Restrictive Spirometry Pattern, Cardiac Structure and Function, and Incident Heart Failure in African Americans

The Jackson Heart Study

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Abstract

Rationale: Although chronic obstructive pulmonary disease has been related to heart failure, the relationship between the restrictive spirometry pattern (forced vital capacity [FVC] < 80% predicted with preserved forced expiratory volume in 1 second [FEV₁]/FVC ratio) and heart failure is poorly understood.

Objectives: To determine whether having a restrictive spirometry pattern is associated with incident heart failure hospitalization.

Methods: Community-dwelling African Americans from the Jackson Heart Study (total $n = 5,306$; analyzed $n = 4,210$ with spirometry and heart failure outcome data) were grouped by restrictive spirometry (FEV₁/FVC ≥ 0.70 , FVC < 80%; $n = 840$), airflow obstruction (FEV₁/FVC < 0.70; $n = 341$), and normal spirometry (FEV₁/FVC ≥ 0.70 , FVC ≥ 80 ; $n = 3,029$) at the time of baseline examination in 2000–2004. We assessed relationships of echocardiographic parameters and biomarkers with spirometry patterns using regression models. Incident heart failure was defined as an adjudicated hospitalization for heart failure after January 1, 2005 in subjects with no self-reported heart failure history. We used multivariable-adjusted Poisson regression models and Cox proportional hazards models, with death treated as a competing risk in the Cox models, to test associations between spirometry patterns and incident heart failure. We also modeled the association of FVC%

predicted with heart failure hospitalization risk using a restricted cubic spline after excluding subjects with airflow obstruction.

Results: At the time of baseline spirometry, participants with restrictive spirometry had a median age of 57.2 years (interquartile range, 47.8–64.1); 38.1% were male. Compared with normal spirometry, restrictive spirometry was associated with a higher transmitral early (E) wave velocity to atrial (A) wave velocity ratio, higher pulmonary artery systolic pressure, and higher endothelin levels. After a median follow-up time of 8.0 years, 8.0% of subjects with restrictive spirometry ($n = 67$) had developed incident heart failure, compared with 3.8% of those with normal spirometry ($n = 115$) and 10.6% of those with airflow obstruction ($n = 36$). After risk adjustment, both a restrictive pattern (hazard ratio [HR], 1.5; 95% confidence interval [CI], 1.1–2.0) and airflow obstruction (HR, 1.7; 95% CI, 1.1–2.5) were associated with increased rates of incident heart failure hospitalization compared with normal spirometry. Using flexible modeling, the lowest hazards of heart failure hospitalization were observed around FVC 90–100%, with lower FVC% values associated with an increased incidence of heart failure.

Conclusions: Both a restrictive pattern on spirometry and airflow obstruction identify African Americans with impaired lung health at risk for heart failure.

Keywords: echocardiography; heart failure; spirometry; vital capacity

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A restrictive spirometry pattern, defined as a reduced forced vital capacity (FVC) in the absence of airflow obstruction, is prevalent in the general population (1) and has been associated with adverse outcomes, including mortality (2–5). Although the association of chronic obstructive pulmonary disease (COPD) with cardiovascular diseases has been well studied (6), our understanding of the cardiovascular risk profile associated with the restrictive spirometry phenotype remains limited. A decline in FVC (with preserved forced expiratory volume in 1 second [FEV₁]/FVC ratio), i.e., in a pattern suggesting incipient restriction, but before abnormal lung function has developed, has been associated with incident hypertension (7) and cardiac remodeling characterized by left ventricular (LV) hypertrophy (8), suggesting the potential for an increased risk of heart failure (HF). Studies have correlated the FVC with other aspects of cardiac structure and function, including higher pulmonary artery pressures (9) and LV end-diastolic dimensions, stroke volumes, and ejection fractions (10). However, there have been few data on the phenotypic aspects of the restrictive spirometry pattern *per se* that may relate to cardiovascular morbidity and mortality. The restrictive spirometry pattern has been associated with echocardiographic pulmonary hypertension (11), and higher levels of troponin and NT-proBNP have been observed with restrictive lung function (12). In a previous study we noted an interaction between plasma endothelin levels and spirometry patterns, such that endothelin-1 was associated with pulmonary hypertension in subjects with restrictive spirometry, but not in those with normal spirometry (13). However, there are relatively few data on other echocardiographic characteristics or biomarkers associated with HF in individuals with this pattern of spirometry, especially in community-based cohorts, and the relationship between a restrictive spirometry pattern and HF remains unclear (12, 14).

Therefore, in the current study, we set out to determine the association between a restrictive spirometry pattern, cardiac structure and function, and subsequent development of incident HF in the Jackson Heart Study (JHS), the largest prospective study of cardiovascular disease in African Americans, a population that has a high prevalence of abnormal spirometry (11) and is also at increased risk of HF (15, 16). We

hypothesized that a restrictive spirometry pattern would be associated with 1) abnormalities of cardiac structure (such as increased LV mass index and increased left atrial [LA] diameter index) and function (such as indices of systolic and diastolic function); 2) increased levels of neurohormonal markers (aldosterone [17] and endothelin [13, 18]); and 3) HF, pulmonary hypertension, and vascular remodeling. We further hypothesized that a restrictive spirometry pattern would be associated with an increased rate of incident HF hospitalization.

