Complimentary roles for N-terminal pro-B-type natriuretic peptide and spirometry to assess functional capacity in patients with complex mixed heart valve disease

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Abstract

Background: Assessing the effects of valvular heart disease on functional capacity is important for optimal timing of surgery.

Aim: To determine whether N-terminal pro-B type natriuretic peptide (NT-proBNP) and lung spirometry predict maximum oxygen consumption (pVO_2) on cardio-pulmonary exercise testing in patients with mixed heart valve disease.

Methods: Forty-five clinically stable patients with moderate-severe stenosis and/or regurgitation of the aortic, mitral and/or tricuspid valves were studied. The ability of echocardiography, NT-proBNP, forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) to predict impaired pVO_2 was determined.

Results: On univariate analysis the natural logarithm of NT-proBNP explained more of the variation in pVO_2 ($r^2 = 0.40$, $p < 0.0001$) than valve severity score ($r^2 = 0.20$, $p = 0.002$), pulmonary artery pressure ($r^2 = 0.21$, $p = 0.005$), left atrial area index ($r^2 = 0.25$, $p = 0.001$) or LV ejection fraction ($r^2 = 0.02$, $p = 0.4$). Low lean body weight ($r^2 = 0.21$, $p = 0.002$), FEV1 ($r^2 = 0.26$, $p = 0.0003$) and FVC ($r^2 = 0.20$, $p = 0.002$) were also associated with pVO_2. In multi-variable analysis independent determinants of pVO_2 were NT-proBNP ($r^2 = 0.27$, $p = 0.001$), FVC ($r^2 = 0.20$, $p = 0.0002$) and lean body weight ($r^2 = 0.23$, $p = 0.001$). NT-proBNP and FVC together were better predictors of $pVO_2 < 60\%$ (C statistic = 0.83, 95% CI 0.71, 0.95) than either NT-proBNP (C = 0.80, 95% CI 0.66, 0.94) or FVC (C = 0.73, 95% CI 0.57, 0.89) alone. NT-proBNP, FVC and age also predicted excessive ventilation on cardio-pulmonary exercise (combined $r^2 = 0.54$, $p < 0.0001$).

Conclusion: In patients with mixed heart valve disease NT-proBNP and spirometry provide a more reliable assessment of functional capacity than assessment by echocardiography and symptoms alone.

Key words: mitral valve, aortic valve, spirometry, BNP, cardio-pulmonary testing

Introduction

Patients with complex mixed lesions of the aortic, mitral and/or tricuspid valves are often more difficult to evaluate than those with single heart valve lesions. Echocardiographic assessment of the combined effects of several valve lesions can be difficult, and assessment of symptoms is less reliable in patients with a chronic disease which progresses slowly. For these reasons objective measures of the impact of the valve disease on functional capacity may be beneficial when deciding on optimal timing of surgery [1, 2].

Cardio-pulmonary exercise testing provides a more objective assessment of functional capacity than assessment of symptoms alone. In patients with heart failure peak oxygen consumption (pVO_2) and the ventilation to CO_2 production slope (VE/VCO_2 slope) are powerful predictors of prognosis [3, 4]. Low pVO_2 also predicts adverse outcomes in patients with mitral regurgitation [5]. However, cardio-pulmonary exercise testing requires sophisticated equipment and skilled technical staff, and is therefore not well suited to the routine outpatient assessment of patients with heart valve

disease. In contrast, brain natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP), and spirometry are simple tests which can be performed during a routine clinic visit. BNP increases with heart failure and is a powerful predictor of adverse outcome in a broad range of cardiac disease. In studies of isolated aortic stenosis [6], aortic regurgitation [7], mitral regurgitation [8, 9] and mitral stenosis [10] plasma levels of BNP or NT-proBNP increase with echocardiographic measures of disease severity, with decreased exercise capacity and with symptoms. These observations suggest that NT-proBNP may increase with the overall severity of valve disease in patients with more complex mixed valve lesions. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) decrease with heart failure and improve with medical treatment [11]. In addition, low FVC predicts new onset heart failure in individuals at increased risk [12]. However, the role of spirometry in evaluation of patients with heart valve disease is uncertain and spirometry is not currently recommended in guidelines for management of heart valve disease except for evaluation of associated pulmonary disease [1, 2].

The aim of this study is to determine whether the plasma level of NT-proBNP and/or simple lung function tests can be used to identify patients with complex mixed heart valve disease who have impaired pVO_2 and an abnormal ventilatory response on cardio-pulmonary exercise testing.

