Aims To examine the value of N-terminal pro-brain natriuretic peptide, abnormal electrocardiogram and other baseline clinical and laboratory variables in identifying patients with left ventricular systolic dysfunction in a high risk population.

Methods and Results We studied 243 patients (129 male, median age 73 years, range 20–94) referred for echocardiography. The relationship between left ventricular wall motion index and log N-terminal pro-brain natriuretic peptide, log creatinine, electrocardiogram, age, history of hypertension, history of ischaemic heart disease, gender, valvular disease and current drug therapy was examined using regression analysis. There was a strong correlation between N-terminal pro-brain natriuretic peptide and left ventricular wall motion index for the whole population (r=0.624, P<0.001) and in those receiving diuretic/angiotensin converting enzyme inhibitor (r=0.661, P<0.005) and in those receiving neither (r=−0.584, P<0.005). On multiple regression analysis, log N-terminal pro-brain natriuretic peptide (P<0.001), age (P=0.015), current diuretic (P=0.002) or angiotensin converting enzyme inhibitor use (P=0.001) and male gender (P=0.026) were independently associated with a low left ventricular wall motion index. Log N-terminal pro-brain natriuretic peptide alone (R²=39%) was a better predictor of left ventricular wall motion index than any other single or combination of factors. Plasma N-terminal pro-brain natriuretic peptide >275 pmol l⁻¹ predicted left ventricular wall motion index ≤ 1.2 with a sensitivity of 93.8%, a specificity of 55% and a negative predictive value of 93%. Left ventricular function was impaired in 18/36 patients with a normal electrocardiogram, in all of whom N-terminal pro-brain natriuretic peptide was >275 fmol ml⁻¹.

Conclusion Of the variables studied, N-terminal pro-brain natriuretic peptide had the strongest correlation with reduced left ventricular wall motion index. The electrocardiogram had a poor predictive value for left ventricular systolic dysfunction in this population. Plasma N-terminal pro-brain natriuretic peptide can usefully predict patients with a reduced left ventricular wall motion index in whom echocardiographic examination may be appropriate.

Introduction Recent years have seen much activity directed towards the search for clinically useful circulating markers of left ventricular systolic dysfunction and heart failure. Plasma levels of a variety of neurohormones such as brain natriuretic peptide, atrial natriuretic peptide and N-terminal pro-atrial natriuretic peptide are raised in patients with both chronic heart failure[1,2] and following acute myocardial infarction[3]. Plasma levels of brain natriuretic peptide-32 may be superior to N-terminal pro-atrial natriuretic peptide in screening for left ventricular systolic dysfunction in the general population[1], in patients with chronic heart failure[4] and following acute myocardial infarction[3]. Assay of brain natriuretic peptide-32 may be as sensitive as echocardiography and superior to clinical examination[5] in this respect. The N-terminal 76 amino acids of prepro-brain natriuretic peptide circulates in plasma in higher concentrations than brain natriuretic peptide-32 in patients with heart failure[6] and in asymptomatic left ventricular systolic dysfunction[7]. Plasma N-terminal prepro-brain natriuretic peptide measured 2–4 days following acute myocardial infarction[3].
myocardial infarction predicts left ventricular function and 2-year survival\[9\]. Thus N-terminal prepro-brain natriuretic peptide may be more useful than brain natriuretic peptide-32 as an indicator of left ventricular systolic dysfunction. However, some studies have failed to show correlation between parameters of left ventricular function and plasma brain natriuretic peptide levels\[9\]. Others have been criticised on the grounds of failing to account for confounding variables which may influence brain natriuretic peptide levels, such as drug therapy and renal impairment\[11\]. Moreover it has been suggested that in survivors of acute myocardial infarction, plasma brain natriuretic peptide cannot discriminate between mild or moderate impairment of left ventricular systolic dysfunction, and preserved ventricular systolic dysfunction on the one hand and preserved systolic function on the other\[9\]. It has also been suggested that a normal ECG virtually excludes left ventricular systolic dysfunction. Other studies have suggested that in survivors of acute myocardial infarction, an abnormal ECG may identify patients with suspected left ventricular systolic dysfunction in whom echocardiography is indicated. A number of studies have suggested that a normal ECG virtually excludes left ventricular systolic dysfunction\[10,11\]. Other studies have suggested that the ECG may be normal in over 10% of patients with significant left ventricular systolic dysfunction\[12\].