Methods

Additional details regarding the methods used in this work are available in the online supplement. We conducted a *post hoc* longitudinal analysis of data from the JHS cohort. The conduct of the JHS was approved by the University of Mississippi Medical Center Institutional Review Board. The participants gave written informed consent. Our analysis of JHS data was reviewed by the Providence VA Medical Center Institutional Review Board and deemed to be exempt from ongoing review as it involved the study of existing data. Some of the data in this work were previously presented in abstract form (19).

Study Participants

The JHS is a longitudinal, population-based cohort study of cardiovascular disease that recruited noninstitutionalized adult participants residing in the Jackson metropolitan area of Mississippi who self-identified as African Americans. Subjects underwent spirometry, echocardiography, and venipuncture at the time of the first/baseline exam in 2000–2004. The participants were followed up at regular intervals for outcomes including HF hospitalization (starting January 1, 2005). Participants with a self-reported HF hospitalization history before January 1, 2005 were excluded.

Outcome

The main outcomes of this analysis were the time to and rate of probable or definite incident HF admission, with outcome adjudication similar to methods used in the ARIC (Atherosclerosis Risk in Communities) study (20). Adjudication of HF outcomes began on January 1, 2005.

HF hospitalizations were defined as hospitalizations for definite or probable decompensated HF as adjudicated by trained medical personnel after review of hospital data. Elements abstracted from the hospital data for HF assessment by trained abstractors included data from history, physical exam, laboratory studies, and chest X-rays, as well as other imaging and diagnostic modalities.

Exposure

The exposure was spirometric lung function classification; restrictive spirometry was defined as an FEV₁/FVC $\geq$ 0.70 and FVC < 80% predicted; an airflow obstruction was defined as an FEV₁/FVC ratio < 0.70; and normal lung function was defined as an FEV₁/FVC $\geq$ 0.70 and an FVC $\geq$ 80%. Detailed spirometry procedures for the JHS are available online (21) and in the online supplement. Spirometry was performed without use of a bronchodilator before measurement.

Echocardiography and neurohormonal biomarkers. Detailed echocardiography procedures for the JHS are available online (22) and in the Supplement. Echocardiograms were recorded by trained sonographers and interpreted by experienced cardiologists blinded to the participants' clinical parameters at the reading center located at the University of Mississippi Medical Center. The echocardiography parameters analyzed included LV ejection fraction (LVEF), LV mass indexed by height in m^{2.7}, LA diameter indexed to height in m², transmitral E and A wave velocity, pulmonary artery acceleration time (in milliseconds), and pulmonary artery systolic pressure (PASP) in mm Hg. A reduced LVEF was defined as an LVEF < 50%. LV hypertrophy was defined as an LV mass index > 51 g/m^{2.7}. Pulmonary hypertension was defined as a PASP > 40 mm Hg.

Log-transformed levels of serum aldosterone and plasma endothelin-1 were analyzed in the study population. High aldosterone and endothelin levels were defined as a value > 75th percentile among all JHS study participants with measured levels. Serum aldosterone was measured by radioimmunoassay (Siemens) in ng/ml. An elevated aldosterone level was defined as an aldosterone level > 7.2 ng/dl (>75th percentile). Endothelin-1 was measured in plasma in picograms per milliliter by QuantiGlo Human ET-1 immunoassay

(R&D Systems Inc.). An elevated endothelin level was defined as an endothelin level $\geq$ 1.7 pg/ml (13) (>75 th percentile).

Clinical Variables

The following covariates were used in the statistical models detailed below: sex at birth, age, education level, coronary heart disease, diabetes (23), systolic blood pressure, blood pressure medication use, heart rate (by electrocardiogram), smoking status (derived from self-report, categorized as never smoker, former smoker, or current smoker), estimated glomerular filtration rate (eGFR), and body mass index (BMI).

Statistical Analysis

Baseline characteristics were summarized by medians, interquartile ranges, and percentages. Differences in echocardiographic findings/biomarkers were compared between spirometry patterns using chi-square tests and Kruskal-Wallis tests. For characteristics that differed among the groups, *post hoc* comparison testing between the restrictive and normal spirometry patterns and the obstructive and normal spirometry patterns was performed using chi-square testing with *P* values adjusted for multiple (two) comparisons and using Dunn's test with Bonferroni adjustment.

The associations between echocardiographic variables/biomarkers and spirometry patterns were further assessed using logistic regression models for binary variables and linear regression models for continuous variables. For all models, normal spirometry was the reference group. Models were initially adjusted for age, sex, and BMI. Then, fully adjusted models (adjusted for age, sex, BMI, coronary heart disease, diabetes, systolic blood pressure, antihypertensive medication use, heart rate by electrocardiogram, smoking status, education category, and eGFR) were examined.