Methods

Study population

Forty-five consecutive patients with at least 2 valve lesions of greater than moderate severity on echo-cardiography using criteria from the American Society of Echocardiography guidelines [13] were recruited from the Green Lane Cardiovascular Service, Auckland, New Zealand. All participants gave written informed consent and the study was approved by the regional ethics committee. Patients were excluded if unable to perform a treadmill exercise, for significant non-valvular heart disease, overt heart failure, previous cardiac surgery, percutaneous coronary intervention or mitral balloon valvotomy, coronary artery stenosis of > 50% of vessel diameter on coronary angiography or primary pulmonary disease. Participants were clinically stable on medication. Each participant completed a symptom questionnaire, clinical examination, 12-lead electrocardiogram, an echocardiogram, blood test for NT-proBNP, spirometry and a cardio-pulmonary exercise test. The percentage body fat was determined using skin-fold thickness with calipers using previously described standard methods [14]. Each subject was classified as symptomatic or asymptomatic by a cardiologist blind to NT-proBNP, lung function and cardio-pulmonary exercise test data.

Measurement of NT-proBNP

NT-proBNP was measured from a venous blood sample taken with the patient supine using the commercially available assay (ProBNP, Roche Diagnostics, Indianapolis, IN, US). To convert NT-proBNP measured in pg/ml to pmol/l multiply by 0.118.

Echocardiography

Standard 2-dimensional and M-mode studies were performed, and measurements were taken in accordance with guidelines of the American Society of Echocardiography (ASE) [15] by an investigator who was blind to all other study data. Valve regurgitation and stenosis were assessed using standard colour-flow Doppler and 2D imaging [16]. The severity of each valve lesion was graded as mild (i), mild to moderate (ii), moderate (iii), moderate to severe (iv), or severe (v), based on criteria described in the ASE guidelines. Valve lesions which satisfied ≥ 2 ASE criteria were classified as mild, moderate or severe. When one criterion from each category was met the lesion was classed as mild-moderate or moderate-severe, as appropriate. The valve severity score was calculated by adding points for all valve lesions. Pulmonary artery systolic pressure was calculated from the tricuspid regurgitation jet velocity and the estimated right atrial pressure from imaging of the inferior vena cava.

Lung function and cardio-pulmonary exercise testing

The FEV1 and FVC were measured by spirometry and the percentage predicted from age, gender and height determined from general population values [17]. The diffusion capacity of carbon monoxide (DLCO) was also measured using standard methods [18]. Symptom-limited treadmill exercise was performed with continuous 12-lead electrocardiographic monitoring and breath-by-breath respiratory gas sampling using an age and sex determined incremental ramp protocol (VMax 229 Console, SensorMedics, Inc.). All subjects had to achieve an RER > 1.1 to ensure maximal effort. This was matched with a rating of perceived exertion according to the Borg dyspnoea scale. Patients had to simultaneously achieve a level of severe exertion and surpass the RER benchmark under continuous ECG monitoring to ensure maximal effort. Peak oxygen consumption was defined as the highest VO_2 achieved during exercise. Results are expressed as the percentage of the value predicted for age, gender and body size. The slope of ventilation to CO_2 production (VE/VCO_2 slope) during the whole exercise was calculated by linear regression.

Follow-up for adverse outcomes

Clinical outcomes were obtained up to March 2008 by contacting patients, their usual doctors and/or from

medical records. The primary outcomes were referral for cardiac surgery, cardiovascular death, including after surgery, and hospital admission for heart failure. The median follow-up was 19 (IQR 18, 21) months. Follow-up could not be obtained for one patient who returned to a Pacific Island.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) for normally distributed variables or median and inter-quartile range for asymmetrically distributed variables. Pearson's correlation coefficients were reported and Spearman correlation coefficients were used where appropriate. NT-proBNP underwent natural log transformation due to its skewed distribution. The associations between functional capacity and NT-proBNP, echocardiographic measurements and lung function measurements were investigated using univariate linear regression. Multiple regressions were applied by retaining independent variables with p values < 0.15 in the univariate models. Receiver operating characteristics (ROC) analyses were conducted to assess the associations between predictors and binary outcomes. Predictive accuracy was assessed by the area under the receiver-operating characteristic curve (C statistic) and its 95%

confidence interval. 1000 bootstrap samples were generated to obtain the estimated standard error of the C statistic and to validate the regression results. Statistical significance was defined as $p \leq 0.05$ and all tests were two tailed. SAS version 9.1 statistical software (SAS Institute Inc., Cary, NC, USA) and R version 2.4.1 (The R Foundation for Statistical Computing ISBN 3-900051-07-0) were used.

