The Relationship of Right- and Left-Sided Filling Pressures in Patients With Heart Failure and a Preserved Ejection Fraction

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Background—Although right-sided filling pressures often mirror left-sided filling pressures in systolic heart failure, it is not known whether a similar relationship exists in heart failure with preserved ejection fraction.

Methods and Results—Eleven subjects with heart failure with preserved ejection fraction underwent right heart catheterization at rest and under loading conditions manipulated by lower body negative pressure and saline infusion. Right atrial pressure (RAP) was classified as elevated when ≥10 mm Hg and pulmonary capillary wedge pressure (PCWP) when ≥22 mm Hg. If both the RAP and the PCWP were elevated or both not elevated, they were classified as concordant; otherwise, they were classified as discordant. Correlation of RAP and PCWP was determined by a repeated measures model. Among 66 paired measurements of RAP and PCWP, 44 (67%) had a low RAP and PCWP and 8 (12%) a high RAP and PCWP, yielding a concordance rate of 79%. In a sensitivity analysis performed by varying the definition of elevated RAP (from 8 to 12 mm Hg) and PCWP (from 15 to 25 mm Hg), the mean±SD concordance of RAP and PCWP was 76±10%. The correlation coefficient of RAP and PCWP for the overall cohort was r=0.86 (P<0.0001).

Conclusions—Right-sided filling pressures often reflect left-sided filling pressures in heart failure with preserved ejection fraction, supporting the role of estimation of jugular venous pressure to assess volume status in this condition. (Circ Heart Fail. 2010;3:202-206.)

Key Words: heart failure ■ hemodynamics ■ physical examination ■ jugular venous pressure

Assessing volume status (left-sided filling pressures) is an important aspect in the care of the patients with heart failure (HF). Estimation of jugular venous pressure is frequently used to accomplish this goal, exploiting the fact that right-sided filling pressures often mirror left-sided filling pressures in patients with HF and reduced left ventricular ejection fraction (LVEF). Although recent data from implantable monitoring have shown that hemodynamics share similarities between patients with HF and a reduced ejection fraction and those with HF and a preserved ejection fraction, to our knowledge, no data demonstrate whether right-sided and left-sided filling pressures mirror each other in the latter patient population. The need to assess this question is highlighted by the observations that the right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP) can be discordant in cardiovascular states, as may occur in acute myocardial infarction, and because HF with preserved ejection fraction (HFPEF) is commonly encountered in the clinical setting. Therefore, we conducted the present study to assess the relationship of the RAP and PCWP in a well-characterized cohort of subjects with HFPEF.

Methods

Study Cohort

This analysis is a substudy of a larger project conducted to compare static and dynamic left ventricular diastolic properties between healthy elderly seniors and those with HFPEF. We screened 2054 patients aged ≥65 years who had been hospitalized within the preceding 9 months and given a discharge diagnosis of HF. Subjects had to have supporting evidence of congestive HF during the index hospitalization, including an elevated B-type natriuretic peptide, x-ray film of the chest indicating pulmonary congestion, or elevated PCWP during cardiac catheterization. Furthermore, they had to have a documented LVEF >50% both during hospitalization and on a screening echocardiogram, the latter obtained by a modified Simpson method as previously and confirmed by a senior investigator (B.D.L.). An LVEF also was obtained immediately after the baseline

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pressure measurements (discussed later). These latter images were analyzed blindly by an experienced sonographer and are the LVEF reported in this study. Subjects were excluded if they had a history or presence of atrial fibrillation/flutter; use of warfarin; previous coronary artery bypass grafting; unrevascularized epicardial coronary stenoses (>50% by prior angiography); angina; myocardial infarction in the past year; creatinine level >2.5 g/dL or end-stage renal disease on dialysis; severe chronic obstructive pulmonary disease or pulmonary disease; moderate or severe valvular heart disease; and an alternative known cause for HF, such as restrictive cardiomyopathy or constrictive pericarditis. Following these exclusion criteria, 23 subjects met the criteria for enrollment, and 11 consented to participate. All studies were performed in the outpatient setting, when patients were clinically stable. Informed consent was obtained from all subjects. The Institutional Review Board of the University of Texas Southwestern (Dallas, Tex) approved this study.

