Submaximal exercise gas exchange is an important prognostic tool to predict adverse outcomes in heart failure

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Aims

Traditionally, $\text{VO}_{2\text{peak}}$ has been used to determine prognosis in heart failure; however, this measure has limitations. Hence, other exercise and gas exchange parameters measured submaximally, e.g. breathing efficiency (V_E/VCO_2), end-tidal CO_2 ($P_{\text{ET}}\text{CO}_2$), oxygen uptake efficiency slope (OUES), and circulatory power [VO_2^* systolic blood pressure (SBP)], have been investigated. The aim of this study was to investigate the prognostic relevance of submaximal exercise gas exchange in heart failure patients.

Method and results

One hundred and thirty-two consecutive heart failure patients (mean age 56 ± 12 years, ejection fraction $29 \pm 11\%$) performed peak treadmill testing. Gas exchange and haemodynamic variables were measured continuously. Gas exchange data obtained from the first 2 min of exercise and at a respiratory exchange ratio (RER) of 0.9 were the measurements of interest. Over a median follow-up period of 62.4 (range 0–114) months, there were 44 endpoints (death or transplant). Univariate analysis demonstrated submaximal predictors of survival, which included V_E/VCO_2 slope and ratio, $P_{\text{ET}}\text{CO}_2$, OUES, and circulatory power ($P \leq 0.01$). When these and additional submaximal variables were included together in the multivariable analysis, the strongest submaximal exercise predictive model (C-statistic 0.75) comprised data from the first stage of exercise (V_E and circulatory power) and at an RER of 0.9 (V_E/VCO_2 ratio). The inclusion of $\text{VO}_{2\text{peak}}$ and demographic data, with submaximal data (V_E/VCO_2 ratio at an RER = 0.9), increased the predictiveness of the model (C-statistic 0.78).

Conclusion

Submaximal exercise measures provide useful prognostic information for predicting survival in heart failure. This form of testing is logistically easier, cheaper, and safer for patients compared with maximal exercise.

Keywords

Heart failure • Submaximal exercise • Outcomes • Gas exchange

Introduction

Heart failure is an increasingly common disorder causing high mortality and morbidity, despite modern developments in medical therapy.¹ As a result, the need for assessing prognosis has become more important, especially when considering high treatment costs and the limited availability of definitive surgical intervention. Cardiopulmonary exercise testing, when performed properly, provides an objective measurement of peak functional capacity and is an important clinical tool assessing disease severity and predicting outcomes in heart failure populations.²

Non-invasive measurements of respiratory and haemodynamic variables at maximal exercise have been shown to be useful in predicting the health status and long-term prognosis of heart failure patients.³ For a long time, peak VO_2 has been seen as the 'gold standard' measure for identifying patients with poorer prognosis;⁴ a lower $\text{VO}_{2\text{peak}}$ ($< 14 \text{ mL/kg/min}$) indicating a more severe heart condition.³ Maximal exertion in heart failure patients is, however, not without risk and is not tolerated well by some patients.^{5,6} In addition, measurements of $\text{VO}_{2\text{peak}}$ may be heavily influenced by patient motivation and can be subject to investigator bias.⁴ As a result, other ventilatory parameters [e.g. breathing efficiency (V_E/VCO_2), oxygen uptake efficiency slope (OUES), and end-tidal

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CO_2 (P_{ETCO_2}) measured at rest and submaximal and peak exercise have been investigated to determine their prognostic values.^{1–6}

Recent studies have investigated ventilatory efficiency, expressed as V_E/VCO_2 slope or ratio, in heart failure patients during submaximal and peak exercise.^{7–10} The majority were in agreement that a steeper slope was an indication of inefficient breathing and poorer prognosis,^{6,11} with submaximal measurements providing results similar to those made at peak exercise.^{4,9,12} Oxygen uptake efficiency slopes have also been identified as good prognostic indicators of health status and outcome in heart failure patients when using either submaximal or peak exercise data.^{1,12} A number of other gas exchange variables have also been investigated, the most recent looking at the prognostic value of P_{ETCO_2} at rest and during exercise.^{13,14} It has been suggested that P_{ETCO_2} is an indirect indicator of cardiac output and is, therefore, considered to be an independent predictor of prognosis in heart failure populations. Although some have suggested that these new prognostic markers of heart failure (V_E/VCO_2 slope, OUES, and P_{ETCO_2}) are more powerful predictors of outcome than $\text{VO}_{2\text{peak}}$,^{12,15} others have disagreed^{5,16} and questions still remain in this particular area.