The incidence rates per 100 person-years of follow-up for congestive HF hospitalization and death for each spirometry pattern were calculated. Rate ratios for congestive HF and death by spirometry pattern were compared in Poisson regression models, adjusted for age, male sex, coronary heart disease, diabetes, systolic blood pressure, blood pressure medication use, heart rate, smoking, and BMI, as well as education level (as a marker of socioeconomic status) and eGFR, with

the log of follow-up time as the offset. Cumulative incidence functions of the probability of HF hospitalization by spirometry pattern were plotted, and differences between the patterns were assessed by log-rank tests. We used Cox proportional hazards models to test for unadjusted and adjusted associations between spirometry patterns and incident HF, with death treated as a competing risk according to the method of Fine and Gray (24). Adjusted models included clinical factors associated with incident HF derived from ARIC (15) (including male sex, coronary heart disease, diabetes, systolic blood pressure, blood pressure medication use, heart rate, smoking, and BMI), as well as education level and eGFR. Secondary analyses were also done that did not include adjustment for hypertension, antihypertensive medication use, diabetes, and coronary heart disease, because it is unclear whether these would be confounding factors in the association between abnormal spirometry and development of incident HF. To account for age-dependent mortality risk, analyses were performed using an age-based timescale (25, 26), where the event age or age at censoring was derived from the baseline age plus the follow-up time in days. We also did a sensitivity analysis using follow-up time as the timescale and adjusting for age as one of the covariates in the model, again treating death as a competing risk.

Multiple imputation by chained equation was used to account for missing data on covariates (27). Twenty imputations were performed for subjects with complete information for the exposure and outcome. All covariates were included in the imputation model, as well as hypertension, diabetes medications, and history of kidney disease as auxiliary variables for blood pressure medications, diabetes, and eGFR, respectively. Sensitivity analyses are presented for the complete cases. A similar methodology was also used to account for missing echocardiography and neurohormonal data in the logistic/linear regression analyses.

Finally, to assess the dose relation between restrictive lung function and the HF outcome, as well as pertinent echocardiographic and biomarker variables, we modeled these outcome variables against FVC% in the study population after excluding subjects with airflow obstruction. FVC% was coded using a restricted cubic

spline function with three knots, located at the fifth, 50th, and 95th percentiles. We used a Cox proportional hazard regression model for HF hospitalization and linear regression models for other continuous outcomes. All models were adjusted for age, sex, BMI, coronary heart disease, diabetes, systolic blood pressure, antihypertensive medication use, heart rate, smoking status, education category, and eGFR.

Analyses were performed using SAS version 9.4, Stata version 14, and R statistical software. A two-sided *P* value of <0.05 was considered significant except for *post hoc* testing (between restrictive and normal spirometry patterns and obstructive and normal spirometry patterns), where a *P* value of 0.025 was considered significant.

Results

Figure 1 illustrates the selection of study participants from the JHS sample population ($n = 5,306$). There were 4,210 participants with complete data on spirometry and HF outcomes (characteristics of the excluded participants are detailed in Table E1 in the online supplement); of these, 556 participants were missing various covariate data (detailed in Table E2) but were included in the primary analysis. Of the 4,210 participants included in the primary analysis, 71.9% had normal spirometry, 8.1% had airflow obstruction, and 20.0% had a restrictive spirometry pattern. The median age of the study population was 55 years (interquartile range, 46–64) and 36.2% were men.

The baseline clinical characteristics of the study population, stratified by spirometry pattern, are shown in Table 1. In this population, 70.2% of subjects with a restrictive spirometry pattern, 71.4% of those with normal spirometry, and 53.6% of those with airflow obstruction were never smokers. Median BMI was highest in the restrictive spirometry group at 32.1 kg/m² and was lowest in the airflow obstruction group at 28.4 kg/m², although a considerable proportion of the study participants in all spirometry groups were overweight or obese. The burden of diabetes was highest in those with a restrictive spirometry pattern. Participants with restrictive and obstructive spirometry patterns had slightly higher systolic blood pressures than those with normal spirometry, and were more often on antihypertensive medication than those

Figure 1. Flow chart of study participant selection. JHS = The Jackson Heart Study.

with normal spirometry. However, eGFRs were similar between the normal and restrictive spirometry groups. A higher proportion of subjects with obstructive and restrictive spirometry had less than a high school education, and those with normal spirometry had attended vocational school, trade school, or college more frequently.

Baseline echocardiography, done at the time of spirometry, revealed differences in echocardiographic characteristics among the spirometry groups (Table 2). The LV mass index was highest in the restrictive spirometry group ($P < 0.001$ compared with normal spirometry). Indices of diastolic function (transmitral early (E) wave velocity to atrial (A) wave velocity ratio and LA diameter index) varied among the spirometry groups, with the airflow obstruction group having the lowest median E/A ratio (median E/A ratio 0.94) and the

normal spirometry group having the highest LA diameter index. In the subgroup of patients with a measurable transtricuspid gradient, PASP was higher and PH (PASP > 40 mm Hg) was more than twice as prevalent in the abnormal spirometry groups ($P < 0.001$ for restrictive vs. normal spirometry and obstructive vs. normal spirometry) (Table 2). In adjusted analyses (Tables 3 and E3), restrictive spirometry was associated with higher mitral E wave velocities, higher E/A ratios, and higher PASP, as well as with increased odds of pulmonary hypertension, but there was no association with the LV mass index. Obstructive spirometry was also associated with higher E/A ratios and PASPs, with pulmonary hypertension, and with lower LA diameter indices.

