Within the NHS there are significant financial incentives for the rapid investigation of suspected malignancy in patients who often have minimal, albeit red-flag, symptoms. In contrast, patients with suspected LVSD are often highly symptomatic, but rapid access to echocardiography remains limited. A chest x ray and a 12 lead electrocardiogram (ECG) are important initial investigations and should be routinely performed in all patients. A normal 12 lead ECG makes significant LVSD unlikely, but minor non-specific abnormalities make this a less useful diagnostic investigation in routine primary care practice.⁵ Within primary care, the use of a blood test to help pre-screen those patients who require referral for further assessment is therefore an attractive proposition. The introduction of the natriuretic peptides, BNP and N-terminal pro B-type natriuretic peptide (NT-proBNP) into clinical practice offers such an opportunity.⁶

METHODS

The aim of this study was to evaluate the predictive value of NT-proBNP reference cut-off values as diagnostic markers for LVSD within two acute NHS trust populations based within the North East of England with a total population of approximately

0.5 million. We undertook a retrospective study assessing our initial 12 month experience of using NT-proBNP in the diagnostic algorithm for the investigation of patients with suspected signs and symptoms of LVSD.

Local guidelines, based on the European Society of Cardiology guidelines for the diagnosis and treatment of chronic heart failure,² recommended referral to secondary care heart failure services if NT-proBNP is ≥ 150 ng/l. Assays of NT-proBNP (Elecys assay system; Roche, Basel, Switzerland) were performed in two central laboratories. Statistical analysis was performed using SPSS version 13. We assessed the diagnostic performance of the NT-proBNP assay by using sensitivity/specificity methods.

Transthoracic echocardiography was performed according to the criteria of the British Society of Echocardiography and a qualitative assessment of overall left ventricular systolic function made.⁷

RESULTS

Two patient cohorts were identified, one from University Hospital North Tees (UHNT) and one from The James Cook University Hospital (JCUH), South Tees. All patients had been initially seen within primary care and judged to have clinical symptoms and signs suggestive of LVSD by the referring general practitioner (GP). The decision to refer for further investigation was at the sole discretion of the GP and only those patients who were referred were investigated further.

A total of 326 patients were identified in the UHNT cohort and 1054 in the JCUH cohort. Results are summarised in tables 1 and 2.

For the JCUH cohort all echocardiograms were stored on a digital on-line database. All the echocardiograms performed on the JCUH patients were retrospectively reviewed for evidence of any cardiac abnormality. Of those patients with an elevated NT-proBNP, 328/492 had normal LV systolic function and of these 252/328 (77%) had other significant echocardiographic

Table 1 Combined crude NT-proBNP results for screening for LVSD in a local population

NT-proBNP	LVSD		
	Positive	Negative	Total
Positive	202	742	944
Negative	48	434	482
Total	250	1176	1426

A NT-proBNP result ≥ 150 ng/l was deemed positive.

Abbreviations: ECG, electrocardiogram; GP, general practitioner; JCUH, The James Cook University Hospital; LVSD, left ventricular systolic dysfunction; NT-proBNP, N-terminal pro B-type natriuretic peptide; UHNT, University Hospital North Tees

Table 2 NT-proBNP results for screening for LVSD in a local population using different cut-off values

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Generic cut-off level: 150 ng/l				
JCUH (n = 1094)	0.94 (0.89–0.96)	0.37 (0.34–0.4)	0.22 (0.19–0.25)	0.97 (0.94–0.98)
UHNT (n = 332)	0.95 (0.84–0.99)	0.45 (0.39–0.5)	0.2 (0.15–0.26)	0.98 (0.95–1.00)
Combined	0.94 (0.9–0.96)	0.39 (0.36–0.42)	0.22 (0.19–0.24)	0.97 (0.95–0.98)
Age and sex specific cut-off levels*				
JCUH (n = 1094)	0.93 (0.87–0.96)	0.36 (0.33–0.39)	0.19 (0.16–0.22)	0.97 (0.94–0.98)
UHNT (n = 332)	0.96 (0.92–0.98)	0.65 (0.58–0.72)	0.67 (0.6–0.73)	0.96 (0.91–0.98)
Combined	0.94 (0.91–0.97)	0.41 (0.38–0.44)	0.29 (0.26–0.32)	0.97 (0.95–0.98)

*Cut-off values used⁸: males aged <60 years, NT-proBNP 100 pg/ml; males aged ≥60 years, NT-proBNP 172 pg/ml; females aged <60 years, NT-proBNP 164 pg/ml; females aged ≥60 years, NT-proBNP 225 pg/ml.

abnormalities. These included left ventricular hypertrophy (LVH) in 152/328 (46%), aortic stenosis in 19/328 (6%), aortic regurgitation in 48/328 (15%), mitral stenosis in 11/328 (3%), mitral regurgitation in 104/328 (32%) and tricuspid regurgitation in 80/328 (24%) with significant pulmonary hypertension in 57/328 (17%); 14 patients had a previous valve replacement. A significant pericardial effusion was found in two patients.

