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# Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction

## A Community-Based Study

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**Objectives** This study sought to define the prevalence, severity, and significance of pulmonary hypertension (PH) in heart failure with preserved ejection fraction (HFpEF) in the general community.

**Background** Although HFpEF is known to cause PH, its development is highly variable. Community-based data are lacking, and the relative contribution of pulmonary venous versus pulmonary arterial hypertension (HTN) to PH in HFpEF is unknown. We hypothesized that PH would be a marker of symptomatic pulmonary congestion, distinguishing HFpEF from pre-clinical hypertensive heart disease.

**Methods** This community-based study of 244 HFpEF patients (age 76 ± 13 years; 45% male) was followed up using Doppler echocardiography over 3 years. Control subjects were 719 adults with HTN without HF (age 66 ± 10 years; 44% male). Pulmonary artery systolic pressure (PASP) was derived from the tricuspid regurgitation velocity and PH defined as PASP >35 mm Hg. Pulmonary capillary wedge pressure (PCWP) was estimated from the ratio of early transmitral flow velocity to early mitral annular diastolic velocity.

**Results** In HFpEF, PH was present in 83% and the median (25th, 75th percentile) PASP was 48 (37, 56) mm Hg. PASP increased with PCWP ($r = 0.21$; $p < 0.007$). Adjusting for PCWP, PASP was higher in HFpEF than HTN ($p < 0.001$). The PASP distinguished HFpEF from HTN with an area under the receiver-operating characteristic curve of 0.91 ($p < 0.001$) and strongly predicted mortality in HFpEF (hazard ratio: 1.3 per 10 mm Hg; $p < 0.001$).

**Conclusions** PH is highly prevalent and often severe in HFpEF. Although pulmonary venous HTN contributes to PH, it does not fully account for the severity of PH in HFpEF, suggesting that a component of pulmonary arterial HTN also contributes. The potent effect of PASP on mortality lends support for therapies aimed at pulmonary arterial HTN in HFpEF. (J Am Coll Cardiol 2009;53:1119–26) © 2009 by the American College of Cardiology Foundation

Left-sided heart failure (HF) is known to cause pulmonary hypertension (PH) (1), but the development and severity of PH in HF is highly variable, and contributing factors are not fully understood. Although initial studies focused on patients with reduced left ventricular ejection fraction (EF) (2), early isolated case reports (3,4) and more recent case series (5–7) have shown that PH can occur in heart failure with preserved ejection fraction (HFpEF). There is now growing appreciation that PH is common and may be severe in elderly patients with HFpEF (8). However, the true prevalence and severity of PH in HFpEF from the general community remain unknown. Previous studies were limited by selection bias, and population-based data have, to date, been lacking.

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Common to left ventricular failure regardless of EF, increased left-sided filling pressure leads to pulmonary venous hypertension (HTN) and post-capillary PH. In the presence of preserved systolic function, the development of pulmonary venous HTN is associated with the severity of left ventricular diastolic dysfunction, as has been shown in patients with aortic stenosis and normal EF (9). Beyond this post-capillary contribution to PH, a reactive increase in pulmonary arterial tone or intrinsic arterial remodeling can result in a superimposed pre-capillary component of pulmonary arterial HTN. This has been shown to occur in patients with mitral stenosis (10) and HF with reduced EF (11). In

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**Abbreviations and Acronyms**

**AUC** = area under the curve
**COPD** = chronic obstructive pulmonary disease
**EF** = ejection fraction
**HF** = heart failure
**HFpEF** = heart failure with preserved ejection fraction
**HTN** = hypertension
**PASP** = pulmonary artery systolic pressure
**PCWP** = pulmonary capillary wedge pressure
**PH** = pulmonary hypertension
**TR** = tricuspid regurgitation

HFpEF without valvular disease, however, the relative contributions of these pre- and post-capillary components to PH are unclear. A population-based approach to discerning the role of PH in HFpEF is to compare hypertensive patients with and without HF from the same community. Because hypertensive heart disease is the most common precursor to HFpEF and because elderly hypertensive patients without HF often show Doppler-echocardiographic features in common with HFpEF, comparisons between these groups of patients can provide insight into mechanisms mediating the progression from hypertensive heart disease to HFpEF and diagnostic features that distinguish pre-clinical hypertensive heart disease from overt HFpEF (12–14).

We hypothesized that both pulmonary venous HTN related to diastolic dysfunction, as well as pulmonary arterial HTN related to increased arterial tone or vascular remodeling, would contribute to PH in HFpEF. Further, we hypothesized that PH would be related to the development and severity of clinically significant pulmonary congestion, thus distinguishing HFpEF from pre-clinical hypertensive heart disease without overt HF. Accordingly, the aims of this population-based study were to measure pulmonary artery systolic pressure (PASP), define the prevalence and severity of PH (PASP >35 mm Hg), and assess the association between PASP and pulmonary venous HTN in patients with a clinical diagnosis of HFpEF compared with hypertensive heart disease without HF from the same community. Finally, we sought to determine whether PH was associated with mortality in HFpEF presenting in the community.

## Methods

This study was conducted in Olmsted County, Minnesota, with the approval of the Mayo Foundation Institutional Review Board. All subjects provided written informed consent. Although data from these patients have previously been published (14,15), many of the indexes proposed here have not.