The main aim of the current study was to test the diagnostic usefulness of circulating levels of N-terminal prepro-brain natriuretic peptide and the ECG as indicators of left ventricular systolic dysfunction in an appropriate population, i.e. a cohort of patients referred by primary and secondary care physicians for echocardiography. In addition we examined the relationship between left ventricular systolic function and a number of routinely available clinical and laboratory parameters including those known to influence circulating natriuretic peptides levels in an attempt to define clinically useful predictors of impaired left ventricular systolic function. We assayed N-terminal prepro-brain natriuretic peptide using a sensitive, immuno-luminometric method\[13\].

**Method**

**Subjects**

We studied 249 consecutive subjects referred for echocardiography to the Cardiology Services Department at Leicester Royal Infirmary. Of these, 243 subjects yielded analysable echocardiograms (129 male, median age 73 years, range 20–94). The majority of the subjects (195) were hospital in-patients at the time of the scan. Patients were selected for study if there was (i) clinical suspicion of heart failure (n=125); (ii) history of ischaemic heart disease i.e. history of myocardial infarction, presence of a pathological Q wave on the ECG, physician diagnosed angina or current use of an oral or sublingual nitrate (n=85); (iii) history of hypertension (n=101); (iv) history of shortness of breath in the absence of chronic airways disease (n=132); (v) current diuretic (n=117), angiotensin converting enzyme inhibitor (n=63) or digoxin (n=29) use. Patients were excluded if there was a history of recent (within 1 month) acute myocardial infarction.

The study was approved by the local ethical and research committee and all subjects gave informed consent.

**Echocardiography**

Echocardiography was performed by a single operator (S.T.) using a Hewlett Packard Sonos 1500 imaging system. Left ventricular wall motion index, a regional measurement of left ventricular systolic dysfunction which correlates to left ventricular ejection fraction by radionuclide cardiography and invasive ventriculography\[14,15\] were calculated using a nine-segment model\[16\]. The scale used for left ventricular wall motion index has been validated\[17,18\]. As in previous large studies\[19\] we defined left ventricular systolic dysfunction as left ventricular wall motion index ≤1.2. Left ventricular wall motion index was analysed by a single investigator (S.T.) blind to patient details and N-terminal prepro-brain natriuretic peptide results.

Colour flow Doppler recordings on the parasternal, apical four-chamber and the apical long axis views enabled semi-quantitative assessment of the severity of mitral, tricuspid and aortic regurgitation. Mitral regurgitation was graded as absence=0, trace=1, moderate=2 or severe=3 on colour flow Doppler analysis based on the area of the jet projecting into the left atrium\[20\].

**Immunoluminometric assay for N-terminal prepro-brain natriuretic peptide**

A 10 ml sample of venous blood was collected into pre-chilled EDTA (1.5 mg . ml⁻¹ blood) tubes containing 500 IU . ml⁻¹ of aprotinin within 24 h of the echocardiogram. Samples were immediately centrifuged and separated and plasma stored at −70°C until assayed. The methodology for assay of N-terminal prepro-brain natriuretic peptide has been described previously\[13\]. We used an in-house rabbit, anti-human N-terminal prepro-brain natriuretic peptide polyclonal antibody directed against a C-terminal domain of N-terminal prepro-brain natriuretic peptide (amino acids 65–76). The peptide was labelled using the chemiluminescent label 4-(2-succinimidyl oxycarbonyl-ethyl)phenyl-10-methylacridinium 9-carboxylate fluorosulfonate and assayed on a LB953 luminometer (Berthold, Germany)\[13\]. N-terminal prepro-brain natriuretic peptide levels were determined blind to patient details and echo findings. Each N-terminal prepro-brain natriuretic peptide value represents the mean of duplicate measurements. The assay is specific for N-terminal prepro-brain natriuretic peptide and...
unreactive with atrial natriuretic peptide, brain natriuretic peptide or CNP. Within and between assay coefficients of variation were 3·0 and 11·2% respectively (at 30 fmol . tube⁻¹). The normal range for N-terminal prepro-brain natriuretic peptide in our laboratory is <200 fmol . ml⁻¹.

