N-terminal pro-brain natriuretic peptide
A new gold standard in predicting mortality in patients with advanced heart failure

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Aims The selection of patients for cardiac transplantation (CTx) is notoriously difficult and traditionally involves clinical assessment and an assimilation of markers of the severity of CHF such as the left ventricular ejection fraction (LVEF), maximum oxygen uptake (peak VO2) and more recently, composite scoring systems e.g. the heart failure survival score (HFSS). Brain natriuretic peptide (BNP) is well established as an independent predictor of prognosis in mild to moderate chronic heart failure (CHF). However, the prognostic ability of NT-proBNP in advanced heart failure is unknown and no studies have compared NT-proBNP to standard clinical markers used in the selection of patients for transplantation. The purpose of this study was to examine the prognostic ability of NT-proBNP in advanced heart failure and compare it to that of the LVEF, peak VO2 and the HFSS.

Methods and results We prospectively studied 142 consecutive patients with advanced CHF referred for consideration of CTx. Plasma for NT-proBNP analysis was sampled and patients followed up for a median of 374 days. The primary endpoint of all-cause mortality was reached in 20 (14.1%) patients and the combined secondary endpoint of all-cause mortality or urgent CTx was reached in 24 (16.9%) patients. An NT-proBNP concentration above the median was the only independent predictor of all cause mortality ($\chi^2=6.03$, $P=0.01$) and the combined endpoint of all cause mortality or urgent CTx ($\chi^2=12.68$, $P=0.0004$). LVEF, VO2 and HFSS were not independently predictive of mortality or need for urgent cardiac transplantation in this study.

Conclusion A single measurement of NT-proBNP in patients with advanced CHF, can help to identify patients at highest risk of death, and is a better prognostic marker than the LVEF, VO2 or HFSS.

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KEYWORDS
BNP; Brain natriuretic peptide; Prognosis; Chronic heart failure; Cardiac transplantation; Mortality

Background

Despite recent advances in medical therapy, the mortality of advanced chronic heart failure (CHF) due to left ventricular systolic dysfunction (LVSD) remains high. Although donor organ availability restricts its use, cardiac transplantation (CTx) remains an option for those patients with advanced CHF who do not respond to medical therapy.

The selection of patients for CTx is notoriously difficult and traditionally involves clinical assessment and an assimilation of markers of the severity of CHF such as the LVEF and peak VO2. Previous studies have shown that those with a peak VO2 ≤14 ml/kg/min benefit in terms of prognosis from transplantation.1-3 More recently, many centres have applied a composite scoring system developed by Aaronson et al.4 to predict those who will benefit from transplantation: the heart failure survival score (HFSS).
However, each of these methods has limitations. Patients with severe CHF often cannot achieve a true peak VO\textsubscript{2} due to leg fatigue, angina or general debilitation. Also, it is well known that an echocardiographic determination of LVEF can only be obtained in 70–85% of patients\textsuperscript{5} and an accurate and reproducible determination of LVEF relies on the availability of radionuclide ventriculography. For these reasons, as well as the limited number of patients who were treated with beta-blockers or spironolactone during the development and validation of the HFSS, an ideal method of deciding who will benefit from transplantation has yet to be found. There would therefore be considerable interest in a biochemical marker, which could simplify this process.

Brain natriuretic peptide (BNP) is well known to be increased in both asymptomatic and symptomatic LVSD\textsuperscript{6,7} and increases in proportion to the severity of chronic heart failure.\textsuperscript{5} It also independently predicts morbidity and mortality in asymptomatic LVSD\textsuperscript{8} and in mild-moderate CHF.\textsuperscript{10–12} In addition, BNP has also been shown to be a strong, independent predictor of sudden death in patients with CHF.\textsuperscript{13} Similarly, the N-terminal portion of pro-brain natriuretic peptide (NT-proBNP) has been shown to be an independent marker of mortality or decompensated heart failure after myocardial infarction\textsuperscript{14} or in those with chronic HFSS was calculated for each patient. Patients were followed up every 3 months or more frequently as required.

HFSS was calculated for each patient. Patients were followed up until the endpoints were reached or 31st January 2003. The median follow-up was 374 days (range=1 to 660). No patients were lost to follow-up.

Follow-up
The primary end point was all-cause mortality. The secondary endpoint was all-cause mortality or urgent transplantation. Urgent transplantation is considered in suitable inotrope dependent patients with end-stage heart failure who have an anticipated life expectancy of less than 1 week. Patients were followed up until the endpoints were reached or 31st January 2003. The median follow-up was 374 days (range=1 to 660). No patients were lost to follow-up.

Statistical analysis
All data analysis was performed using the Statistical Package for Social Sciences (SPSS 9.0) software (SPSS Inc., Chicago, Illinois). Normally distributed, continuous data, unless otherwise stated, are expressed as mean values (±SD). Non-normally distributed continuous data are expressed as medians [25th and 75th percentiles].