Results

Clinical characteristics of the 45 study patients are described in Table I. The aetiology was chronic rheumatic heart disease for 41 (91%) patients. Seventeen patients were of European decent, 17 Pacific Islanders, 3 New Zealand Maori, and 8 from other ethnic groups. Seventeen (38%) patients did not have cardiac symptoms and 28 (62%) had New York Heart Association class II symptoms. Fifteen (33%) patients had at least moderate severity isolated mixed mitral valve disease, 13 (29%) disease of the aortic and mitral valves, 2 (4%) mixed aortic valve disease and 15 (33%) disease of the aortic, mitral and tricuspid valves. The dominant lesion was mitral regurgitation in 12 (27%), mitral stenosis in 12 (27%), aortic stenosis in 8 (18%), aortic regurgitation in 9 (20%) and tricuspid regurgitation in 4 (9%). Thirteen (29%) subjects were in atrial fibrillation. Fifteen (33%) were taking a beta

Table I. Description of study population and comparison of asymptomatic with symptomatic patients

	All subjects	Asymptomatic	Symptomatic	p*
Number of subjects	45	17	28	
Age [years]	56 ± 16	52 ± 16	58 ± 16	0.2
Gender, male (%)	22 (49)	10 (59)	13 (46)	0.4
History of smoking, n (%)	20 (44)	6 (35)	14 (50)	0.3
BMI [kg/m^2]	27 ± 6	24 ± 4	28 ± 7	0.07
Lean body weight [kg]	51 ± 12	49 ± 11	52 ± 12	0.4
pVO$_2$, % predicted	60 ± 23	70 ± 25	55 ± 19	0.05
VE/VCO$_2$ slope, units	35 (32, 39)	32 (31, 34)	37 (35, 45)	0.0005
NT-proBNP [pg/ml]	693 (313, 1717)	372 (195, 846)	1049 (440, 2317)	0.02
LV ejection fraction [%]	56 ± 11	59 ± 8	54 ± 12	0.3
Left atrial area index [cm^2/m^2]	19 (14, 23)	17 (12, 25)	19 (15, 23)	0.6
LVESV index [cm^2/m^2]	31 (19, 41)	25 (19, 40)	32 (20, 45)	0.3
LVEDV index [cm^2/m^2]	64 (52, 98)	63 (51, 97)	67 (60, 101)	0.7
Valve severity score, units	8 (7, 11)	7 (6, 8)	9 (7, 11)	0.09
Pulmonary artery pressure [mmHg]	43 (34, 54)	34 (30, 41)	49 (36, 61)	0.003
Atrial fibrillation, n (%)	17 (38)	5 (29)	12 (43)	0.4
FEV1, % predicted	87 ± 22	99 ± 19	80 ± 20	0.008
FVC, % predicted	84 ± 19	95 ± 14	77 ± 18	0.002
FEV1/FVC [%]	74 ± 11	76 ± 6	72 ± 12	0.5
DLCO, % predicted	86 ± 23	102 ± 21	77 ± 18	0.0005

* Mann-Whitney U test
Results are mean ± standard deviation or median (inter-quartile range).

blocker, 14 (31%) an angiotensin-converting enzyme inhibitor and 16 (35%) a loop diuretic. Five study participants were current smokers and 15 subjects had a prior history of smoking. For all analyses results were not changed after adjusting for smoking status.

Comparison of symptomatic and asymptomatic patients

Clinical characteristics, echocardiography, lung function, NT-proBNP and cardio-pulmonary exercise tests for asymptomatic and symptomatic patients are also presented in Table I. Symptomatic compared to asymptomatic patients had a lower pVO_2, higher VE/VCO_2 slope on cardio-pulmonary exercise testing, higher plasma NT-proBNP, higher pulmonary artery pressure, and lower FEV1, FVC and DLCO.

Associations with NT-proBNP

There were statistically significant correlations between NT-proBNP and left atrial area index and valve severity score (Table II). In contrast, there was no statistically significant association between NT-proBNP and LV ejection fraction or LV end systolic volume index, LV end diastolic volume index, pulmonary artery pressure, FEV1, DLCO, age, gender or lean body weight.

### Associations with FVC and FEV1

Lower FVC was associated with increase in pulmonary artery pressure and a higher valve severity score (Table II).

There was no statistically significant correlation between FVC and LV ejection fraction, LV end systolic volume index, LV end diastolic volume index, or left atrial area index. FEV1 was strongly correlated with FVC and had similar associations with valve severity score (r = –0.36, p = 0.02) and pulmonary artery pressure (r = –0.56, p < 0.001). There was no significant association between FEV1 and LV ejection fraction, LV end systolic or LV end diastolic volume.

