ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 2731–2740
Published online 1 May 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13342

ORIGINAL RESEARCH ARTICLE

All-cause mortality predicted by peak oxygen uptake differs depending on spirometry pattern in patients with heart failure and reduced ejection fraction

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Abstract

Aims In patients with heart failure and reduced ejection fraction (HFrEF), it remains unclear how exacerbated impairments in peak exercise oxygen uptake ($\dot{V}O_{2peak}$) caused by coexistent obstructive or restrictive ventilatory defects affect mortality risk. We evaluated in patients with HFrEF, whether demonstrating either an obstructive or restrictive-patterned ventilatory defect on spirometry affects $\dot{V}O_{2peak}$ to yield all-cause mortality risk predicted by $\dot{V}O_{2peak}$ that is spirometry pattern specific.

Methods and results We retrospectively analysed resting spirometry and treadmill cardiopulmonary exercise testing data of patients with HFrEF (left ventricular ejection fraction $\leq$ 40%). The study sample (N = 329) was grouped by spirometry pattern: normal [Group 1: N = 101; forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) $\geq$ 0.70; FVC $\geq$ 80% predicted], restrictive without airflow obstruction (Group 2: N = 104; FEV_1/FVC $\geq$ 0.70; FVC $<$ 80% predicted), or obstructive (Group 3: N = 124; FEV_1/FVC $<$ 0.70). Patients were followed up to 1 year for the endpoint of all-cause mortality. $\dot{V}O_{2peak}$ was higher in Group 1 versus Groups 2 and 3 (13.4 ± 4.0 vs. 12.1 ± 3.7 and 12.2 ± 3.3 mL/kg/min, respectively; P = 0.014). Over the 1 year follow-up, n = 9, n = 16, and n = 12 deaths occurred in Groups 1–3, respectively, with corresponding crude survival rates of 88%, 81%, and 92%, respectively (log-rank; P = 0.352). $\dot{V}O_{2peak}$ was associated with all-cause mortality (crude hazard ratio = 0.77; P $<$ 0.001). In multivariate analyses, a significant $\dot{V}O_{2peak}$-by-spirometry group interaction yielded 1.99 (95% confidence interval, 1.14–3.46) and 2.43 (95% confidence interval, 1.44–4.11) higher mortality risk associated with $\dot{V}O_{2peak}$ in Group 2 versus Groups 1 and 3, respectively.

Conclusions Demonstrating a restrictive pattern on spirometry yields the severest mortality risk associated with $\dot{V}O_{2peak}$. Using spirometry to screen patients with HFrEF for ventilatory defects has a potential role in improving risk stratification based on $\dot{V}O_{2peak}$.

Keywords HFrEF; Spirometry; Exercise capacity; Exercise intolerance; CPET

Received: 12 October 2020; Revised: 9 February 2021; Accepted: 23 March 2021
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Introduction

Approximately one-third of patients with heart failure and reduced ejection fraction (HFrEF) demonstrate overlapping obstructive airflow defects on spirometry.[1–5] In these patients, severe limitations in airflow and central and peripheral oxygen transport yield excessive losses in aerobic exercise capacity and an impairment in peak exercise oxygen uptake ($\dot{V}O_{2peak}$) exceeding that observed in HFrEF alone.[1–3] Little is known, however, whether the unique loss of aerobic exercise capacity caused by HFrEF and coexistent obstructive airflow defect pathology predicts increased mortality risk as compared with levels reported for the general HFrEF population.[6–8] There remains a clinical need to clarify

whether mortality risk linked to severely impaired $\dot{V}O_{2peak}$ is worsened secondary to overlapping effects of specific spirometric phenotypes in patients with HFrEF.

In addition to the possibility of obstructive airflow defect pathology in HFrEF, it is also not uncommon for patients to demonstrate signs of restrictive ventilatory defect pathology.[9–11] Although the modern incidence of this heart–lung overlap phenotype has not been well defined, past estimates suggest at least 10–12% of previously healthy adults eventually develop a restrictive ventilatory defect with the lengthy latency period between disease development and diagnosis coinciding with the aging transition across mid-to-late adulthood.[12–18] The temporality of this process is important because throughout the period of lung disease development and functional decline is where patients not only experience a gradual worsening of symptoms, typically involving dyspnoea and fatigue, but the presence of signs of subclinical left-sided heart dysfunction, including incipient HFrEF, is also not rare.[12–18]

Testing for the degree of $\dot{V}O_{2peak}$ impairment has long been considered a crucial part of standard of care for patients with HFrEF. However, a similarly strong body of evidence is not available to support the medical necessity of dedicated spirometry testing for identifying possible signs of restrictive or obstructive ventilatory defects as part of routine HFrEF management. This also means it is unclear whether acquiring basic spirometric data in the setting of cardiopulmonary exercise testing (CPET) and HFrEF would strengthen the understanding of the clinical implications associated with $\dot{V}O_{2peak}$ responses that typically fall within a narrow range.[7,19] The pragmatic knowledge gained as a result of testing this knowledge gap also has immediate clinical value because,[12–18] unlike specialized whole-body plethysmography, flow-volume loop spirometry can be routinely performed by patients using the standard metabolic cart system in a CPET laboratory.