### *Study Design and Subject Groups*

In this population-based observational study, subject groups included the following.

**Hypertensive control (HTN) group.** A random sample (n = 2,042, studied between June 1997 and September 2000) of the Olmsted County, Minnesota, population ages ≥45 years underwent medical review, echocardiography, and spirometry. From this cohort, 719 subjects with a history of HTN but without HF (all EF ≥50%) constituted the HTN group.

**HFpEF group.** Consecutive HFpEF patients (n = 244) were identified (between September 2003 and October 2005) in an Olmsted County, Minnesota, HF surveillance study as previously described (14). Both inpatients and outpatients were identified by real-time interrogation of electronic medical records using natural language processing techniques. All patients underwent medical review and echocardiography. The HF diagnosis was validated using the Framingham criteria, and EF ≥50% without hemodynamically significant left-sided valve disease was confirmed by echocardiography.

### *Doppler Echocardiography*

All echocardiograms were performed by registered diagnostic cardiac sonographers using standardized instruments and protocols, and interpreted by a blinded echocardiologist (C.S.P.L. and M.M.R.). All parameters were measured in triplicate and averaged. In addition to standard M-mode, 2-dimensional, and color Doppler imaging, continuous-wave Doppler examination of tricuspid flow, pulsed-wave Doppler examination of mitral inflow, and Doppler tissue imaging of the medial mitral annulus were performed in each subject as previously described (14,15).

**Determination of PH.** Because PASP is equal to right ventricular systolic pressure in the absence of pulmonary stenosis, PASP was estimated using Doppler echocardiography by calculating the right ventricular to right atrial pressure gradient during systole, approximated by the modified Bernoulli equation as $4v^2$, where v is the velocity of the tricuspid regurgitation jet in m/s. Right atrial pressure, estimated based on echocardiographic characteristics of the inferior vena cava and assigned a standardized value (16), was then added to the calculated gradient to give PASP. The PH was defined as PASP >35 mm Hg (17). Echocardiographic estimates of PASP obtained in this fashion have been shown to correlate well with invasively measured values on right heart catheterization with a sensitivity and specificity of 0.79 to 1.0 and 0.6 to 0.98, respectively, for predicting PH (18).

**Assessment of left ventricular diastolic function.** The ratio of early transmitral flow velocity (E) to early mitral annular (medial) diastolic velocity (e′) was used to estimate pulmonary capillary wedge pressure (PCWP) (= 11.96 + 0.596 · E/e′) based on prior Doppler and invasive measurements at our institution (19). This index has also been shown to reliably detect pulmonary venous HTN in patients with elevated echocardiography-derived PASP undergoing right heart catheterization (20). Other parameters included left atrial volume as calculated by the ellipse formula and left ventricular mass, both indexed to body surface area (21).

### *Spirometry*

Spirometry was performed in accordance with recommended techniques (22) and measurements standardized as percentages of predicted normal values (23). Chronic obstructive pulmonary disease (COPD) was defined as either a forced expiratory volume in 1 s to forced vital capacity ratio of <70% (24) or the presence of a clinical diagnosis of COPD.

### *Follow-Up*

The HFpEF patients were followed up from baseline echocardiography at enrollment to death (all-cause mortality) or last contact, at which time they were censored. Follow-up was 100% complete with vital status (March 2008) determined from the Mayo Clinic registration database and the Rochester Epidemiology Project death database, where mortality data on Olmsted County residents are routinely collected by reviewing community medical records, death certificates, and obituary notices (15).

### *Statistical Methods*

Groups were compared using the Pearson chi-square test for categorical variables and *t* test for normally distributed continuous variables. The association between PASP (log transformed to satisfy normality assumptions) and PCWP was investigated by calculating the Pearson correlation coefficient. Regression analyses were used for adjusted comparisons, in which the dependent variable was the normally distributed continuous (linear least-squares regression) or categorical (logistic regression) outcome variable of interest, whereas factors entered into the model included age, sex, PCWP, group (dummy variable), and appropriate interaction terms. Receiver-operating characteristic curve analyses were used to determine the ability of echocardiographic parameters (PASP, E/e′, left atrial volume index, relative wall thickness, left ventricular mass index) to distinguish HFpEF from HTN. The optimal cutoff value for each parameter was defined as the value giving the largest area under the curve (AUC) for the parameter. The derived mean ± standard error AUC for each parameter was compared with that of PASP using *t* tests as well as paired analyses by the method of DeLong et al. (25), with Bonferroni correction to control for multiple comparisons. The effect of PH on survival was assessed by Kaplan-Meier analysis. The association of PASP with mortality was assessed by Cox regression analysis, before and after adjusting for age and other echocardiographic parameters. All analyses were 2-sided, and significance was judged at $p < 0.05$.