Predictors of pVO_2

Predictors of impaired pVO_2 were increased NT-proBNP, decrease in FEV1 or FVC, left atrial enlargement, higher valve severity score, higher pulmonary artery pressure, lower lean body mass and presence of symptoms (Table III). There was no statistically significant association between pVO_2 and body mass index, LV ejection fraction and LV end systolic or LV end diastolic volume. Associations between pVO_2 and NT-proBNP and FVC in symptomatic and asymptomatic patients are shown in Figure 1.

In a multivariable model which included age, gender, smoking history, NT-proBNP, echocardiographic, and lung function measurements the statistically significant independent determinants of pVO_2 were NT-proBNP (partial r^2 = 0.27, p = 0.001), lung function (FVC, partial r^2 = 0.20, p = 0.0002) and lean body weight (partial r^2 = 0.23, p = 0.001), with an overall R^2 of 0.59. Presence of symptoms, valve severity score, LV ejection fraction, left atrial area index and pulmonary artery pressure did not improve prediction of peak VO_2 with NT-proBNP, FVC and
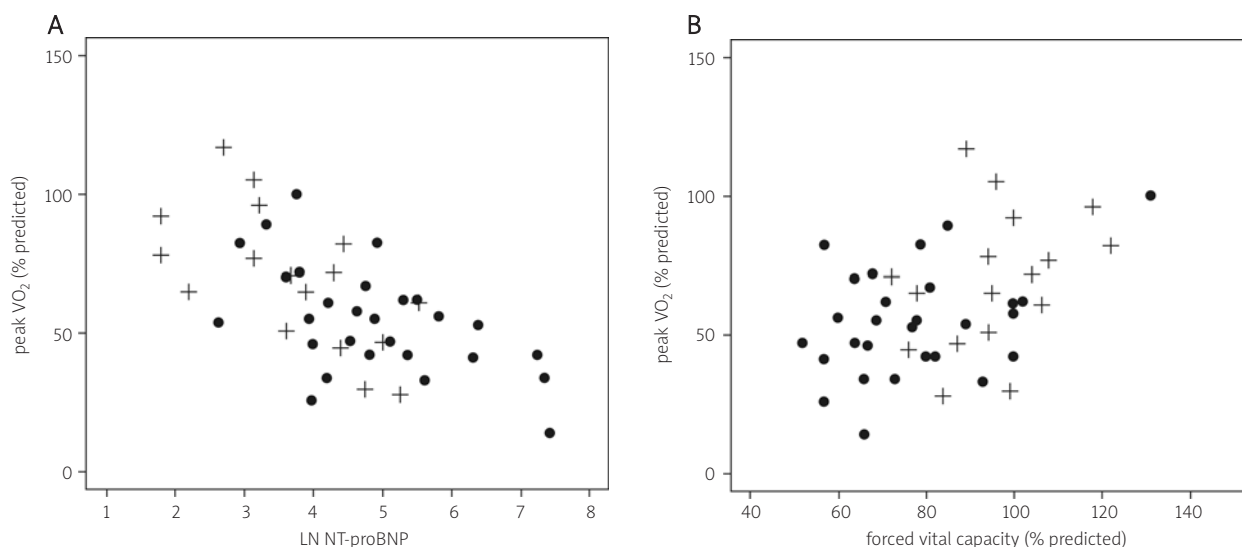
Figure 1. A – association between the natural logarithm of NT-proBNP and maximum oxygen consumption expressed as a percentage of the normal predicted value for age and gender for symptomatic (•) and asymptomatic (+) patients. Symptomatic patients on average have lower peak VO_2 and higher plasma levels of NT-proBNP than asymptomatic patients, but there is considerable overlap, particularly for intermediate values. **B** – association between the peak VO_2 and FVC for symptomatic (•) and asymptomatic (+) patients

lean body weight in the model. A model which included FEV1 in place of FVC was similar (with an overall r^2 of 0.64).

The predictive accuracy of NT-proBNP and FVC together for a $pVO_2 < 60\%$, the median level for the study population (C statistic = 0.83, 95% CI 0.71, 0.95), was slightly better than for NT-proBNP (C statistic = 0.80, 95% CI 0.66, 0.94) or FVC (C statistic = 0.73, 95% CI 0.57, 0.89) alone.

Predictors of VE/VCO_2 slope

Predictors of the VE/VCO_2 slope on cardio-pulmonary exercise were similar to predictors of pVO_2 (Table IV). Significant predictors of VE/VCO_2 slope were NT-proBNP, FEV1, FVC, age, valve severity score, pulmonary artery pressure, and presence or absence of symptoms. Lean body mass, gender, left atrial area index, LV end systolic and LV end diastolic volumes were not significant predictors of the VE/VCO_2 slope. Association between VE/VCO_2 slope and FVC is shown in Figure 2.

