

# The prognostic value of estimated glomerular filtration rate, amino-terminal portion of the pro-hormone B-type natriuretic peptide and parameters of cardiopulmonary exercise testing in patients with chronic heart failure

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## Abstract

The aim of this study was to evaluate the prognostic value of renal function in relation to amino-terminal portion of the pro-hormone B-type natriuretic peptide (NT-proBNP) and parameters of cardiopulmonary exercise testing in predicting mortality and morbidity in patients with moderate chronic heart failure (CHF). Sixty-one CHF patients

were included in the study. Patients' characteristics were: age  $64.3 \pm 11.6$  years; New York Heart Association class *III/III*: 14/37/10; left ventricular ejection fraction:  $0.30 \pm 0.13$  (%); NT-proBNP:  $252.2 \pm 348.0$  (ng/L); estimated creatinine clearance (e-CC):  $73.6 \pm 31.4$  (mL/min); estimated glomerular filtration rate (e-GFR):  $66.1 \pm 24.6$  (mL/min/1.73 m<sup>2</sup>); the highest O<sub>2</sub> uptake during exercise (VO<sub>2-peak</sub>):  $1.24 \pm 0.12$  mL/kg/min; VO<sub>2</sub>/workload:  $8.52 \pm 1.81$  (mL/min/W)]. During follow up (59.5 ± 4.0 months) there were 15 cardiac deaths and 16 patients were hospitalized due to progression of heart failure. NT-proBNP and VO<sub>2</sub>/workload were independently associated with cardiac death (P=0.007 and P=0.006, respectively). Hospitalization for progressive CHF was only associated with NT-proBNP (P=0.002). The combined cardiac events (cardiac death and hospitalization) were associated with NT-proBNP and VO<sub>2</sub>/workload (P=0.007 and P=0.005, respectively). The addition of estimates of renal function (neither serum creatinine nor e-GFR) did not improve the prognostic value for any of the models. In conclusion, in patients with moderate CHF, increased NT-proBNP and reduced VO<sub>2</sub>/workload identify those with increased mortality and morbidity, irrespective of estimates of renal function.

approximately 20%.<sup>2</sup>

Left ventricular ejection fraction (LVEF) and several cardiopulmonary exercise test (CPET) parameters, such as the highest O<sub>2</sub> uptake during exercise (VO<sub>2-peak</sub>), have been identified as prognostic variables. Both a lower LVEF and VO<sub>2-max</sub> are associated with reduced survival.<sup>3</sup> Activation of several neurohormonal axes and changes in the autonomic nervous system play a pivotal role in the decline of cardiac function and are also associated with prognosis. For example, the plasma concentration of amino-terminal portion of the pro-hormone B-type natriuretic peptide (NT-proBNP),<sup>4</sup> and the cardiac sympathetic neuronal function as assessed with <sup>123</sup>I-metaiodobenzylguanidine (<sup>123</sup>I-MIBG)<sup>5</sup> were shown to be associated with outcome in CHF patients. Renal dysfunction is often present in CHF patients with reported creatinine clearance lower than 60 mL/min in up to 50% of patients.<sup>6,7</sup> Although the mechanisms behind this so-called cardio-renal syndrome are not fully understood, the serum creatinine-based estimates of renal function in particular were shown to be independently related to mortality.<sup>8-12</sup> Despite a real wealth of data, few studies compare the contribution of each prognostic indicator in predicting mortality and morbidity in CHF patients. In particular, there is a lack of data on the prognostic value of estimates of renal function in relation to CPET derived parameters. Therefore, the goal of this study was to evaluate the prognostic value of the CPET derived parameters, NT-proBNP and LVEF in relation to renal function in CHF patients.

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## Introduction

Chronic heart failure (CHF) is a disorder associated with high mortality and prolonged hospitalizations and affects more than 10 million people in the countries represented by the European Society of Cardiology and almost 6 million people in the US.<sup>1,2</sup> Over the last decades, the number of CHF deaths has increased steadily despite advances in treatment. CHF still carries a high risk of death with a reported 1-year mortality rate of

## Materials and Methods

Between 1 January 2001 and 31 December 2002, 61 consecutive patients with recently diagnosed heart failure were included in the

study and were subjected to cardiopulmonary exercise testing. The study protocol was approved by the local ethics committee and the procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 2008. All subjects gave their written informed consent to take part in the study. Plasma NT-proBNP and serum creatinine values were measured before exercise testing. Glomerular filtration rate was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation.

