

ORIGINAL RESEARCH

**OPEN ACCESS**  
Full open access to this and  
thousands of other papers at  
<http://www.la-press.com>.

## Prognostic Value of Resting Pulmonary Function in Heart Failure

Thomas P. Olson<sup>1</sup>, Dustin L. Denzer<sup>2</sup>, William L. Sinnett<sup>2</sup>, Ted Wilson<sup>2</sup> and Bruce D. Johnson<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Mayo Clinic, Rochester, MN. <sup>2</sup>Department of Biology, Winona State University, Winona, MN. Corresponding author email: [johnson.bruce@mayo.edu](mailto:johnson.bruce@mayo.edu)

### Abstract

**Background:** The heart and lungs are intimately linked anatomically and physiologically, and, as a result, heart failure (HF) patients often develop changes in pulmonary function. This study examined the prognostic value of resting pulmonary function (PF) in HF.

**Methods and results:** In all, 134 HF patients (enrolled from January 1, 1999 Through December 31, 2005; ejection fraction (EF) = 29% ± 11%; mean age = 55 ± 12 years; 65% male) were followed for 67 ± 34 months with death/transplant confirmed via the Social Security Index and Mayo Clinic registry. PF included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV<sub>1</sub>), diffusing capacity of the lungs for carbon monoxide (DL<sub>CO</sub>), and alveolar volume (VA). Patients were divided in tertiles according to PF with survival analysis via log-rank Mantel-Cox test with chi-square analysis. Groups for FVC included (1) >96%, (2) 96% to 81%, and (3) <81% predicted (chi-square = 18.9, *P* < 0.001). Bonferroni correction for multiple comparisons (BC) suggested differences between groups 1 and 3 (*P* < 0.001) and 2 and 3 (*P* = 0.008). Groups for FEV<sub>1</sub> included (1) >94%, (2) 94% to 77%, and (3) <77% predicted (chi-square = 17.3, *P* < 0.001). BC suggested differences between groups 1 and 3 (*P* < 0.001). Groups for DL<sub>CO</sub> included (1) >90%, (2) 90% to 75%, and (3) <75% predicted (chi-square = 11.9, *P* = 0.003). BC suggested differences between groups 1 and 3 (*P* < 0.001). Groups for VA included (1) >97%, (2) 97% to 87%, and (3) <87% predicted (Chi-square = 8.5, *P* = 0.01). BC suggested differences between groups 1 and 2 (*P* = 0.014) and 1 and 3 (*P* = 0.003).

**Conclusions:** In a well-defined cohort of HF patients, resting measures of PF are predictive of all-cause mortality.

**Keywords:** lung volume, lung diffusing capacity, mortality, left ventricular dysfunction

*Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine* 2013:7 35–43

doi: [10.4137/CCRPM.S12525](https://doi.org/10.4137/CCRPM.S12525)

This article is available from <http://www.la-press.com>.

© the author(s), publisher and licensee Libertas Academica Ltd.

This is an open access article published under the Creative Commons CC-BY-NC 3.0 license.



## Introduction

Chronic heart failure (HF) is a progressive disease resulting in severe morbidity and mortality.<sup>1,2</sup> Although cardiac dysfunction is clearly an initiating process, HF becomes a systemic illness that impacts multiple organ systems.<sup>3-5</sup> One such system is the pulmonary system, which lies in series with the heart, accepts nearly all of the cardiac output, is exposed to similar intrathoracic pressure changes, and shares a closed anatomical space. Thus, it would be expected that adverse changes the cardiac system may have consequences on the pulmonary system. Correspondingly, it could be hypothesized that these known changes in pulmonary function may provide insight to HF patient clinical status.

It has been previously determined that patients with HF develop mild to moderate changes in the pulmonary system including restrictive and obstructive changes, alveolar-capillary diffusion abnormalities, tachypneic breathing pattern, and ventilation/perfusion inhomogeneities ( $\dot{V}_A/\dot{Q}_c$ ).<sup>6-9</sup> The etiology for these changes in lung function have traditionally been linked to respiratory muscle weakness, chronic pulmonary hypertension with pulmonary vasculature remodeling, changes in lung fluid balance, altered receptor function, and progressive cardiac enlargement within a closed thoracic cavity leading to pulmonary displacement.<sup>10-14</sup> Importantly, many HF patients present with additional comorbid diseases such as diabetes and chronic obstructive disease, which influence pulmonary function.<sup>15,16</sup> For example, Iversen and colleagues demonstrated, in a cohort of HF patients admitted to the hospital for acute decompensation, that simple spirometry provides useful prognostic information for all-cause mortality.<sup>15</sup> The authors demonstrated that the measure of forced expiratory volume in 1 second ( $FEV_1$ ) was predictive of survival in these patients. However, the study by Iversen also included patients with self-reported and medically diagnosed chronic obstructive pulmonary disease (COPD), which was also demonstrated to be prognostic of survival.<sup>15</sup>

This study examined the utility of resting measures of pulmonary function in predicting all-cause mortality in a homogenous cohort of patients with stable HF who did not present with other comorbidities. We hypothesized that the commonly measured indices of pulmonary function would have significant prognostic value in these patients.