Median serum aldosterone and plasma endothelin levels varied among the spirometry groups, with the restrictive

spirometry group having the highest aldosterone levels (Table 2). A higher proportion of restrictive spirometry patients had a high serum aldosterone level (> 7.2 ng/dl) (28.3% with restriction, vs. 23.0% with normal spirometry and 23.5% with airflow obstruction; $P = 0.002$ for comparison of restrictive and normal spirometry groups). Significantly higher proportions of participants with obstructive (30.0%) and restrictive (26.2%) spirometry had elevated endothelin levels (≥ 1.7 pg/ml) compared with those with normal spirometry (20.1%). In adjusted analyses (Table E3), the association of restrictive spirometry with high aldosterone levels persisted after adjustment for age, sex, and BMI, but became nonsignificant in the fully adjusted model. Both restrictive spirometry and obstructive spirometry were associated with higher log-transformed endothelin levels and with increased odds of having a high endothelin level (Tables 3 and E3).

At a median age at follow-up of 62.8 years for the overall study population (median follow-up time for HF outcome, 8.0 yr), 8.0% of subjects with the restrictive spirometry pattern were hospitalized for incident, compared with 10.6% of those with airflow obstruction and 3.8% of those with normal spirometry (Table 4). Over this period, 10.1% of subjects with the restrictive spirometry pattern died, compared with 19.6% of those with obstructive spirometry and 5.7% of those with normal spirometry (Table 4). Over 31,001 person-years of follow-up, the incidence rates for HF hospitalization were 1.11 per 100 person-years for participants with the restrictive spirometry pattern, 0.51 per 100 person-years for those with normal spirometry, and 1.53 per 100 person-years for those with airflow obstruction (Table 4). Rate ratios for incident HF for obstructive and restrictive spirometry, adjusted for potential confounders, were significantly higher than in the normal spirometry group (adjusted rate ratio for restrictive spirometry: 1.49, 95% confidence interval [CI], 1.09–2.03) (Table 4). A cumulative incidence plot of HF hospitalization by spirometry pattern is shown in Figure 2; the incidence of HF events differed by spirometry pattern ($P < 0.01$ by log-rank).

After adjustment for clinical factors associated with HF, education level, and eGFR, and accounting for death as a competing risk, the hazard ratio (HR) for incident HF hospitalization for subjects with

Table 1. Baseline characteristics of the subjects

Characteristic*	Normal Spirometry	Airflow Obstruction	Restrictive Spirometry
Total number	3,029	341	840
Age, years	53.8 (44.6, 63.6)	62.9 (53.1, 70.7)	57.2 (47.8, 64.1)
Male	34.9%	43.7%	38.1%
Coronary heart disease	6.2%	12.7%	11.2%
Diabetes	17.4%	20.4%	30.6%
Smoking status			
Never	71.4%	53.6%	70.2%
Former	18.3%	24.0%	16.2%
Current	10.3%	22.5%	13.6%
Antihypertensive medication use	45.5%	56.5%	59.3%
Education level			
Less than high school	15.9%	37.1%	21.5%
High school graduate or equivalent	18.2%	16.5%	19.0%
Vocational school or college	65.9%	46.5%	59.4%
BMI in kg/m ²	30.4 (26.9, 35.0)	28.4 (24.6, 32.6)	32.1 (28.1, 37.4)
Systolic blood pressure, mm Hg	124 (115, 135)	128 (118, 139)	127 (117, 139)
Heart rate, per minute	63 (57, 70)	63 (56, 70)	65 (58, 72)
Estimated GFR, ml/min/1.73 m ²	96.7 (83, 109.8)	93.0 (77, 104.8)	97.5 (81.5, 110.8)
FEV ₁ , L	2.49 (2.11, 3.03)	1.71 (1.37, 2.24)	1.92 (1.59, 2.33)
FEV ₁ % predicted	98.6% (91.4%, 107.1%)	72.9% (59.5, 85.6)	76.1% (69.2, 81.1)
FVC, L	3.01 (2.58, 3.69)	2.95 (2.25, 3.67)	2.31 (1.93, 2.79)
FVC% predicted	95.5% (88.4, 103.6)	91.2% (76.5, 106.8)	72.9% (66.9, 76.6)
FEV ₁ /FVC ratio	0.82 (0.79, 0.86)	0.64 (0.57, 0.68)	0.83 (0.79, 0.87)

Definition of abbreviations: BMI = body mass index; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; GFR = glomerular filtration rate. Continuous data are presented as medians and interquartile ranges. Categorical data are presented as frequencies and percentages.

