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Spirometric Volumes and Breathlessness across Levels of Airflow Limitation: The COPDGene Study

To the Editor:

Breathlessness is the cardinal symptom in people with chronic obstructive pulmonary disease (COPD) and is strongly associated with adverse health outcomes (1–3). Activity-related breathlessness, measured using the modified Medical Research Council (mMRC) breathlessness scale, is about twice as common among women as among men in the population for unclear reasons (1, 3).

Mechanistic and population-based data suggest that women are more prone to experience breathlessness in daily life owing to their lower absolute lung volumes and ventilatory capacity (3–6). No study has evaluated whether absolute lung function is related to breathlessness independent of the level of lung function impairment, and whether absolute volume may explain the higher breathlessness prevalence in women compared with men in COPD across severities of airflow limitation.

The aim of the present work was to evaluate whether the higher prevalence of breathlessness in women is related to their lower absolute spirometric lung volumes as measured by FEV_1, and whether this is seen both in people with normal lung function ($FEV_1 \geq 80\%$ of predicted) and across severities of lung function impairment due to COPD.

Methods

This was a cross-sectional analysis of the COPDGene (Genetic Epidemiology of COPD) study (7). Inclusion criteria were as follows: age, 45–80 years; ethnic category, non-Hispanic white or African-American; and at least 10 years of smoking (COPD cohort) or no smoking (never-smoking control subjects), as detailed elsewhere (7). Exclusion criteria for the present analysis were as follows: missing data on spirometry ($n = 63$) or mMRC breathlessness score ($n = 14$).

Participants completed a modified American Thoracic Society Respiratory Questionnaire including smoking status, physician-diagnosed asthma, COPD, and emphysema. Activity-related breathlessness was self-rated on the mMRC scale (8). Post-bronchodilator spirometry was performed with an EasyOne spirometer (ndd Medizintechnik AG) according to American Thoracic Society standards (7). Predicted FEV_1 and FVC were calculated (9).

The sex difference in breathlessness was analyzed as the odds ratio (OR) of higher mMRC scores for women compared with men, using ordinal logistic regression. All models were adjusted for age, level of chronic airflow limitation (FEV_1/FVC), body mass index, pack-years of smoking, current smoking, and physician-diagnosed asthma, COPD, chronic bronchitis, emphysema, congestive heart failure, ischemic heart disease, and diabetes mellitus. No data were imputed. The impact of lung function on the sex difference in breathlessness was evaluated as the change in the sex estimate when adding each lung function measure to the fully adjusted model. Analyses were performed for the whole population, and in people with impaired lung function ($FEV_1 < 80\%$ of predicted) and normal lung function ($FEV_1 \geq 80\%$ of predicted). Statistical analyses were conducted with SAS version 9.4 (SAS Institute, Inc.).

Results

In total, 10,223 participants were included, with a mean age of 59.6 years; 53.2% were men, and 4,935 (48.3%) had an FEV_1 less than 80% of predicted. Despite a similar FEV_1% predicted in men ($76.2 \pm 26.3\%$) and women ($77.2 \pm 24.8\%$), women had a mean 0.7-L lower absolute FEV_1 (1.9 ± 0.9 vs. 2.6 ± 1.0 L).

Higher absolute FEV_1 was associated with lower likelihood of breathlessness (Figure 1) (adjusted OR, 0.41; 95% confidence interval [95% CI], 0.37–0.44). This was consistent in both men (OR, 0.44; 95% CI, 0.40–0.49) and women (0.33; 95% CI, 0.28–0.38), and in people with normal lung function (OR, 0.53; 95% CI, 0.46–0.61) and people with impaired lung function (OR, 0.30; 95% CI, 0.26–0.35). Women were more likely to have breathlessness than men (46.1% vs. 37.4% had mMRC ≥ 2) (adjusted OR, 1.75; 95% CI, 1.62–1.90) (Table 1). Adding FEV_1% predicted to the model did not decrease the sex difference (adjusted OR, 1.72; 95% CI, 1.59–1.86). However, when instead adjusting for the absolute FEV_1, sex difference disappeared (adjusted OR, 0.93; 95% CI, 0.84–1.03) ($P = 0.147$). Adjusting for absolute FEV_1, breathlessness was similar in men and women with normal lung function, whereas breathlessness was even slightly lower among women in people with lung function