In a multivariable model which included echocardiographic, clinical and lung function measurements the statistically significant independent determinants of increased VE/VCO_2 slope were NT-proBNP ($r^2 = 0.27$, p = 0.001), FEV1 ($r^2 = 0.24$, p = 0.001) and age ($r^2 = 0.26$, p = 0.001), with an overall r^2 of 0.62. A model which included FVC in place of FEV1 was similar ($r^2 = 0.54$).

Outcomes

Clinical outcomes were obtained for 44 patients during a median follow-up of 19 (IQR 18, 21) months. Twenty-two patients were referred for valve surgery (n = 22). Three patients suffered cardiac death (n = 2) or death within 30 days of valve surgery (n = 1), and 4 patients had a hospital admission with heart failure in 1 patient before and in 3 after valve surgery. Sixteen patients had none of
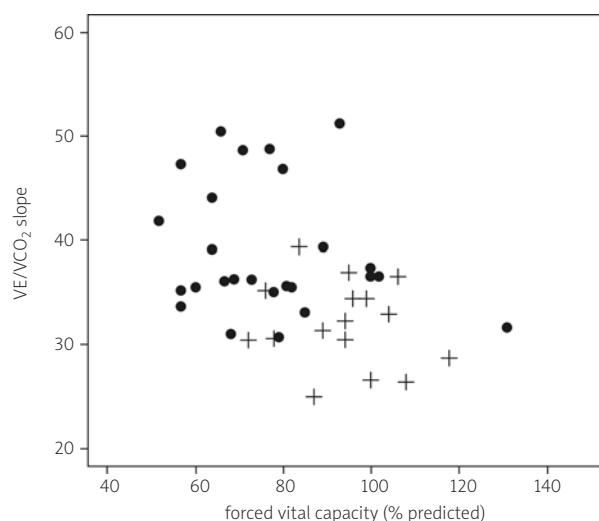
Figure 2. Association between FVC and VE/VCO_2 for symptomatic (•) and asymptomatic (+) patients

these adverse outcomes. Variables associated with a statistically significant increased hazard ratio for surgery, and for cardiac death or heart failure (n = 7) during follow-up, are presented in Table V. The cumulative freedom from cardiovascular death or hospital admission with heart failure is plotted by NT-pro-BNP and FVC in Figures 3 and 4 respectively.

Discussion

In this study there was a strong association between higher plasma levels of NT-proBNP and both pVO_2 and VE/VCO_2 slope on cardio-pulmonary exercise testing in patients with mixed valvular heart disease. Other markers of severity of cardiac disease including the valve severity

Table II. Associations of N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) and lung forced vital capacity (FVC) with echocardiographic, cardio-pulmonary exercise test and lung function measurements