With this in mind, the aims of the present study were to (i) identify which submaximal exercise gas exchange variables were the strongest univariate predictors of survival in patients with heart failure and (ii) create a model using the best predictors of prognosis to see whether a combination of parameters could better predict outcomes. We hypothesize that submaximal exercise data would have similar or greater prognostic values when compared with peak exercise data.

Methods

One hundred and thirty-two consecutive patients with a history of stable heart failure and ischaemic or non-ischaemic cardiomyopathy performed cardiopulmonary exercise testing with respiratory gas analysis, as part of their clinical evaluation, between August 1999 and August 2005. Patients with primary lung disease, morbid obesity (body mass index $>40 \text{ kg/m}^2$), musculoskeletal disease, valvular heart disease, peripheral vascular disease, chest pain, pacemaker dependency, atrial fibrillation, a history of complex ventricular arrhythmias, or the inability to perform exercise testing were not included in this study. Follow-up data for all-cause mortality or transplant was obtained through the Mayo Clinic database and confirmed through the social security index periodically, the most recent being January 2009. All participants gave written informed consent after being provided with a description of study requirements. The study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Mayo Clinic Institutional Review Board.

Cardiopulmonary exercise testing

All patients performed graded treadmill exercise testing to volitional fatigue. For the first 2 min, patients exercised at a constant treadmill speed of 2.0 m.p.h. with 0% grade. After this, the speed and/or grade was increased every 2 min to yield an approximate 2-MET increase in each exercise stage. Participants were verbally encouraged to continue the exercise protocol to maximal exertion, which was confirmed by a rating of perceived exertion >18 on the Borg 6–20 scale and a respiratory exchange ratio (RER) of >1.15 . After achieving peak

workload, treadmill speed was reduced to 1.7 m.p.h. and 0% grade for a cool down period that lasted for 3 min and which was followed by seated rest for a further 3 min.

Ventilatory expired gas analysis was performed at rest and throughout exercise using a metabolic measurement system (Medgraphics CPX/D, Medical Graphics, St Paul, MN, USA). Patients were fitted with a nose clip and a standard mouthpiece attached to a PreVent pneumotach (Medical Graphics), which was worn for the duration of the test. Manual flow calibrations were performed with a 3 L syringe, and gas calibrations performed with manufacturer-recommended gases of known concentrations. Calibrations were made prior to the start of every test. Additional measurements of heart rate (electrocardiogram), oxygen saturation (pulse oximetry), and blood pressure (manual sphygmomanometry) were made throughout the exercise test.

Data collection and analysis

Data obtained from the first 2 min of exercise and data corresponding to an RER of 0.9 were the primary interest of this study, with the aim of identifying which submaximal exercise parameters were the strongest predictors of survival.

Minute ventilation (V_E), oxygen consumption (VO_2), carbon dioxide production (VCO_2), RER, end-tidal CO_2 (P_{ETCO_2}), and breathing frequency were acquired and averaged over 30 s intervals. From these data-derived variables such as V_E/VCO_2 ratio, oxygen pulse, circulatory power (VO_2^*SBP) and respiratory drive (V_T/TI , where V_T is the tidal volume and TI is the inspiratory time) were calculated at rest and during exercise.

Ventilatory efficiency slopes (V_E/VCO_2 slope) [V_E , L/min = $m(\text{VCO}_2$, L/min) + b , where $m = V_E/\text{VCO}_2$ slope] were calculated using data from the first 2 min of exercise ($V_E/\text{VCO}_2\text{stage1}$) and up to an RER of 0.9 ($V_E/\text{VCO}_2\text{RER0.9}$) via least-squares linear regression. Oxygen uptake efficiency slopes [VO_2 , L/min = $m(\log^{10} V_E) + b$, where $m = \text{OUES}$] and oxygen uptake relative to work rate (VO_2/WR) were similarly calculated using data from the first 2 min (OUESstage1 and $\text{VO}_2/\text{WRstage1}$) and up to an RER of 0.9 (OUESRER0.9 and $\text{VO}_2/\text{WRER0.9}$).