*Across all spirometry groups, for coronary heart disease, there were a total of 185 missing values; for diabetes, there were 38 missing values; for smoking status, there were 36 missing values; for antihypertensive medication use, there were 302 missing values; for education category, there were 12 missing values; for systolic blood pressure, there were seven missing values; for heart rate, there were two missing values; and for estimated glomerular filtration rate, there were 34 missing values. The remaining variables had no missing values.

the restrictive spirometry pattern relative to normal spirometry was 1.5 (95% CI, 1.1–2.0) (Table E4). Secondary analysis excluding adjustments for hypertension, blood pressure medication use, diabetes, and coronary heart disease yielded somewhat higher HR estimates for HF hospitalization (adjusted HR for restrictive spirometry, 1.7; 95% CI, 1.3–2.3). The HRs for HF with obstructive spirometry were similar in the primary (Table E4) and secondary analyses. Sensitivity analyses using the follow-up time as the timescale and adjusting for age in the model did not substantially change the results (adjusted HR for HF for restriction, 1.5; 95% CI, 1.1–2.0; for airflow obstruction, 1.7; 95% CI, 1.1–2.5). Sensitivity analyses using complete cases only (no missing covariate data) ($n = 3,654$) also did not change the results appreciably (Table E4).

In models assessing the linearity of the relationship between FVC% and outcomes among those with normal or restrictive spirometry (Figures 3A–3D), there was an inverse nonlinear relationship between FVC% and PASP, with a steeper upward slope for PASP at FVC% below 100% predicted. The

relationship between FVC% and log endothelin levels was essentially an inverse linear relationship, with steadily increasing log endothelin levels as FVC% decreased. The relationship with log aldosterone and FVC% was more complex, with higher aldosterone levels associated with lower FVC%, although this relationship became flatter and CIs widened at lower FVC% levels. Finally, the hazard of HF hospitalization was lowest in the region of FVC% levels around 90–100%, with steadily higher HRs as FVC% decreased, especially elevated >1 below an FVC% of about 70%. Interestingly, there was a trend of increasing HF HRs at supranormal FVC% levels, although not to the extent seen with low FVC%. The CIs were also wider in this range, making these estimates less precise.

Discussion

In the current study, we report that participants in the JHS with a restrictive spirometry pattern have an increased hazard of being hospitalized for HF. We also report

differences in the clinical, neurohormonal, and echocardiographic characteristics of patients with restrictive and normal spirometry. Lastly, we describe the relationships between predicted FVC% and endothelin/aldosterone levels, pulmonary artery systolic pressure, and hazard of HF. Our results further refine the understanding of the connection between abnormal lung function and cardiovascular disease, and, in particular, the risk for HF hospitalization that is associated with the restrictive spirometry pattern, a common but poorly understood pattern of low lung function that is prevalent in many populations worldwide (28).

Little is known about the relationship between the restrictive spirometry pattern and HF, despite reported associations between this abnormal spirometry pattern and cardiovascular disease, as well as mortality (1). Early data from the Framingham Heart Study demonstrated an association between a low VC and incident HF. In a study of the Framingham cohort, both a decrease in VC over time and a persistently low VC were associated with HF

Table 2. Echocardiography and neurohormonal data by spirometry category

Characteristic*	Normal Spirometry	Airflow Obstruction	Restrictive Spirometry	P Value†
Total number	3,029	341	840	
LV ejection fraction, %	65 (55, 65)	65 (55, 65)	65 (55, 65)	0.60
LV ejection fraction < 50%	1.8%	2.8%	2.9%	0.08
LVMI, g/m ^{2.7}	33.4 (28.8, 39.6)	34.5 (29.1, 39.5)	35.4 [‡] (30.2, 41.8)	<0.001
LV hypertrophy (LVMI > 51 g/m ^{2.7})	5.3%	7.0%	7.1%	0.21
Peak mitral E wave velocity, cm/s	0.83 (0.71, 0.96)	0.80 (0.66, 0.94)	0.86 [‡] (0.73, 0.98)	<0.001
Peak mitral A wave velocity, cm/s	0.78 (0.66, 0.92)	0.84 [‡] (0.67, 0.99)	0.81 [‡] (0.68, 0.96)	<0.001
E/A ratio (unitless)	1.07 (0.87, 1.29)	0.94 [‡] (0.77, 1.20)	1.04 (0.87, 1.23)	<0.001
Left atrial diameter index, mm/m ²	17.6 (16.1, 19.1)	17.5 (15.9, 19.1)	17.4 [‡] (15.8, 18.7)	0.01
Pulmonary acceleration time, ms	125 (105, 150)	120 (100, 140)	120 (100, 145)	0.01
Pulmonary artery systolic pressure, mm Hg	26 (23, 30)	29 [‡] (24, 35)	27 [‡] (23, 33)	<0.001
Pulmonary hypertension (PASP > 40 mm Hg)	3.3%	9.2% [‡]	7.4% [‡]	<0.001
Aldosterone, ng/dl	4.2 (2.5, 6.9)	4.4 (2.4, 7.0)	4.6 [‡] (2.7, 7.6)	0.04
High aldosterone (>7.2 ng/dl)	23.0%	23.5%	28.3% [‡]	0.006
Endothelin, pg/ml	1.2 (0.9, 1.5)	1.3 [‡] (1.0, 1.7)	1.3 [‡] (1.0, 1.7)	<0.001
High endothelin (≥1.7 pg/ml)	20.1%	30.0% [‡]	26.2% [‡]	<0.001

Definition of abbreviations: E/A = transmitral early wave velocity to atrial wave velocity; LV = left ventricular; LVMI = left ventricular mass index; PASP = pulmonary artery systolic pressure.