	NT-proBNP		FVC	
	r	p	r	p
NT-proBNP	1	-	−0.31	0.04
VE/VCO_2 slope	0.60	<0.0001	−0.33	0.03
pVO_2	−0.64	<0.0001	0.44	0.002
Lean body weight	−0.27	0.07	−0.08	0.6
LV ejection fraction	−0.24	0.12	0.25	0.10
LVEDV index	−0.02	0.91	−0.14	0.37
LVESV index	0.14	0.38	−0.25	0.12
Left atrial area index	0.41	0.01	−0.08	0.61
Valve severity score	0.31	0.04	−0.31	0.03
Pulmonary artery pressure	0.15	0.39	−0.56	0.0004
FEV1	−0.19	0.20	0.83	< 0.0001
DLCO	−0.23	0.13	0.39	0.009
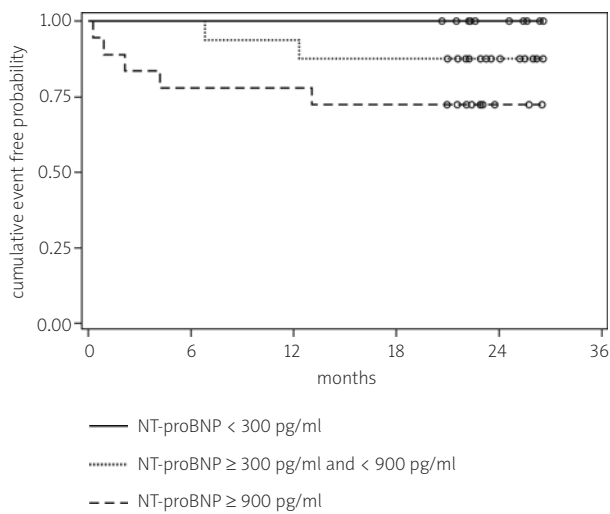
Figure 3. Freedom from cardiovascular death or hospital admission with heart failure during follow-up by plasma level of NT-proBNP. Cut-off levels are < 300 pg/ml, the upper limit of the normal reference range (n = 10), 300 to 900 pg/ml (n = 16), and ≥ 900 pg/ml, the optimal level for diagnosing heart failure in a published meta-analysis (n = 18) [31]
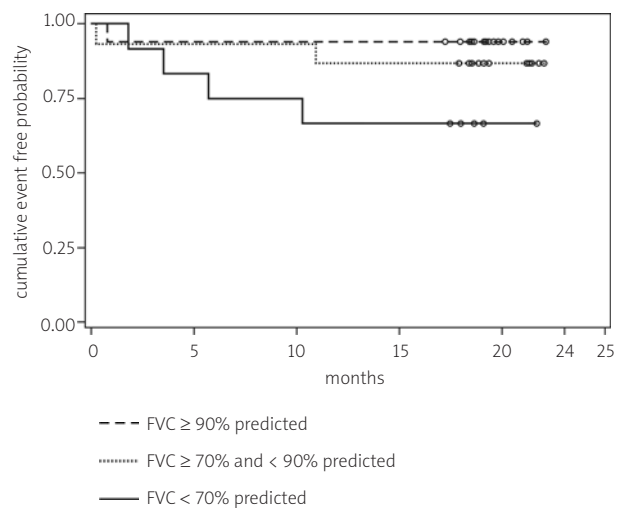
Figure 4. Freedom from cardiovascular death (n = 3) or hospital admission with heart failure (n = 4) during follow-up by forced vital capacity expressed as the percentage of the predicted measurement for age, gender and height. Cut-off levels are > 90% of predicted normal (n = 12), > 70% and ≤ 90% of predicted normal (n = 15), and ≤ 70% of predicted normal (n = 17)

Table III. Univariate predictors of lower peak oxygen consumption (pVO_2) on cardio-pulmonary exercise testing

Predictors of pVO_2	Decrease in pVO_2% (SE)*	p	Variability explained (r^2)
NT-proBNP, 2 fold increase	7.4 (1.3)	< 0.0001	40%
Valve severity score, 2 unit increase	7.9 (2.4)	0.002	20%
Pulmonary artery pressure, 10 mmHg increase	5.1 (1.7)	0.005	21%
Symptoms, Yes vs. No	15.0 (6.6)	0.03	11%
Left atrial area, 5 cm^2/m^2 increase	7.4 (2.1)	0.001	25%
FEVl, 10% decrease	5.4 (1.4)	0.0003	26%
FVC, 10% decrease	5.4 (1.7)	0.002	20%
Lean body weight, 5 kg decrease	4.4 (1.3)	0.002	21%

Peak VO_2 is the % predicted value for age and gender.
* SE – standard error
Variables included are those which were statistically significant (p < 0.05) on univariate analysis.

score, left ventricular ejection fraction, left atrial area, and pulmonary artery systolic pressure were also associated with pVO_2 and VE/VCO_2 slope. However, NT-proBNP was a stronger predictor than these echocardiographic measures, and with the exception of LV ejection fraction echocardiographic measures did not independently predict pVO_2 or VE/VCO_2 slope when NT-proBNP was included in the model. These observations suggest that NT-proBNP provides a better global measure of the effects of heart valve disease on functional capacity than any single echocardiographic measurement.

There were modest correlations between plasma NT-proBNP and left atrial size, valve severity score and LV ejection fraction. However, there was no significant association between LV end systolic or LV end diastolic volume index and NT-proBNP, consistent with studies in patients with single valve lesions [7, 8, 19]. In patients with mitral or aortic regurgitation increase in LV volume may be a less reliable measure of LV systolic function because LV modelling in part reflects the adaptive response to the volume load. In previous studies of mitral [20] and aortic regurgitation [7] changes in LV function on exercise stress

Table IV. Univariate predictors of increased VE/CO$_2$ slope on cardio-pulmonary exercise testing

Variables	Increase in VE/VCO$_2$ (SE)	p	Variability explained r^2
Ln (NBNP), 2 fold increase	2.1 (0.4)	< 0.0001	39%
Valve severity score, 2 unit increase	1.7 (0.7)	0.03	11%
Pulmonary artery pressure, 10 mmHg increase	1.5 (0.6)	0.02	15%
Ejection fraction 10% decrease	2.2 (0.9)	0.02	13%
Symptoms, Yes vs. No	6.7 (1.7)	0.0002	28%
FEV1, 10% decrease	1.2 (0.4)	0.006	17%
FVC, 10% decrease	1.3 (0.5)	0.01	14%
Age, 10 years older	1.4 (0.5)	0.01	14%

SE – standard error
Variables included are those which were statistically significant (p < 0.05) on univariate analysis.

