The relationship of right- and left-sided filling pressures in patients with heart failure and a preserved ejection fraction

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Running title: Right- and left-sided filling pressures in HFPEF
Abstract

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 a preserved ejection fraction (HFPEF).

Methods and Results
Eleven subjects with HFPEF 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 \( \geq 10 \) mm Hg and pulmonary capillary wedge pressure (PCWP) when \( \geq 22 \) mm Hg. If both the RAP and PCWP were elevated or both not elevated, the RAP and PCWP were classified as concordant; otherwise, they were classified as discordant. Correlation of RAP and PCWP was determined by a one factor 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 ± standard deviation 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 HFPEF, supporting the role of estimation of jugular venous pressure to assess volume status in this condition.

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 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 a reduced left ventricular ejection fraction. 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 (HFPEF), to our knowledge there are no data demonstrating 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 HFPEF is commonly encountered in the clinical setting. We therefore conducted the following 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 had screened 2,054 patients > 65 years of age who had been hospitalized within the preceding 9 months with a discharge diagnosis of HF. Subjects had to have supporting evidence of CHF during the index hospitalization including an elevated BNP, pulmonary congestion on chest X-ray, or elevated pulmonary capillary wedge pressure during cardiac catheterization. Further, they had to have a documented LVEF > 50% both during hospitalization and on a screening echocardiography, the latter obtained by a modified Simpson’s method as before and confirmed by a senior investigator (BDL). LVEF was also obtained immediately following the baseline pressure measurements (see below). 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, prior coronary artery bypass grafting, unrevascularized epicardial coronary stenoses (>50% by prior angiography), angina, myocardial infarction in the last year, creatinine > 2.5 g/dl or ESRD on dialysis, severe COPD or pulmonary disease, ≥ moderate valvular heart disease, and an alternative known etiology for HF such as restrictive cardiomyopathy or constrictive pericarditis. Following these exclusion criteria, 23 subjects met criteria for enrollment and 11 subjects 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 UT Southwestern approved this study.

Right heart catheterization
Beta 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 anti-hypertensive drugs such as vasodilators and ACE inhibitors/ARBs were continued as prescribed. A 6 French balloon-tipped fluid filled catheter (Edwards Lifesciences, Irvine, California) was placed under fluoroscopic guidance through an antecubital vein into the pulmonary artery. The wedge position of the catheter was confirmed by both 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 pulmonary capillary wedge pressure and mean right atrial pressures were determined in triplicate visually at the end of expiration from paper recordings amplified to 0.4 mmHg resolution. The right atrial pressure was measured from the proximal port of the catheter.

**Manipulation of volume status**

Central blood volume was manipulated to allow six individual measurements across a broad physiological range of LV filling pressure ranging from about 3 mmHg to a maximum of 29 mm Hg. As previously described,\textsuperscript{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 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 achieved by a vacuum pump controlled with a variable autotransformer. If baseline PCWP was $\leq$ 16 mmHg, this was accomplished by 2 levels of LBNP (-15 and -30 mmHg) and 2 levels of saline infusion (approximately 10 and 20 ml/kg at a rate of 100-200 ml/min). If baseline PCWP was $>$ 16 mmHg, an additional level of LBNP was used (-40 mmHg) and only 1 dose of saline was infused (10 ml/kg) to avoid the risk of acute pulmonary edema. Two of our 11 subjects were too obese to fit into the LBNP chamber; for these two subjects, head up tilt was substituted for LBNP. The position of the right atrium was marked on the chest.
using biplane fluoroscopy as described. Subjects underwent head-up tilt to 20, 40, and 60 degrees, with the transducer carefully re-leveled to the right atrial position in each case, and measurements were then obtained after waiting 5 minutes.

**Data analysis**

For our primary analysis, we used dichotomous threshold values of RAP and PCWP as before. RAP was classified as elevated when \( \geq 10 \) mm Hg and PCWP when \( \geq 22 \) 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 from 8 to 12 mm Hg and PCWP from 15 to 25 mm Hg) of threshold values. Values of PCWP and RAP at different loading conditions are reported as mean ± standard deviation. Pairwise PCWP was compared at different loading conditions via the Wilcoxon signed-rank test. To determine the effect of RAP on PCWP, given that multiple measurements were made on each subject, a one factor repeated measures model was implemented using the Mixed procedure of SAS (Version 9.1; SAS Institute Inc, Cary, North Carolina). PCWP was the outcome variable, and RAP was the fixed effect. Random effects for the patient and patient*RAP were also 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 alpha=0.05.
Results