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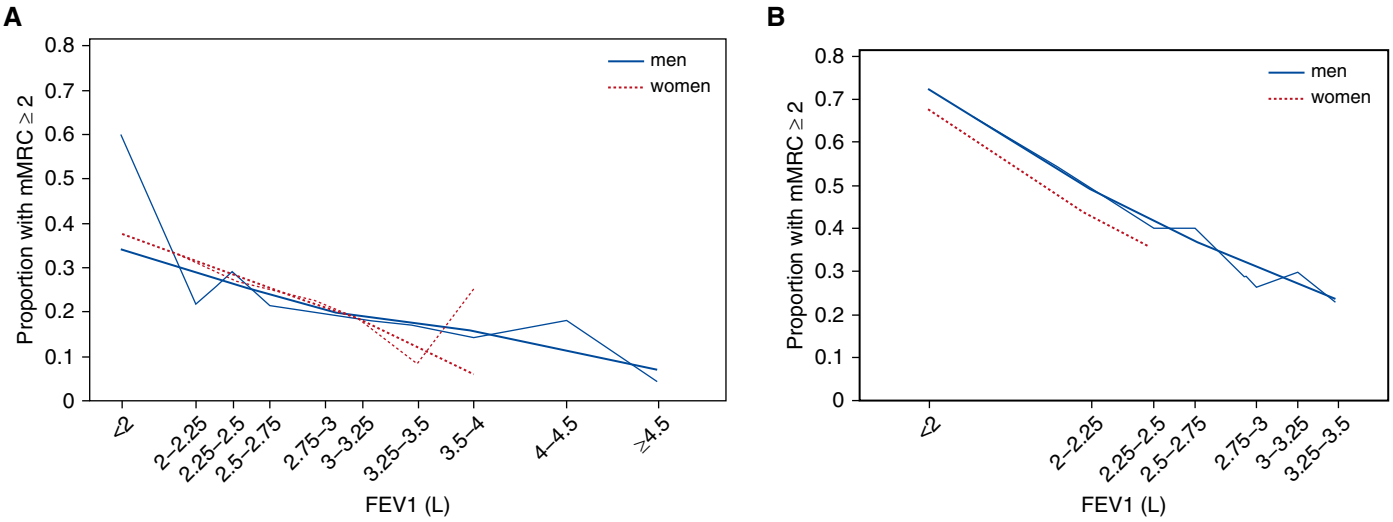

Figure 1. The relationship between absolute FEV_1 and breathlessness (mMRC ⩾ 2) by sex in people with (*A*) normal FEV_1 (⩾80% of predicted) and (*B*) impaired FEV_1 (<80% of predicted). Lower FEV_1 was associated with more breathlessness, both among men and women. When compared at a similar absolute FEV_1, breathlessness was similar between men and women. mMRC = modified Medical Research Council breathlessness scale.

impairment (Table 1). Using FVC instead of FEV_1, there was no sex difference even in people with impaired lung function (OR, 0.84; 95% CI, 0.71–1.01), and all other findings were similar when using FVC compared with FEV_1. Findings were robust when also adjusting for ethnicity, and when not including FEV_1/FVC in the models. Analysis using multinomial and dichotomous logistic regression had similar findings as reported with ordinal logistic regression.

Discussion: Main Findings

The key findings are that the markedly increased prevalence of breathlessness in women is related to their lower absolute lung function measured as FEV_1 or FVC. People with smaller spirometric lung volumes have a higher prevalence of breathlessness, both in men and in women. When matched on absolute spirometric lung volume, men and women have similar (or near similar) likelihoods of breathlessness both in people with normal lung function and in people with lung function impairment due to COPD.