## Methods

### Population characteristics

This study recruited a total of 134 patients with compensated HF recruited from the Mayo Clinic Heart Failure Service and the Cardiovascular Health Clinic (a preventive and rehabilitative center, Rochester, MN). Participants were prospectively recruited in the years from 1999 through 2005 and followed until December 31, 2005 if seen at the Mayo Clinic. Participants were included in this cohort if they met our inclusion criteria. Inclusion criteria included all of the following: a history of ischemic or dilated cardiomyopathy, stable HF symptoms (>3 months), duration of HF symptoms >1 year, left ventricular ejection fraction (EF)  $\leq$  35%, body mass index (BMI) <35 kg/m<sup>2</sup>, nonsmoking status with a smoking history of <15 pack years, and no medical diagnosis of chronic obstructive pulmonary disease or other pulmonary diseases (asthma, pulmonary fibrosis, cystic fibrosis, etc.), diabetes, or musculoskeletal diseases. Patients were treated with standard optimized medications for HF at the time of entry to the study.

All participants gave written informed consent after being provided a description of study requirements. This study was conducted in accordance with the Declaration of Helsinki and approved by the Mayo Clinic Institutional Review Board; all procedures followed institutional and Health Insurance Portability and Accountability Act (HIPAA) guidelines.

### Measurement of pulmonary function

All participants underwent spirometry evaluation including forced vital capacity (FVC) and assessment of forced expiratory volume in 1 second ( $FEV_1$ ). Participants also underwent assessment of the diffusing capacity of the lungs for carbon monoxide ( $DL_{CO}$ ) and measurement of alveolar volume (VA) using the single breath method. Spirometry and  $DL_{CO}$  measures were collected according to the American Thoracic Society (ATS) standards.<sup>17,18</sup>

### Statistical analysis

All-cause mortality was determined using the Mayo Clinic death database as well as the United States Social Security Death Index. Due to the inherent limitations of these databases, all-cause mortality was used as the primary end point. Statistical analysis and graphic presentation were accomplished using



SPSS (version 12.0, Chicago, IL) and GraphPad Prism (version 4.0, San Diego, CA). Kaplan-Meier analysis assessed survival characteristics of evenly distributed tertile expression of resting pulmonary function variables. The Mantel-Cox log-rank test determined statistical significance of the Kaplan-Meier analysis via chi-square analysis. When the log-rank test was significant, Bonferroni correction for multiple comparisons was applied. Significance was set at an alpha level of 0.05 for all comparisons. When the Bonferroni correction was applied, the alpha level was set at 0.017.

## Results

### Population characteristics

The patient demographics, clinical characteristics, medications in use at the time of recruitment, and resting pulmonary function data are reported in Table 1. The cohort consisted of predominantly male patients (65% male). By definition, these patients had a significantly reduced EF% and  $VO_2$  peak although the majority of patients were of moderate symptomology (66% New York Heart Association [NYHA] class I or II). The majority of these patients were prescribed angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, digoxin, and diuretics, while only 11% of patients were prescribed angiotensin II receptor blockers. This cohort of stable HF patients presented with mild reductions in pulmonary function.

### Heart failure mortality analysis

There were 34 deaths and 11 heart transplants resulting in a total of 45 adverse events during the  $67.1 \pm 33.5$  month follow-up period (range of follow-up = 1–114 months). This resulted in an annual event rate of 5.6%. All patients who did not suffer an adverse event were followed for a minimum of 36 months.

### Resting pulmonary function predictors of survival in patients with heart failure

Figures 1–4 present the results of the Kaplan-Meier analysis for patients grouped by equally distributed tertiles of FVC,  $FEV_1$ ,  $DL_{CO}$ , and VA, respectively. The results of the chi-square analysis suggested an overall log-rank value of 18.9 ( $P < 0.001$ ) for FVC, 17.3 ( $P < 0.001$ ) for  $FEV_1$ , 11.0 ( $P = 0.003$ ) for  $DL_{CO}$ , and 8.5 ( $P = 0.01$ ) for VA, respectively.