CHF severity was clinically evaluated according to the New York Heart Association (NYHA) classification. The census date for follow up was set at 1 February 2008. The mean follow up after spirometry was 59.5±4.0 months (range 53-66 months) and at the census date complete follow-up data could be obtained for all subjects.

#### Cardiopulmonary exercise testing

All subjects underwent CPET using a bicycle ergometer with a ramp protocol in accordance with the recommendations of the American Thoracic Society/American College of Chest Physicians.<sup>13</sup> The incremental symptom-limited exercise protocol consisted of a 5-15 Watt stepwise increase of workload, depending on the individually predicted maximum exercise capacity and in such a way that the calculated maximal effort could be attained in approximately 10-15 min. Heart rate, ST-T changes, and arrhythmias were checked using a 12-lead echocardiogram. Blood pressure was measured and recorded every minute by an automatic sphygmomanometer. All patients were exercised to their maximum exercise capability.

$VO_{2\text{-peak}}$  was determined as the largest value in the terminal phase of exercise. Measured cardiopulmonary exercise test parameters were compared with predicted normal values from Wasserman and co-workers and reported as percentages of the predicted values.<sup>14</sup> The system was calibrated before each test according to the manufacturer's specifications.

#### Measurements of pulmonary function during exercise

Expired gas analysis was performed throughout the exercise session on a breath-by-breath basis with an Aeromonitor AE-280 (Minato Medical Science). The system was calibrated before each study. The minute ventilation (VE), oxygen uptake ( $VO_2$ ), and carbon dioxide output ( $VCO_2$ ) were used to calculate the anaerobic threshold (AT), peak  $VO_2$  ( $VO_{2\text{-peak}}$ ), and the rate of change in  $VO_2$  divided by the rate of change in external workload ( $VO_2/\text{workload}$ ). The AT was determined by the V-slope method.

#### Amino-terminal portion of the pro-hormone B-type natriuretic peptide and serum creatinine

Serum concentrations of creatinine and NT-proBNP were determined according to routine hospital procedure. Reference levels for creatinine were 75-110  $\mu\text{mol/L}$  for men and 65-95  $\mu\text{mol/L}$  for women.

#### Renal function

The estimated glomerular filtration rate (e-GFR) was calculated using the abbreviated MDRD-formula:<sup>15</sup>

$$\text{e-GFR} = 32788 \times [\text{serum creatinine } (\mu\text{mol/L})]^{-1.154} \times [\text{age}(\text{years})]^{-0.203} \times [0.742 \text{ for females}] \times [1.212 \text{ for blacks}]$$

The e-GFR was expressed per 1.73 m<sup>2</sup> of body surface area (mL/min/1.73 m<sup>2</sup>).

Patients were stratified into those with a moderate impairment of kidney function or worse (e-GFR <60 mL/min/1.73 m<sup>2</sup>) and those with a relative normal e-GFR (*i.e.*  $\geq 60$  mL/min/1.73 m<sup>2</sup>).<sup>16</sup>

#### Follow up

Follow-up data were obtained from at least one of four sources: visit to the outpatient clinic; review of the patient's hospital records; personal communication with the patient's physician; a telephone interview with the patient conducted by trained personnel. Outcome was defined as the occurrence of any of the following events during follow up: cardiac death and/or hospitalization for the progression of heart failure.

#### Statistical analysis

Cox's proportional hazard regression analysis was used to investigate the relationship between several variables and the combined end point of cardiac death or hospitalization. Each individual parameter was entered in the Cox's proportional hazard regression analysis if  $P < 0.05$ . First, several variables of heart failure (LVEF, NYHA, NT-proBNP) and CPET parameters ( $VO_2/\text{workload}$  and  $VO_{2\text{-peak}}$ ) were entered into the model according to a stepwise forward likelihood ratio based method. Secondly, the possible additional value of an estimate of renal function (*i.e.* e-GFR) was determined. These data were added to the first model according to the enter method (forced addition to the model). The proportional hazards assumption was tested using the partial residuals of the multivariate Cox's analyses for each covariate. The partial residual for each covariate was plotted against time to event (*i.e.*