This is the first study of breathlessness in relation to sex and spirometric lung volumes across severities of chronic airflow limitation, using data from the well-characterized COPDGene study. The likely mechanism underpinning the sex difference in breathlessness is that women have smaller airways and less respiratory musculature than men, even when matched for height and lung size, resulting in a lower ventilator capacity (4, 5). For a given level of work and ventilation, women experience more breathlessness as they use a greater fraction of their ventilatory capacity than men (4, 5). Despite similar lung function impairment (% of predicted) between the sexes, women may have markedly lower absolute FEV_1. This could explain the sex disparity in breathlessness seen in previous studies matching on the FEV_1% predicted (10). By matching on absolute spirometric volumes, this sex bias can be overcome.

Data were unavailable on breathlessness measured using a standardized exercise test, as well as on static lung volumes and diffusion capacity. The impact on the sex difference in breathlessness has been found to be similar for FEV_1 and FVC to that of static lung volumes (6).

The impact of a given lung function impairment on symptoms and function likely depends on the absolute lung volume and remaining ventilatory reserve. Relative and absolute lung volumes provide complementary information on the lung volume impairment and remaining ventilatory reserve and should be evaluated in both research and clinical care. ■

Table 1. FEV_1 and Sex Difference in Breathlessness

Models, All Adjusted for Confounders*	Sex Difference in mMRC Breathlessness Scale Score, for Women vs. Men [*OR (95% CI)*]
All participants (*N* = 10,223)	
Without any FEV_1 measure	1.75 (1.62–1.90)
With FEV_1% predicted	1.72 (1.59–1.86)
With FEV_1, L	0.93 (0.84–1.03)
Participants with FEV_1 ⩾ 80% predicted (*n* = 5,288)	
Without any FEV_1 measure	1.95 (1.73–2.19)
With FEV_1, L	1.11 (0.94–1.31)
Participants with FEV_1 < 80% predicted (*n* = 4,935)	
Without any FEV_1 measure	1.57 (1.41–1.75)
With FEV_1, L	0.84 (0.73–0.95)

Definition of abbreviations: CI = confidence interval; mMRC = modified Medical Research Council; OR = odds ratio.
*All models were adjusted for age, body mass index, pack-years of smoking, current smoking, FEV_1/FVC, asthma, chronic obstructive pulmonary disease or emphysema, chronic bronchitis, heart failure, cardiovascular disease, and diabetes mellitus.

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Metformin Therapy for Pulmonary Hypertension Associated with Heart Failure with Preserved Ejection Fraction versus Pulmonary Arterial Hypertension

To the Editor:

Pulmonary arterial hypertension (PAH; World Health Organization group 1) is a disease of the small pulmonary arteries, characterized by vasoconstriction, vascular proliferation, and remodeling. Although at present there are 14 drugs approved by the U.S. Food and Drug Administration for the treatment of PAH available on the U.S. market, the morbidity and mortality of PAH remain high. Pulmonary hypertension associated with heart failure with preserved ejection fraction (PH-HFpEF) (also referred to as combined pre- and postcapillary PH or CpcPH; World Health Organization group 2) is known to occur secondary to the left ventricular diastolic dysfunction and is recognized as a clinical complication of the metabolic syndrome (1). At present, there are no approved therapies for PH-HFpEF. We have recently reported that metformin, the first-line antidiabetic drug and the canonical AMP-activated protein kinase (AMPK) activator, exhibits therapeutic efficacy in the early treatment of PH-HFpEF in preclinical rat models (2). Because PH-HFpEF shares many pathophysiological characteristics with PAH, and many patients with PAH exhibit signs of insulin resistance and glucose intolerance in the absence of obesity and diabetes (3, 4), we evaluated metformin in the treatment of group 1 PH.