We aimed to evaluate in patients with HFrEF, whether the loss in $\dot{V}O_{2peak}$ associated with demonstrating a spirometry pattern classified as a ventilatory defect observed as a restrictive pattern in the absence of airflow obstruction as compared with an obstructive airflow pattern alone yields ventilatory defect-specific differences in all-cause mortality risk predicted by $\dot{V}O_{2peak}$.

Methods

In this retrospective study, we analysed clinical and physiological data of patients with moderate-to-severe HFrEF who were selectively referred to undergo outpatient CPET as part of standard management of care in the Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH (demographics, *Table 1*). Data analyses and CPET reporting were only performed on those who, based on the clinical judgement of the referring provider, had also been referred for flow-volume loop spirometry testing. More than 87% of selected CPETs analysed for this study were performed during or after the year 2010.[19]

Patients included in the study sample had an established diagnosis of chronic heart failure (HF), documented left ventricular ejection fraction (LVEF) $\leq$ 40%, were stable on standard pharmacotherapies for the management of HFrEF, New York Heart Association functional class II through IV, and were outpatients.[20,21] Patients were not considered to be in the decompensated state at the time of CPET given that this testing is contraindicated in such a context, and CPET also would not be performed as a result of being admitted to the hospital for an acute bout of exacerbated HF or related unscheduled emergency medical care.

In addition to studying patients with HFrEF, as part of a sub-analysis, we included a control group of patients without HFrEF and with normal spirometry who were selectively matched to HFrEF *Group 1* (described below) for age, body size, and sex (demographics, Supporting Information, *Table S1*). These patients had been referred to undergo outpatient CPET in the Department of Cardiovascular Medicine as part of a workup to evaluate whether cardio-centric limitations were the primary cause of symptoms, typically including dyspnoea, fatigue, and exercise intolerance. Patients also received a referral for flow-volume loop spirometry testing.

This study was reviewed and approved by the Cleveland Clinic Institutional Review Board (#18-1260) and complies with the Declaration of Helsinki.

Spirometry testing and patient stratification

Patients performed flow-volume loop spirometry (MGC Diagnostics, St. Paul, MN) while at rest and in the upright seated position.[22,23] Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) could be well visualized on spirograms. The FEV_1 to FVC ratio (FEV_1/FVC) was calculated. Per cent predicted equations referenced were those recommend by the European Respiratory Society.[24]

Spirometry patterns were classified and patients were stratified by airflow and ventilation function as normal (Group 1: FEV_1/FVC $\geq$ 0.70 and FVC $\geq$ 80% predicted), restricted in the absence of airflow obstruction (Group 2: FEV_1/FVC $\geq$ 0.70 and FVC $<$ 80% predicted), or obstructed airflow alone (Group 3: FEV_1/FVC $<$ 0.70).[15,22] Controls demonstrated normal spirometry (Group 4: FEV_1/FVC $\geq$ 0.70 and FVC $\geq$ 80% predicted).

Exercise testing

All patients performed treadmill (GE CASE, Milwaukee, WI) CPET while in the post-absorptive state (no caffeine $>$ 12 H)

Table 1 Baseline characteristics of patients with heart failure and reduced ejection fraction