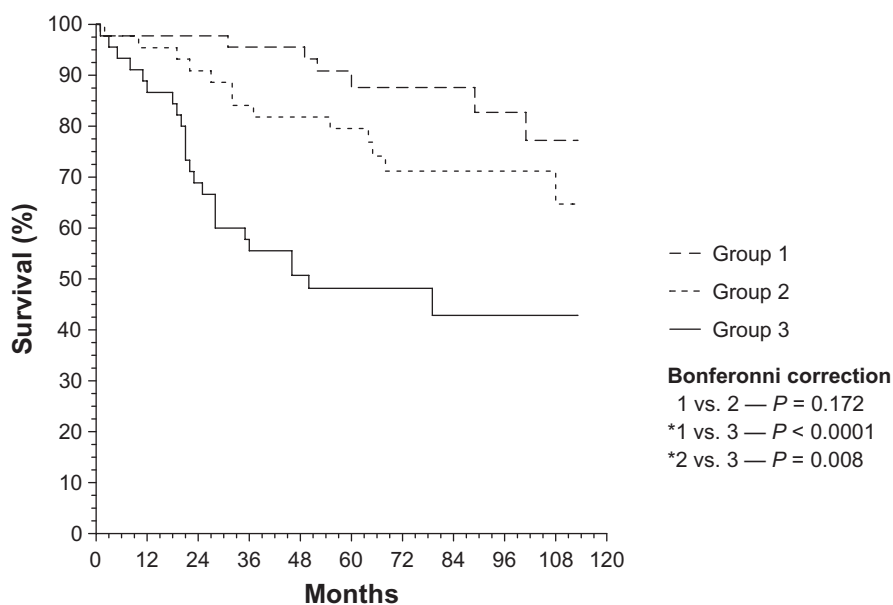
**Table 1.** Participant characteristics.

Demographics	Mean $\pm$ SD
Number	134
Male/female	83/51
Age (yr)	55 $\pm$ 12
Height (cm)	172.7 $\pm$ 9.9
Weight (kg)	84.8 $\pm$ 17.2
BMI (kg/m <sup>2</sup> )	28.3 $\pm$ 4.6
Body fat (%)	27.1 $\pm$ 6.8
Smoking Hx (pack yrs)	4.4 $\pm$ 10.0
Exercise Hx (min/wk)	72.2 $\pm$ 95.8
<b>Clinical characteristics</b>	
EF (%)	28.8 $\pm$ 11.3
Peak $VO_2$ (mL/kg/min)	19.0 $\pm$ 6.2
NYHA class	class I = 45 (34) class II = 43 (32) class III = 35 (26) class IV = 11 (8)
Medications	Number (% of population)
ACE inhibitor	98 (74)
All receptor blocker	15 (11)
Beta-blocker	100 (76)
Digoxin	86 (65)
Diuretic	89 (67)
Resting pulmonary function	Mean $\pm$ SD (Range)
FVC (L)	3.71 $\pm$ 1.12 (1.4–7.8)
%pred	86.7 $\pm$ 17.4 (41–134)
$FEV_1$ (L/sec)	2.88 $\pm$ 0.89 (1.1–5.8)
%pred	84.5 $\pm$ 18.6 (39–124)
$DL_{CO}$ (mL/min/mmHg)	22.28 $\pm$ 5.70 (10.2–36.2)
%pred	82.7 $\pm$ 16.5 (46–122)
VA (L)	5.58 $\pm$ 1.31 (3.1–9.0)
%pred	90.6 $\pm$ 13.8 (55–125)

**Abbreviations:** BMI, body mass index; BF, body fat; EF, left ventricular ejection fraction; NYHA, New York Heart Association;  $VO_2$ , volume of oxygen consumed; ACE, angiotensin converting enzyme; All, angiotensin II.

### Group 1

Patients with a FVC of  $>96\%$  predicted comprised 33.6% of the population and had 7 events resulting in an event-free survival of 84.4%. Patients with a  $FEV_1$  of  $>94\%$  predicted comprised 34.3% of the population and had 6 events resulting in 87.0% event-free survival. For  $DL_{CO}$ , patients with  $>90\%$  predicted comprised 32.1% of the population and had 9 events resulting in 79.1% event-free survival. Finally, patients with an VA of  $>97\%$  predicted comprised approximately 34.3% of the population and had 9 events resulting in an event-free survival of 80.4%.



Group	Characteristics	Participants meeting criteria	Number of events	Percent event free
1	FVC %pred >96	45	7	84.4
2	FVC %pred = 96–81	44	13	70.5
3	FVC %pred <81	45	24	46.7

**Figure 1.** Kaplan-Meier analysis for patients grouped by FVC. Log rank: 18.9,  $P < 0.001$ .

**Abbreviation:** FVC, forced vital capacity.

### Group 2

Patients presenting with a FVC between 96% and 81% predicted comprised 32.8% of the population and had 13 events resulting in 70.5% event-free survival. Similarly, patients with a FEV<sub>1</sub> between 94% and 77% predicted comprised 31.3% of the population and had 14 events resulting in an event free survival of 66.7%. Patients with a DL<sub>CO</sub> between 90% and 75% predicted comprised 35.1% of the population and had 14 events resulting in 70.2% event free survival. The patients with an VA between 97% and 87% predicted comprised 32.8% of the population and had 17 events resulting in an event free survival of 61.4%.