Statistical analysis

Descriptive information was expressed as mean $\pm$ standard deviation or frequency (per cent), unless otherwise stated. Univariate Cox regression analysis of time to death or transplant was used both to compare demographics between survivors and non-survivors and to assess the prognostic ability of submaximal (first stage of exercise and at an RER of 0.9) and maximal gas exchange data. Selected clinically interesting and statistically significant univariate predictors of survival were then entered into multivariable models, and using a backwards selection procedure (on a complete data set for all variables of interest in all patients; $n = 119$), variables were eliminated from the model until only those with a significance level $P < 0.05$ remained. Multivariable models were constructed in the first instance using just submaximal data. After the strongest possible model had been formulated, demographic information and $\text{VO}_{2\text{peak}}$ (mL/min/kg) were added and backwards selection repeated, to determine whether these variables enhanced the prognostic utility of the model. Prognostic utility was assessed using C -statistics. This is a measure of concordance and refers to the ability of a parameter or model to distinguish between high- and low-risk patients. These values are typically between 0.5 and 1, where 0.5 offers no prognostic information. Prognostic utility was also assessed using the likelihood ratio index (McFadden's pseudo- R^2), which is a model comparison tool that is the survival

analysis analogue to R^2 . This demonstrates the 'goodness-of-fit' of non-linear models, and a higher value indicates the better model for predicting survival. Formal statistical comparisons between models based on different types of variables (stage 1 exercise, submaximal exercise, maximal exercise, and demographic information) were performed by using mutually nested versions of these models. Finally, Kaplan–Meier curves were constructed using the three tertiles of the predicted values from the submaximal model, as well as the corresponding tertiles from the complete model to visualize the spread between the survival curves. Analysis of data was performed using SAS Version 9.1 (SAS Institute Incorporated, Cary, NC, USA).

Results

Univariate predictors of survival from demographic data

Patient demographics are summarized in Table 1. In total, there were 44 outcomes, 33 deaths, and 11 urgent heart transplants, over a median follow-up period of 62.4 (range 0–114) months. The age, height, weight, and body mass index of the survivors and non-survivors were similar. A reduced left ventricular ejection fraction (LVEF, $P = 0.004$), lower VO_{2peak} ($P < 0.001$), higher New York Heart Association (NYHA) class ($P = 0.002$), and being male were associated with increased risk of death ($P = 0.021$). Males were 2.47 times more likely to have adverse outcomes, a 10% decrease in LVEF was associated with 1.61 times the risk of death, and a 1 U decrease in VO_{2peak} (mL/min/kg) was associated with 1.15 times the risk of death. The majority of the heart failure (HF) cohort had a diagnosis of non-ischaemic aetiology.

Univariate predictors of survival from submaximal and maximal exercise data

Gas exchange data from two submaximal exercise levels, from the first 2 min stage of exercise and at an RER of 0.9, are reported in Table 2. Following univariate Cox regression analysis of time to death or transplant, the strongest predictors of survival, based on the level of significance (i.e. P -value), were V_E/VCO_2 slope and ratio, $P_{ET}CO_2$, OUES, and circulatory power (Table 3). Some of the additional variables that offered prognostic value were RER and V_E from the first 2 min of exercise, and VO_2/kg , heart rate, and $VO_2/work$ at an RER of 0.9 (Table 3). Peak VO_2 (mL/min/kg) was also a univariate [hazard ratio (HR) 0.87, 95% confidence interval (CI) 0.80–0.94, $P < 0.001$] predictor of survival.

Multivariable Cox regression analysis

The strongest univariate predictors of survival (in terms of the significance level achieved) from the two submaximal exercise levels were entered into multivariable models using backwards selection (Table 4). The first model (Model 1) incorporated data from the first stage of exercise only, and the variables retained in this model were V_E and circulatory power (C -statistic 0.755; McFadden's $R^2 = 0.079$). The second model was created using data from an RER of 0.9 only (Model 2). Following backwards selection at a retention significance level $P < 0.05$, the only variable retained was V_E/VCO_2 ratio (C -statistic 0.716; McFadden's $R^2 = 0.069$). When a model was built considering all 14 variables from both the first 2 min of exercise and at an RER of 0.9 (Model 3), the variables retained were $V_E/VCO_2RER0.9$ ratio, $V_{Estage1}$, and circulatory powerstage1. This was a better model for predicting

Table 1 Patient demographics

	All patients (n = 132)	Survivors (n = 88)	Non-survivors (n = 44)
Gender (male)	88 (67%)	52 (59%)	36 (82%)
Age (years)	56 ± 12	55 ± 11	57 ± 12
Height (cm)	172.5 ± 9.9	171.9 ± 10.2	173.6 ± 9.3
Weight (kg)	84.5 ± 17.3	83.4 ± 17.8	86.7 ± 16.4
Body mass index (kg/m ²)	28.3 ± 4.7	28.1 ± 4.7	28.7 ± 4.6
Ischaemic HF	41 (31%)	19 (22%)	22 (50%)
NYHA class			
I	45 (34%)	35 (40%)	10 (22%)
II	42 (32%)	28 (32%)	14 (32%)
III	35 (27%)	22 (25%)	13 (30%)
IV	10 (8%)	3 (3%)	7 (16%)
LVEF (%)	29 ± 11	30 ± 10	25 ± 12
VO_{2peak} (mL/min/kg)	19.0 ± 5.9	20.4 ± 5.9	16.2 ± 4.7
Therapy distribution			
ACE inhibitors (%)	73	72	77
Beta-blockers (%)	76	77	72
Angiotensin II blocker (%)	12	11	14
Digitalis (%)	63	64	65
Diuretics (%)	67	58	86