	All (N = 329)	Group 1 (N = 101)	Group 2 (N = 104)	Group 3 (N = 124)	P-value
LVEF, %	23 ± 9	23 ± 9	24 ± 8	22 ± 8	0.523
LVEF ≤ 30%, %	81	80	81	82	0.919
Sex, % men	76	72	77	77	0.630
Age, years	63 ± 7	63 ± 8	61 ± 8*	64 ± 7	0.005
Min/max	45/84	45/84	45/82	47/79	
Height, cm	175 ± 10	174 ± 10	175 ± 9	175 ± 10	0.965
Weight, kg	88 ± 20	88 ± 17	91 ± 22	87 ± 22	0.270
BMI, kg/m^2	28.8 ± 5.7	28.7 ± 4.8	29.7 ± 6.0	28.2 ± 6.1	0.143
Obese, %	40	34	48	37	0.085
Haemoglobin, g/dL	12.8 ± 1.8	12.9 ± 1.9	12.8 ± 1.8	12.7 ± 1.8	0.866
Haematocrit, %	39 ± 5	39 ± 5	39 ± 5	39 ± 6	0.481
eGFR, mL/min per 1.73 m^2	55.8 ± 21.8	54.9 ± 20.0	57.9 ± 23.1	54.7 ± 22.2	0.502
CKD ≥ 3, %	59	61	53	62	0.312
NT-proBNP, pg/mL Med. (25–75th IQR)	1679 (548, 4529)	2235 (784, 5592)	1994 (1005, 5488)	2520 (1158, 5709)	0.576
Ischaemic aetiol., %	44	38	52	47	0.256
Diastolic dysfunc., 0/I/II/III/NA, %	2/17/12/26/43	2/17/9/24/48	5/13/14/30//38	0/20/12/24/44	0.173
NYHA class, II/III/IV, %	29/67/4	32/66/2	27/68/5	30/65/5	0.613
ICD/CRT-D, %	83	88	83	80	0.250
A-fib, %	36	40	38	30	0.239
Asthma, %	10	7	7	16	0.027
Diabetes (I or II), %	42	35	55‡	37	0.005
Hypertension, %	88	87	88	90	0.709
Ex-smoker, %	60	55	50	73♦	<0.001
Spirometry					
FVC, L	3.22 ± 0.87	3.74 ± 0.75	2.75 ± 0.67	3.19 ± 0.88	<0.001
FEV_1, L	2.29 ± 0.71	2.85 ± 0.58#	2.14 ± 0.54	1.95 ± 0.66	<0.001
FEV_1/FVC	0.71 ± 0.10	0.76 ± 0.04	0.78 ± 0.05	0.61 ± 0.09♦	<0.001
FVC, %pred	79 ± 16	92 ± 10	66 ± 10	78 ± 16	<0.001
FEV_1, %pred	72 ± 18	91 ± 11	66 ± 10	62 ± 17	<0.001
FEV_1/FVC, %pred	91 ± 13	98 ± 5	100 ± 7	79 ± 11♦	<0.001
Drug therapy, %					
Beta-blocker (non-select or cardioselect)	87	86	88	88	0.921
ACEi	59	62	57	59	0.709
ARBs	28	33	24	28	0.386
Loop diuretics	92	91	91	94	0.582
K^+ sparing diuretics	61	64	62	58	0.626
Ca^{2+} ch. blockers	5	7	5	2	0.258
NO promoters	31	27	34	31	0.548
Digoxin	39	37	39	40	0.888

ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor antagonists; CKD, chronic kidney disease; CRT-D, cardiac resynchronization therapy defibrillator; eGFR, estimated glomerular filtration rate calculated using the modification of diet and renal disease formula; Ex-smoker, smoked >100 lifetime cigarettes (yes/no); FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; Obesity, body mass index (BMI) ≥ 30 kg/m^2.

Continuous data are means ± standard deviation. Spirometric patterns were normal (*Group 1*: FEV_1/FVC ≥ 0.70 and FVC ≥ 80% predicted), restrictive in the absence of obstruction (*Group 2*: FEV_1/FVC ≥ 0.70 and FVC < 80% predicted), or obstructive (*Group 3*: FEV_1/FVC < 0.70). Diastolic dysfunction grade was evaluated according to the American Society of Echocardiography/European Association of Cardiovascular Imaging Guidelines and Standards in Nagueh *et al*.[29] In addition to severity grades I to III, 0 indicates no diastolic function and NA indicates could not be determined due to technical and/or physiological factors. Table P-value is the main effect of spirometric group tested for patients with heart failure and reduced ejection fraction. For FVC (L and %pred) and FEV_1 (%pred), all groups are significantly different. Table symbols represent significant pairwise differences following post hoc testing and correcting for multiple comparisons.

*Group 2 vs. Group 3.
#Group 1 vs. Groups 2 and 3.
♦Group 3 vs. Groups 1 and 2.
‡Group 2 vs. Groups 1 and 3.
†Group 1 vs. Group 3.

in an environmentally controlled stress laboratory.[19] The Modified Naughton or Naughton protocols were used for HFrEF, whereas other clinically validated protocols were also considered for controls where appropriate.[19]

Continuous heart rate and rhythm monitoring occurred throughout CPET using standard 12-lead electrocardiography. Continuous breath-to-breath ventilation and gas-exchange measurements (MGC Diagnostics) were acquired throughout

CPET, and data were visually inspected post hoc for the presence and removal of non-physiological breaths.[25] A peak effort was classified as a respiratory exchange ratio $\geq$ 1.10 and/or rating of perceived exertion $>$ 17 (Borg scale, 6–20).[19] Reported data reflect 15 s averages where appropriate.