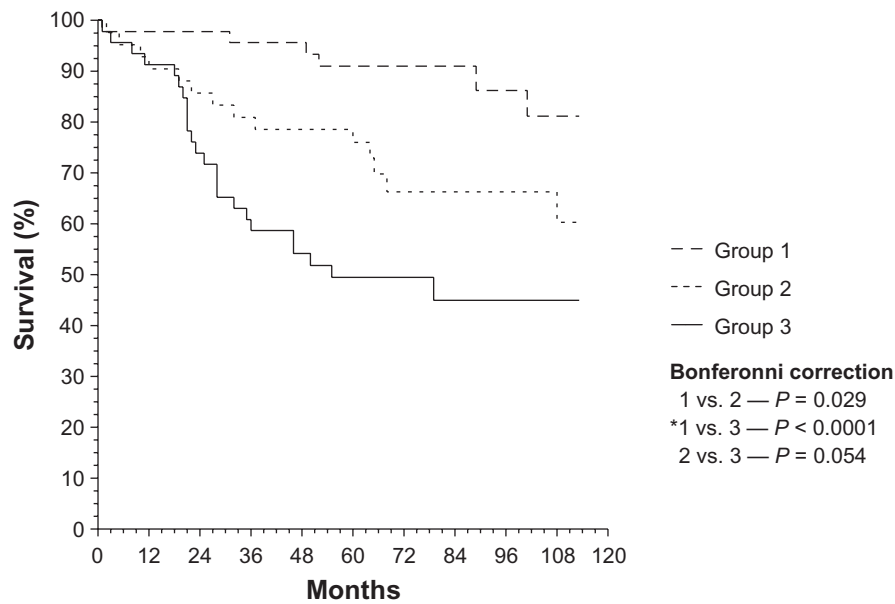
### Group 3

Patients with a FVC of <81% predicted comprised 33.6% of the population and had 24 events resulting in an event-free survival of 46.7%. Similarly, patients with a FEV<sub>1</sub> of <77% predicted comprised 34.3% of the population and had 24 events resulting in 47.8% event-free survival. Patients with a

DL<sub>CO</sub> of <75% predicted comprised 33.6% of the population and had 21 events resulting in 53.3% event-free survival whereas those with an VA of <87% predicted comprised 32.8% of the population and had 19 events resulting in an event-free survival of 56.8%.

### Comparisons

For FVC, there was no significant difference between groups 1 and 2 for survival ( $P = 0.17$ ); however, there were significant differences between groups 1 and 3 ( $P < 0.001$ ) as well as groups 2 and 3 ( $P = 0.008$ ). When examining FEV<sub>1</sub>, there also was no difference between groups 1 and 2 ( $P = 0.03$ ) or groups 2 and 3 ( $P = 0.05$ ), whereas there was a significant difference between groups 1 and 3 ( $P < 0.001$ ). There was no difference between groups 1 and 2 ( $P = 0.13$ ) or groups 2 and 3 ( $P = 0.09$ ) for DL<sub>CO</sub>. There was, however, a significant difference between groups 1 and 3 ( $P = 0.002$ ). The VA demonstrated a significant difference between groups 1 and 2 ( $P = 0.014$ ) and groups



Group	Characteristics	Participants meeting criteria	Number of events	Percent event free
1	FEV <sub>1</sub> %pred >94	46	6	87.0
2	FEV <sub>1</sub> %pred = 94–77	42	14	66.7
3	FEV <sub>1</sub> %pred <77	46	24	47.8

**Figure 2.** Kaplan-Meier analysis for patients grouped by FEV<sub>1</sub>. Log rank: 17.3,  $P < 0.001$ .  
**Abbreviation:** FEV<sub>1</sub>, forced expiratory volume in one second.

1 and 3 ( $P = 0.003$ ); however, there was no difference between groups 2 and 3 ( $P = 0.70$ ).

## Discussion

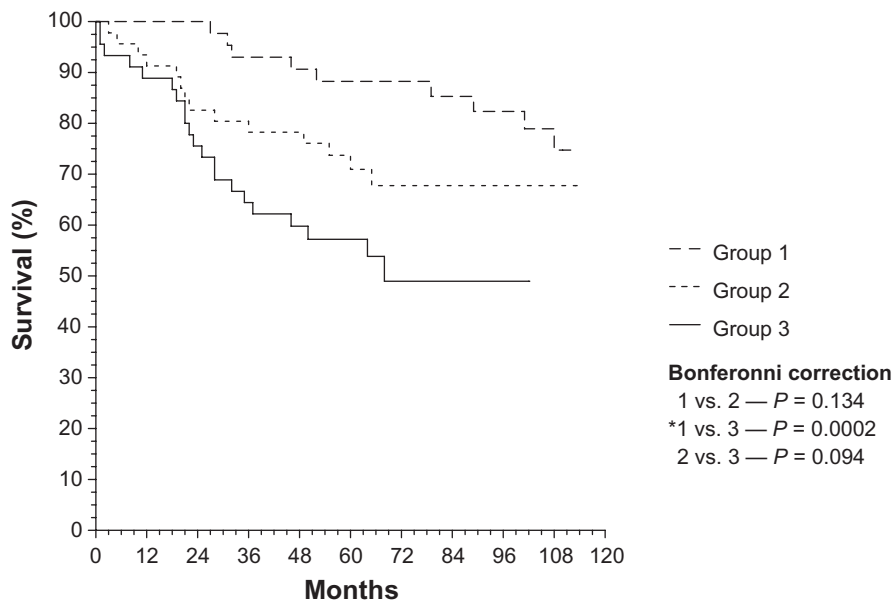
### Primary findings

This study examined the utility of resting pulmonary function measures in predicting event-free survival in patients with HF. Our data suggest that resting measures of pulmonary function are useful markers of prognosis in a well-defined cohort of HF patients. Specifically, resting measures of FVC, FEV<sub>1</sub>, DL<sub>CO</sub>, and VA can be used to stratify prognosis and highlight the close interaction between the cardiac and pulmonary systems as it relates to HF prognosis.