combined end point of cardiac death or hospitalization). The resulting scatter plot was then used to assess the proportional hazards assumption. If the proportional hazards assumption is correct with respect to the covariate, then the scatter plot should show no pattern (*i.e.* random distribution). All covariates selected for our analysis were tested in this way and none showed a pattern indicating dependency between the tested covariate and time to event. Therefore, we concluded that for all covariates the proportional hazards assumptions were fulfilled. The  $\chi^2$  test, Cox's proportional hazard regression coefficient (coefficient B) and exponent (exponent B) were used to describe the model and relative contribution of the parameters to the model. Exponent B can, therefore, be considered to be the predicted change in hazard for a unit change in the predictor.  $P < 0.05$  was considered statistically significant. All statistical analyses were performed with SPSS software (SPSS for Windows, version 16.0, SPSS Inc., Chicago, IL, USA).

## Results

### Baseline characteristics

Sixty-one consecutive patients with a history of CHF were included with a mean age of 64.3±11.6 years. The etiology of CHF was almost equally divided between ischemic and non-ischemic causes (51% *vs* 49%, respectively). The majority of patients were in NYHA class II (61%,  $n=37$ ) while there were no patients in NYHA class IV. The majority of patients (56%) had severe left ventricular dysfunction (*i.e.* LVEF<35%). The majority of the patients were on beta-blockers, diuretics and angiotensin-converting-enzyme-inhibitors/AT-II receptor blockers. At baseline, only a minority of patients had implanted devices (15%,  $n=9$ ). Baseline characteristics are shown in Table 1.

CPET parameters were available in all study patients and are shown in Table 2.

### Renal function related parameters

The serum creatinine level and the e-GFR are shown in Table 3. Twenty-three male patients (50%) had an increased serum creatinine concentration (*i.e.*  $>110$   $\mu\text{mol/L}$ ) and 5 female patients (33%) had an increased serum creatinine concentration (*i.e.*  $>95$   $\mu\text{mol/L}$ ). Twenty-seven patients (44%) showed signs of a moderate impairment of renal function or worse according to e-GFR (*i.e.* e-GFR <60 mL/min/1.73m<sup>2</sup>).

### Follow up and cardiac events

During follow up there were 31 cardiac events (15 cardiac deaths and 16 hospitaliza-

tions for progression of CHF, Table 4). The mean follow up to a cardiac event after spirometry was  $43.8 \pm 22.1$  months (median 54.0 months, range 1-66 months).

### Cox's proportional hazard regression analysis

Cox's proportional hazard regression analysis showed that NT-proBNP and  $VO_2$ /workload were associated with the combined end point: cardiac death and hospitalization ( $\chi^2$  of the model: 26.76, Table 5). The e-GFR was not associated with the combined end point (Table 5) and the addition of the e-GFR did not significantly improve the predictive power of the model ( $\chi^2$  27.51,  $P=0.555$  compared to the model including NT-proBNP and  $VO_2$ /workload).

## Discussion

The present study demonstrates that NT-proBNP and CPET derived parameters are independent predictors of mortality and morbidity in CHF. However, e-GFR as an estimate of renal function did not appear to have additional value in predicting cardiac events.

There is much evidence to support the use of LVEF to risk-stratify patients with CHF. Although low LVEF (<40%) identifies a group with relatively increased risk, the majority of sudden cardiac deaths (SCD) occur in patients with more preserved LVEF (*i.e.* >40%). This highlights the limited sensitivity of LVEF as a marker of prognosis in CHF.<sup>17</sup> In addition, in patients with CHF, renal dysfunction is highly prevalent and has been shown to be a risk factor for in-hospital mortality, regardless of left ventricular function.<sup>18</sup> Our results are in line with this and indicate that, regardless of left ventricular function, NT-proBNP and  $VO_2$ /workload appear to be independent predictors of mortality and morbidity in patients with CHF.