## Results

The tricuspid regurgitation (TR) jets were analyzable in 470 (65%) of HTN and 203 (83%) of HFpEF patients. Compared with patients in whom TR jets could not be analyzed, those with analyzable TR jets were older (age 64 ± 10 years vs. 70 ± 12 years; $p < 0.001$), were more often female (46% vs. 60%; $p < 0.001$), had smaller body size (2.08 ± 0.28 $m^2$ vs. 1.91 ± 0.25 $m^2$, $p < 0.001$), were more likely to have coronary artery disease (21% vs. 28%; $p = 0.029$) or chronic renal disease (glomerular filtration rate ≤60 ml/min/1.73 $m^2$ in 16% vs. 36%; $p < 0.001$), and were similarly likely to have diabetes (20% vs. 17%; $p = 0.36$) or COPD (23% vs. 20%; $p = 0.29$).

### *Distribution of PASP and Prevalence of PH*

Median (25th, 75th percentile) PASP was 28 (24, 32) mm Hg in HTN and 48 (37, 56) mm Hg in HFpEF ($p < 0.001$) (Fig. 1A) patients; PH was present in 8% (n = 38) of HTN and 83% (n = 169) of HFpEF ($p < 0.001$) (Fig. 1B) patients. Clinical and echocardiographic characteristics of subjects with and without PH in each group are provided in Table 1. In both groups, patients with PH were older and had higher systolic blood pressure, wider pulse pressure, higher PCWP, and larger left atria compared with those without PH. There was no difference in left ventricular systolic function (EF, stroke volume index, cardiac index) or structural characteristics (mass, relative wall thickness, volume) between those with and without PH in either group. Among HFpEF patients, the prevalence of atrial fibrillation, coronary artery

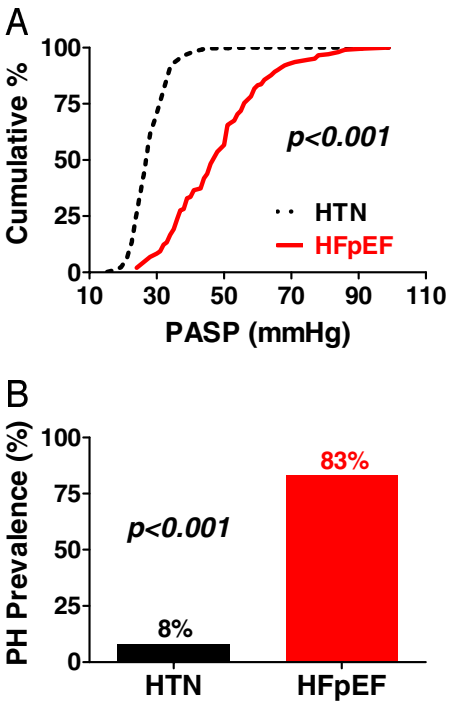


**Figure 1** **Cumulative Frequency Distribution of PASP and Prevalence of PH by Subject Group**

In patients with heart failure and preserved ejection fraction (HFpEF) (in **red**), the cumulative frequency distribution of pulmonary artery systolic pressure (PASP) was shifted toward higher pressures **(A)**, whereas the prevalence of pulmonary hypertension (PH) was markedly increased **(B)** compared with subjects with hypertension (HTN) (in **black**) without heart failure in the community.

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**Table 1 Characteristics of Subjects With Measurable PASP**

| | HTN | | HFpEF | |
|---|---|---|---|---|
| | PH Absent | PH Present | PH Absent | PH Present |
| N (% group) | 432 (92) | 38 (8) | 34 (17) | 169 (83) |
| PASP, mm Hg | 28 ± 4 | 40 ± 5* | 30 ± 3 | 52 ± 13* |
| Clinical characteristics | | | | |
| Age, yrs | 67 ± 10 | 72 ± 9* | 74 ± 11 | 79 ± 12* |
| Male, % | 40 | 32 | 47 | 41 |
| Height, m | 1.66 ± 0.10 | 1.62 ± 0.08* | 1.66 ± 0.10 | 1.65 ± 0.14 |
| Weight, kg | 79.6 ± 16.9 | 75.3 ± 14.5 | 84.8 ± 17.9 | 81.6 ± 23.0 |
| BSA, $m^2$ | 1.91 ± 0.23 | 1.83 ± 0.20 | 1.97 ± 0.24 | 1.92 ± 0.29 |
| Body mass index, $kg/m^2$ | 28.8 ± 5.5 | 28.8 ± 5.2 | 30.9 ± 6.3 | 29.6 ± 7.2 |
| Systolic blood pressure, mm Hg | 141 ± 21 | 153 ± 27* | 125 ± 20 | 134 ± 24* |
| Diastolic blood pressure, mm Hg | 75 ± 11 | 75 ± 11 | 69 ± 13 | 67 ± 14 |
| Pulse pressure, mm Hg | 66 ± 18 | 78 ± 20* | 56 ± 18 | 67 ± 20* |
| Heart rate, beats/min | 65 ± 11 | 65 ± 13 | 68 ± 15 | 71 ± 16 |
| Hypertension, % | 100 | 100 | 91 | 97 |
| Atrial fibrillation, % | 5 | 13* | 22 | 31 |
| Coronary artery disease, % | 16 | 21 | 59 | 53 |
| Diabetes mellitus, % | 10 | 13 | 27 | 34 |
| Chronic kidney disease,† % | 29 | 43 | 50 | 51 |
| Chronic obstructive lung disease,‡ % | 14 | 21 | 29 | 32 |
| Echocardiographic characteristics | | | | |
| Ejection fraction, % | 65 ± 5 | 65 ± 7 | 63 ± 5 | 62 ± 7 |
| Stroke volume/BSA, $ml/m^2$ | 46.8 ± 9.3 | 48.9 ± 10.5 | 42.7 ± 10.3 | 43.2 ± 9.8 |
| Cardiac index, $l/min/m^2$ | 3.0 ± 0.7 | 3.1 ± 0.8 | 2.8 ± 0.7 | 3.0 ± 0.8 |
| LV mass/BSA, $g/m^2$ | 99.6 ± 22.4 | 107.4 ± 31.0 | 99.7 ± 27.2 | 103.3 ± 30.1 |
| Relative wall thickness | 0.42 ± 0.07 | 0.42 ± 0.08 | 0.46 ± 0.11 | 0.45 ± 0.09 |
| LV end-diastolic volume/BSA, $ml/m^2$ | 59.2 ± 12.2 | 60.7 ± 11.1 | 54.5 ± 11.4 | 57.4 ± 15.0 |
| E/e′ ratio | 9.3 ± 3.3 | 12.8 ± 4.7* | 15.7 ± 9.8 | 19.6 ± 9.6* |
| PCWP, mm Hg | 18 ± 2 | 20 ± 3* | 21 ± 6 | 24 ± 6* |
| Left atrial volume/BSA, $ml/m^2$ | 26.2 ± 7.8 | 32.7 ± 8.5* | 32.1 ± 11.4 | 38.1 ± 14.3* |