Continuous data are presented as medians and interquartile ranges. Categorical data are presented as frequencies and percentages.

*Across all spirometry groups, there were 139 missing values for LV ejection fraction, 1,418 missing values for LV mass index, 366 missing values for peak mitral E wave velocity, 367 missing values for peak mitral A wave velocity, 371 missing values for E/A ratio, 163 missing values for left atrial diameter index, 587 missing values for pulmonary artery acceleration time, 1,567 missing values for PA systolic pressure, 71 missing values for aldosterone, and 66 missing values for endothelin-1.

†Kruskal-Wallis test for continuous variables and chi-square for categorical variables.

‡*P* < 0.025 for comparison with normal spirometry. Dunn's test for continuous and chi-square for categorical variables.

development (29). Interestingly, the association between low VC and HF was not believed to be due to airflow obstruction, as the FEV₁/VC ratio was not related to HF risk. However, that analysis did not examine whether a restrictive spirometry pattern *per se* was associated with HF.

Although Engström and colleagues, using data from the Malmö Preventive Project, also showed an association between low FVC and incident HF (30), studies examining the specific relationship between the restrictive spirometry pattern (nonobstructive FEV₁/FVC ratio but low FVC) and HF have had contradictory results. Wannamethee and colleagues found in the British Regional Heart Study cohort that having a restrictive spirometry pattern was associated with elevated levels of cardiac biomarkers (N-terminal pro-BNP and cardiac troponin-T), but that restrictive spirometry was not associated with incident HF after adjustment for traditional HF risk factors (12). In contrast, Georgiopoulos and colleagues, analyzing data from the Health ABC (Health, Aging, and Body Composition) study, noted an increased risk of incident HF in participants with a restrictive spirometry pattern compared with those with normal lung function (14). These contrasting results could be related to

the populations studied (mean age >73 years at baseline in Health ABC, vs. upper 60s in the British Regional Heart Study cohort). We observed an elevated hazard of incident HF in JHS participants with restrictive spirometry compared with participants with normal spirometry, even though the participants in this cohort were younger (median age at baseline in the JHS study cohort: 55 yr) than the subjects examined by Georgiopoulos and colleagues, and Wannamethee and colleagues. Our results provide some of the first evidence that in a study cohort with a high prevalence of abnormal spirometry, the restrictive spirometry pattern is associated with the risk of developing HF.

Why individuals with restrictive lung function have an elevated risk of developing cardiovascular disease, including incident HF, is a topic of interest. In the CARDIA (Coronary Artery Risk Development in Young Adults) study, a greater decline in FVC (with a preserved FEV₁/FVC ratio) from peak lung function in youth was associated with increased LV mass and decreased E/A ratio on echocardiography after 20 years of follow-up (8). In our study, we observed an association between a restrictive spirometry pattern and higher mitral E wave velocities and higher E/A

ratios, possibly indicative of more advanced diastolic impairment with established restriction. Notably, there was no relationship between LV systolic function and restrictive spirometry. Although the median LV mass index was higher in the restrictive spirometry group, in adjusted analyses we found no significant relationship between LV mass and restrictive spirometry. Restrictive spirometry was, however, associated with higher PASPs and increased prevalence of pulmonary hypertension, and there was a relationship between higher PASP and decreased lung function across the full range of FVCs. These findings suggest potential linkages among impaired lung function, LV diastolic impairment, and (perhaps consequently) increased pulmonary artery pressures preceding the development of HF.

Furthermore, we found that subjects with restrictive spirometry more often had high levels of aldosterone and endothelin (>75th percentile)—neurohormonal factors associated with vascular and LV remodeling—in the period preceding the development of HF. Although the association between restrictive spirometry and aldosterone levels was nonsignificant in fully adjusted models, with a complex nonlinear relationship observed between

Table 3. Adjusted mean differences of echocardiographic and neurohormonal data between spirometry groups