In a sub-analysis of the ProBNP Investigation of Dyspnea in the Emergency Department study, multivariate analysis showed that NT-proBNP was the strongest overall independent risk factor for 60-day mortality (HR 1.6; 95% confidence interval (95% CI): 1.2-2.0;  $P=0.0004$ ) and remained so even in those patients with GFR less than 60 mL/min/1.73 m<sup>2</sup> (HR 1.6; 95% CI: 1.1-2.3;  $P=0.006$ ).<sup>19</sup> However, this study focused on acute CHF. In a study by Gardner *et al.* NT-proBNP was superior to GFR estimated by MDRD in patients with advanced CHF evaluated for cardiac transplantation.<sup>20</sup> Multivariate analysis showed that NT-proBNP was the only independent predictor of all-cause mortality (HR 2.5; 95% CI: 1.0-6.2;  $P=0.04$ ). Furthermore, NT-proBNP was able to identify patients with a poor prognosis whose GFR was

**Table 1. Cardiopulmonary exercise parameters.**

Baseline characteristics	Patients
Male/Female	46/15 (75/25%)
Age, years [range]	64.3±11.6 [40-86]
Length, cm	171.6±9.4
Weight, kg	80.2±17.9
Body mass index	27.1±5.1
Etiology of CHF:	
Ischemic	31 (51%)
Non-ischemic	30 (49%)
NYHA, I/II/III	14/37/10 (23/61/16%)
NT-proBNP, ng/L [range]	252.2±348.0 [8-1886]
LVEF:	
Normal LV, >60%	1 (2%)
Mild LV dysfunction, 46-60%	10 (16%)
Moderate LV dysfunction, 35-45%	16 (26%)
Severe LV dysfunction, <35%	34 (56%)
Mitral valve regurgitation (MVR):	
No MVR	4 (7%)
Mild MVR, <20%	27 (44%)
Moderate MVR, 20-40%	20 (33%)
Severe MVR, <40%	10 (16%)
Medication:	
Beta-blockers:	
Selective	35 (57%)
Non-selective	16 (26%)
ACE inhibitor	45 (74%)
ATII receptor blockers	16 (26%)
Diuretics	57 (93%)
Digoxine	23 (38%)
Aldactone	33 (54%)
Amiodarone	9 (15%)
Devices:	
ICD	4 (7%)
Bi-ventricular pacemaker	5 (8%)

CHF, chronic heart failure; NYHA, New York Heart Association; Nt-proBNP, amino-terminal portion of the pro-hormone B-type natriuretic peptide; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator.

**Table 2. Functional lung parameters.**

Parameters	Patients
Vital capacity (VC), L	3.28±0.82
FEV1, L/s	2.36±0.72
FEV1/VC, %	70.3±10.5
MVV, L/s	92.9±28.0
Exercise:	
Peak heart rate, min <sup>-1</sup>	131±24
Systolic BP at peak exercise, mmHg	168±82
Rate pressure product, mmHg/min	22011±6913 [10296-41832]
$VO_{2-peak}$ ml/kg/min	1.24±0.12
Predicted $VO_{2-peak}$ %	57.7±17.8
$VO_2$ /workload, ml/min/W	8.52±1.81
Anaerobic threshold (AT)	0.77±0.28

VC, vital capacity (L); FEV1, forced expiratory volume in one second (L/s); FEV1/VC%, % of VC expired in one second (%); MVV, maximal voluntary ventilation: breathing as deeply and as rapidly as possible for 15 s (average air flow in L/s); BP, blood pressure;  $VO_{2-peak}$  the peak capacity to transport and use oxygen during incremental exercise (mL/kg/min); predicted  $VO_{2-peak}$  (%), percentage of age predicted  $VO_{2-peak}$ ;  $VO_2$ /workload,  $VO_2$  in relation to workload (mL/min/W); AT, ventilatory anaerobic threshold is defined as the point at which minute ventilation increases disproportionately in relation to  $VO_2$ .

already low. More recently, Bruch *et al.* showed that NT-proBNP was an independent predictor of cardiac events both in patients with and without renal dysfunction.<sup>21</sup> Our findings are in line with these publications and show that, irrespective of renal function, NT-proBNP appears to be an independent predictor of events in an outpatient CHF population with relatively mild disease.