CONCLUSION

Importantly, this study was conducted under the same constraints GPs face in everyday clinical practice. As with all tests used for triage and screening purposes, appropriate cut-off levels need to be identified. Some suggest that gender and age specific cut-off values should be adopted as NT-proBNP concentrations are generally higher in females and rise with age.⁸ In our two cohorts, we used our daily clinical generic cut-off value of 150 ng/l (equivalent to 150 pg/ml). In addition, we analysed our data using age and sex specific cut-off levels that previously have been shown to be of use in screening individuals for cardiovascular disease in an unselected UK population aged >45 years.⁸ Re-analysing our data using these recommended specific cut-off values provided no additional benefit over our simple generic cut-off level when using NT-proBNP as a triage tool for screening patients with signs and symptoms suggestive of LVSD for further investigation.

The North East of England has a higher than average incidence of coronary artery disease, type II diabetes and hypertension, all aetiological factors in the development of LVSD. As the prevalence of disease varies geographically, cut-off values may need to be determined at a local rather than a national or international level. In our population there was a

high prevalence of LVH, and hypertension with associated LVH is likely to be a common cause for false positive results.⁹

Government policies and national guidelines have led to a national expansion in the provision of services for patients with heart failure.¹⁰ These services are primarily concerned with the identification of patients with LVSD. In this setting, NT-proBNP is a “rule-out” test that should be used to identify those individuals who need further assessment with echocardiography. It is not a diagnostic test, like troponin, since its true value lies in its negative predictive value (if it is not elevated the probability the patient has LVSD is low). If a patient has an NT-proBNP value above the local level for action, then we must ensure that there are systems so that this patient is promptly referred for appropriate detailed assessment and investigation. This includes echocardiography either within secondary care or in specialised community clinics. Anecdotal evidence suggests that this message is still not clear within both primary and secondary care.

The potential use of NT-proBNP extends far wider than just identifying this select group of patients and it has been proposed that we should be using the test to screen populations for cardiovascular disease.⁸ Our data confirm that NT-proBNP is elevated in a wide spectrum of cardiac diseases including LVH, valvular lesions and secondary pulmonary hypertension, highlighting the importance of referring patients with an NT-proBNP level above the locally defined limit for detailed cardiac assessment. In addition to cost effectiveness issues, general principles dictate that if you are to screen for a condition then that condition needs an effective treatment. This holds for

What is already known on the subject

- The diagnosis of left ventricular systolic dysfunction can be clinically difficult and relies on a collection of non-specific clinical symptoms and signs.
- To diagnose left ventricular systolic dysfunction objective evidence of systolic dysfunction is required.
- Echocardiographic investigation is the gold standard for left ventricular systolic dysfunction.
- Rapid access to echocardiography is limited within primary care.
- The neurohormone N-terminal pro B-type natriuretic peptide (NT-proBNP) is predominantly released from the left ventricle in response to increasing wall tension, and is suggested as a useful screening test for suspected left ventricular systolic dysfunction.

What this study adds

- This study was conducted under the same constraints that GPs face in everyday clinical practice and as such represents daily clinical practice.
- NT-proBNP is a “rule-out” test that should be used to identify those individuals who need further assessment with echocardiography.
- The true value of NT-proBNP lies in its negative predictive value.
- Appropriate local cut-off levels for NT-proBNP need to be identified.
- When using NT-proBNP as a triage tool for screening patients with signs and symptoms suggestive of LVSD, a simple generic cut-off level is comparable to age and sex specific cut-off values.
- NT-proBNP is elevated in a wide spectrum of cardiac diseases other than left ventricular systolic dysfunction.

many cardiovascular conditions. However there is no clear evidence that screening asymptomatic individuals for LVSD ultimately improves clinical outcome.

We believe that NT-proBNP is a useful "rule-out" test for the diagnosis of LVSD in the primary care setting whose usefulness and potential cost effectiveness would be further enhanced by setting appropriate local cut-off levels.

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