Cumulative univariate adverse event rates were compared by use of \( \chi^2 \) tests with risk ratios and 95% confidence intervals quoted. Kaplan–Meier survival curves were calculated with the data dichotomized at the mean or median values for each parameter as appropriate. The mean values of clinical variables for patients with and without the primary or secondary endpoints were compared by the use of independent \( t \)-tests and median values by the Mann–Whitney \( U \)-test.

To compare the predictive value of NT-proBNP, LVEF, peak VO\textsubscript{2} and the HFSS, receiver operating characteristic (ROC) analysis was performed and the area under the curves calculated.\textsuperscript{15}

To identify predictors of death, Cox proportional hazards analysis was used and variables achieving \( P<0.10 \) on univariate analysis were then tested in a stepwise (forward) multiple Cox regression survival model to determine the independent predictors of both the primary and secondary endpoints. A \( P<0.05 \) was considered statistically significant.

Results
The baseline clinical and demographic features of the patients are described in Table 1. The population was
Values were skewed with the median concentration being the mean peak VO2 was 11.8 ml/kg/min. The NT-proBNP in NYHA classes III and IV, the mean LVEF was 14.9% and predominantly male (82.4%). Over 85% of patients were in NYHA classes III and IV, the mean LVEF was 14.9% and the mean peak VO2 was 11.8 ml/kg/min. The NT-proBNP values were skewed with the median concentration being 1490 [511–3887] pg/ml.

Of the 142 patients, 20 (14.1%) reached the primary endpoint of death (16.7% 1-year mortality) and 4 (2.1%) were urgently transplanted. The secondary endpoint of death or urgent CTx occurred in 24 (16.9%). A further 17 patients (12%) were transplanted during the study, but these subjects were considered survivors.

Markers of prognosis in advanced heart failure

**Table 2** shows the relative risk ratios of various traditional and potential prognostic markers in CHF dichotomized about their median values. The only significant univariate predictor of all cause mortality was an NT-proBNP level above the median value (RR=5.0 [1.6–15.9], P=0.006)–out of 20 deaths, 16 (80%) had an NT-proBNP concentration above the median, compared with four deaths below the median level.

The significant univariate predictors of the secondary endpoint of all cause mortality or urgent cardiac transplantation were a RVEF, HFSS and serum sodium below the median and an NT-proBNP level above the median. Most notably, 83% of patients who reached the combined endpoint had an NT-proBNP level above the median value.

**Table 3** describes the mean and median values of various clinical parameters, including the LVEF, peak VO2, HFSS, and NT-proBNP, in survivors, non-survivors and in those who died or were urgently transplanted. The median NT-proBNP level in patients who died was 3052 pg/ml, compared to that of survivors of 1222 pg/ml (P<0.001) and the median NT-proBNP level in patients who died or required urgent transplantation was 5518 pg/ml, compared to that of survivors of 1177 pg/ml (P<0.001).

The area under the curve on ROC analysis for NT-proBNP, the LVEF, peak VO2 and HFSS, for the prediction of the primary and secondary endpoints are shown in Fig. 1 and Fig. 2. The greatest area under the curve for both endpoints was NT-proBNP (AUC=0.738 and 0.786, respectively).

Multiple Cox proportional hazards regression analysis was performed using the above univariate predictors (systolic BP, serum sodium, Peak VO2, HFSS and RVEF)
and repeated to force the LVEF into the model. The analysis was first performed with variables dichotomized about their median value and then repeated using continuous variables with identical results. NT-proBNP remained the only independent predictor of all cause mortality ($\chi^2=6.03$, $P=0.01$). For the combined endpoint of all-cause mortality or urgent cardiac transplantation, the only independent predictor was again an NT-proBNP.