Renal dysfunction probably affects the concentrations of NT-proBNP. However, it is not clear whether this effect reflects the increased release of NT-proBNP due to the presence of cardiac disease in patients with renal dysfunction or due to reductions in the clearance of NT-proBNP. It is, therefore, tempting to speculate that this has significant implications for the use of NT-proBNP for the evaluation of patients with renal dysfunction. Although the clearance of NT-proBNP is not well understood, there are indications for renal dependency. Small amounts of NT-proBNP may be recovered in urine, and in hemodialysis patients NT-proBNP levels are markedly elevated.<sup>22-28</sup> Thus, renal clearance is likely to play a role in the removal of NT-proBNP and, therefore, elevated levels of NT-proBNP in patients with CHF and renal dysfunction can at least in part be explained by a decreased clearance. However, there is a wide variety of NT-proBNP levels among patients with renal dysfunction and CHF.<sup>19</sup> This suggests that reduced clearance is only one mechanism of the increased NT-proBNP levels in these patients. Furthermore, the high prevalence of both structural and functional cardiac abnormalities among those with renal insufficiency suggests that the increased levels of NT-proBNP are likely to reflect structural heart disease.<sup>19,23,24,26</sup>

Cardiopulmonary exercise testing (CPET) with gas-exchange analysis has become a routine clinical tool for the evaluation of patients with CHF.<sup>13</sup> Because of its direct relationship with cardiac output one of the most widely accepted CPET derived parameter is  $VO_{2\text{-peak}}$ . This is traditionally defined as the highest  $O_2$  uptake for a given subject during exercise. Another CPET derived parameter is  $VO_2$  in relation to external workload. Normally,  $VO_2$  increases almost linearly with external workload. The slope of  $VO_2$  versus external work rate reflects the efficiency of the metabolic conversion of chemical potential energy to mechanical work and the mechanical efficiency of the musculoskeletal system. The slope determined from the rate of change in  $VO_2$  divided by the rate of change in external work is independent of age, gender and height. In addition to this, there are also few processes that affect the metabolic efficiency of muscles and, therefore, a reduction in the value of this relationship most often indicates inadequacies of  $O_2$  transport, which may make  $VO_2$  workload

superior to  $VO_{2\text{-peak}}$ . Reports have shown that the ratio of increase in  $VO_2$  to the increase in external workload rate is decreased in patients with CHF.<sup>29,30</sup> However, CPET has a number of disadvantages: it is time-consuming, expensive, not readily available, and not routinely applicable as a rapid diagnostic test in an ambulatory setting of a CHF clinic. However, despite these limitations and based on the results of the current findings we advocate the use of CPET in this patient population.

### Study limitations

The main limitation of our study was the relatively small size of the study group which limited the statistical power. Only consecutive CHF patients who were able to undergo cardiopulmonary exercise testing were included. This may have resulted in a selection bias

leading to differences in patients' characteristics between the present study and other heart failure populations in the community or hospitals. Our results do not apply to severe heart failure because the majority of our patients were in NYHA classes II and III. In addition, the majority of our patients had a reduced systolic left ventricular function (82%). Therefore, the extrapolation of our results to CHF patients with a more or less preserved left ventricular function is problematic.

### Conclusions

Although the findings of this study should be considered to be preliminary, the observations indicate that in patients with relatively mild CHF, NT-proBNP and  $VO_2$  workload can

**Table 3. Estimates of renal function.**

Estimates of renal function	Overall N=61	Male >110 $\mu\text{mol/L}$ N=23	Female >95 $\mu\text{mol/L}$ N=5
Creatinine, mol/L [range]	109.6±38.4 [49-224]	143.9±32.5 [112-224]	129.4±33.8 [101-180]
	Overall N=61	<60 mL/min/1.73m <sup>2</sup> N=27	≥60 mL/min/1.73m <sup>2</sup> N=34
e-GFR, mL/min/1.73m <sup>2</sup> [range]	66.1±24.6 [26-154]	45.3±10.7 [26-59]	83.4±19.0 [61-154]

Estimated glomerular filtration rate (e-GFR) according to the modification of diet in renal disease equation.

**Table 4. Cardiac events.**

Events	Patients
Death from heart failure	9
Death from other cardiac related causes	6
Non-cardiac deaths	3
Hospitalization for progression of heart failure	16
Hospitalization for other cardiac related diseases	6

**Table 5. Cox's proportional hazard regression analysis.**

Model for combined cardiac events (death and hospitalization)	Coefficient B	SE Coeff B	Exponent B [95%CI]	P
$VO_2$ workload, mL/min/W	-0.703	0.249	0.495 [0.304-0.806]	0.005
NT-proBNP, ng/L	0.002	0.001	1.002 [1.001-1.003]	0.007
e-GFR, mL/min/1.73m <sup>2</sup>	0.008	0.010	1.008 [0.988-1.028]	0.444

identify CHF patients at risk of increased mortality and morbidity, irrespective of estimates of renal function.

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