**Electrocardiogram (ECG)**

Only ECGs performed within 2 weeks of the echocardiogram were analysed and were available for 222/243 (91·3%) of the subjects. Each ECG was categorized as normal, minor abnormality (sinus bradycardia, sinus tachycardia, poor R wave progression, right axis deviation, non-specific ST/T changes, first-degree heart block, or atrial enlargement) or major abnormality (atrial fibrillation, evidence of a past myocardial infarction, voltage criteria for left ventricular hypertrophy, left axis deviation or left bundle branch block).

**Relationship between left ventricular wall motion index and physiological variables**

Concentrations of N-terminal prepro-brain natriuretic peptide, serum creatinine and left ventricular wall motion index were not normally distributed and were log transformed before analysis. For the categorical variables gender (male/female), past history of ischaemic heart disease or hypertension, current use of diuretic, ACE inhibitor, beta-blocker and digoxin, ECG (normal/minor abnormality/major abnormality) and severity of mitral regurgitation (none/mild/moderate/severe), log-left ventricular wall motion index were compared and 95% confidence intervals calculated for the difference in medians between groups for each variable. The strength of association between left ventricular wall motion index and each of the continuous variables log N-terminal prepro-brain natriuretic peptide, age, aortic valve gradient and log creatinine concentration was quantified using the Pearson rank correlation coefficient. Predictive models for the response variable (left ventricular wall motion index) were developed using multiple linear regression analysis and stepwise logistic regression analysis. All statistical analyses were carried out using the software package Minitab (Minitab Inc., PA, U.S.A.). Comparisons with P < 0·05 were considered significant.

Receiver operating characteristic curves were constructed to assess the ability of N-terminal prepro-brain natriuretic peptide throughout the range of concentrations to detect left ventricular systolic dysfunction. The area under the curve, estimated by the method of Hanley and McNeil, provides a measure of the overall diagnostic accuracy of the test.

**Results**

The characteristics of the study population (243 subjects) are shown in Table 1. Ninety-six (39·5%) of the patients had a left ventricular wall motion index ≤1·2. Of these, 64 (66·6%) were taking a diuretic, 43 (44·7%) an ACE inhibitor, 76 (79·1%) gave a history of shortness of breath and 71 (73·9%) had clinical evidence of heart failure. The concentration of N-terminal prepro-brain natriuretic peptide (median range) was higher in subjects with a left ventricular wall motion index ≤1·2 (509·6 fmol . ml⁻¹ [195·2–1619·3]) compared to those with a left ventricular wall motion index ≥1·3 (255·2 fmol . ml⁻¹ [65·5–1175·9] fmol . ml⁻¹, P < 0·0001).

**Determinants of left ventricular wall motion index — Univariate analysis**

On univariate analysis for the whole study population there was a negative correlation between log N-terminal prepro-brain natriuretic peptide and left ventricular wall motion index (r = −0·624, P < 0·001) (Fig. 1). Left ventricular wall motion index also correlated with age (r = −0·15, P = 0·01), serum creatinine (r = −0·29, P < 0·001), past history of ischaemic heart disease (r = −0·29, P < 0·001), male gender (r = 0·23, P < 0·001) and current treatment with a diuretic (r = 0·34, P < 0·001), or ACE inhibitor (r = 0·38, P < 0·001). One hundred and thirty-two (54%) patients were treated with an ACE inhibitor and/or diuretic (48 both, 69 diuretic alone, 15 ACE inhibitor alone). Those treated were older (74 ± 10 years) than those untreated (66 ± 17 years, P < 0·0005). N-terminal prepro-brain natriuretic peptide levels (fmol . ml⁻¹; median, range) were similar in untreated (368, 78–1047) compared to patients receiving either an ACE inhibitor or diuretic (355, 65–1619), an ACE inhibitor alone (382, 84–1619), a diuretic alone (398, 65–1609) or both (332, 124–1293) (P = 0·981, Kruskal–Wallis). Left ventricular wall motion index did not differ among groups (P = 0·941, Kruskal–Wallis). The correlation between log N-terminal prepro-brain natriuretic peptide and left ventricular wall motion index was similar for both treated (r = −0·661, P < 0·005) and untreated (r = −0·584, P < 0·005) patients (Fig. 1).