Ventilatory (in)efficiency was estimated using exercise onset to peak data in the calculation of the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$) slope.[26]

Clinical data and study endpoint

Patients were retrospectively followed for up to 1 year for the endpoint of all-cause mortality identified via the Social Security Death Index and electronic medical records review of the Cleveland Clinic Health System Institutional Death Index.[27] Electronic medical records review was also used to acquire baseline clinical, demographic, and physiological data summarized in *Table 1*.

Statistical analyses

Data are presented as means ± SD, percentages, or median and interquartile range (25–75th) where appropriate. Single-factor ANOVA tests were performed to evaluate the main effect of spirometry group (i.e. normal pattern, restrictive pattern in the absence of airflow obstruction, or obstructive pattern) on continuous variables. Tukey's post hoc tests were performed to assess between-group differences when the main effect was significant. Either Kruskal–Wallis or χ^2 tests were performed to evaluate the effect of spirometry group on categorical or non-parametric variables.

Event-free survival (absence of death from any cause), stratified by spirometry group, was estimated using Kaplan–Meier curves. Cox proportional hazard regression analyses were also performed to estimate both crude and adjusted hazard ratios associated with spirometry group, $\dot{V}O_{2peak}$, or the $\dot{V}O_{2peak}$-by-spirometry group interaction. The clinical relevance of the $\dot{V}O_{2peak}$-by-spirometry group interaction term was further evaluated via multivariate Cox regression analyses involving the backwards stepwise variable selection process,[28] accounting for possible confounding effects of baseline variables, including age, diastolic dysfunction grade (severity I to III or not present or definable as outlined in the latest guidelines from the American Society of Echocardiography and European Association of Cardiovascular Imaging),[29] ex-smoking history (defined by the Centers for Disease Control and Prevention as having smoked $\geq$100 lifetime cigarettes but not currently smoking),[30] asthma history, diabetes (type I or II), haemoglobin content, beta-blocker (non-selective or β_1-selective), sex, LVEF, N-terminal pro-brain natriuretic peptide, estimated glomerular filtration rate calculated based on the modification of diet and renal disease formula,[31] and body mass index. At each stage of the backwards stepwise selection process, the variable with the highest *P*-value greater than 0.05 was removed, and this process continued until achieving the final model where remaining variables demonstrated a *P*-value less than 0.05.

The concordance statistic (c-statistic) was generated from Cox regressions in order to evaluate for each model the overall accuracy, calibration, and discriminative performance for predicting 1 year all-cause mortality. Likelihood ratio (LR) testing involving the comparison of log-likelihood statistics between Cox models was also performed in order to improve the interpretability of c-statistics and to test the assumption that regression coefficients for $\dot{V}O_{2peak}$ and spirometry group produced by Cox models varied by group and required interaction testing. When comparing the overall fit of Cox models, the model with the smaller log-likelihood statistic provides the better fit of the data.

The proportionality assumption was confirmed for each Cox regression via visual inspection of Cumulative Martingale Residual Plots coupled with results from both Kolmogorov-type supremum and Shoenfeld testing.

With the exception of the multivariate Cox regression analyses involving the backwards stepwise variable selection process, a complete sub-analysis involving each of the aforementioned statistical tests was performed where we included the control group in addition to each of the three HFrEF groups. Complete results of those tests are reported in Supporting Information, *Tables S1–S4*.

Two-tailed significance was determined using an alpha level set at 0.05. Analyses were performed using SAS statistical software v.9.4 (SAS Institute, Cary, NC).

Results

Baseline demographic, clinical, and physiological profiles in *Table 1* were not significantly different between groups for LVEF, sex, body mass index/obesity, New York Heart Association class, HF aetiology, asthma history, blood labs, and device and pharmacological therapies. However, Group 3 (i.e. obstructive spirometry pattern) patients were more likely to be ex-smokers and older than those in Group 2 (i.e. restrictive spirometry pattern without airflow obstruction). Diabetes prevalence was also highest in Group 2, whereas diastolic dysfunction grade distribution was not significantly different across groups. The addition of controls detailed in Supporting Information, *Table S1* did not wash out significant group differences reported in *Table 1*.