Data are mean ± SD. *$p < 0.05$ versus PH absent. †Glomerular filtration rate ≤60 ml/min/1.73 $m^2$ (National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines [26]). ‡Forced expiratory volume in 1 s/forced vital capacity <70% (24) or clinical diagnosis.

BSA = body surface area; E/e′ = the ratio of early transmitral flow velocity to early mitral annular velocity; HFpEF = heart failure with preserved ejection fraction; HTN = hypertension; LV = left ventricular; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension.

disease, diabetes, chronic kidney disease, and COPD were similarly high in those with and without PH.

### *Association of PASP With PCWP*

The PASP increased with PCWP in both HTN and HFpEF ($r = 0.318$ and $r = 0.209$, respectively; both $p < 0.007$) (Fig. 2). After adjusting for PCWP, PASP was still higher in HFpEF compared with HTN ($p < 0.001$), suggesting that beyond the post-capillary contribution of pulmonary venous congestion, a pre-capillary component of pulmonary arterial HTN contributed to greater PH in HFpEF.

### *Utility of PASP in Distinguishing HFpEF From HTN*

The PASP distinguished HFpEF from HTN with an AUC of 0.91 ($p < 0.001$) and optimal cutoff of 35 mm Hg, coinciding with the definition of PH (17).The presence of PH (PASP >35 mm Hg) distinguished HFpEF from HTN with a sensitivity of 83% and a specificity of 92%. In univariate analysis, other significant distinguishing markers included E/e′, left atrial size, and relative wall thickness, whereas left ventricular mass was not a significant distinguishing marker (Table 2) (26). The largest AUC was obtained with PASP (Bonferroni-adjusted $p < 0.01$ vs. each of the other markers in pairwise comparisons) (Fig. 3). In multivariate analysis involving the 443 subjects in whom all parameters were measurable, only PASP and E/e′ remained significant markers of HFpEF (odds of HFpEF vs. HTN = 1.22× higher per 1-mm Hg increase in PASP and 1.15× higher per unit increase in E/e′, respectively; both $p < 0.001$). Excluding patients with atrial fibrillation ($n = 26$ in HTN; $n = 54$ in HFpEF) from the analysis gave similar results (data not shown).

### *Effect of PH on Survival*

In HFpEF, there were 84 deaths over a median follow-up of 2.8 years (mean 2.4 ± 1.2 years). By Kaplan-Meier analysis, mortality was higher in those with a PASP above the median value of 48 mm Hg (log-rank $p = 0.002$) (Fig. 4). The presence of PH as defined by PASP above 35 mm Hg was similarly strongly associated with mortality in HFpEF (log-rank $p = 0.003$). Among echocardiographic parame-

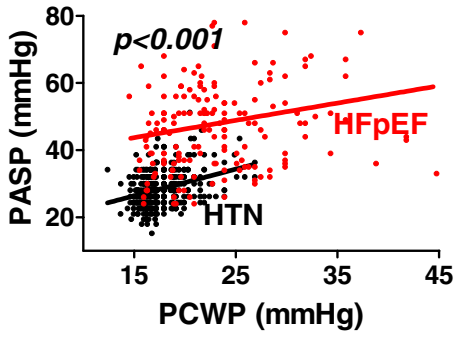


**Figure 2** Association of PASP With Pulmonary Venous Hypertension

PASP increased with pulmonary capillary wedge pressure (PCWP) in patients with HFpEF, as well as in subjects with HTN without heart failure, but remained higher in HFpEF than HTN after adjusting for PCWP ($p < 0.001$). Raw data points and linear regression line for the association are shown for HFpEF (in **red**) and HTN (in **black**). Abbreviations as in Figure 1.