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VO_{2peak} , peak oxygen consumption.

Table 2 Gas exchange data from first stage of exercise and at an RER of 0.9

	First stage of exercise		RER at 0.9	
	Survivors (n = 88)	Non-survivors (n = 44)	Survivors (n = 83)	Non-survivors (n = 40)
VO ₂ (mL/min/kg)	10.8 ± 2.1	10.4 ± 2.0	15.8 ± 4.0	13.0 ± 3.8
VCO ₂ (mL/min)	738 ± 248	762 ± 189	1181 ± 399	1003 ± 335
V _T (mL)	1119 ± 400	1154 ± 340	1514 ± 565	1453 ± 528
V _E (L/min)	24.3 ± 7.4	28.6 ± 10.0	36.0 ± 10.8	34.3 ± 9.6
RER	0.81 ± 0.09	0.86 ± 0.1	0.90 ± 0.01	0.90 ± 0.02
P _{ET} CO ₂ (mmHg)	36 ± 4	33 ± 6	38 ± 4	34 ± 6
Heart rate (b.p.m.)	96 ± 21	94 ± 19	111 ± 19	101 ± 21
Respiratory drive	0.95 ± 0.30	1.07 ± 0.36	1.35 ± 0.41	1.29 ± 0.35
O ₂ pulse	9.8 ± 3.6	9.8 ± 3.0	12.1 ± 4.2	11.3 ± 3.8
V _E /VCO ₂ ratio	34 ± 5	38 ± 8	31 ± 4	35 ± 7
V _E /VCO ₂ slope	29 ± 6	35 ± 9	28 ± 4	33 ± 8
OUES	1.9 ± 0.8	1.6 ± 0.5	2.0 ± 0.6	1.7 ± 0.5
VO ₂ /work	7.9 ± 2.3	7.5 ± 2.1	8.1 ± 1.8	7.3 ± 2.0
Circulatory power	109 ± 44	96 ± 37	171 ± 79	130 ± 62

OUES, oxygen uptake efficiency slope; P_{ET}CO₂, end-tidal partial pressure of carbon dioxide; RER, respiratory exchange ratio; VCO₂, carbon dioxide production; V_E, minute ventilation; V_E/VCO₂, breathing efficiency; V_T, tidal volume.

Table 3 Univariate Cox regression analysis of time to death or transplant from submaximal exercise gas exchange data

	First stage of exercise		RER at 0.9, adjusted for work (W)	
	HR (CI 95%)	P-value	HR (CI 95%)	P-value
VO ₂ (mL/min/kg)	0.87 (0.75–1.01)	0.07	0.85 (0.76–0.94)	<0.001
VCO ₂ (mL/min) (per 10 U change)	1.00 (0.99–1.01)	0.90	0.98 (0.97–1.00)	0.021
V _T (mL) (per 10 U change)	1.00 (0.99–1.01)	0.91	1.00 (0.99–1.01)	0.07
V _E (L/min) (per 10 U change)	1.72 (1.26–2.34)	<0.001	1.27 (0.81–1.99)	0.051
RER (per 0.1 U change)	1.60 (1.21–2.12)	0.001	1.43 (0.18–11.67)	0.07
P _{ET} CO ₂ (mmHg)	0.88 (0.83–0.93)	<0.001	0.88 (0.83–0.94)	<0.001
Heart rate (b.p.m.) (per 10 U change)	0.96 (0.83–1.11)	0.62	0.82 (0.69–0.97)	0.004
Respiratory drive	3.23 (1.25–8.38)	0.016	2.09 (0.64–6.84)	0.049
O ₂ pulse	0.97 (0.89–1.06)	0.56	1.04 (0.91–1.18)	0.06
V _E /VCO ₂ ratio	1.09 (1.05–1.13)	<0.001	1.12 (1.07–1.18)	<0.001
V _E /VCO ₂ slope (per 10 U change)	2.12 (1.59–2.83)	<0.001	2.78 (1.88–4.12)	<0.001
OUES (per 0.1 U change)	0.91 (0.86–0.97)	0.004	0.90 (0.85–0.96)	0.002
VO ₂ /work	0.90 (0.79–1.04)	0.15	0.80 (0.67–0.95)	0.011
Circulatory power (per 10 U change)	0.90 (0.83–0.97)	0.01	0.89 (0.81–0.97)	0.004