In contrast to Groups 2 and 3, Group 1 (i.e. normal spirometry pattern) demonstrated the least impaired aerobic exercise capacity (*Table 2*). Group 1 also exhibited the most balanced rate and volume contributions to peak minute

Table 2 Peak exercise responses

	All (N = 329)	Group 1 (N = 101)	Group 2 (N = 104)	Group 3 (N = 124)	P-value
$\dot{V}O_2$, mL/kg/min	12.6 ± 3.7	13.4 ± 4.0$^{\#}$	12.1 ± 3.7	12.2 ± 3.3	0.014
≤12 or ≤14 mL/kg/min, %	54	40$^{\#}$	63	57	0.002
$\dot{V}O_2$, L/min	1.11 ± 0.40	1.19 ± 0.40‡	1.09 ± 0.41	1.07 ± 0.39	0.047
$\dot{V}CO_2$, L/min	1.24 ± 0.48	1.35 ± 0.51‡	1.21 ± 0.46	1.18 ± 0.44	0.018
RER	1.12 ± 0.12	1.13 ± 0.11	1.11 ± 0.12	1.11 ± 0.11	0.533
f_B, br/min	34 ± 8	33 ± 7	37 ± 8*	33 ± 7	<0.001
V_T, L	1.47 ± 0.47	1.66 ± 0.50$^{\#}$	1.34 ± 0.37	1.42 ± 0.46	<0.001
$\dot{V}_E$, L/min	49 ± 17	53 ± 19‡	48 ± 16	45 ± 15	0.002
f_B/V_T, br/L/min	26 ± 14	22 ± 13†	30 ± 15	26 ± 13	<0.001
$\dot{V}_E/\dot{V}O_2$	46 ± 11	46 ± 10	46 ± 12	45 ± 11	0.389
$\dot{V}_E/\dot{V}CO_2$	41 ± 9	41 ± 8	42 ± 10	41 ± 9	0.633
$\dot{V}_E/\dot{V}CO_2$ slope	39 ± 9	40 ± 8	40 ± 10	38 ± 9	0.390
$PETCO_2$, mm Hg	30.1 ± 5.6	29.6 ± 5.0	29.9 ± 5.7	30.8 ± 5.8	0.210
HR, b.p.m.	111 ± 20	111 ± 19	110 ± 19	111 ± 21	0.789
SBP, mmHg	124 ± 25	125 ± 26	122 ± 23	125 ± 25	0.693
DBP, mmHg	70 ± 11	70 ± 11	70 ± 11	71 ± 12	0.679
MAP, mmHg	88 ± 14	88 ± 15	87 ± 14	89 ± 15	0.702
SaO_2, %	94 ± 5	95 ± 4†	92 ± 6	94 ± 4	0.045
RPE, 6–20 scale	19.5 ± 2.0	19.4 ± 2.1	19.3 ± 2.3	19.8 ± 1.4	0.114

DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; RER, respiratory exchange ratio; RPE, rating of perceived exertion; SBP, systolic blood pressure.
Continuous data are means ± standard deviation. Spirometric patterns were normal [*Group 1*: forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ≥ 0.70 and FVC ≥ 80% predicted], restrictive in the absence of obstruction (*Group 2*: FEV_1/FVC ≥ 0.70 and FVC < 80% predicted), or obstructive (*Group 3*: FEV_1/FVC < 0.70). For $\dot{V}O_2$, ≤12 or ≤14 mL/kg/min, the % was calculated according to the presence or absence of beta-blocker therapy, respectively. Table *P*-values represent the main effect of group. Table symbols represent significant pairwise differences following post hoc testing and correcting for multiple comparisons.
[#]Group 1 vs. Groups 2 and 3.
[‡]Group 1 vs. Group 3.
[*]Group 2 vs. Groups 1 and 3.
[†]Group 1 vs. Group 2.

ventilation, whereas Group 2 demonstrated the highest respiratory rate and the smallest tidal volume. However, the main effect of spirometry group was not significant for the $\dot{V}_E/\dot{V}CO_2$ slope or basic cardiovascular function (*Table 2*). The addition of control data detailed in Supporting Information, *Table S2* to HFrEF comparisons did not alter significant group differences reported in *Table 2*.

No patient demonstrated absolute indications requiring the immediate termination of CPET. Patients with a clinical history of asthma did not require use of inhaler therapy before or after CPET.