### Traditional predictors of mortality in heart failure

A number of studies have sought to determine the critical predictors of survival in the HF population.<sup>19</sup> Initially, the majority of these predictors centered on measures of cardiac performance and functional capacity.

Specifically, measures with well-established prognostic value include NYHA class,<sup>20</sup> peak  $\dot{V}O_2$ ,<sup>21</sup> and left ventricular ejection fraction,<sup>22</sup> although a number of emerging measures are becoming more prominent. Emerging measures have included heart rate recovery,<sup>23</sup> ventilatory efficiency slope,<sup>24</sup> and partial pressure of end-tidal carbon dioxide ( $P_{ET}CO_2$ ) at rest and during exercise.<sup>25,26</sup> In addition, a number of plasma markers have also been suggested to provide prognostic information in the HF population including norepinephrine,<sup>27</sup> brain natriuretic peptide (BNP),<sup>28</sup> and urea nitrogen.<sup>29</sup> While limited cardiac function is clearly an initiating process, it is evident that HF becomes a systemic illness that impacts multiple organ systems. One system that is particularly influenced in the cascade of pathophysiology is the pulmonary system. The pulmonary and cardiac systems are intimately linked anatomically and hemodynamically, and, as such, changes in the cardiac system have profound effects on the pulmonary system. This creates a unique condition where the pulmonary system may be used as a window to assess the HF disease process.



Group	Characteristics	Participants meeting criteria	Number of events	Percent event free
1	DL <sub>CO</sub> %pred >90	43	9	79.1
2	DL <sub>CO</sub> %pred = 90–75	46	14	69.6
3	DL <sub>CO</sub> %pred <75	45	21	53.3

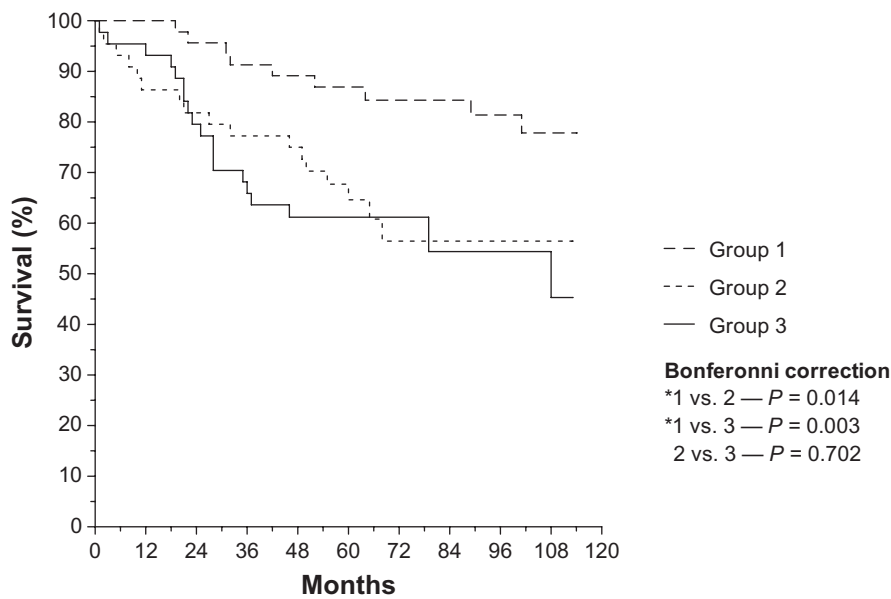
**Figure 3.** Kaplan-Meier analysis for patients grouped by DL<sub>CO</sub>. Log rank: 11.9,  $P = 0.003$ .  
**Abbreviation:** DL<sub>CO</sub>, diffusing capacity of the lungs for carbon monoxide.

### Pulmonary system related predictors of mortality in heart failure

Due to the close interactions between the pulmonary and cardiac systems, measures of pulmonary function may also provide novel, useful, and noninvasive measures of prognosis in patients with HF. Gas exchange measures such as diffusion capacity of the lungs for carbon monoxide and  $P_{ET}CO_2$  have been shown to be effective predictors in heart failure and have been suggested for use in clinical settings.<sup>26,30,31</sup> The ventilatory efficiency slope during exercise also has shown particular prognostic usefulness in heart failure patients.<sup>32</sup> Altered breathing architecture such as exertional periodic breathing, periodicity of breathing during sleep, and the apnea-hypopnea index may also be significant factors predictive of heart failure disease status.<sup>33</sup> Pulmonary function is closely related to cardiac function and the clinical understanding of its relevance to HF prognosis is rapidly becoming apparent.