HR, Cox proportional hazard ratio; CI, confidence interval.

survival than using just either stage of submaximal exercise data only (C-statistic 0.745, McFadden's $R^2 = 0.092$; $P = 0.031$ when compared with Model 1 and $P = 0.019$ when compared with Model 2). The prognostic utility of Model 3 is illustrated by the Kaplan–Meier survival plot (Figure 1), in which the sample was split into three equal groups based on the distribution of the composite prediction (risk) score generated by the model. The spread among the lines shows that despite the lack of demographic or

VO_{2peak} data, the model has substantial discriminating ability about which patients are at highest mortality risk.

Interestingly, when only VO_{2peak} was included with the candidate variables from Model 3, it was not retained following backwards selection and only the submaximal variables were retained in the model (Model 4). However, when demographic information was included with Model 3, the only variables retained were V_E/VCO₂ ratio at RER 0.9 and NYHA class (Model 5). In addition,

Table 4 Multivariable Cox proportional hazard model summary (death or transplant) following backwards selection

Model no.	Description (candidate variables)	Number of Variables retained in model	Explanatory variables in final model	McFadden's R^2	C-statistic
Model 1	1st stage of exercise ($V_E VCO_2$ slope; $V_E VCO_2$ ratio; V_E ; circulatory power; $P_{ET}CO_2$; OUES; RER)	2	$V_{Estage1}$; circulatory powerstage1	0.079	0.755
Model 2	$RER = 0.9$ ($V_E VCO_2$ slope; $V_E VCO_2$ ratio; heart rate; circulatory power; $P_{ET}CO_2$; OUES; VO_2)	1	$V_E VCO_2$ ratio RER0.9	0.069	0.716
Model 3	1st stage of exercise and $RER = 0.9$ (all variables from Models 1 and 2 included together)	3	$V_E VCO_2$ ratio RER0.9; $V_{Estage1}$; circulatory powerstage1	0.092	0.745
Model 4	Model 3 and VO_{2peak} (mL/min/kg), ($V_E VCO_2$ ratio RER0.9; $V_{Estage1}$; circulatory powerstage1; VO_{2peak})	3	$V_E VCO_2$ ratio RER0.9; $V_{Estage1}$; circulatory powerstage1	0.092	0.745
Model 5	Model 3 and demographics ($V_E VCO_2$ ratio RER0.9; $V_{Estage1}$; circulatory powerstage1; NYHA class; LVEF; age; sex)	2	$V_E VCO_2$ ratio RER0.9; NYHA class	0.084	0.739
Model 6	VO_{2peak} (mL/min/kg) and demographics (NYHA class; LVEF; age; sex; VO_{2peak})	3	NYHA class; sex; VO_{2peak}	0.088	0.756
Model 7	Model 3, VO_{2peak} (mL/min/kg), and demographics ($V_E VCO_2$ ratio RER0.9; $V_{Estage1}$; circulatory powerstage1; NYHA class; LVEF; age; sex; VO_{2peak})	5	$V_E VCO_2$ ratio RER0.9; age; NYHA class; sex; VO_{2peak}	0.116	0.781

when VO_{2peak} and demographic candidate variables were included together in a separate model and underwent backwards selection (Model 6), the predictive power (C-statistic 0.756, McFadden's $R^2 = 0.088$) was not better than that based on submaximal variables (Model 3). Finally, when demographic information and VO_{2peak} , as well as submaximal exercise gas exchange data (stage 1 and RER 0.9), were included together as candidates and underwent backwards selection (Model 7), the strongest model was produced (C-statistic 0.781, McFadden's $R^2 = 0.116$). This incorporated data ($V_E VCO_2$) from an RER of 0.9, as well as demographic information and VO_{2peak} . The need for RER 0.9 $V_E VCO_2$ in this model was indicated by its P -value ($\chi^2 = 15.9$ on 4 d.f., $P = 0.003$), whereas the need for demographic information and VO_{2peak} was demonstrated by comparing Cox regression χ^2 values for Model 7 with the model of only RER 0.9 $V_E VCO_2$ ($\chi^2 = 8.2$ on 1 d.f., $P = 0.004$). Figure 2 suggests that inclusion of maximal data and demographics may serve to further identify low- and medium-risk patients.