All-cause mortality

In patients with HFrEF, more than 40% of all deaths observed over the 1 year tracking period were in Group 2 (n = 16), whereas deaths in Group 1 (n = 9) and Group 3 (n = 12) accounted for ~24% and ~32%, respectively. The corresponding estimated crude 1 year survival rate for Group 2 (81%) was lower than that of both Group 1 (88%) and Group 3 (89%), whereas the main effect of spirometry group was not significant (log-rank, χ^2 = 2.09; P = 0.352). A single patient died in the control group over the 1 year tracking period, and this event had no effect on differences in estimated crude 1 year survival rates for HFrEF groups.

In univariate Cox regressions involving only HFrEF, there was no significant association between spirometry group and all-cause mortality (χ^2 = 1.99; *Table 3*). However, the inverse association between $\dot{V}O_{2peak}$ and all-cause mortality was significant, amounting to a 23% decrease in the expected crude hazard per 1.0 unit (mL/kg/min) rise in $\dot{V}O_{2peak}$ (χ^2 = 21.63; *Table 3*). Cox modelling that included both HFrEF and control patients also yielded a significant inverse association between $\dot{V}O_{2peak}$ and all-cause mortality (χ^2 = 37.88, P < 0.001; Supporting Information, *Table S3*).

In multivariate Cox regression analysis involving only HFrEF, the main effect of spirometry group joined with $\dot{V}O_{2peak}$ yielded a significant $\dot{V}O_{2peak}$-by-spirometry group interaction (χ^2 = 8.98; *Table 3*) and the strongest overall model fit of the data (*Table 4*). The corresponding expected hazards associated with $\dot{V}O_{2peak}$ were significantly increased in Group 2 as compared with Groups 1 and 3, respectively (*Table 3*). Differences in expected hazards associated with $\dot{V}O_{2peak}$ between Groups 1 and 3 were not significant (*Table 3*). Data and differences reported in Supporting Information, *Tables S3* and *S4* were also consistent with *Tables 3 and 4* even after accounting for variance associated with controls.

The final model resulting from multivariate Cox regression using the backwards step-wise selection process detailed in *Table 3* confirmed that there was a significant prognostic

Table 3 Predictors of all-cause mortality for patients with heart failure and reduced ejection fraction

	HR (95% CI)	c-statistic (95% CI)	*P*-value
Univariate			
$\dot{V}O_{2peak}$, (1.0 unit) mL/kg/min	0.77 (0.68, 0.87)	0.71 (0.63, 0.79)	<0.001
Univariate			
Spirometry phenotype		0.56 (0.44, 0.68)	0.370
Multivariate (restricted adj. model)			
Overall model fit		0.72 (0.62, 0.81)	<0.001
$\dot{V}O_{2peak}$, (1.0 unit) mL/kg/min	0.78 (0.69, 0.88)		<0.001
Spirometry phenotype			0.809
Multivariate (fully adj. model)			
Overall model fit		0.73 (0.65, 0.81)	<0.001
$\dot{V}O_{2peak}$			<0.001
Spirometry phenotype			0.022
$\dot{V}O_{2peak}$-by-spirometry interaction			0.011
Group 2 vs. Group 1	1.99 (1.14, 3.46)		0.015
Group 3 vs. Group 1	1.32 (0.74, 2.38)		0.354
Group 2 vs. Group 3	2.43 (1.44, 4.11)		<0.001
Multivariate (backward stepwise)			
Initial full model fit (all covariates)		0.79 (0.69, 0.89)	<0.001
Variables removed ($P > 0.05$)			
Step 1 Haemoglobin			0.901
Step 2 Diastolic dysfunction grade			0.877
Step 3 Ex-smoker			0.663
Step 4 Asthma			0.598
Step 5 eGFR			0.426
Step 6 Beta-blocker			0.357
Step 7 Sex			0.382
Step 8 BMI			0.264
Step 9 Diabetes			0.139
Step 10 LVEF			0.116
Final model fit		0.77 (0.65, 0.89)	<0.001
Age	1.06 (1.01, 1.11)		0.017
NT-proBNP	>1.00 (>1.00, >1.00)		<0.001
$\dot{V}O_{2peak}$-by-spirometry interaction			0.042
Group 2 vs. Group 1	1.77 (1.04, 3.02)		0.035
Group 3 vs. Group 1	1.18 (0.68, 2.06)		0.550
Group 2 vs. Group 3	2.46 (1.36, 4.43)		0.003