### Relationship between resting pulmonary function and morbidity and mortality

Previous studies have suggested that deterioration of pulmonary function in the general population is a useful indicator of prognosis.<sup>34–36</sup> Beaty and colleagues prospectively followed 2500 community dwelling individuals over 5 years and demonstrated that impairment of pulmonary function is a significant risk factor for both short- and long-term morbidity and mortality, independent of traditional risk factors.<sup>36</sup> It is suggested that maladaptations of the pulmonary system not only contribute to morbidity and mortality independently, but also through specific pathogenic contributions to a number of nonrespiratory diseases.<sup>36</sup> Not only is this true for the general population, but also for patients at risk for myocardial infarction and sudden death,<sup>37</sup> those with obstructive airway disease,<sup>38</sup> and those with lung cancer.<sup>39</sup> Thus, it is apparent that detrimental changes in pulmonary function not only act as markers of underlying disease



Group	Characteristics	Participants meeting criteria	Number of events	Percent event free
1	VA %pred >97	46	9	80.4
2	VA %pred = 97–87	44	17	61.4
3	VA %pred <87	44	19	56.8

**Figure 4.** Kaplan-Meier analysis for patients grouped by VA. Log rank: 8.5,  $P = 0.014$ .  
**Abbreviation:** VA, alveolar volume.

but also have the capacity to significantly and independently elevate an individual's risk for morbidity and mortality.

### Alterations of pulmonary function in heart failure

A number of studies have demonstrated that patients with HF often develop significant pulmonary function abnormalities.<sup>13,14,40–43</sup> These changes range from relatively minimal dysfunction when compared with age- and height-predicted measures<sup>44</sup> to more significant restrictive abnormalities,<sup>45</sup> obstructive changes,<sup>46</sup> and combined restrictive and obstructive alterations.<sup>40</sup> Although the specific mechanisms leading to altered lung function in HF are not entirely clear, these changes have been attributed to neurohumoral changes,<sup>11,12,47</sup> lung fluid imbalance,<sup>12</sup> chronic pulmonary congestion and hypertension,<sup>48</sup> respiratory muscle weakness,<sup>11</sup> cardiomegaly,<sup>13,14</sup> altered receptor function,<sup>10</sup> and possibly inflammatory mediators.<sup>49</sup> Despite the lack

of clarity regarding the underlying mechanism(s), it is clear that changes in the pulmonary system reflect the disease severity of the HF patient. As such, the results of this study clearly demonstrate the utility of resting pulmonary function measures in stratifying risk for mortality in these patients.

In the general population, impaired pulmonary function, particularly reductions in FVC and FEV<sub>1</sub>, have been shown to be predictive of mortality, especially in smokers and persons under the age of 70.<sup>34,35</sup> In the healthy aging population, FEV<sub>1</sub> and FVC are known to be progressively diminished with progressing age.<sup>50,51</sup> However, these studies did not include DL<sub>CO</sub> and VA in their analyses. Moreover, Sorlie and colleagues demonstrated that dyspnea, commonly associated with reduced pulmonary function in patients with HF, is also associated with mortality.<sup>35</sup> However these seminal studies did not indicate HF as a study subset within their population. Our study consisted of a relatively homogeneous group of HF



patients with patients excluded for morbid obesity, extensive smoking history, and heart rhythm abnormalities. As such, it may be warranted to include a more heterogeneous and larger cohort of patients in follow-up studies.

### Clinical implications and study limitations

Our results suggest that in patients with stable heart failure of duration >1 year pulmonary function measures significantly predict mortality. These results are specific to HF patients who present without other significant comorbidities such as preexisting COPD, asthma, diabetes, or other diseases that may influence pulmonary function. As such, these results should be seen as a key step in understanding the influence of HF on pulmonary function and its implications for survival. Importantly, the inclusion criteria for this study were narrow to ensure patients with significant comorbidities were not included. As such, these findings are only generalizable to the cohort studied. Future studies might include wider inclusion criteria with a more heterogeneous HF population, which would permit the study of how multiple comorbidities influenced the impact of pulmonary function measures to predict mortality.

### Conclusion

The results of this study demonstrate that classical measures of lung function are useful in predicting prognosis in patients with HF. In particular, both the FVC and FEV<sub>1</sub> demonstrated the strongest relationship with event-free survival; however DL<sub>CO</sub> and V<sub>A</sub> also appear to be important prognostic markers.

### Acknowledgements

The authors would like to thank Minelle Hulsebus and Kathy O'Malley for their help with study recruitment and database management. The abstract of this paper was previously published as a meeting abstract in FASEB J. April 2009 23 (Meeting Abstract Supplement) 812.15.

### Author Contributions

Conceived and designed the experiments: TPO, TW, BDJ. Analyzed the data: TPO, DLD, WLS, TW. Wrote the first draft of the manuscript: TPO, DLD, WLS. Contributed to the writing of the manuscript: TPO, DLD, WLS, TW, BDJ. Agree with the manuscript

results and conclusions: TPO, DLD, WLS, TW, BDJ. Jointly developed the structure and arguments for the paper: TPO, DLD, WLS, TW, BDJ. Made critical revisions and approved final version: TPO, DLD, WLS, TW, BDJ. All authors reviewed and approved of the final manuscript.