Table V. Hazard ratios for cardiac surgery, and for cardiac death or hospital admission with heart failure during follow-up by echocardiographic, lung function, NT-proBNP and cardio-pulmonary exercise test measurements

	Cardiac surgery	p	Death or CHF+	p
Number of subjects	22		7	
Valve severity score, 2 unit increase	1.39 (0.99, 1.96)	0.06	1.83 (1.01, 3.30)	0.05
LVEDV index, +10 cm^2/m^2	1.06 (1.00, 1.13)	0.04	0.80 (0.61, 1.05)	0.10
Pulmonary artery pressure, + 10 mmHg	1.11 (0.89,1.38)	0.36	1.61 (1.18, 2.20)	0.003
NT-proBNP, 2 fold increase	1.25 (1.00, 1.57)	0.05	2.10 (1.31, 3.37)	0.002
FVC, 10% decrease	1.30 (1.02, 1.66)	0.04	1.63 (0.98, 2.71)	0.06
FEV1, 10% decrease	1.27 (1.06, 1.52)	0.009	1.56 (1.09, 2.24)	0.02
pVO$_2$, 10% decrease	1.18 (0.98, 1.43)	0.09	2.15 (1.27, 3.62)	0.004
VE/VCO$_2$ slope, +10 units	1.81 (0.93, 3.51)	0.08	5.82 (1.86, 18.17)	0.002

Variables with a statistically significant (p < 0.05) increase in hazard for cardiac surgery or for cardiac death/CHF are presented
for FVC and pVO$_2$ the units of measurement are the % of the predicted value for age, gender and height (for FVC).
CHF+ – treatment for congestive heart failure (n = 4)
Death – cardiac death (n = 2) or death early after cardiac surgery (n = 1)

echocardiography were more strongly associated with the plasma level of BNP than resting measures of LV function.

Previous studies have not combined evaluation of BNP and simple measures of lung function. In patients with heart failure FEV1 and FVC may be reduced with a normal FEV1 to FVC ratio, and this correlates with the severity of functional impairment [21, 22]. Decreases in FEV1, FVC and DLCO have also been described in patients with severe mitral stenosis [18, 23]. In the current study FEV1 and FVC were lower than predicted normal values in patients with symptoms and were strong independent predictors of pVO$_2$ and VE/VCO$_2$ slope. However, the associations between NT-proBNP and both FVC and FEV1 were modest, suggesting that NT-proBNP and spirometry provide information on different pathophysiological pathways by which heart valve disease causes symptoms and limits functional capacity.

Restrictive lung function may be explained in part by the homeostatic mechanisms which maintain alveolar ventilation–perfusion matching when cardiac output decreases. Decrease in alveolar blood flow results in a relative excess in alveolar ventilation and a fall in alveolar PCO$_2$. This stimulates constriction of alveolar ducts to reduce alveolar ventilation. The result is an increase in the physiological dead space and a decrease in the forced vital capacity and FEV1, with a normal FEV1/FVC. During exercise the increase in ventilation relative to CO$_2$ production is greater because of the increased physiological dead space [21]. In experimental models abrupt reduction in pulmonary artery blood flow results in an increase in lung impedance, a decrease in vital capacity and an increase in residual volume, changes which are reversed by increasing inspired CO$_2$ [24, 25]. Impaired lung function may also result from an increase in alveolar-capillary membrane conductance due to increased pulmonary venous congestion which also decreases DLCO [26, 27]. In the current study DLCO and FVC were both lower in symptomatic patients but FVC and FEV1 were better predictors of pVO$_2$ and VE/VCO$_2$ slope.

While on average pVO_2 was lower in symptomatic compared to asymptomatic patients, there was considerable overlap between individual subjects. Echocardiographic measurements of the severity of valve disease and LV function were only modest predictors of pVO_2 and VE/VCO$_2$ slope on cardio-pulmonary exercise testing. These observations are consistent with studies in heart failure populations in which there may be large differences in pVO_2 between patients in the same symptom class, and echocardiographic measures such as LV ejection fraction correlate poorly with objective measures of functional capacity [28]. In heart failure populations LV ejection fraction, NT-proBNP, pVO_2 and VE/VCO$_2$ slope each provide independent prognostic information [3, 29]. Lower lean body mass from skeletal muscle deconditioning is also associated with decreased pVO_2 and a poorer prognosis independent of cardiac output [30]. In the current study lower lean body mass was an independent predictor of low pVO_2 but not increase in VE/VCO$_2$ slope.