	Airflow Obstruction		Restrictive Spirometry	
	Mean Difference (95% CI)	P Value	Mean Difference (95% CI)	P Value
LV ejection fraction, %				
Model 1	−0.21 (−1.0 to 0.6)	0.60	−0.47 (−1 to 0.1)	0.09
Model 2	−0.09 (−0.9 to 0.7)	0.81	−0.39 (−0.9 to 0.1)	0.16
LV mass index, g/m ^{2.7}				
Model 1	0.53 (−0.4 to 1.4)	0.35	0.34 (−0.3 to 1)	0.32
Model 2	0.11 (−0.8 to 1)	0.60	−0.13 (−0.7 to 0.5)	0.61
Peak mitral E wave velocity, m/s				
Model 1	0.01 (−0.01 to 0.03)	0.34	0.028 (0.01 to 0.04)	<0.01
Model 2	0.011 (−0.01 to 0.03)	0.29	0.03 (0.02 to 0.04)	<0.01
Peak mitral A wave velocity, m/s				
Model 1	0.002 (−0.02 to 0.02)	0.78	0.014 (0 to 0.03)	0.05
Model 2	−0.002 (−0.02 to 0.02)	0.79	0.001 (−0.01 to 0.01)	0.75
E/A ratio (unitless)				
Model 1	0.033 (0 to 0.07)	0.07	0.016 (−0.01 to 0.04)	0.18
Model 2	0.039 (0 to 0.07)	0.03	0.035 (0.01 to 0.06)	<0.01
Left atrial diameter index, mm				
Model 1	−0.47 (−0.7 to −0.2)	<0.01	−0.11 (−0.3 to 0.1)	0.20
Model 2	−0.54 (−0.8 to −0.3)	<0.01	−0.14 (−0.3 to 0)	0.12
Pulmonary acceleration time, ms				
Model 1	−2.18 (−5.6 to 1.2)	0.26	0.16 (−2.2 to 2.5)	0.74
Model 2	−1.6 (−5 to 1.8)	0.38	1.29 (−1 to 3.6)	0.32
Pulmonary artery systolic pressure, mm Hg				
Model 1	2.02 (1.3 to 2.7)	<0.01	0.92 (0.4 to 1.4)	<0.01
Model 2	1.91 (1.2 to 2.6)	<0.01	0.83 (0.3 to 1.3)	<0.01
Log aldosterone, ng/ml				
Model 1	0.005 (−0.07 to 0.08)	0.87	0.046 (0 to 0.1)	0.08
Model 2	0.008 (−0.06 to 0.08)	0.83	0.019 (−0.03 to 0.07)	0.44
Log endothelin, pg/ml				
Model 1	0.082 (0.04 to 0.13)	<0.01	0.056 (0.03 to 0.09)	<0.01
Model 2	0.055 (0 to 0.1)	0.02	0.047 (0 to 0.1)	<0.01

Definition of abbreviations: CI = confidence interval; E/A = transmitral early wave velocity to atrial wave velocity; LV = left ventricular.

The reference group is the normal spirometry group for all analyses.

Model 1 adjusted for age, sex, and body mass index.

Model 2 adjusted for age, sex, body mass index, coronary heart disease, diabetes, systolic blood pressure, antihypertensive medication use, heart rate by electrocardiogram, smoking status, education category, and estimated glomerular filtration rate.

FVC and aldosterone levels, the relationship between log endothelin levels and FVC was a strikingly inverse, essentially linear relationship. We note that an inverse relationship between FEV₁ and log endothelin levels in African Americans was reported in a previous study (31), but subjects with restrictive spirometry were excluded from that study. Although neurohormonal factors such as endothelin could contribute to the development of LV remodeling, pulmonary vascular remodeling, and eventual HF (13), this cannot be determined using cross-sectional data and requires further study.

Overall, however, these results contribute to an increased understanding of the clinical, laboratory, and imaging phenotype associated with the restrictive spirometry pattern. Recent data from the COPDGene study examined the prevalence

and characteristics of current and former smokers with preserved ratio impaired spirometry, defined as a preserved FEV₁/FVC ratio with a reduced FEV₁ (32), i.e., a form of restrictive spirometry. This group (with a mean FVC of 71.5%) constituted 12.3% of the COPDGene cohort and was characterized by higher BMIs, decreased total lung capacities as measured by computed tomography volumetry, and less emphysema, but greater dyspnea and lower exercise capacities compared with those with normal spirometry (32). Our study also showed higher BMIs and a higher prevalence of diabetes in subjects with a restrictive spirometry pattern, although most participants with this spirometry pattern in the JHS cohort were never smokers. Further attention must be given to individuals with this abnormal spirometry pattern to determine the origins and best

management of this form of impaired lung health.

Our analysis confirms prior reports of associations between airflow obstruction and incident HF. Obstruction and HF are frequent comorbid conditions (6, 33–40) and their coexistence is associated with more dyspnea (34) and worse outcomes (33, 41). Both lower FEV₁/FVC ratios (10, 42) and COPD (12, 43–45) have been associated with the risk of developing HF. In the JHS, we demonstrate that participants with obstructive spirometry had a 70% higher hazard of HF hospitalization. Interestingly, among those with obstructive spirometry in the JHS, about half were never smokers and the HF risk associated with obstructive spirometry persisted after adjustment for smoking status, suggesting that the association between airflow obstruction and HF is not mediated by smoking-related

Table 4. Associations of spirometry group with heart failure hospitalization and all-cause mortality