### Funding

This work was supported by: National Institutes of Health grant HL71478, National Center for Research Resources (NCRR) grant 1KL2RR024151 (<http://www.ncrr.nih.gov>), and the Winona State Office of Academic Affairs.

### Competing Interests

Author(s) disclose no potential conflicts of interest.

### Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

### References

1. Brunwald E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med.* 1997;337:1360–9.
2. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2006;113:e85–151.
3. Johnson RLJ. Gas exchange efficiency in congestive heart failure. *Circulation.* 2000;101:2774–6.
4. Johnson RLJ. Gas exchange efficiency in congestive heart failure ii. *Circulation.* 2001;103:916–8.
5. Witte KK, Clark AL. Why does chronic heart failure cause breathlessness and fatigue? *Prog Cardiovasc Dis.* 2007;49:366–84.
6. Dimopoulou I, Daganou M, Tsintzas OK, Tzelepis GE. Effects of severity of long-standing congestive heart failure on pulmonary function. *Respir Med.* 1998;92:1321–5.
7. Kindman LA, Vagelos RH, Willson K, Prikazky L, Fowler M. Abnormalities of pulmonary function in patients with congestive heart failure and reversal with ipratropium bromide. *Am J Cardiol.* 1994;73:258–62.
8. Light RW, George RB. Serial pulmonary function in patients with acute heart failure. *Arch Intern Med.* 1983;143:429–33.