Study limitations

There are currently no clear guidelines on how to accurately summarize the severity of multiple valve lesions. For this study a valve severity score based on the ASE severity classifications [13] for single valve lesions was developed, but further research is needed to validate this approach. The study was too small for reliable subgroup analysis of different valve lesions. In addition the observational study design does not allow assessment of the effects of medical treatments including beta-blockers, angiotensin-converting inhibitors and diuretics. The study included subjects with a history of smoking, which may cause obstructive airways disease and a reduction in FEV1 and FEV1/FVC. However, FVC, pVO_2 and VE/VCO$_2$ slope were similar for subjects with and without a history of smoking, and statistical adjustment for smoking status did not change the study results. The number of patients who suffered adverse outcomes was small. Despite this NT-proBNP, FVC, VE/VE slope and pVO_2 on cardio-pulmonary exercise testing each predicted risk of heart failure or cardiac death during follow-up, suggesting that these are important prognostic measures in patients with valvular heart disease as well as heart failure.

Conclusions

NT-proBNP and spirometry provide additional information to echocardiography on the overall severity of the heart disease and its impact on functional capacity. These simple, widely available tests may be useful for monitoring patients in the community to identify those who should be referred for specialist cardiology assessment and aid decisions on optimal timing of surgical intervention.

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Pomiar stężenia NT-proBNP i badanie spirometryczne pozwalają na dokładniejszą ocenę wydolności wysiłkowej chorych ze złożoną wadą serca

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Streszczenie

Wstęp: Ocena wpływu zastawkowej wady serca na wydolność wysiłkową jest istotna dla ustalenia optymalnego momentu wykonania zabiegu operacyjnego.

Cel: Ustalenie, czy pomiar stężenia NT-proBNP i wyniki spirometrii są pomocne w przewidywaniu maksymalnego pochłaniania tlenu (pVO_2) podczas spiroergometrycznego testu wysiłkowego u chorych ze złożoną wadą serca.

Metody: Grupa badana obejmowała 45 stabilnych klinicznie chorych z umiarkowaną lub ciężką stenozą i/lub niedomykalnością aortalną, mitralną i/lub trójdzielną. Oceniono znaczenie parametrów echokardiograficznych, stężenia NT-proBNP, jednosekundowej natężonej objętości wydechowej (FEV1) oraz natężonej pojemności życiowej (FVC) dla przewidywania zaburzonych wartości pVO_2.

Wyniki: Analiza jednoczynnikowa wykazała, że naturalny logarytm NT-proBNP lepiej przewidywał zmiany wartości pVO_2 ($r^2 = 0,40$, $p < 0,0001$) niż wskaźnik nasilenia wady zastawkowej ($r^2 = 0,20$, $p = 0,002$), ciśnienie w tętnicy płucnej ($r^2 = 0,21$, $p = 0,005$), powierzchnia lewego przedsionka ($r^2 = 0,25$, $p = 0,001$) lub frakcja wyrzutowa lewej komory ($r^2 = 0,02$, $p = 0,4$). Niska waga ciała ($r^2 = 0,21$, $p = 0,002$), FEV1 ($r^2 = 0,26$, $p = 0,0003$) i FVC ($r^2 = 0,20$, $p = 0,002$) były również związane z wartościami pVO_2. Analiza wieloczynnikowa wykazała, że stężenie NT-proBNP ($r^2 = 0,27$, $p = 0,001$), FVC ($r^2 = 0,20$, $p = 0,0002$) i waga ciała ($r^2 = 0,23$, $p = 0,001$) były niezależnymi czynnikami predykcyjnymi dla wartości pVO_2. Wartości stężeń NT-proBNP i FVC razem lepiej przewidywały obniżone wartości $pVO_2 < 60\%$ (statystyka C = 0,83, 95% CI 0,71, 0,95) niż osobno wynik proBNP (C = 0,80, 95% CI 0,66, 0,94) lub FVC (C = 0,73, 95% CI 0,57, 0,89). Wartości stężeń NT-proBNP, FVC i wiek przewidywały również nadmierną wentylację podczas wysiłkowego testu spiroergometrycznego (złożone $r^2 = 0,54$, $p < 0,0001$).

Wnioski: U chorych ze złożoną, mieszaną wadą serca analiza stężenia NT-proBNP i wyników spirometrii pozwala na dokładniejszą ocenę wydolności wysiłkowej niż analiza parametrów echokardiograficznych i objawów klinicznych.

Słowa kluczowe: wada serca, spirometria, NT-proBNP, test spiroergometryczny

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