95% CI, confidence interval, lower and upper bounds; Asthma, clinical history not of the chronic obstructive pulmonary disease variant; BMI, body mass index; c-statistic, concordance statistic; eGFR, estimated glomerular filtration rate calculated based on the modification of diet and renal disease formula; Ex-smoker, defined as having smoked >100 lifetime cigarettes (yes/no); HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; $\dot{V}O_{2peak}$, peak exercise oxygen uptake.
Patients with heart failure and reduced ejection fraction were classified by spirometric patterns as follows: normal [*Group 1*: forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) $\geq$ 0.70 and FVC $\geq$ 80% predicted], restrictive in the absence of obstruction (*Group 2*: FEV_1/FVC $\geq$ 0.70 and FVC < 80% predicted), or obstructive (*Group 3*: FEV_1/FVC < 0.70). Diastolic dysfunction grade was evaluated according to the American Society of Echocardiography/European Association of Cardiovascular Imaging Guidelines and Standards in Nagueh *et al*.[29] Control group patients were not included in statistical testing and results reported within the table. Table *P*-values represent the overall Cox model fit, level of significance for explanatory variables in Cox models, level of significance for pairwise group comparisons of hazards, or level of significance for an explanatory variable removed at each step of backward stepwise multivariate regression.

association involving the $\dot{V}O_{2peak}$-by-spirometry group interaction term and risk of 1 year all-cause mortality. The inclusion of age and N-terminal pro-brain natriuretic peptide as the other final model covariates provided further strength to the overall model (ΔLR statistic = 15.78; $P < 0.001$) but had no relevant effect on changing the increased expected hazard predicted by an impaired $\dot{V}O_{2peak}$ linked to Group 2 as compared with Groups 1 and 3.

Discussion

We demonstrate in this study that when patients with moderate-to-severe HFrEF are subclassified according to basic flow-volume loop spirometry patterns, 1 year all-cause mortality risk estimated by $\dot{V}O_{2peak}$ is severest in individuals exhibiting a restrictive ventilatory defect in the absence of airflow obstruction. Each of the three spirometric patterns

Table 4 Comparison of Cox regression models using likelihood ratio testing

	ΔLR statistic	*P*-value
Cox model comparisons		
$\dot{V}O_{2peak}$ (univariate) versus $\dot{V}O_{2peak}$-by-spirometry interaction (fully adjusted multivariate)	9.38	<0.001
Spirometry group (univariate) versus $\dot{V}O_{2peak}$-by-spirometry interaction (fully adjusted multivariate)	29.02	<0.001
$\dot{V}O_{2peak}$ + Spirometry phenotype (restricted adjusted multivariate) versus $\dot{V}O_{2peak}$-by-spirometry interaction (fully adjusted multivariate)	8.95	<0.001

LR, likelihood ratio; $\dot{V}O_{2peak}$, peak exercise oxygen uptake.
ΔLR statistic $= -2 \ln L_R - (-2 \ln L_F)$, where R = either the univariate or restricted adjusted Cox regression model without the $\dot{V}O_{2peak}$-by-spirometry interaction term and F = full adjusted Cox regression model containing the $\dot{V}O_{2peak}$-by-spirometry interaction term. Cox regression model and comparisons include only patients with heart failure and reduced ejection fraction.

yielded a different direct effect on both $\dot{V}O_{2peak}$ and the prognostic power of $\dot{V}O_{2peak}$ for the study endpoint; key results which are not otherwise observable when $\dot{V}O_{2peak}$ is simply adjusted for the main effect of spirometry pattern. The significant $\dot{V}O_{2peak}$-by-spirometry interaction and the lack of wide disparity in aerobic exercise impairment across groups also showed that there does not need to be obvious differences in the deterioration of $\dot{V}O_{2peak}$ to observe unique associations with mortality risk. Integrating pragmatic spirometry testing into the CPET clinical practice model can aid HF specialists identify insipient signs of coexistent airflow and ventilatory defect pathology, which is information that can be used to strengthen the risk stratification process involving classical $\dot{V}O_{2peak}$ thresholds known to fall within narrow lower and upper limits.

Studies reporting on clinical exercise physiological testing continue to provide evidence highlighting that abnormal heart–lung interactions exert potent whole-body circulatory effects resulting in limited aerobic exercise capacity in HFrEF.[1,2,11,32–36] This body of knowledge is extended with this study. We address a major 'lab-to-practice' knowledge gap by demonstrating that the direct effect of a restrictive-patterned ventilatory defect on the strength of the inverse association between $\dot{V}O_{2peak}$ and mortality risk is clinically relevant and not generalizable to similarly aerobically impaired counterparts classified with one of the other spirometric phenotypes. That the unique joint effects of severe aerobic impairment and restrictive-patterned ventilatory function continued to estimate the highest mortality risk even after accounting for typical HFrEF risk factors or adding a control group, it is clear that having on-hand basic spirometry data provides valuable information that is straightforward and impactful to the sector of possible transplant eligible patients where the definition of moderate-to-severely impaired $\dot{V}O_{2peak}$ has quantifiably narrow margins.