**Table 3** Mean values of variables for patients incurring or spared primary and secondary endpoints

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death</th>
<th>Survivor</th>
<th>$P$</th>
<th>Secondary endpoint</th>
<th>No secondary endpoint</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>78.9±15.5</td>
<td>74.1±15.5</td>
<td>ns</td>
<td>81.4±16.3</td>
<td>73.4±15.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>101.1±16.7</td>
<td>111.4±17.9</td>
<td>0.02</td>
<td>100.2±15.5</td>
<td>112.0±17.9</td>
<td>0.003</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>12.3±6.7</td>
<td>15.3±7.1</td>
<td>0.09</td>
<td>11.5±6.4</td>
<td>15.6±7.1</td>
<td>0.01</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>18.7±10.4</td>
<td>22.6±10.1</td>
<td>ns</td>
<td>17.5±9.9</td>
<td>23.0±10.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Peak VO$_2$ ml/kg/min</td>
<td>10.0±2.7</td>
<td>12.0±3.6</td>
<td>0.04</td>
<td>10.2±2.8</td>
<td>12.0±3.7</td>
<td>0.04</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>148.0±46.1</td>
<td>129.8±35.3</td>
<td>0.055</td>
<td>141.4±45.2</td>
<td>130.5±35.5</td>
<td>ns</td>
</tr>
<tr>
<td>HFSS$^a$</td>
<td>7.38 [6.00–8.03]</td>
<td>7.72 [7.23–8.27]</td>
<td>0.03</td>
<td>7.36 [5.97–7.73]</td>
<td>7.77 [7.23–8.29]</td>
<td>0.004</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)$^a$</td>
<td>3052 [1511–12405]</td>
<td>1222 [423–2753]</td>
<td>&lt;0.001</td>
<td>5518 [1467–11618]</td>
<td>1117 [406–2597]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>136.5±4.2</td>
<td>139.0±3.7</td>
<td>0.007</td>
<td>136.1±4.2</td>
<td>139.2±3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mol/l)</td>
<td>138.3±38.8</td>
<td>122.8±31.9</td>
<td>0.053</td>
<td>132.8±38.6</td>
<td>123.4±32.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

$^a$HFSS and NT-pro-BNP values expressed as median [interquartile range]. ns denotes not-significant ($P>0.1$).

**Fig. 1** ROC curves of NT-proBNP, left ventricular ejection fraction (LVEF), maximum oxygen uptake (peak VO$_2$) and heart failure survival score (HFSS) against all-cause mortality in 142 patients with advanced heart failure.
value above the median ($\chi^2=12.68$, $P=0.0004$). LVEF, Peak VO$_2$ and HFSS were not independently predictive of mortality or need for urgent transplantation.

Kaplan–Meier survival curves for all-cause mortality are depicted in Fig. 3 for the variables most commonly associated with a poor outcome in advanced heart failure (LVEF, Peak VO$_2$ and HFSS), as well as NT-proBNP. The only predictor of all-cause mortality was an NT-proBNP above the median value (log rank statistic=10.99, $P=0.0009$). Kaplan–Meier survival curves for all-cause mortality and urgent transplantation are shown in Fig. 4 for the same variables. The predictors of mortality or urgent CTx were LVEF (log rank statistic=5.92, $P=0.015$) and NT-proBNP (log rank statistic=15.36, $P=0.0001$).

Fig. 5 shows poorer outcome associated with increasing NT-proBNP concentrations represented as quartiles (log rank statistic=12.7 ($P=0.005$) for all-cause mortality and 21.22 ($P=0.0001$) for all-cause mortality and urgent transplantation).

Discussion

This study first of all confirms the poor prognosis associated with advanced heart failure; in the cohort, 14.1% of patients died in the median follow up period of 374 days and 16.9% either did not survive or were urgently transplanted. The 1-year mortality rate of 16.7% is in keeping with mortality rates reported in a recent trial of beta-adrenoreceptor antagonists in advanced heart failure—the COPERNICUS Study$^{16}$—where the annual mortality rates were 18.5% in the placebo group and 11.4% in the carvedilol treated group. The truly advanced nature of the LVSD in this transplant referral population is also highlighted by the fact that 85% of patients were either in NYHA Classes III or IV, and the mean LVEF was 14.9% and the mean peak VO$_2$ was 11.8 ml/kg/min.

Our study has also demonstrated for the first time that NT-proBNP concentrations are independent markers of both mortality and death or urgent transplantation in
patients with advanced heart failure referred for consideration of cardiac transplantation. As such, this work confirms previous research which has demonstrated that an increased BNP concentration is associated with a poorer survival rate in patients with CHF due to systolic dysfunction in NHYA Classes II and II, in minimally symptomatic LVD and indeed, in the general population. Interestingly Pacher's group have also very recently demonstrated that BNP is a predictor of sudden death in heart failure. Our study was not sufficiently powered to comment on the mode of death in this heart failure population and we have restricted our analyses to all cause mortality. Atrial natriuretic peptide (ANP) has also been shown to be an independent predictor of mortality in a cohort of patients referred for further hospital assessment of their heart failure. However, in that study only 38% of patients were in NYHA Classes III/IV compared to 85% in this work and the mean LVEF was 27% and mean peak VO₂ 17.1 ml/kg/min indicating they were not as severe a group of patients. This study also extends our current knowledge of the prognostic power of NT-proBNP into the advanced heart failure arena. Richards et al. have shown that NT-proBNP is an independent predictor of both adverse prognosis and the development of heart failure after myocardial infarction and in patients with CHF of ischaemic aetiology. In contrast, our study includes patients with both ischaemic and dilated cardiomyopathies. Stanek et al. have recently reported that NT-proBNP (as well as BNP) is an independent predictor of prognosis in 91 patients with advanced LV dysfunction. However, the work described here is in a more severe group than in Stanek's paper, where 86% of subjects were in NHYA Class II. Interestingly Zugck et al. have also published on a cohort of 408 patients referred for out-patient or in-patient hospital assessment of heart failure and shown that NT-proBNP was an independent predictor of cardiac events (hospitalization for heart failure or cardiovascular death) in the total cohort but not in the subgroup receiving beta-blocker therapy. In contrast, in this study, NT-proBNP predicted a poor outcome independent of treatment. In addition, once again Zugck's observations were in a cohort with less severe CHF; the mean NHYA was 2.3 compared with 3.0 in this work and the mean LVEF and peak VO₂ levels were 22% and 14.9 ml/kg/min.