Discussion

Main findings

The present study demonstrated a number of gas exchange parameters, taken from two different submaximal exercise levels, that were univariate predictors of adverse outcomes in heart failure patients. The strongest univariate predictors of survival (based on the level of significance) were $V_E VCO_2$ slope or ratio, $P_{ET}CO_2$, OUES, and circulatory power. In addition, $V_{Estage1}$ and $VO_2 RER0.9$ were also strong predictors of outcome. Interestingly, these submaximal exercise gas exchange variables had a prognostic utility that was similar to VO_{2peak} .

Following multivariable analysis of selected statistically significant univariate parameters, it was apparent that the best model to predict survival using just submaximal exercise was a combination of data taken from the first stage of exercise and at an RER of 0.9. The variables retained as part of this model were $V_{Estage1}$, circulatory powerstage1, and $V_E VCO_2 RER0.9$ ratio. This model has good clinical value (C-statistic = 0.745, McFadden's $R^2 = 0.092$) for predicting adverse outcomes. Interestingly, when looking at a model incorporating demographic information and VO_{2peak} , data that are commonly recorded in a clinical setting, no extra prognostic information (C-statistic = 0.756, McFadden's $R^2 = 0.088$) was obtained in comparison to the model using just submaximal exercise data. When including demographic (NYHA class, age, and sex), maximal exercise (VO_{2peak}), and submaximal exercise ($V_E VCO_2$ at an RER of 0.9) data together, the model created (C-statistic = 0.781, McFadden's $R^2 = 0.116$) was better than when submaximal exercise data were used alone. This would suggest that submaximal exercise testing may be used to provide useful prognostic information, in the absence of peak exercise measurements, to predict adverse outcomes in heart failure patients. Examination of Figures 1 and 2 suggests that submaximal data alone may be sufficient to identify high-risk patients, whereas the addition of maximal exercise plus demographic data allows further identification of low- and medium-risk patients.

Previous literature

Cardiopulmonary exercise testing in heart failure patients has been utilized in a clinical environment for a number of years.^{17,18} This symptom-limited exercise test demonstrates the maximum functional capacity, commonly known as VO_{2max} or peak, of an individual and has been used to classify heart failure severity as well

Figure 1 Kaplan–Meier survival plot based on submaximal exercise data. The spread of the lines in this plot demonstrates that the submaximal exercise model (Model 3) has discriminating ability in regard to high-risk patients.

Figure 2 Kaplan–Meier survival plot based on submaximal exercise data, maximal exercise data, and demographic information. The spread of the lines in this plot demonstrates that the full model (Model 7) has discriminating ability in regard to low-, medium-, and high-risk patients.

as to predict adverse events.³ Although the prognostic usefulness of this technique has been previously shown, problems have been noted with the logistics of performing maximal exercise testing in a clinical setting.¹⁹ It is time-consuming, expensive, and requires additional laboratory staffing to perform the test under safe conditions. In addition, there is considerable patient anxiety

and risk associated with the measurement.⁵ Maximal exercise testing is also dependent on patient motivation and can be subject to investigator bias.^{1,4} As a result of these problems, the use of submaximal exercise testing and the measurement of gas exchange in clinical practice have gathered pace, and the expanding literature suggests that there are numerous ventilatory parameters, the most common including V_E/VCO_2 slope or ratio,^{4,6,11,19} OUES,^{1,5,12} and $P_{ET}CO_2$ ^{13,19} that are useful univariate predictors of survival in heart failure populations. Some have suggested that these variables, measured at low levels of exercise, provide more prognostic information than VO_{2peak} ,^{12,15} while being much easier to measure.^{20,21} The current study demonstrated similar results, following univariate and multivariate analyses of a range of gas exchange parameters, showing that a number of submaximal exercise-derived variables were predictors of survival, including V_E/VCO_2 slope and ratio, OUES, $P_{ET}CO_2$, and circulatory power. These variables had a similar prognostic value as VO_{2peak} . When multivariate models were created using just a combination of submaximal exercise data, a good clinical model was produced (C -statistic 0.745, McFadden's $R^2 = 0.092$), which was marginally improved when both demographic information (age, sex, and NYHA class) and VO_{2peak} were considered with submaximal data (C -statistic 0.781, McFadden's $R^2 = 0.113$). This would suggest that submaximal exercise data provide useful prognostic information in the absence of maximal exercise testing.