| Table 1 Patient characteristics |
|-----------------|-----------------|
| Total patients  | 243             |
| Age, median (range) | 73 years (20-94) |
| Male            | 129             |
| History of shortness of breath | 132 |
| History of ischaemic heart disease | 85 |
| History of hypertension | 101 |
| Clinical heart failure | 102 |
| Diuretic use    | 117             |
| ACE inhibitor use | 63             |
| Digoxin use     | 29              |
| Beta-blocker use | 32             |
| Creatinine, median (range) | 106 μmol . l⁻¹ (37–316) |
| Wall motion index, median (range) | 1.6 (0.2–2) |
Multivariate analysis

On multiple regression analysis in the whole population, log N-terminal prepro-brain natriuretic peptide ($P<0.001$), age ($P=0.015$), diuretic use ($P=0.002$), ACE inhibitor use ($P=0.001$) and male gender ($P=0.026$) were independently associated with a low left ventricular wall motion index. Serum creatinine ($P=0.09$) and an abnormal ECG ($P=0.27$) were not predictors of a left ventricular wall motion index in the multivariate model. Using best subsets analysis, log N-terminal prepro-brain natriuretic peptide alone ($R^2=39\%$) was a better predictor of left ventricular wall motion index than any other single factor (ACE inhibitor $R^2=15\%$; mitral regurgitation $R^2=15\%$; diuretic $R^2=12\%$). The predictive value of the model was improved slightly by consideration of combinations of variables, all of which included log N-terminal prepro-brain natriuretic peptide: log N-terminal prepro-brain natriuretic peptide + ACE inhibitor $R^2=44\%$; log N-terminal prepro-brain natriuretic peptide + ACE inhibitor + male gender $R^2=47\%$; log N-terminal prepro-brain natriuretic peptide + ACE inhibitor + male gender + diuretic $R^2=48\%$.

Independent predictors of left ventricular wall motion index in patients treated with ACE inhibitor and/or diuretic were N-terminal prepro-brain natriuretic peptide ($P<0.001$) and age ($P<0.001$). Using best subsets analysis, log N-terminal prepro-brain natriuretic peptide alone ($R^2=26.3\%$) was again the best predictor of left ventricular wall motion index than any other single or combination of factors. In untreated patients only N-terminal prepro-brain natriuretic peptide ($P<0.001$) independently predicted wall motion index. On best subsets analysis, log N-terminal prepro-brain natriuretic peptide alone ($R^2=42.8\%$) was the best predictor of left ventricular wall motion index. Thus, in both treated and untreated patients, log N-terminal prepro-brain natriuretic peptide accounted for a substantial proportion of
the total variance in left ventricular wall motion index. There was a weak but statistically significant correlation between plasma N-terminal prepro-brain natriuretic peptide and log creatinine concentration \( (r=0.28, P<0.001) \).

Figure 2 shows the receiver operating characteristic curve for various concentrations of N-terminal prepro-brain natriuretic peptide in the diagnosis of left ventricular systolic dysfunction in the whole study population. Plasma N-terminal prepro-brain natriuretic peptide > 275 fmol \( \cdot \) ml \( ^{-1} \) predicted left ventricular wall motion index \( \leq 1 \cdot 2 \) with a sensitivity of 93.8%, a specificity of 55%, a positive predictive value of 58% and a negative predictive value of 93%. The area under the receiver operating characteristic curve in the whole population was 0.854. A similar area under the curve of 0.856 was seen for N-terminal prepro-brain natriuretic peptide in the diagnosis of left ventricular systolic dysfunction as compared to the hypertension group (median 446.4, range 121.1–1292.6 vs median 336.5, range 79.2–1052.8, \( P<0.005 \)).

**Aetiology of left ventricular systolic dysfunction**

In the study 47 patients were identified with a history of ischaemic heart disease and no history of hypertension and 63 had a history of hypertension with no history of ischaemic heart disease. The left ventricular wall motion index was lower in the ischaemic heart disease group compared to the hypertension group (median 1, range 0.2–2 vs median 1.8, range 0.2–2, \( P<0.005 \)). N-terminal prepro-brain natriuretic peptide was higher in the ischaemic heart disease group as compared to the hypertension group (median 1.8, range 0.2–2, \( P<0.005 \)).