Right Heart Catheterization

β-blockers were held for at least 24 to 48 hours, and diuretics were delayed to the end of the study on the morning of the examination. Other antihypertensive drugs such as vasodilators and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers were continued as prescribed. A 6F balloon-tipped fluid-filled catheter was placed under fluoroscopic guidance through an antecubital vein into the pulmonary artery. The wedge position of the catheter was confirmed by fluoroscopy and the presence of typical wave forms. The pressure transducer was set with the zero reference point at 5.0 cm below the sternal angle. Mean PCPw and mean RAPs were determined in triplicate visually at the end of expiration from paper recordings amplified to 0.4 mm Hg resolution. The RAP was measured from the proximal port of the catheter.

Manipulation of Volume Status

Central blood volume was manipulated to allow 6 individual measurements across a broad physiological range of left ventricular filling pressure, ranging from ~3 mm Hg to a maximum of 29 mm Hg. As previously described,10–13 we followed a general protocol of baseline supine measurements, the use of lower body negative pressure (LBNP) to reduce cardiac filling, a repeat set of baseline measurements, and the rapid infusion of warm saline to increase cardiac filling. To achieve LBNP, subjects were placed in an acrylic plastic box sealed at the level of the iliac crest, and suction was applied by a vacuum pump controlled with a variable auto-

Table. Baseline Characteristics and Hemodynamic Response to Volume Changes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>73±7</th>
<th>Women 64</th>
<th>Race</th>
<th>White 55</th>
<th>Black 27</th>
<th>Hispanic 18</th>
<th>Hypertension 100</th>
<th>Diabetes mellitus 55</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>PCWP, mm Hg</td>
<td>9.5±3</td>
<td>15±5</td>
<td>4±3</td>
<td>6.6±3</td>
<td>13±3</td>
<td>22±3</td>
<td></td>
<td></td>
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<tr>
<td>Lowest filling pressures* RAP, mm Hg</td>
<td>30 mm Hg</td>
<td>15 mm Hg</td>
<td>13 mm Hg</td>
<td>22 mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>6.6±3</td>
<td>13±3</td>
<td>22±3</td>
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Data Analysis

For our primary analysis, we used dichotomous threshold values of RAP and PCWP as before.1 The RAP was classified as elevated when ≥10 mm Hg and PCWP when ≥22 mm Hg. We determined how often RAP and PCWP were concordant (both elevated or both not elevated) using these threshold values. In a sensitivity analysis, we assessed the concordance rate of RAP and PCWP over a broad range (RAP, 8 to 12 mm Hg; PCWP, 15 to 25 mm Hg) of threshold values. Values of RAP and PCWP at different loading conditions are reported as mean±SD. Pairwise PCWP was compared at different loading conditions with the Wilcoxon signed-rank test. To determine the effect of RAP on PCWP, given that multiple measurements were made on each subject, a repeated measures model was implemented using the MIXED procedure of SAS version 9.1. PCWP was the outcome variable, and RAP was the fixed effect. Random effects for the patient and patient*RAP also were included, with the covariance parameter of patient*RAP significant (P=0.027). The covariance structure of the random effects was variance components. Using these models, scatterplots with the estimated regression equations were produced for each subject and in toto. The correlation coefficient was calculated using a multivariate mixed model to account for the repeated measures within subject. The structure for the multivariate repeated measures was constructed by taking the Kronecker product of an unstructured matrix with a first-order autoregressive structure. This adequately takes into account the covariance design both between RAP and PCWP measurements at specific loading conditions and across the various loading conditions. Significance was determined by 2-tailed tests, with α=0.05.

Results

The baseline characteristics and hemodynamic responses to volume changes are shown in the Table. The 11 subjects were elderly, hypertensive, and predominantly diabetic and women. Three were black, 2 were Hispanic, and 6 were white. The B-type natriuretic peptide at the time of the index hospitalization was 448±374 pg/mL. The range of LVEF was 51 to 70%.

The baseline RAP was 9.5±3.3 mm Hg, and the baseline PCWP was 15.2±5.1 mm Hg. The lowest filling pressure achieved after LBNP or head-up tilt is shown in the Table, as is the highest filling pressure after saline infusion. The efficacy of the LBNP and head-up tilt was confirmed as the PCWP decreased to 10.6±3.7 mm Hg at LBNP −15 mm Hg, 7.2±3.3 mm Hg at LBNP −30 mm Hg, and 6.7±0.9 mm Hg at LBNP −40 mm Hg (P<0.001). In the 2 subjects who underwent head-up tilt, the PCWP decreased from 12.9±2.3 mm Hg to 6.6±3.2 mm Hg, and the RAP from...
7.7±1.9 mm Hg to 4.8±1.6 mm Hg. The adequacy of volume challenge was confirmed by the increase in RAP to 13.4±2.9 mm Hg (P=0.002) and the increase in PCWP to 21.7±2.9 mm Hg after peak saline infusion (P=0.02).