Underlying physiology

Valuable information can be obtained from gas exchange measurements, as pulmonary structure and function, and hence ventilation, are altered greatly in heart failure patients. Heart failure patients have been shown to develop lung restrictive defects resulting from pulmonary fibrosis, elevated pulmonary vasoconstriction, and increased pulmonary congestion.^{22,23} In addition, previous studies have suggested that ventilatory drive is increased, due in part to a greater sensitivity or stimulation of cardiac or pulmonary receptors, central and peripheral chemoreceptors, and skeletal muscle ergoreceptors.^{8,24–26} A reduced lung perfusion and diffusion capacity resulting in inefficient gas exchange has also been evident.²⁷ Physiologically, the changes noted in the pulmonary structure and function and ventilatory control are typically manifest as an altered breathing pattern (lower tidal volumes and greater breathing rates), greater ventilation in relation to metabolic demand (i.e. a higher V_E/VCO_2 slope), elevated dead space to tidal volume ratio (V_D/V_T), hyperventilation (reduced $P_{ET}CO_2$), and a reduced oxygen uptake in relation to ventilation (OUES). In more severe cases, these signature changes are noticeable at rest, but for the majority of patients, they are evident from the onset of exercise. These physiological measures can, therefore, be obtained during submaximal exercise to provide useful prognostic information to predict survival in heart failure patients.

Clinical implications

The present study suggests that submaximal exercise testing can be performed in place of maximal testing, while retaining a similar prognostic utility for identifying high-risk patients. There are seemingly many advantages to the use of submaximal exercise testing in clinical practice, including more reproducible measures

that unlike maximal exercise testing are effort-independent, exercise levels that correspond more to normal daily activities, better patient compliance, and a reduced potential for adverse events.¹ This form of testing is also logistically easier to organize, less time-consuming and considerably cheaper to perform, pertinent issues in view of current economic instabilities.

Limitations

A relatively small sample size was used in this study, particularly when looking to ascertain the prognostic utility of certain gas exchange variables. Yet despite this, it was evident that a number of gas exchange parameters were predictive of adverse events in heart failure patients, and when examined together, good models were generated to predict survival. Further analysis with larger data sets is required to fully elucidate the prognostic utility of submaximal gas exchange variables and to ascertain the best parameters to be incorporated into predictive models.

At the present time, there are no standardized submaximal exercise testing protocols. In the present study, we retrospectively selected two submaximal levels of exercise, taking data at the end of the first 2 min of constant exercise and at an RER of 0.9, from a maximal cardiopulmonary test. If submaximal testing is to be utilized in future clinical practice, standardized protocols that can be easily implemented by all clinicians need to be formulated.

Conclusion

Submaximal exercise gas exchange measures are good predictors of survival in heart failure patients that offer considerable advantages to both the patient and the clinician. Compared with traditional maximal exercise testing, submaximal tests are logistically easier, cheaper, and safer to perform and may be considered as good assessment tools to be used in a clinical setting to evaluate and monitor heart failure severity and prognosis.

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References

1. Davies LC, Wensel R, Georgiadou P, Cicoira M, Coats JSC, Piepoli MF, Francis D. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur Heart J* 2006;**27**:684–690.
2. Corra U, Mezzani A, Bosimini E, Giannuzzi P. Cardiopulmonary exercise testing and prognosis in chronic heart failure: a prognosticating algorithm for the individual patient. *Chest* 2004;**126**:942–950.
3. Mancini DM, Eisen H, Kussmaul WV, Mull R, Edmunds LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991;**83**:778–786.
4. Koike A, Itoh H, Kato M, Sawada H, Aizawa T, Fu LT, Watanabe H. Prognostic power of ventilatory responses during submaximal exercise in patients with chronic heart disease. *Chest* 2002;**121**:1581–1588.
5. Pardaens K, Cleemput JV, Vanhaecke J, Fagard RH. Peak oxygen uptake better predicts outcome than submaximal respiratory data in heart transplant candidates. *Circulation* 2000;**101**:1152–1157.
6. Ingle L, Goode K, Carroll S, Sloan R, Boyes C, Cleland JGF, Clark AL. Prognostic value of the V_E/VCO_2 slope calculated from different time intervals in patients with suspected heart failure. *Int J Cardiol* 2007;**118**:350–355.
7. Metra M, Cas LD, Panina G, Visioli O. Exercise hyperventilation in chronic congestive heart failure, and its relation to functional capacity and hemodynamics. *Am J Cardiol* 1992;**70**:622–628.

8. Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, Clark AL, Poole-Wilson PA, Coats AJS. Clinical correlates and prognostic significance of the ventilatory response to exercise in CHF. *J Am Coll Cardiol* 1997;**29**:1585–1590.
9. Robbins M, Francis G, Pashkow FJ, Snader CE, Hoercher K, Young JB, Lauer MS. Ventilatory and heart rate response to exercise: better predictors of heart failure mortality than peak oxygen consumption. *Circulation* 1999;**100**:2411–2417.
10. Guazzi M, Reina G, Tumminello G, Guazzi MD. Exercise ventilation inefficiency and cardiovascular mortality in heart failure: the critical independent prognostic value of the arterial CO₂ partial pressure. *Eur Heart J* 2005;**26**:472–480.
11. Jankowska EA, Witkowski T, Ponikowska B, Reczuch K, Borodulin-Nadzieja L, Anker SD, Piepoli MF, Banasiak W, Ponikowski P. Excessive ventilation during early phase of exercise: a new predictor of poor long-term outcome in patients with chronic heart failure. *Eur J Heart Fail* 2007;**9**:1024–1031.
12. Arena R, Myers J, Hsu L, Peberdy MA, Pinkstaff S, Bensimhon D, Chase P, Vicenzi M, Guazzi M. The minute ventilation/carbon dioxide production slope is prognostically superior to the oxygen uptake efficiency slope. *J Card Fail* 2007;**13**:462–469.
13. Arena R, Guazzi M, Myers J. Prognostic value of end-tidal carbon dioxide during exercise testing in heart failure. *Int J Cardiol* 2007;**117**:103–108.
14. Arena R, Myers J, Abella J, Pinkstaff S, Brubaker P, Moore B, Kitzman D, Peberdy MA, Bensimhon D, Chase P, Guazzi M. The partial pressure of resting end-tidal carbon dioxide predicts major cardiac events in patients with systolic heart failure. *Am Heart J* 2008;**156**:982–988.
15. Kleber FX, Vietzke G, Wernecke KD, Bauer U, Opitz C, Wensel R, Sperfeld A, Glaser S. Impairment of ventilatory efficiency in heart failure: prognostic impact. *Circulation* 2000;**101**:2803–2809.
16. Ingle L, Witte KK, Cleland JGF, Clark AL. Combining the ventilatory response to exercise and peak oxygen consumption is no better than peak oxygen consumption alone in predicting mortality in chronic heart failure. *Eur J Heart Fail* 2008;**10**: 85–88.
17. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL. ACC/AHA 2002 guidelines update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2002;**40**:1531–1540.
18. Arena R, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, Collins E, Fletcher G. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council of Clinical Cardiology and the Council of Cardiovascular Nursing. *Circulation* 2007;**116**:329–343.
19. Arena R, MacCarter D, Olson TP, Lalande S, Ceridon ML, Olson LJ, Johnson BD. Ventilatory expired gas at constant rate low intensity exercise predicts adverse events and is related to neurohormonal markers in patients with heart failure. *J Card Fail* 2009;**15**:482–488.
20. Johnson RL. Gas exchange efficiency in congestive heart failure. *Circulation* 2000;**101**:2774–2776.
21. Miller AD, Woods PR, Olson TP, Hulsebus ML, Malley KA, MacCarter D, Johnson BD. Validation of a simplified, portable cardiopulmonary gas exchange system for submaximal exercise testing. *Open Sports Med J* 2010;**4**:34–40.
22. Wasserman K, Zhang YY, Gitt A, Belardinelli R, Koike A, Lubarsky L, Agostoni PG. Lung function and exercise gas exchange in chronic heart failure. *Circulation* 1997;**96**:2221–2227.
23. Johnson BD, Beck KC, Olson LJ, O'Malley KA, Allison TG, Squires RW, Gau GT. Ventilatory constraints during exercise in patients with chronic heart failure. *Chest* 2000;**117**:321–332.
24. Ponikowski P, Francis DP, Piepoli MF, Davies LC, Chua TP, Davos CH, Florea V, Banasiak W, Poole-Wilson P, Coats AJS, Anker SD. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation* 2001;**103**:967–972.
25. Naeije R, van de Borne P. Clinical relevance of autonomic nervous system disturbances in pulmonary arterial hypertension. *Eur Respir J* 2009;**34**:792–794.
26. Olson TP, Joyner MJ, Johnson BD. Influence of locomotor muscle metaboreceptor stimulation on the ventilatory response to exercise in heart failure. *Circulation* 2010;**3**:212–219.
27. Guazzi M. Alveolar gas diffusion abnormalities in heart failure. *J Card Fail* 2008;**14**: 695–702.