Our observations and interpretation of the current data are consistent with studies on otherwise healthy middle-to-elderly aged adults where it is suggested that there is prognostic value associated with identifying abnormal spirometric patterns and increased risk of cardiovascular disease.[12,14,16–18] Even more specific to our study rationale and key outcomes is the collective body of evidence suggesting that not only does the risk of developing restrictive ventilatory defects increase as previously healthy adults age into and across mid-to-late adulthood, but it is not rare for these individuals to exhibit coexistent left-sided heart disease, ventricular dysfunction, and increased risk of HFrEF and early death.[12,14–18] This study extends that body of evidence as we demonstrate what are likely to be the exercise physiological, clinical, and terminal consequences associated with the next logical sequence of multi-organ disease progression for those where restrictive ventilatory defect pathology overlaps with confirmed HFrEF. Thus, while the need for performing the full spectra of pulmonary function and lung volume testing plays a critical role in formally diagnosing respiratory morbidity,[22,37] consistent with the methodology of spirometric studies performed on healthy adults before us, it is also practically and clinically relevant that basic spirometry testing greatly simplifies the ability to routinely screen patients for possible overlapping airflow and ventilatory defects while concurrently improving the understanding of the clinical severity implied by an impaired $\dot{V}O_{2peak}$.

Limitations

We did not perform advanced pulmonary function testing to confirm our interpretations of airflow and ventilatory patterns resulting from basic spirometry testing.[22,23,37] However, advanced pulmonary function testing that also includes quantifying lung volumes is labour intensive, requires special equipment with functions not available on a metabolic cart, and is not routinely available in HF clinics. The present application of spirometry testing coupled with CPET is

immediately clinically translational, and observations discussed herein are useful in continuing to advance the understanding of how to interpret and apply information generated by the typical range of $\dot{V}O_{2peak}$ responses observed in moderate-to-severe HFrEF. Identifying deteriorated pulmonary function consistent with restrictive ventilatory defect pathology lends information that is dually influential to exercise physiological and adverse event risk interpretations, which collectively have not even been reported in studies involving other HFrEF subgroups, such as the HFrEF–chronic obstructive pulmonary disease overlap.[1–5]

In contrast to our interpretations and views of these data, there is the possibility that other pathophysiological reasons may explain these data. This could include, for example, a still to be well-accepted haemodynamic-based restrictive mimicking effect stemming from coexistent diabetes, renal dysfunction, hypertension, and diastolic dysfunction disproportionately affecting patients demonstrating a restrictive-patterned ventilatory defect.[9,38,39] While Group 2 patients demonstrated the highest overall prevalence of diabetes, the proportional distribution of renal dysfunction, hypertension, and diastolic dysfunction grade severity did not differ significantly across groups, and both diabetes and diastolic dysfunction grade did not persist as significant covariates in multivariate Cox regression testing.

There is also the possibility that non-pathophysiological reasons (e.g. poor effort) may account for our observed spirometry patterns. However, spirometry manoeuvres and acquired measurements met procedural standards of the European Respiratory Society.[22,23] We also propose that if technical and non-pathophysiological factors, such as poor effort, played the main explanatory role in this study, it is unlikely that this source of variability would have led to such a distinct statistical interaction involving $\dot{V}O_{2peak}$ and spirometry group as joined factors in representing the strongest overall model for predicting all-cause mortality.

Conclusions

In patients with moderate-to-severe HFrEF, an impaired $\dot{V}O_{2peak}$ coupled with a resting spirometry pattern resembling a restrictive ventilatory defect significantly increases the risk of 1 year all-cause mortality as compared with that of counterparts similarly aerobically impaired but while exhibiting an obstructive airflow pattern. Patients classified with a normal spirometry pattern demonstrate the least impaired aerobic exercise capacity and a mortality risk associated with $\dot{V}O_{2peak}$ that does not differ from that of counterparts exhibiting an obstructive spirometry pattern. Evaluating airflow and ventilatory patterns using basic spirometry testing can provide clinicians with unique information that helps to refine the understanding of mortality risk associated with $\dot{V}O_{2peak}$ thresholds commonly referenced to indicate severe aerobic capacity impairment in patients with moderate-to-severe HFrEF.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Funding

None.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of control patients.
Table S2. Peak exercise responses of control patients.
Table S3. Predictors of all-cause mortality in patients with either heart failure and reduced ejection fraction or no heart failure.
Table S4. Comparison of Cox regression models using likelihood ratio testing.

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