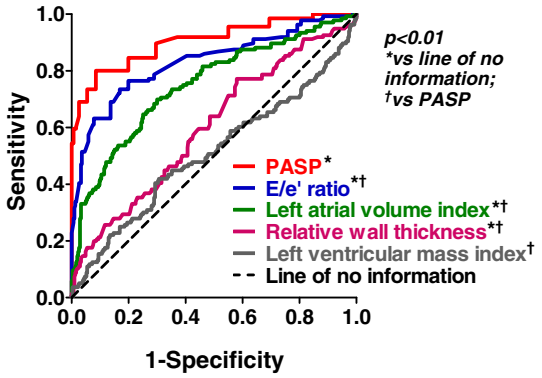


**Figure 3** Receiver-Operating Characteristic Curves of Echocardiographic Parameters for the Diagnosis of HFpEF

By receiver-operating characteristic curve analysis, echocardiographic parameters that distinguished HFpEF from HTN heart disease without heart failure included PASP, the ratio of early transmittal flow velocity to early mitral annular diastolic velocity (E/e′), left atrial volume index, and relative wall thickness. The largest area under curve was obtained with PASP, with the optimal cutoff value of 35 mm Hg. Abbreviations as in Figure 1.

ters, only PASP was associated with mortality in HFpEF (unadjusted hazard ratio: 1.28 per 10 mm Hg; $p < 0.001$) (Table 3), and this association persisted after adjustment for age (age-adjusted hazard ratio: 1.22 per 10 mm Hg; $p = 0.005$).

### *Subanalysis Excluding Patients With COPD and Other Potential Causes of PH*

Among subjects with measurable PASP, COPD was present in 15% (n = 69) of HTN (13 with the clinical diagnosis of COPD, 67 with abnormal spirometry, 69 with either, and 11 with both diagnostic criteria) and 32% (n = 64) of HFpEF (46 with the clinical diagnosis of COPD, 34 with abnormal spirometry, 64 with either, and 16 with both diagnostic criteria). Restricting the analysis to patients without COPD (n = 401 in HTN; n = 139 in HFpEF), the HFpEF group still had a greater prevalence of PH (83% vs. 8%; $p < 0.001$) and a higher PASP (48 ± 14 mm Hg vs. 28 ± 5 mm Hg; $p < 0.001$) compared with HTN, even after adjusting for age and PCWP ($p < 0.001$). The presence of PH remained a significant predictor of mortality in HFpEF ($p = 0.018$) independent of age (age-adjusted hazard ratio: 1.27 per 10 mm Hg increase in PASP; $p = 0.014$).

A further 11 HFpEF patients had other potential causes of PH (5 with obstructive sleep apnea, 4 with history of pulmonary embolism, 1 with scleroderma, and 1 with liver disease). Excluding these subjects gave similar results, with a greater prevalence of PH (82% vs. 8%; $p < 0.001$) and higher PASP (47 ± 14 mm Hg vs. 28 ± 5 mm Hg; $p < 0.001$) in HFpEF compared with HTN, even after adjusting for age and PCWP ($p < 0.001$), as well as a negative impact of increasing PASP on survival in HFpEF, independent of age (age-adjusted hazard ratio: 1.28 per 10 mm Hg increase in PASP; $p = 0.019$).

## Discussion

In these first population-based data regarding pulmonary pressures in HFpEF, PH was highly prevalent and often severe in HFpEF presenting in the general community. The development of PH was related to the extent of pulmonary venous HTN as estimated by Doppler indexes. However, after accounting for this post-capillary component of PH, the severity of PH in HFpEF still exceeded that of hypertensive control subjects without HF from the same community, suggesting the contribution of a pre-capillary component of pulmonary arterial HTN to PH in HFpEF. The severity of PH distinguished HFpEF from hypertensive control subjects with excellent diagnostic accuracy, superior to traditional indexes of cardiac remodeling (left atrial

**Table 2** Receiver-Operating Characteristic Curve of Echocardiographic Parameters Distinguishing HFpEF From HTN

| Parameter | Number Available | AUC (Mean ± SE) | p Value | Optimal Cutoff | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| PASP, mm Hg | 673 | 0.91 ± 0.02 | <0.001 | 35 | 83 | 92 |
| E/e′ ratio | 808 | 0.83 ± 0.02 | <0.001 | 12.5 | 70 | 85 |
| Left atrial volume/BSA, ml/m$^2$ | 848 | 0.75 ± 0.02 | <0.001 | 29 | 66 | 74 |
| Relative wall thickness | 759 | 0.60 ± 0.03 | <0.001 | 0.39 | 80 | 36 |
| LV mass index, g/m$^2$ | 756 | 0.52 ± 0.03 | 0.497 | 105 | 42 | 68 |

AUC = area under curve; other abbreviations as in Table 1.