The baseline characteristics and hemodynamic responses to volume changes are shown (Table). The 11 subjects were elderly, hypertensive, and predominantly diabetic and female. Three were African-American, 2 Hispanic, and 6 were white. The BNP at the time of the index hospitalization was 448 ± 374 pg/ml. The range of left ventricular ejection fraction 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 following LBNP or head up tilt is shown (Table), as is the highest filling pressure following saline infusion. The efficacy of the LBNP/head up tilt was confirmed as the PCWP fell to 10.6 ± 3.7 mm Hg at LBNP -15 mmHg, 7.2 ± 3.3 mm Hg at LBNP -30 mmHg, and 6.7 ± 0.9 mm Hg at LBNP -40 mmHg (p<0.001). In the two subjects who underwent head up tilt, the PCWP fell 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 rise in RAP to 13.4 ± 2.9 mm Hg (p=0.002) and by the rise 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 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 obese subjects who had head up tilt done instead of lower body negative pressure, the concordance rate was 78% (65% with high RAP and high PCWP, and 13% in low RAP and low PCWP). In a sensitivity analysis, we varied the definition of elevated RAP from 8 mm Hg to 12 mm Hg and the definition of elevated PCWP
from 15 mm Hg 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 either 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 (e.g., 8 or 9 mm Hg) and PCWP at the higher 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 the RAP and PCWP is shown for each individual subject and for the overall cohort (Figure 2, r = 0.86 for the overall cohort). Representative RAP and PCWP tracings from 2 subjects under various loading conditions are shown (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 are often concordant (~80% of cases are either both elevated or both not elevated) when previously chosen^3^ clinically relevant dichotomous cut points are used. Further, 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 CHF and severely reduced LVEF (mean <22%) have demonstrated a significant correlation between the RAP and PCWP with a correlation coefficient of 0.64.\textsuperscript{2,3} Despite the difference in LVEF between those studies and the current one, the correlation of RAP to PCWP remains significant in the present cohort ($r=0.86$). Furthermore, the discordance rate (i.e., when the RAP is not elevated but the PCWP is elevated, or the RAP is elevated and the PCWP is not elevated) in the present study is 21%, remarkably consistent to what we previously reported (21%) in those with largely systolic HF.\textsuperscript{3} 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 above, there was one apparent difference between the relationship of RAP and PCWP found in the present study of HFPEF as compared to that previously reported in systolic heart failure. Specifically, there were no paired measurements where the RAP was low and the PCWP was elevated in the patients with HFPEF. In contrast, in those with systolic heart failure, the RAP was low with an elevated PCWP in 13\%\textsuperscript{2} and 15\%\textsuperscript{3} 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 the present 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\textsuperscript{15,16} as has been shown in HF patients with a reduced LVEF.\textsuperscript{15} 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, as has been shown in subjects with advanced HF and severely depressed LVEF. However this possibility is less likely in this population given that patients with more than minimal valve disease were excluded.

Limitations

The number of subjects included in the present 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 patient, there were multiple filling states induced in each patient, thus improving the interpretation of changes in RAP and PCWP pressures with changes in pre-load. Patients treated for HFPEF in the general community may have a variety of comorbid conditions for which we excluded subjects from enrollment, and the study subjects may therefore 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 right atrial pressure can be estimated noninvasively by 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 filling pressures and left-sided filling pressures in patients with HFPEF, similar to what has been observed previously in patients 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 left ventricular ejection fraction.
Funding sources

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Disclosures

None
References


Table. Baseline characteristics and hemodynamic response to volume changes.

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<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Baseline hemodynamics (mm Hg)</td>
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<tr>
<td>Right atrial pressure</td>
<td>9.5 ± 3</td>
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<tr>
<td>Pulmonary capillary wedge pressure</td>
<td>15 ± 5</td>
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<td>Lowest filling pressures* (mm Hg)</td>
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<td>Right atrial pressure</td>
<td>4 ± 3</td>
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<tr>
<td>Pulmonary capillary wedge pressure</td>
<td>6.6 ± 3</td>
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<tr>
<td>Highest filling pressures* (mm Hg)</td>
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</table>
Right atrial pressure 13 ± 3

Pulmonary capillary wedge pressure 22 ± 3

Data are presented as mean (standard deviation) or percentages. *Lowest filling pressures following lower body negative pressure (n=9) or head up tilt (n=2). Highest filling pressures following normal saline infusion.
**Figure legends**

Figure 1. Classification of 66 paired measurements of RAP and PCWP from the 11 subjects in the study cohort as to whether RAP was elevated (> 10 mm Hg) and PCWP was elevated (> 22 mm Hg).

Figure 2. Scatterplot of RAP versus PCWP in individual patients (light gray lines) and the overall cohort (black line) using all loading conditions. The blue line indicates the overall regression equation in the entire cohort and the red lines the 95% confidence intervals. The symbols represent data points from individual patients.

Figure 3: Representative hemodynamic pressure waveforms of RAP and PCWP in two individual patients under various loading conditions. LBNP30 signifies lower body negative pressure at -30 mm Hg; LBNP15 at -15 mm Hg. NS1 signifies a normal saline infusion of approximately 10 ml/kg at 100-200 ml/min; NS2 an infusion of approximately 20 ml/kg at the same rate. A simultaneous electrocardiogram (ECG) is shown at the top. Numbers represent pressure measurements. Note that as the RAP increases, the PCWP increases in concert in both cases.
Figure 1

<table>
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*Concordant measurements
Figure 2
Figure 3A.
Figure 3B.
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