**The ECG in screening for left ventricular systolic dysfunction**

In this largely hospital based population, a normal ECG was found in 36/222 (16%), a minor abnormality in 36/222 (16%) and a major abnormality in 150/222 (68%). Of the 36 patients with a normal ECG, 18 had a left ventricular wall motion index \( \leq 1 \cdot 3 \), six (17%) had a left ventricular wall motion index of 1.3–1.9 and 12 (33%) of \( \leq 1 \cdot 2 \). Thus the ECG alone would have failed to identify 18 patients (50%) in whom left ventricular function was impaired. In all of these patients N-terminal prepro-brain natriuretic peptide was > 275 fmol \( \cdot \) ml \( ^{-1} \). Of the further 36 patients with minor ECG abnormalities, 10 (28%) had a left ventricular wall motion index of 1.3–1.9
N-terminal prepro-brain natriuretic peptide was >275 fmol . ml⁻¹ in 7/10. Fifteen of 36 (42%) patients had a left ventricular wall motion index of ≤1·2 and of these N-terminal prepro-brain natriuretic peptide was >275 fmol . ml⁻¹ in 13. Of the 150 patients whose ECG showed a major abnormality, 52 had a left ventricular wall motion index=2, in 29 of whom N-terminal pro-brain natriuretic peptide was <275 fmol . ml⁻¹. 36/150 (24%) had a left ventricular wall motion index of 1·3–1·9, in 26 (72%) of whom N-terminal pro-brain natriuretic peptide was >275 fmol . ml⁻¹. N-terminal pro-brain natriuretic peptide was >275 fmol . ml⁻¹ in all 62 patients with a major ECG abnormality and a left ventricular wall motion index of 1·2.

**Influence of mitral regurgitation**

Mitral regurgitation was graded as 0 in 44 (18%), 1 in 145 (60%), 2 in 40 (16%) and 3 in 14 (6%) patients. The estimated severity of mitral regurgitation correlated with plasma N-terminal prepro-brain natriuretic peptide (r=0·389, P<0·0005). Mean N-terminal prepro-brain natriuretic peptide differed among groups (P<0·0005, Kruskal–Wallis) and between all pairs except mitral regurgitation=2 and mitral regurgitation=3 (Fig. 3). However, there was a correlation between the severity of mitral regurgitation and wall motion index (r=−0·365, P<0·0005). Thus although elevated N-terminal prepro-brain natriuretic peptide largely reflects reduced wall motion index it is affected by the presence and severity of mitral regurgitation.

**Discussion**

Our study has confirmed the previously established relationship between plasma levels of natriuretic peptides and measures of left ventricular dysfunction[11–7,22]. Moreover our study indicates that plasma N-terminal prepro-brain natriuretic peptide remains a strong predictor of left ventricular function when confounding variables such as renal function and concomitant drug therapy are taken into account. Our study also indicates that, at least in a population at relatively high risk of left ventricular dysfunction, consideration of the ECG does not add to the predictive value of plasma N-terminal prepro-brain natriuretic peptide.

Our study has confirmed a linear relationship between N-terminal prepro-brain natriuretic peptide and left ventricular function as assessed by left ventricular wall motion index, a relationship previously reported for left ventricular ejection fraction[3]. We have demonstrated the strong, independent predictive value of plasma N-terminal prepro-brain natriuretic peptide in the identification of left ventricular dysfunction. Previous studies on the use of natriuretic peptides for detecting left ventricular systolic dysfunction have utilized echocardiographic ejection fraction and fractional shortening[2,5] or radionuclide ventriculography[3]. Echocardiographic measures of left ventricular dysfunction have, with rare exceptions, failed to predict prognosis in multivariate models[23]. This perhaps reflects the inaccuracy of current methods for measuring ejection fraction. On the other hand, the left ventricular wall motion index is a relatively simple, robust and reproducible measurement[18,19] and the nine segment model has been shown to contain prognostic information in patients with heart failure[24].

Figure 3  Box plot showing relationship of log N-terminal prepro-brain natriuretic peptide levels and its relationship to the severity of mitral regurgitation.

