

SCIENTIFIC LETTER

N-terminal brain natriuretic peptide is predictive of death after cardiac transplantation

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Cardiac transplantation is an important treatment option for those patients with end stage heart failure who have failed to respond to disease modifying treatment. However, cardiac transplantation is not without risk, with the one year mortality around 19%,¹ and identifying patients at the highest risk of death is notoriously difficult.

Brain natriuretic peptide (BNP) and the N-terminal portion of pro-brain natriuretic peptide (NT-proBNP) are now well established diagnostic and adverse prognostic markers in all stages of congestive heart failure. Indeed, we have shown that NT-proBNP is predictive of death before cardiac transplantation.² Studies have also shown that increasing BNP concentrations precede cardiac allograft rejection and are associated with poor survival late after transplantation.³ However, the prognostic ability of NT-proBNP immediately after cardiac transplantation has not been evaluated. The goal of this study was therefore to assess the short term prognostic ability of NT-proBNP in patients after cardiac transplantation.

METHODS

We prospectively studied 26 consecutive patients undergoing orthotopic cardiac transplantation in the Scottish Cardiopulmonary Transplant Unit between September 2001 and September 2003. The primary end point was all cause mortality. The median follow up was 477 days (range 20–922 days). No patients were lost to follow up.

Blood for NT-proBNP was collected in EDTA containing tubes before each routine right ventricular endomyocardial biopsy. The samples were then spun at 3000 rpm for 10 minutes at 0°C. Plasma was extracted and frozen in aliquots at –70°C until analysis. NT-proBNP was measured by chemiluminescent immunoassay kits (Roche Diagnostics) on an Elecsys 2010 analyser. The clinicians caring for the patients were blinded to the neurohormone concentrations obtained. The local research ethics committee approved the study protocol and all patients gave written informed consent. The study complies with the Declaration of Helsinki.

All data were analysed by SPSS version 11.5 software (SPSS Inc, Chicago, Illinois, USA). Normally distributed continuous data, unless otherwise stated, are expressed as mean (SD). Non-normally distributed continuous data are expressed as median (25th to 75th centiles). The mean values of clinical variables were compared by the use of independent *t* tests, and median values by the Mann-Whitney U test. 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 mortality. A probability value of $p < 0.05$ was considered significant.

RESULTS

Table 1 describes the mean and median values of various clinical parameters for survivors and those who died, both at listing and one week after cardiac transplantation. The

population was predominantly male (84.6%), with a mean age of 49.3 years. Of the 26 patients, five reached the primary end point of death (19.2% one year mortality). The causes of death were right heart dilatation in two, multiorgan failure in two, and respiratory syncytial virus infection in one.

The median NT-proBNP concentration one week after cardiac transplantation was 12 184 (6464–25 485) pg/ml. However, the median NT-proBNP concentration in patients who died was 32 930 (18 260–69 935) pg/ml compared with that of survivors of 10 713 (6029–18 646) pg/ml ($p = 0.008$); all five patients who died had an NT-proBNP concentration above the median. The other univariate markers of outcome one week after cardiac transplantation were troponin T and C reactive protein above their median concentrations and diastolic blood pressure below its median value. Haemofiltration, days in the intensive treatment unit, and prolonged need for inotropes were not correlated with outcome.

Figure 1 depicts the change in NT-proBNP concentration in all 26 patients. NT-proBNP concentrations were much higher one week after cardiac transplantation than on listing and, unlike patients who survived, in those who died these concentrations failed to fall. Multiple Cox proportional hazards regression analysis of the above univariate predictors was repeated to force ischaemia time, donor age, and postoperative creatinine into the model. NT-proBNP remained the only independent predictor of all cause mortality ($\chi^2 = 6.9$, $p = 0.009$).

DISCUSSION

This study first of all highlights the fact that cardiac transplantation is not a benign procedure and confirms the significant one year mortality after cardiac transplantation found from registry data of about 19%.¹ In keeping with these registry data, univariate markers of outcome in this study included trends both for ischaemia time and donor age; however, we found no significant difference in recipient age or pulmonary vascular resistance preceding cardiac transplantation in patients who died. Significant univariate markers in this study not discussed in the aforementioned registry were diastolic blood pressure, C reactive protein, and NT-proBNP measured at the time of the first endomyocardial biopsy. Indeed, in this study, NT-proBNP was found to be the only independent predictor of mortality one week after transplantation.