There were a total of 66 paired measurements of RAP and PCWP (Figure 1). Of these, 44 (67%) occurred with a low RAP and a low PCWP and 8 (12%) with a high RAP and a high PCWP, yielding a concordance rate of 79%. Of the discordant group, all 14 were with an elevated RAP but not an elevated PCWP (21% of all measurements), and there were no cases of an elevated PCWP with a low RAP (0%). When we excluded the 2 subjects with obesity who had head-up tilt done instead of LBNP, the concordance rate was 78% (65% with high RAP and high PCWP and 13% with low RAP and low PCWP). When we excluded the 2 subjects with obesity who had head-up tilt done instead of LBNP, the concordance rate was 78% (65% with high RAP and high PCWP and 13% with low RAP and low PCWP). When we excluded the 2 subjects with obesity who had head-up tilt done instead of LBNP, the concordance rate was 78% (65% with high RAP and high PCWP and 13% with low RAP and low PCWP). In a sensitivity analysis, we varied the definition of elevated RAP from 8 to 12 mm Hg and the definition of elevated PCWP from 15 to 25 mm Hg. Among these 55 different combinations, the concordance of elevated RAP and PCWP was 76±10%. In the cases when elevated RAP was defined as 10, 11, or 12 mm Hg, the concordance rate with elevated PCWP when defined at any value from 15 to 25 mm Hg was between 71% and 89%. The utility of the RAP to PCWP relationship was suboptimal only when an elevated RAP was defined at the low end of its range (eg, 8 or 9 mm Hg) and PCWP at the high end of its range (from 20 to 25 mm Hg). In these cases, the concordance rate of RAP and PCWP varied between 52% and 67%.

The relationship of RAP and PCWP is shown for each individual subject and for the overall cohort in Figure 2 (r=0.86 for the overall cohort). Representative RAP and PCWP tracings from 2 subjects under various loading conditions are shown in Figure 3. In both cases, a decrease (with LBNP) or an increase (with saline infusion) in RAP from baseline was associated with a change in PCWP in the same direction.

Discussion

The relationship of RAP to PCWP has not been well explored in patients with HFPEF. Herein, we demonstrate in a well-characterized cohort of subjects with HFPEF that the RAP and PCWP are correlated significantly (r=0.86) and often are concordant (≈80% of cases are either both elevated or both not elevated) when previously chosen, clinically relevant dichotomous cut points are used. Furthermore, by manipulating loading conditions with LBNP (n=9) or head-up tilt (n=2) and with saline loading, we demonstrate that dynamic changes in RAP often mirror those of the PCWP. These findings were unaltered when those with head-up tilt were excluded from analysis.

Previous studies of patients with HF and severely reduced LVEF (mean ±22%) have demonstrated a significant correlation between RAP and PCWP, with a correlation coefficient of 0.64.2,3 Despite the difference in LVEF between those studies and the present one, the correlation of RAP to PCWP remains significant in the present cohort (r=0.86). Furthermore, the discordance rate (ie, when the RAP is not elevated but the PCWP is, or the RAP is elevated but the PCWP is not) in this study is 21%, remarkably consistent to what we
previously reported (21%) in those with largely systolic HF. Overall, these data suggest that monitoring the RAP by estimation of jugular venous pressure would provide insights into left-sided filling pressures in HFPEF that were equally useful to that in systolic HF.

In contrast to the similarities noted earlier, there was one apparent difference between the relationship of RAP and PCWP found in this study of HFPEF compared with that previously reported in systolic HF. Specifically, there were no paired measurements where the RAP was low and the PCWP was elevated in the subjects with HFPEF. In contrast, in those with systolic HF, the RAP was low with an elevated PCWP in 13% and 15% of subjects. The basis of this difference is uncertain, and we cannot exclude the possibility that this finding is simply due to the small sample size of this study. Nevertheless, if confirmed, this observation suggests that the presence of low jugular venous pressure in a patient with HFPEF may be a useful tool to exclude elevated left-sided filling pressures.