9. Wright RS, Levine MS, Bellamy PE, et al. Ventilatory and diffusion abnormalities in potential heart transplant recipients. *Chest*. 1990;98:816–20.
10. Snyder EM, Turner ST, Johnson BD. Beta2-adrenergic receptor genotype and pulmonary function in patients with heart failure. *Chest*. 2006;130:1527–34.
11. Daganou M, Dimopoulou I, Alivizatos PA, Tzelepis GE. Pulmonary function and respiratory muscle strength in chronic heart failure: comparison between ischaemic and idiopathic dilated cardiomyopathy. *Heart*. 1999;81:618–20.
12. Puri S, Baker BL, Oakley CM, Hughes JM, Cleland JG. Increased alveolar/capillary membrane resistance to gas transfer in patients with chronic heart failure. *Br Heart J*. 1994;72:140–4.
13. Olson TP, Beck KC, Johnson BD. Pulmonary function changes associated with cardiomegaly in chronic heart failure. *J Card Fail*. 2007;13:100–7.
14. Olson TP, Beck KC, Johnson JB, Johnson BD. Competition for intrathoracic space reduces lung capacity in patients with chronic heart failure: a radiographic study. *Chest*. 2006;130:64–71.
15. Iverson KK, Kjaergaard J, Akkan D, et al; ECHOS Lung Function Study Group. The prognostic importance of lung function in patients admitted with heart failure. *Eur J Heart Fail*. 2010;12:685–91.
16. Ehrlich SF, Quesenberry CPJ, Van Den Eeden SK, Shan J, Ferrara A. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia, but not lung cancer. *Diabetes Care*. 2010;33:55–60.
17. ATS. Single breath carbon monoxide diffusing capacity (transfer factor). Recommendations for a standard technique. Statement of the American Thoracic Society. *Am Rev Respir Dis*. 1987;136:1299–307.
18. American Thoracic Society. Standardization of spirometry, 1994 update. American Thoracic Society. *Am J Respir Crit Care Med*. 1995;152:1107–36.
19. Rector TS, Cohn JN. Prognosis in congestive heart failure. *Annu Rev Med*. 1994;45:341–50.
20. Scrutinio D, Lagioia R, Ricci A, Clemente M, Boni L, Rizzon P. Prediction of mortality in mild to moderately symptomatic patients with left ventricular dysfunction. The role of the New York Heart Association classification, cardiopulmonary exercise testing, two-dimensional echocardiography and Holter monitoring. *Eur Heart J*. 1994;15:1089–95.
21. Ciccoira M, Davos CH, Francis DP, et al. Prediction of mortality in chronic heart failure from peak oxygen consumption adjusted for either body weight or lean tissue. *J Card Fail*. 2004;10:421–6.
22. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation*. 1993;87:VI17–23.
23. Kubrychtova V, Olson TP, Bailey KR, Thapa P, Allison TG, Johnson BD. Heart rate recovery and prognosis in heart failure patients. *Eur J Appl Physiol*. 2009;105:37–45.
24. Tabet JY, Beauvais F, Thabut G, Tartiere JM, Logeart D, Cohen-Solal A. A critical appraisal of the prognostic value of the VE/VCO<sub>2</sub> slope in chronic heart failure. *Eur J Cardiovasc Prev Rehabil*. 2003;10:267–72.
25. Arena R, Guazzi M, Myers J. Prognostic value of end-tidal carbon dioxide during exercise testing in heart failure. *Int J Cardiol*. 2007;117:103–8.
26. Arena R, Myers J, Abella J, et al. The partial pressure of resting end-tidal carbon dioxide predicts major cardiac events in patients with systolic heart failure. *Am Heart J*. 2008;156:982–8.
27. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med*. 1984;311:819–23.
28. Berger R, Huelsman M, Strecker K, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation*. 2002;105:2392–7.
29. Kerzner R, Gage BF, Freedland KE, Rich MW. Predictors of mortality in younger and older patients with heart failure and preserved or reduced left ventricular ejection fraction. *Am Heart J*. 2003;146:286–90.
30. Guazzi M, Pontone G, Brambilla R, Agostoni P, Reina G. Alveolar-capillary membrane gas conductance: a novel prognostic indicator in chronic heart failure. *Eur Heart J*. 2002;23:467–76.
31. Myers J, Guija P, Neelagaru S, et al. End-tidal CO<sub>2</sub> pressure and cardiac performance during exercise in heart failure. *Med Sci Sports Exerc*. 2009;41:19–25.
32. Arena R, Humphrey R, Peberdy MA. Prognostic ability of VE/VCO<sub>2</sub> slope calculations using different exercise test time intervals in subjects with heart failure. *Eur J Cardiovasc Prev Rehabil*. 2003;10:463–8.
33. Corra U, Pistono M, Mezzani A, et al. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. *Circulation*. 2006;113:44–50.
34. Ashley F, Kannel W, Sorlie PD, Masson R. Pulmonary function: relation to aging, cigarette habit, and mortality. *Ann Intern Med*. 1975;82:739–45.
35. Sorlie PD, Kannel W, O'Connor G. Mortality associated with respiratory function and symptoms in advancing age. The Framingham Study. *Am Rev Respir Dis*. 1989;140:379–84.
36. Beaty TH, Cohen BH, Newill CA, Menkes HA, Diamond EL, Chen CJ. Impaired pulmonary function as a risk factor for mortality. *Am J Epidemiol*. 1982;116:102–13.
37. Friedman GD, Klatsky AL, Siegel AB. Lung function and risk of myocardial infarction and sudden cardiac death. *N Engl J Med*. 1976;13:1071–5.
38. Menkes HA, Cohen BH, Beaty TH, Newill CA, Khoury MJ. Risk factors, pulmonary function, and mortality. *Prog Clin Biol Res*. 1984;147:501–21.
39. Eberly LE, Ockene J, Sherwin R, Yang L, Kuller L. Pulmonary function as a predictor of lung cancer mortality in continuing cigarette smokers and in quitters. *Int J Epidemiol*. 2003;32:592–9.
40. Dimopoulou I, Daganou M, Tsintzas OK, Tzelepis GE. Effects of severity of long-standing congestive heart failure on pulmonary function. *Respir Med*. 1998;92:1321–5.
41. Kindman LA, Vagelos RH, Willson K, Prikazky L, Fowler M. Abnormalities of pulmonary function in patients with congestive heart failure and reversal with ipratropium bromide. *Am J Cardiol*. 1994;73:258–62.
42. Light RW, George RB. Serial pulmonary function in patients with acute heart failure. *Arch Intern Med*. 1983;143:429–33.
43. Wright RS, Levine MS, Bellamy PE, et al. Ventilatory and diffusion abnormalities in potential heart transplant recipients. *Chest*. 1990;98:816–20.
44. Collins JV, Clark TJ, Brown DJ. Airway function in healthy subjects and patients with left heart disease. *Clin Sci Mol Med*. 1975;49:217–28.
45. Cabanes LR, Weber SN, Matran R, et al. Bronchial hyperresponsiveness to methacholine in patients with impaired left ventricular function. *N Engl J Med*. 1989;321:1756–8.
46. Petermann W, Barth J, Entzian P. Heart failure and airway obstruction. *Int J Cardiol*. 1987;17:207–9.
47. Abraham MR, Olson LJ, Joyner MJ, Turner ST, Beck KC, Johnson BD. Angiotensin-converting enzyme genotype modulates pulmonary function and exercise capacity in treated patients with congestive stable heart failure. *Circulation*. 2002;106:1794–9.
48. Dembinski R, Henzler D, Rossaint R. Modulating the pulmonary circulation: an update. *Minerva Anesthesiol*. 2004;70:239–43.
49. Sierra-Johnson J, Romero-Corral A, Somers VK, Olson LJ, Johnson BD. Leptin, a novel predictor of lung function in heart failure. *Chest*. 2008;134:346–50.
50. Enright PL, Kronmal RA, Higgins MW, Schenker M, Haponik EF. Spirometry reference values for women and men 65 to 85 years of age. Cardiovascular health study. *Am Rev Respir Dis*. 1993;147:125–33.
51. Griffith KA, Sherrill DL, Siegel EM, Manolio TA, Bonekat HW, Enright PL. Predictors of loss of lung function in the elderly: the Cardiovascular Health Study. *Am J Respir Crit Care Med*. 2001;163:61–8.