Fig. 3 Kaplan–Meier survival curves for left ventricular ejection fraction (LVEF), maximum oxygen uptake (peak VO₂), heart failure survival score (HFSS) and NT-proBNP stratified above (broken line) and below (solid line) the median value against all-cause mortality.
The usefulness of the traditional markers of the severity of heart failure in predicting prognosis in this cohort of patient is worthy of discussion. We did not find either the LVEF, peak VO₂, RVEF, serum sodium, or systolic blood pressure to be independent predictors of death. This may of course be due to the relatively small numbers of deaths or insufficient length of follow up to date. Alternatively, the explanation may lie in the severity of the patient population referred-with a mean LVEF of 14.9±7.1% and a mean peak VO₂ of 11.8±3.6 ml/kg/min. We may have insufficient spread of these parameters to allow adequate discrimination to be seen. However, this reflects the real life situation of trying to predict prognosis in a transplant referral setting as opposed to a more heterogeneous heart failure population. NT-proBNP was clearly able to assign a poor survival with far greater power.

Because of the difficulties in trying to predict an adverse outcome in advanced heart failure by relying on single parameters of severity, the HFSS has been developed to try and predict more reliably those who will have a definite survival advantage from cardiac transplantation. This is the first study to our knowledge to compare NT-proBNP concentrations with the HFSS in terms of their usefulness in assigning a poorer survival. NT-proBNP emerged as the superior modality, indeed it was the only independent predictor of all-cause mortality or the combine endpoint of all-cause mortality and urgent transplantation in our study. With the one year mortality rate post transplantation being in the region of 15–20%,²⁰ it is of vital importance to try and select those for the procedure whose mortality rate exceeds this. Of note in this group of patients the mortality rate at our median follow-up of 374 days was 22.5% in those with a NT-proBNP concentration greater than the median value, compared to 5.6% in those with a NT-proBNP concentration less than the median value, and 80% of the deaths and 83% of the secondary endpoints occurred in this group with an NT-proBNP above the median level for the cohort.

This study has demonstrated for the first time that NT-proBNP may well have significant potential in helping to decide which of our advanced heart failure patients may benefit from the scarce resource of a cardiac transplant. Much work still needs to be done in greater numbers of patients referred in for cardiac transplantation to
help identify how this test could fit in clinically. In particular we need to know if a certain concentration of NT-proBNP at referral would be useful or whether a value that is rising or failing to fall with optimization of heart failure therapy would be superior. It is likely that BNP would produce similar results. However, NT-proBNP may be a more useful marker of prognosis than BNP especially if future treatment with intravenous BNP or neutral endopeptidase inhibition (which could interfere with the measurement of BNP, but not NT-proBNP) become routinely used in clinical practice. Bigger studies are therefore needed to compare NT-proBNP and BNP in terms of their prognostic potential in this patient group, and to determine if we can use these natriuretic peptides in isolation and, if not, which clinical, invasive and non-invasive parameters would be useful to use in combination with them.

Although there are differences in the absolute concentrations of BNP and NT-proBNP between normal men and women, as far as we are aware, there are no inter-gender differences in the prognostic power of NT-proBNP in CHF patients; however, our numbers are too small to test for this formally. Similarly, BNP and NT-proBNP concentrations are also higher in patients with significant renal impairment. However, in this cohort of patients the median creatinine was 120 µmol/l (interquartile range 100–140). The absence of significant renal impairment in our cohort presumably reflects the fact that renal dysfunction is a relative contra-indication for subsequent cardiac transplantation.

In this study plasma was taken for NT-proBNP analysis on first contact with each patient, before any changes in therapy were made. Whilst adjustments to therapy may well influence both outcome and the NT-proBNP concentration, in this paper we are only addressing the hypothesis that an increased baseline NT-proBNP concentration would be predictive of an adverse outcome.

As the natriuretic peptides and in particular BNP and NT-proBNP are coming into clinical use for the diagnosis of heart failure and rapid assays are now available, it is tantalizing to think that we now may well have a simple, non-invasive marker of the severity of heart failure to help unravel the complex problem of whom to refer for cardiac transplantation.

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