There are several potential explanations for the relationship of right- and left-sided filling pressures in HF. Backward transmission of elevated left-sided filling pressures can lead to pulmonary hypertension, in turn causing progressive right ventricular failure and an elevated RAP. An alternative explanation is diastolic ventricular interaction, which has been shown in patients with HF and a reduced LVEF. Here, an increased right ventricular end-diastolic volume due to worsening right HF (and manifest as increased RAP) can impinge on the left ventricular volume due to pericardial constraint and lead to a secondary increase in the PCWP. A third possibility is that increased left-sided filling pressures can lead to progressive mitral annular dilation and mitral regurgitation, which has been shown in subjects with advanced HF and severely depressed LVEF. However, this possibility is less likely in this population where subjects with more than minimal valve disease were excluded.

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Figure 3. Representative hemodynamic pressure waveforms of RAP and PCWP in 2 individual subjects under various loading conditions. A simultaneous ECG is shown at the top. Numbers represent pressure measurements. Note that as the RAP increases, the PCWP increases in concert in both cases. LBNP30 indicates LBNP at −30 mm Hg; LBNP15, LBNP at −15 mm Hg; NS1, a normal saline infusion of −10 mL/kg at 100 to 200 mL/min; and NS2, an infusion of −20 mL/kg at 100 to 200 mL/min.

Limitations
The number of subjects included in this study is small (n=11), and the relationship between RAP and PCWP may have been different had 66 independent subjects been studied. However, in contrast to other larger studies in which single measurements of RAP and PCWP were made per subject, there were multiple filling states induced in each subject, thus improving the interpretation of changes in RAP and PCWP pressures with changes in preload. Patients treated for HFPEF in the general community may have a variety of comorbid conditions for which we excluded subjects from enrollment; therefore, the study subjects may not represent the full spectrum of the broad population of patients with HFPEF. If so, then the relationships we describe from a small study cohort may not be generalizable. Our data are based on invasive hemodynamic measurements. Whether the RAP can be estimated noninvasively by the assessment of the jugular venous pressure in this patient population is not known. Finally, we have demonstrated the relationship of RAP and PCWP with acute changes in loading conditions. Whether this represents the conditions present in the setting of chronic changes in volume in patients with HFPEF is not known.

Conclusion
There is a strong relationship between right-sided and left-sided filling pressures in subjects with HFPEF similar to what has been observed previously in subjects with systolic HF. These data support the role of estimation of jugular venous pressure in assessing the volume status of patients with HF, irrespective of their LVEF.

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Disclosures
None.

References
Assessment of the left ventricular filling pressure in patients with heart failure (HF) often includes examination of the jugular veins to estimate the central venous pressure (right ventricular filling pressure). This approach has been shown to be useful in patients with systolic HF because right and left ventricular filling pressures often mirror each other in this setting. However, it is not known whether this relationship exists in patients with HF and a preserved left ventricular ejection fraction. In this study, 11 subjects with HF with preserved ejection fraction underwent right heart catheterization at rest and under loading conditions manipulated by lower body negative pressure or head-up tilt and by saline infusion. Right atrial pressure (RAP) was classified as elevated when ≥10 mm Hg, and pulmonary capillary wedge pressure (PCWP) when ≥22 mm Hg. If both the RAP and the PCWP were elevated or both not elevated, the RAP and PCWP were classified as concordant; otherwise, they were classified as discordant. Among 66 paired measurements of RAP and PCWP, 44 (67%) had a low RAP and PCWP and 8 (12%) a high RAP and PCWP, yielding a concordance rate of 79%. The correlation coefficient of RAP and PCWP for the overall cohort was \( r = 0.86 \) (\( P < 0.0001 \)). We conclude that right-sided filling pressures often reflect left-sided filling pressures in HF with preserved ejection fraction, supporting the role of estimation of jugular venous pressure to assess volume status in this condition.

**CLINICAL PERSPECTIVE**

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In the article, “The Relationship of Right- and Left-Sided Filling Pressures in Patients With Heart Failure and a Preserved Ejection Fraction” by Drazner et al, which appeared in the March 2010 issue of the journal (Circ Heart Fail. 2010;3;202–206), the wrong DOI was displayed. The correct DOI for this article should be 10.1161/CIRCHEARTFAILURE.109.876649.

The online version of the article has been corrected.

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