Although small, this study extends the prognostic properties of NT-proBNP into the post-cardiac transplantation arena. It should be noted that this reflects the relatively small numbers of cardiac transplants carried out in most centres around the world: 77% of reporting centres averaged fewer than 20 procedures a year (and 45% fewer than 10 a year).¹

Previous research has shown that an increased BNP or NT-proBNP concentration is associated with a poorer survival rate in all stages of congestive heart failure. The B-type

Table 1 General characteristics of 26 patients receiving a cardiac transplant

Demographic	Overall	Dead	Survivors	p Value
On listing for cardiac transplantation				
Age (years)	49.3 (12.1)	49.2 (13.6)	49.3 (12.1)	NS
Male sex	22 (84.6%)	5 (100%)	17 (80.9%)	NS
Weight (kg)	79.2 (14.1)	72.0 (16.0)	80.9 (13.5)	NS
Aetiology (IHD/DCM)	57.7%/42.3%	60%/40%	57%/43%	NS
LVEF (%)	13.4 (11.8)	10.5 (4.7)	14.0 (12.9)	NS
Peak VO ₂ (ml/kg/min)	10.4 (2.3)	10.0 (2.8)	10.4 (2.3)	NS
HFSS*	6.86 (6.30–7.35)	6.46 (6.00–7.62)	7.76 (7.31–8.38)	NS
GFR (ml/min/1.73 m ²)	50.9 (14.3)	44.8 (13.6)	52.3 (14.4)	NS
NT-proBNP (pg/ml)	4 041 (945–6408)	3 541 (1 578–7360)	2 215 (911–6667)	NS
One week after transplantation				
Heart rate (beats/min)	90.1 (13.7)	91.0 (17.5)	89.7 (12.7)	NS
Systolic BP (mm Hg)	125.8 (18.0)	123.4 (23.2)	126.9 (16.3)	NS
Diastolic BP (mm Hg)	67.6 (15.7)	54.2 (11.6)	73.6 (13.6)	0.02*
Ischaemia time (min)	249.2 (75.4)	301.8 (111.7)	236.1 (60.4)	0.08
Donor age (years)	37.6 (12.4)	45.2 (9.3)	35.8 (12.5)	0.10
Donor sex male	13 (50%)	5 (100%)	8 (38%)	NS
GFR (ml/min/1.73 m ²)	36.9 (13.4)	35.4 (11.9)	37.2 (14.0)	NS
NT-proBNP (pg/ml)	12184 (6464–25485)	32930 (18260–69935)	10713 (6029–18646)	0.008*
CRP (mg/l)	34 (24–64)	63 (49–117)	28 (17–38)	0.014*
Troponin T (µg/l)	1.05 (0.51–1.71)	2.82 (1.74–5.66)	0.78 (0.23–1.26)	0.007*

Values are expressed as mean (SD), number (%), or median (interquartile range) for non-normally distributed variables.

*Univariate markers of outcome.

BP, blood pressure; CRP, C reactive protein; DCM, dilated cardiomyopathy; GFR, glomerular filtration rate; HFSS, heart failure survival score; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; NS, not significant ($p < 0.1$); NT-proBNP, N-terminal portion of pro-brain natriuretic peptide; VO₂, oxygen consumption.