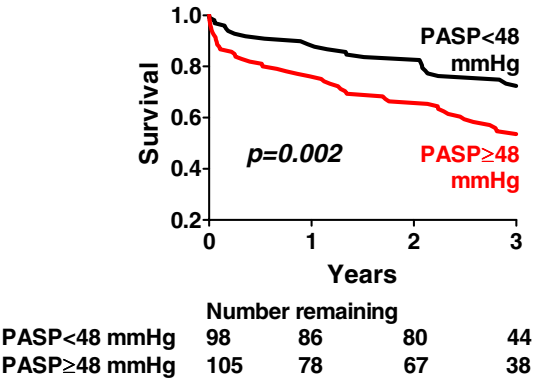


**Figure 4** Kaplan-Meier Survival Curves in HFpEF Patients With PASP Above and Below the Median

HFpEF patients with PASP above the median value of 48 mm Hg (in **red**) had reduced survival compared with patients with PASP <48 mm Hg (in **black**) over 3 years (log-rank p = 0.002). Abbreviations as in Figure 1.

volume, relative wall thickness, left ventricular mass) and of incremental value to Doppler indexes of diastolic dysfunction (E/e′). Further, the presence of PH was a potent adverse prognostic factor in HFpEF, independent of age. The implications of these data for PH as a pathophysiologic factor and therapeutic target in HFpEF deserve further study.

**Prevalence and significance of PH in HFpEF.** That severe PH could develop in HFpEF was described in early isolated case reports of elderly hypertensive patients with HFpEF (3,4). In a subsequent series of patients hospitalized in the New York metropolitan area for HFpEF, Klapholz et al. (5) reported a mean PASP of 47 ± 17 mm Hg by echocardiography in the 44% (272 of 619) of patients in whom measurements were available. More recently, Kjaergaard et al. (7) obtained PASP measurements by echocardiography in 38% (388 of 1,022) of Danish patients hospitalized for symptomatic HF, 25% (n = 96) of whom had preserved EF, and found a median (25th, 75th percentile) PASP of 39 (31, 50) mm Hg. Of note, the latter study also identified elevated PASP as an independent predictor of mortality in HFpEF. Although important, the generalizability of these previous findings was limited by selection bias and the low proportions of patients in whom PASP estimates were available. Our current findings therefore serve to confirm and extend the prior studies by including all inpatients and outpatients with HFpEF presenting in the community, thus providing the first community-based estimates of the prevalence, severity, and prognostic significance of PH in HFpEF to date.

**Mechanism of PH in HFpEF.** The development of PH in HFpEF has largely focused on the role of left ventricular diastolic dysfunction and the passive effect of pulmonary venous HTN. Aragam et al. (9) showed that in patients with aortic stenosis, most of whom had normal EF, it was the severity of diastolic dysfunction, rather than the severity of aortic stenosis, that correlated better with the severity of PH. Kessler et al. (3) attributed the reversible severe PH in an elderly hypertensive man to abnormal left ventricular filling that was treated with long-acting nifedipine. Kjaergaard et al. (7) alluded to the contribution of diastolic dysfunction to PH by showing that HF patients (25% HFpEF) with restrictive filling had higher PASP compared with those with nonrestrictive patterns. Finally, Bouchard et al. (27) showed a close correlation between PASP and PCWP by echocardiography in 69 patients with normal systolic function (not all with HF) and concluded that PASP could be used as a surrogate of left ventricular filling pressure when pulmonary vascular resistance was assumed normal. Our data, while consistent with the prior data, importantly highlight that the passive contribution of pulmonary venous HTN may not by itself account for the increased PASP in HFpEF compared with elderly hypertensive subjects without overt HF. Beyond this postcapillary component of PH, we postulate that the greater severity of PH in HFpEF may be caused by an additional pre-capillary component of pulmonary arterial HTN. In longstanding pulmonary congestion, pre-capillary PH may be mediated by reactive increases in pulmonary arterial tone or development of a congestive arteriopathy characterized by pulmonary arteriolar remodeling, medial hyperplasia, and intimal fibrosis, as shown to occur in patients with mitral stenosis (10) or systolic HF (11). The presence of PH may therefore carry important clinical implications for the diagnosis and treatment of the syndrome as elaborated in the following text.

**Diagnostic utility.** The difficulties and controversies surrounding the optimal diagnostic approach to HFpEF have

**Table 3** Predictors of Mortality in HFpEF

| | Univariate Analysis* | | | Multivariate Analysis* | | |
|---|---|---|---|---|---|---|
| Variable | n | Hazard Ratio | p Value | n | Hazard Ratio | p Value |
| PASP, mm Hg | 203 | 1.28 per 10 mm Hg | <0.001 | 136 | 1.20 per 10 mm Hg | 0.028 |
| E/e′ ratio | 208 | 1.01 per U | 0.496 | 136 | 0.98 per U | 0.199 |
| Left atrial volume/BSA, ml/m$^2$ | 185 | 1.12 per 10 ml/m$^2$ | 0.140 | 136 | 1.12 per 10 ml/m$^2$ | 0.237 |
| Relative wall thickness | 211 | 1.18 per 0.1 U | 0.108 | 136 | 1.26 per 0.1 U | 0.121 |
| LV mass index, g/m$^2$ | 207 | 1.00 per 10 g/m$^2$ | 0.946 | 136 | 0.96 per 10 g/m$^2$ | 0.383 |

*Cox regression analysis, in which multivariate model includes all 5 variables.
Abbreviations as in Table 1.