N-terminal prepro-brain natriuretic peptide was >275 fmol . ml⁻¹ in 7/10. Fifteen of 36 (42%) patients had a left ventricular wall motion index of ≤1·2 and of these N-terminal prepro-brain natriuretic peptide was >275 fmol . ml⁻¹ in 13. Of the 150 patients whose ECG showed a major abnormality, 52 had a left ventricular wall motion index=2, in 29 of whom N-terminal pro-brain natriuretic peptide was <275 fmol . ml⁻¹. 36/150 (24%) had a left ventricular wall motion index of 1·3–1·9, in 26 (72%) of whom N-terminal pro-brain natriuretic peptide was >275 fmol . ml⁻¹. N-terminal pro-brain natriuretic peptide was >275 fmol . ml⁻¹ in all 62 patients with a major ECG abnormality and a left ventricular wall motion index of 1·2.
therapy on plasma hormone levels. Our study has addressed both of these issues. We identified a correlation between log creatinine and log N-terminal prepro-brain natriuretic peptide. However, we also identified a correlation between log creatinine and left ventricular wall motion index \( (r^2 = 0.29, P<0.001) \). Moreover, while creatinine concentration was a univariate predictor of left ventricular wall motion index, this parameter was not significant in multivariate analysis. While we accept that serum creatinine concentration represents a crude measure of renal function, this is the measure that is usually applied clinically. Moreover we have no reason to think that a more sensitive measure of renal function such as creatinine clearance would have significantly reduced the predictive value of N-terminal prepro-brain natriuretic peptide in our population.

Concerns have been expressed that drug treatment, in particular diuretic or ACE inhibitor therapy\[^{25}\], beta-blockers\[^{9,26}\], and digoxin\[^{27}\] may modify plasma levels of natriuretic peptides and nullify their potential as markers for left ventricular systolic dysfunction. We have observed the correlation of N-terminal prepro-brain natriuretic peptide with left ventricular wall motion index to be as strong in the group who were being treated with a diuretic or an ACE inhibitor when compared to those patients who were receiving neither. Similarly we detected no influence of concomitant beta-blocker or digoxin therapy. Although our study does not indicate whether N-terminal prepro-brain natriuretic peptide levels had been altered by these therapies, our data suggest that the utility of this measurement is not significantly reduced in the presence of appropriate treatment for left ventricular systolic dysfunction or ischaemic heart disease.

Our study population contained 101 patients who had a history of hypertension which on its own can increase the levels of N-terminal prepro-brain natriuretic peptide\[^{25}\]. In addition approximately 20% of the patients had moderate to severe mitral regurgitation and a similar proportion had a plasma creatinine level of 130 \( \mu \text{mol.l}^{-1} \) or above, both of which are associated with elevated levels of natriuretic peptides\[^{28}\]. Despite the confounding effect of all these important variables, N-terminal prepro-brain natriuretic peptide was strongly correlated to left ventricular wall motion index and emerged as the strongest independent predictor of left ventricular systolic dysfunction in a multivariate model. The area under the receiver operating characteristic curve for N-terminal prepro-brain natriuretic peptide in the diagnosis of left ventricular systolic dysfunction was similar to that for brain natriuretic peptide-32 in previous studies\[^{8,3}\].

While the relationship between plasma levels of natriuretic peptides and measures of left ventricular dysfunction is well established\[^{11-7,22}\], concerns have been expressed regarding the use of such measures in routine clinical practice\[^{8}\]. McClure \textit{et al.}\[^{9}\] studied a population that may be regarded as being at high risk of left ventricular systolic dysfunction i.e. survivors of acute myocardial infarction. These authors found that the plasma brain natriuretic peptide level was unable to differentiate between patients with mildly or moderately impaired left ventricular function and those with preserved function. Our study, on the other hand, indicates a linear relationship between N-terminal prepro-brain natriuretic peptide and left ventricular wall motion index. Methodological differences, including the method of assessment of left ventricular function, may explain these differences. In addition, while the study of McClure \textit{et al.}\[^{9}\] and the present study looked at high risk populations, differences in the patient populations are likely to explain at least part of the difference in results.