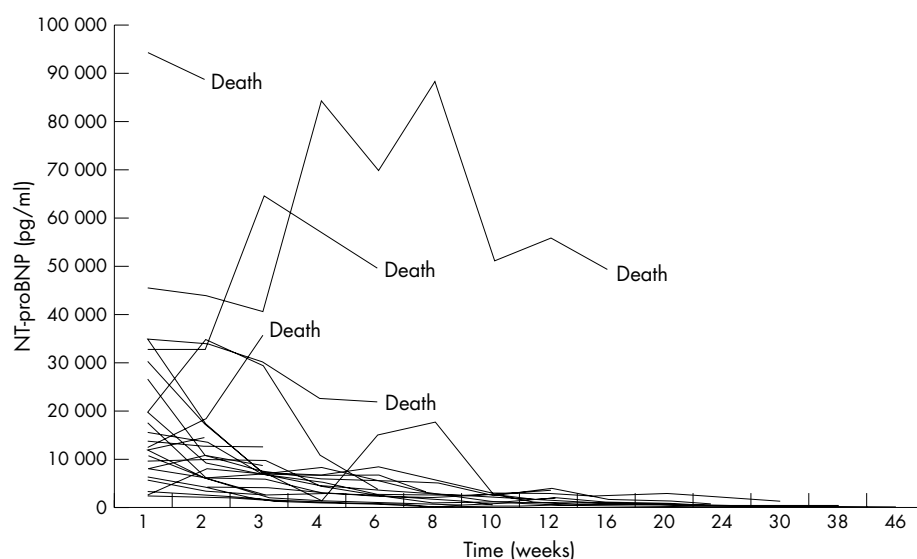


Figure 1 Line graph depicting change in N-terminal portion of pro-brain natriuretic peptide (NT-proBNP) concentrations in 26 patients after cardiac transplantation. Lines indicating patients who died are marked accordingly.

natriuretic peptides have also been studied in patients after cardiac transplantation. BNP has been shown to be slightly higher in patients with treatable allograft rejection.⁴ Work by Mehra *et al*⁵ has shown that BNP is independently predictive of survival of patients long after cardiac transplantation. A recent study has also shown that administration of nesiritide (recombinant BNP) can improve haemodynamic function, as well as renal function, immediately after cardiac transplantation in patients with increased filling pressures.⁵

Why NT-proBNP should be predictive of death in this population is uncertain, particularly given the heterogeneous modes of death. However, patients who died had greatly raised NT-proBNP concentrations that failed to fall before death. A raised NT-proBNP concentration may indicate left or right ventricular dysfunction secondary to myocardial insult, renal dysfunction, or multiorgan failure. Larger studies are therefore needed to determine where this test can fit in clinically and whether methods now used in heart failure

studies to “drive down” BNP and NT-proBNP concentrations would alter the subsequent prognosis.

In summary, this study has shown that a single measurement of NT-proBNP one week after cardiac transplantation can help to identify patients at the highest risk of death. Patients at the highest risk of death were shown to have persistently increased concentrations of NT-proBNP. As the natriuretic peptides, in particular BNP and NT-proBNP, are coming into clinical usage for the diagnosis and prognosis of heart failure and rapid assays are now available, it is tantalising to think that we now may well have another potential use for this simple, non-invasive marker.

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IMAGES IN CARDIOLOGY

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Acute recoil in sirolimus eluting stent: real time, in vivo assessment with optical coherence tomography

In coronary arteries, final stent area is an important predictor for subsequent clinical events and restenosis. Acute stent recoil has been identified as a contributor for inadequate stent expansion. However, assessment of acute recoil is complex. We describe a method for real time imaging of acute recoil with optical coherence tomography (OCT) in a patient treated for a significant lesion in the left circumflex artery.

Panels A and B illustrate the principle. The dedicated OCT imaging wire (diameter 0.014 inch; light source 1300 nm; LightLab Imaging LLC, Westford, Massachusetts, USA) is introduced into the guidewire shaft of an over-the-wire balloon. Cross sectional images of the artery are obtained by imaging through the inflated balloon (mixture of contrast medium and saline). Panels C, D, and E demonstrate the OCT findings during postdilatation of the stent (Cypher 3.0 mm diameter/18 mm length; Cordis, Johnson & Johnson, Warren, New York, USA). The balloon (3.0 mm diameter, Open sail, Guidant, Diegem, Belgium) was stepwise inflated at 9 atm and 22 atm and then deflated to a pressure of 5 atm with the OCT imaging wire in place. At each pressure level, the maximum stent diameter was measured online by OCT. Stent diameter was 3.04 mm at 9 atm, increased to 3.50 mm at 22 atm, and decreased to 2.94 mm immediately after deflating the balloon to 5 atm. This corresponds to acute stent recoil of 16%.

Our case illustrates a new approach with OCT to image stent expansion directly during balloon inflation. This might be useful to study stent behaviour in the clinical setting and to guide improvements of stent characteristics based on in vivo findings.

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