been the subject of recent debate (28,29). In the most current consensus statement from the European Society of Cardiology (30), a variety of echocardiographic markers of diastolic dysfunction (chiefly the mitral E/e′ ratio) or cardiac remodeling (left atrial size, left ventricular mass) were proposed to aid in the diagnosis of HFpEF. However, the specificity of these markers has been questioned, because elderly hypertensive patients frequently show abnormal mitral Doppler profiles and cardiac remodeling in the absence of clinical HF (15). As shown in our study and others (27), PASP elevation was a good surrogate measure of clinically significant pulmonary venous HTN in HFpEF. The present data further showed the utility of PH in distinguishing HFpEF from HTN independent of E/e′, as well as its potent independent impact on survival, suggesting that PH may play a primary role in the pathophysiology of HFpEF. Importantly, these findings need to be prospectively validated in other populations, ideally using invasive gold-standard measurements.

**Therapeutic implications.** The presence of a pre-capillary component in addition to post-capillary PH in HFpEF raises the potential that aside from therapies aimed at reducing pulmonary venous congestion, those aimed at pulmonary arterial HTN may also have a role in the treatment of HFpEF. To date, there are no proven therapies in HFpEF. Treatment recommendations as outlined in HF guidelines are empiric and have not changed over time. Specific therapy aimed at PH in HFpEF is therefore an appealing consideration but has been tempered by concern that increases in right heart output with pulmonary vasodilators may result in further increases in left atrial pressure in patients with left heart disease and HF (31). Indeed, the use of epoprostenol was associated with increased mortality in systolic HF (32), although the mechanism for increased mortality was unclear. Similarly, despite early data showing the deleterious effect of endothelin and potential benefit of endothelin antagonism in HF, a trial of the selective endothelin receptor A antagonist darusentan in systolic HF failed to show clinical benefit (33). However, there remains room for cautious optimism. Recent seminal trials using phosphodiesterase-5 inhibitors in systolic HF (34,35) have shown beneficial effects, including improvement in exercise capacity and quality of life. In fact, evidence exists that phosphodiesterase-5 inhibition may not only improve pulmonary tone and right heart function but also exert pleiotropic effects on left ventricular structure (36), ventricular function (36,37), and peripheral vascular function (38). These data lend support for the ongoing trial of phosphodiesterase-5 inhibition in HFpEF (the RELAX [Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure] trial [39]).

**Study limitations.** The feasibility of obtaining tricuspid regurgitation signals may potentially have led to overestimation of the prevalence of PH, but estimations of PASP were obtained in the majority of subjects including a larger proportion of participants than in previous studies. Although known causes of PH were excluded by careful clinical review in the subanalyses, occult diagnoses may have been missed in some patients. Lack of invasive measurements of pulmonary artery characteristic impedance or pulmonary arteriolar resistance precluded assessment of pulmonary artery stiffening or pulmonary arteriolar tone. However, this study could not have been performed using an invasive approach. The potential limited precision of echocardiography-derived PASP is acknowledged (18). Similarly, although the E/e′ ratio provides an estimate of PCWP (19), it is not a perfect measure of PCWP. Further, resting measures of PCWP do not reflect activity related increases in PCWP that may contribute to reactive PH and congestive pulmonary arterial remodeling and weaken the correlation between resting PCWP and PASP. Finally, the single time-point measurements in this study did not allow assessment for time-dependence of PASP in Cox regression analysis and may have led to underestimation of the prognostic significance of PH.

## Conclusions

Pulmonary HTN is common and can be severe in HFpEF presenting in the community. In addition to pulmonary venous HTN from diastolic dysfunction, a component of pulmonary arterial HTN may contribute to PH in HFpEF, distinguishing these patients from hypertensive control subjects without HF. The potent association between PH and mortality suggests that PH may contribute to the progression of HF in patients with HFpEF, and thus PH may represent a therapeutic target in HFpEF.

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### REFERENCES

1. Thompson W, White PD. Commonest cause of hypertrophy of the right ventricle-left ventricular strain and failure. Am Heart J 1936;12:641–9.
2. Abramson SV, Burke JF, Kelly JJ Jr., et al. Pulmonary hypertension predicts mortality and morbidity in patients with dilated cardiomyopathy. Ann Intern Med 1992;116:888–95.
3. Kessler KM, Willens HJ, Mallon SM. Diastolic left ventricular dysfunction leading to severe reversible pulmonary hypertension. Am Heart J 1993;126:234–5.
4. Willens HJ, Kessler KM. Severe pulmonary hypertension associated with diastolic left ventricular dysfunction. Chest 1993;103:1877–83.
5. Klapholz M, Maurer M, Lowe AM, et al. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. J Am Coll Cardiol 2004;43:1432–8.
6. Ghali JK, Kadakia S, Cooper RS, Liao YL. Bedside diagnosis of preserved versus impaired left ventricular systolic function in heart failure. Am J Cardiol 1991;67:1002–6.