Outcome	Normal	Airflow Obstruction	Restrictive Spirometry
Heart failure hospitalization			
Number at risk	3,029	341	840
Number of events	115	36	67
Person-years	22,612	2,354	6,035
Crude rate, 95% CI*	0.51 (0.42–0.61)	1.53 (1.10–2.12)	1.11 (0.87–1.41)
Unadjusted rate ratio, 95% CI	Ref	3.01 (2.07–4.37)	2.18 (1.62–2.94)
Adjusted rate ratio [†] , 95% CI	Ref	1.83 (1.23, 2.70)	1.49 (1.09, 2.03)
All-cause mortality			
Number at risk	3029	341	840
Number of events	173	67	85
Person-years	22,887	2,437	6,197
Crude rate, 95% CI*	0.76 (0.65–0.88)	2.75 (2.16–3.49)	1.37 (1.11–1.70)
Unadjusted rate ratio, 95% CI	Ref	3.64 (2.75–4.81)	1.81 (1.40–2.35)
Adjusted rate ratio [†] , 95% CI	Ref	1.82 (1.35, 2.46)	1.31 (1.01, 1.71)

Definition of abbreviations: CI = confidence interval; Ref = referent group.

*Per 100 person-years.

[†]Adjusted for age, sex, body mass index, coronary heart disease, diabetes, systolic blood pressure, antihypertensive medication use, heart rate by electrocardiogram, smoking status, education category, and estimated glomerular filtration rate.

effects. JHS participants with obstructive spirometry had similar aldosterone levels, but were more likely to have high endothelin levels than those with normal spirometry. The question of whether endothelin mediates the development of the cardiac structural (13) and functional (10, 46, 47) abnormalities noted in COPD requires further study.

The limitations of our study include the fact that some covariate data were missing; however, this was minimal for most covariates (see Table E2) and was managed by using a multiple imputation

methodology that allowed for the inclusion of more participants in the primary outcome analysis. This would tend to minimize the selection bias associated with including only complete cases. We did not impute data if they were missing for HF outcomes or spirometry values, and thus excluded potential participants on this basis. These excluded participants tended to be older, with more heart disease and diabetes, and this may have resulted in an underestimate of the potential association of abnormal spirometry with HF outcomes, and could reduce the generalizability of our results. We

cannot exclude the possibility of residual confounding, especially by unmeasured factors. We also cannot establish causal relationships between impaired lung function and incident HF given the observational nature of the study data. Spirometry was performed in the standing position in overweight and obese participants, versus the sitting position in normal-weight participants; however, positioning should not have affected spirometric values to a significant extent (48). Spirometry was performed without the use of a bronchodilator, and this may have resulted in the inclusion of subjects with potentially reversible airflow obstruction in the obstructive spirometry group, and also may have resulted in an overdiagnosis of restriction in those whose VC might have improved after treatment with a bronchodilator. Despite this potential limitation, abnormal spirometry patterns remained associated with HF hospitalization. There was a lack of repeated spirometry measurements over time, so we were unable to determine whether participants remained in the same spirometry category during follow-up (the restrictive spirometry pattern may not always be stable over time) (4, 5). Similarly, we lacked repeated echocardiography measurements to assess how cardiac function may have evolved over time. Nevertheless, a single baseline spirometry measurement was predictive of subsequent incident HF over an extended follow-up

Figure 2. Cumulative incidence of heart failure hospitalization by spirometry pattern. Blue: normal spirometry; green: restrictive spirometry; red: obstructive spirometry. *P* by log-rank < 0.01.

Figure 3. Restricted cubic spline models of forced vital capacity (FVC) as a percentage of predicted, with 95% confidence intervals (in gray), for (A) pulmonary artery systolic pressure, (B) log aldosterone, (C) log endothelin, and (D) hazard ratio of heart failure hospitalization. FVC% predicted was coded using a restricted cubic spline function with three knots located at 66.3%, 91.5%, and 116% predicted. Models were adjusted for age, sex, body mass index, coronary heart disease, diabetes, systolic blood pressure, antihypertensive medication use, heart rate, smoking status, education, and estimated glomerular filtration rate.

period. Information regarding the type of HF, i.e., preserved versus reduced ejection fraction, was not available for all participants, and whether the association of HF with a particular spirometry classification may vary by the type of HF pattern cannot be assessed. We used a standard definition of the restrictive spirometry pattern ($FEV_1/FVC < 0.70$, $FVC < 80\%$) that has been used in multiple prior studies (1) and has been associated with adverse outcomes, including mortality, but other definitions—for example, based on the lower limit of normal—may have resulted in alternative

classifications of the study participants. Plots of predicted FVC% against the hazard of HF hospitalization suggest that risk may increase above unity at slightly lower levels of FVC than 80% predicted. Finally, the generalizability of our findings to other races/ethnicities and age groups is uncertain.

In summary, we found that having a restrictive spirometry pattern was associated with an increased rate of incident HF hospitalization in the JHS cohort. Lower FVCs in general were associated with higher PASPs, endothelin levels, and HF hospitalization risk, whereas the lowest risk

of HF was noted at FVCs in the 90–100% range. Further research is needed to explore and define mechanisms leading to cardiovascular morbidity in the setting of the restrictive spirometry pattern and airflow obstruction, and to determine whether the cardiovascular risk associated with abnormal lung function is modifiable. ■

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