Although metformin has been found to prevent the development of PAH in hypoxia and monocrotaline rat models (5) and reverse PAH in SU5416/hypoxia (SuHx) rats (6), and is currently in a phase 2 clinical trial for the treatment of PAH (NCT01352026), our data showed that metformin treatment failed to reverse pulmonary pressures and vascular remodeling in mice with SuHx-induced PAH (Figure 1). In this experimental model, 6-week-old male C57BL/6J mice were injected subcutaneously with SU5416 (20 mg/kg) or vehicle buffer once per week during the first 3-week exposure to hypoxia (10% oxygen). Metformin (100 mg/kg) was given in drinking water and continued for 2-week exposure to hypoxia (Figure 1A). We observed no changes in right ventricular systolic pressure (RVSP) in metformin-treated SuHx mice compared with untreated animals (Figure 1A), nor did we detect changes in right ventricular hypertrophy (Figure 1B) or pulmonary vascular remodeling in metformin-treated SuHx mice (Figure 1C).

To further validate these unexpected findings, we evaluated the preventative effect of metformin in the conventional SuHx rat model of PAH with a higher dose of metformin (300 mg/kg, the effective dose used in the rat model of PH-HFpEF, drinking water, starting at Day 1). In this experimental model, 8-week-old male Sprague Dawley rats were single-injected with SU5416 (20 mg/kg), followed by 3 weeks of exposure to hypoxia (10% oxygen) and an additional 3 weeks of exposure to normoxia. We further compared the effect of metformin with the effect of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR, an AMPK agonist) and nitrite (a drug that can be reduced to nitric oxide under hypoxia and that has been shown to improve hypoxia- and monocrotaline-induced PAH) (7) in the SuHx rat model of PAH. In line with our observations in mice with SuHx-induced PAH, no significant difference in RVSP (Figure 2A) was observed in metformin-treated SuHx rats compared with untreated animals. Right ventricular hypertrophy, fastest rate of pressure change in the right ventricle (RV dP/dt max), and pulmonary vascular remodeling were not affected in metformin-treated SuHx rats compared with untreated animals (Figures 2B–2D). In addition, the AMPK agonist AICAR (500 mg/kg, intraperitoneally, daily, starting at Day 1) did not reduce RVSP in SuHx rats, whereas nitrite (100 mg/L, drinking water, starting at Day 1) treatment significantly lowered RVSP and pulmonary vascular remodeling in rats with SuHx-induced PAH (Figures 2A and 2D). Collectively, these data demonstrate a lack of efficacy of metformin in prevention or reversal of PAH induced by SuHx, in contrast to clear beneficial effects in PH-HFpEF rat models with metabolic syndrome. These data suggest that metformin therapy for PH may be limited to PH associated with metabolic syndrome.

Recently, we have also reported that metformin limits PH-HFpEF by a mechanism involving, at least in part, activation of SIRT3 in skeletal muscle (2). SIRT3 is a member of the sirtuin family of protein deacetylases that is preferentially localized in mitochondria and known to regulate reactive oxygen species levels and global respiration. Dysregulation of SIRT3 has been implicated in the development of insulin resistance and diabetes both in humans and rodents (8). In addition, SIRT3 deficiency in pulmonary artery smooth muscle cells has been shown to promote PAH (4). Decreased levels of SIRT3 in skeletal muscle have been associated with the development of insulin resistance and diabetes, whereas caloric restriction- and exercise-induced increase in skeletal muscle SIRT3 leads to multiple health benefits within the cardiovascular and the musculoskeletal system (9). Our previously published data demonstrated that in rats with PH-HFpEF, the levels of activated SIRT3 are decreased specifically in skeletal muscle (not in the pulmonary vasculature and the heart), concomitant with robust increase in pulmonary pressures and vascular remodeling (2). Restoration of SIRT3 in skeletal muscle with nitrite and metformin improved insulin sensitivity and reduced pulmonary pressures (2). Because insulin resistance and exercise intolerance are key features of PAH (3, 4, 10), we next assessed the activation levels of skeletal muscle SIRT3 in SuHx rats. Consistent with our previous findings, our new data show that skeletal muscle SIRT3 activation is reduced in

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