7. Kjaergaard J, Akkan D, Iversen KK, et al. Prognostic importance of pulmonary hypertension in patients with heart failure. Am J Cardiol 2007;99:1146–50.
8. Shapiro B, Nishimura R, McGoon M, Redfield M. Diagnostic dilemmas: diastolic heart failure causing pulmonary hypertension, pulmonary hypertension causing diastolic dysfunction. Adv Pulmon Hypertens 2006;5:13–20.
9. Aragam JR, Folland ED, Lapsley D, Sharma S, Khuri SF, Sharma GV. Cause and impact of pulmonary hypertension in isolated aortic stenosis on operative mortality for aortic valve replacement in men. Am J Cardiol 1992;69:1365–7.
10. Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. Circulation 2000;102:1718–23.
11. Delgado JF, Conde E, Sanchez V, et al. Pulmonary vascular remodeling in pulmonary hypertension due to chronic heart failure. Eur J Heart Fail 2005;7:1011–6.
12. Maurer MS, El Khoury Rumbarger L, King DL. Ventricular volume and length in hypertensive diastolic heart failure. J Am Soc Echocardiogr 2005;18:1051–7.
13. Melenovsky V, Borlaug B, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus non-failing hypertensive left ventricular hypertrophy in the urban Baltimore community. J Am Coll Cardiol 2007;49:198–207.
14. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 2007;115:1982–90.
15. Redfield MM, Jacobsen SJ, Burnett JC Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.
16. Ommen SR, Nishimura RA, Hurrell DG, Klarich KW. Assessment of right atrial pressure with 2-dimensional and Doppler echocardiography: a simultaneous catheterization and echocardiographic study. Mayo Clin Proc 2000;75:24–9.
17. Rich SE. Executive summary from the World Symposium on Primary Pulmonary Hypertension, Evian, France, September 6–10, 1998. Geneva: The World Health Organization.
18. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:14S–34S.
19. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788–94.
20. Willens HJ, Chirinos JA, Gomez-Marin O, et al. Noninvasive differentiation of pulmonary arterial and venous hypertension using conventional and Doppler tissue imaging echocardiography. J Am Soc Echocardiogr 2008;21:715–9.
21. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. Eur J Echocardiogr 2006;7:79–108.
22. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995;152:1107–36.
23. Miller A, Thornton JC, Warshaw R, Bernstein J, Selikoff IJ, Teirstein AS. Mean and instantaneous expiratory flows, FVC and FEV1: prediction equations from a probability sample of Michigan, a large industrial state. Bull Eur Physiopathol Respir 1986;22:589–97.
24. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001;163:1256–76.
25. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.
26. National Kidney Foundation. K/DOQI Clinical Practice Guidelines. Available at: www.kidney.org/professionals/kdoqi/guidelines.cfm. Accessed January 1, 2009.
27. Bouchard JL, Aurigemma GP, Hill JC, Ennis CA, Tighe DA. Usefulness of the pulmonary arterial systolic pressure to predict pulmonary arterial wedge pressure in patients with normal left ventricular systolic function. Am J Cardiol 2008;101:1673–6.
28. Maurer MS, Spevack D, Burkhoff D, Kronzon I. Diastolic dysfunction: can it be diagnosed by Doppler echocardiography? J Am Coll Cardiol 2004;44:1543–9.
29. Oh JK, Hatle L, Tajik AJ, Little WC. Diastolic heart failure can be diagnosed by comprehensive two-dimensional and Doppler echocardiography. J Am Coll Cardiol 2006;47:500–6.
30. Paulus WJ, Tschope C, Sanderson JE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 2007;28:2539–50.
31. Semigran MJ, Cockrill BA, Kacmarek R, et al. Hemodynamic effects of inhaled nitric oxide in heart failure. J Am Coll Cardiol 1994;24:982–8.
32. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997;134:44–54.
33. Anand I, McMurray J, Cohn JN, et al., EARTH Investigators. Long-term effects of darusentan on left-ventricular remodelling and clinical outcomes in the Endothelin A Receptor Antagonist Trial in Heart Failure (EARTH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364:347–54.
34. Guazzi M, Samaja M, Arena R, Vicenzi M, Guazzi MD. Long-term use of sildenafil in the therapeutic management of heart failure. J Am Coll Cardiol 2007;50:2136–44.
35. Lewis GD, Shah R, Shahzad K, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation 2007;116:1555–62.
36. Takimoto E, Champion HC, Li M, et al. Chronic inhibition of cyclic GMP phosphodiesterase-5A prevents and reverses cardiac hypertrophy. Nat Med 2005;11:214–22.
37. Borlaug BA, Melenovsky V, Marhin T, Fitzgerald P, Kass DA. Sildenafil inhibits beta-adrenergic-stimulated cardiac contractility in humans. Circulation 2005;112:2642–9.
38. Katz SD, Balidemaj K, Homma S, Wu H, Wang J, Maybaum S. Acute type 5 phosphodiesterase inhibition with sildenafil enhances flow-mediated vasodilation in patients with chronic heart failure. J Am Coll Cardiol 2000;36:845–51.
39. Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX). Available at: http://clinicaltrials.gov/ct2/show/NCT00763867?term=Phosphodiesterase-5+Inhibition+to+Improve+Clinical&rank=1. Accessed March 3, 2009.

**Key Words:** pulmonary hypertension ■ diastolic heart failure ■ heart failure with preserved ejection fraction.