It has been suggested that left ventricular systolic dysfunction is unlikely to be present if the ECG is normal or shows only minor abnormalities\[^{11,29}\], that there is usually a major ECG abnormality in the presence of left ventricular systolic dysfunction\[^{11,29}\] and that the consideration of the ECG in addition to natriuretic peptide levels can increase overall accuracy and specificity in diagnosing left ventricular systolic dysfunction\[^{8}\]. These findings have led to the suggestion that patients with a normal ECG are unlikely to have heart failure and therefore should not be considered for further investigation. However other studies have suggested that 10% of patients with left ventricular systolic dysfunction have a normal ECG\[^{12}\]. Our data indicate that consideration of the ECG as a screening tool would indeed have led to the failure to diagnose 12 patients with significant systolic impairment (left ventricular wall motion index \( \leq 1.2 \)) out of 36 with a normal ECG. A further six patients had a left ventricular wall motion index between 1.3 and 1.9. In each case, plasma N-terminal prepro-brain natriuretic peptide identified these patients as being likely to have left ventricular systolic dysfunction. As in previous studies, an abnormal ECG had a low specificity in the prediction of left ventricular systolic dysfunction. Moreover, an abnormal ECG was not a predictor of low left ventricular wall motion index on either univariate or multivariate analysis, in contrast to previous studies\[^{8,11}\]. However one study\[^{8}\] did not show any association between pro-brain natriuretic peptide and left ventricular dysfunction, in contrast to the strength of association between N-terminal prepro-brain natriuretic peptide and left ventricular wall motion index in the current study. Further to this, the other two studies\[^{10,11}\] did not assess the value of natriuretic peptides in identifying left ventricular dysfunction. One likely reason for the discrepancy is the large proportion of ECGs with a major abnormality in our study; essentially very few of the patients in this high risk population had a normal ECG.

N-terminal prepro-brain natriuretic peptide had a sensitivity of approximately 95% and a specificity of 55% for the detection of left ventricular systolic dysfunction. The sensitivity and specificity, respectively, of various natriuretic peptides has been reported as 77% and 87%\[^{3}\], 97% and 84\%\[^{9}\] for brain natriuretic peptide in primary care, 91% and 72% for N-terminal brain natriuretic peptide following myocardial infarction\[^{3}\]. The
variability in reported sensitivity and specificity is likely to reflect differences in the selection of study populations. Of more clinical importance is the high negative predictive value (93%) of N-terminal prepro-brain natriuretic peptide in the diagnosis of left ventricular systolic dysfunction in our study. This compares to previously reported values of 97%[6], 98%[7] and 97%[8].

Our study has a number of limitations. Firstly, we studied a group of patients at high risk of having left ventricular systolic dysfunction and the findings may not be applicable to the identification of left ventricular systolic dysfunction in a low risk group, such as an unselected community population. The aim of the study was to evaluate the ability of plasma N-terminal pro-brain natriuretic peptide to identify patients with left ventricular systolic dysfunction in the presence of possible confounding variables, namely drug therapy and concomitant disease. In this respect the findings of the study are unequivocal: very few patients with left ventricular systolic dysfunction will not be identified by measurement of N-terminal pro-brain natriuretic peptide. Secondly, we did not compare the predictive value of N-terminal proBNP to that of other natriuretic peptides such as brain natriuretic peptide-32. However brain natriuretic peptide-32 has been evaluated as a marker of left ventricular systolic dysfunction in both a hospital population and in primary care[11–13]. The measurement of N-terminal prepro-brain natriuretic peptide has the advantage that it is present in quantities that are tenfold higher than brain natriuretic peptide, potentially improving ease of detection. This would make the development of a near patient test for left ventricular systolic dysfunction a distinct possibility, since existing methods for capturing and colorimetric detection of N-terminal pro-brain natriuretic peptide are capable of rapid measurement at the high plasma concentrations present in patients with heart failure.

In summary, we have demonstrated in a high risk population that N-terminal pro-brain natriuretic peptide is a powerful predictor of the degree of left ventricular systolic dysfunction as measured by left ventricular wall motion index. N-terminal pro-brain natriuretic peptide strongly predicts left ventricular wall motion index even in the presence of concomitant drug therapy. Moreover we have shown that consideration of the ECG alone in such patients may be misleading and that consideration of the ECG in addition to the plasma N-terminal pro-brain natriuretic peptide level adds little to the identification of patients with left ventricular systolic dysfunction. The possibility of developing an accurate, reliable and cost effective blood test for both the diagnosis and prognostic evaluation of heart failure is a current challenge in the field of cardiovascular medicine. There may also be a role for the natriuretic peptides in the therapeutic monitoring of patients with heart failure and we have demonstrated that N-terminal pro-brain natriuretic peptide measurements are still predictive of left ventricular systolic dysfunction in treated patients. The role and cost-effectiveness of N-terminal prepro-brain natriuretic peptide as a diagnostic tool for detection of left ventricular systolic dysfunction in other, particularly community based populations, needs to be established.

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