Relationship of Right- to Left-Sided Ventricular Filling Pressures in Advanced Heart Failure
Insights From the ESCAPE Trial

Mark H. Drazner, MD, MSc; Mariella Velez-Martinez, MD; Colby R. Ayers, MS; Sharon C. Reimold, MD; Jennifer T. Thibodeau, MD; Joseph D. Mishkin, MD; Pradeep P.A. Mammen, MD; David W. Markham, MD, MSc; Chetan B. Patel, MD

Background—Although right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP) are correlated in heart failure, in a sizeable minority of patients, the RAP and PCWP are not tightly coupled. The basis of this variability in the RAP/PCWP ratio, and whether it conveys prognostic value, is not known.

Methods and Results—We analyzed the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial database. Baseline characteristics, including echocardiographic assessment of right ventricular (RV) structure and function, and invasively measured hemodynamic parameters, were compared among tertiles of the RAP/PCWP ratio. Multivariable Cox proportional hazard models assessed the association of RAP/PCWP ratio with the primary ESCAPE outcome (6-month death or hospitalization [days]) adjusting for systolic blood pressure, blood urea nitrogen, 6-minute walk distance, and PCWP. The RAP/PCWP tertiles were 0.27 to 0.4 (tertile 1); 0.41 to 0.615 (tertile 2), and 0.62 to 1.21 (tertile 3). Increasing RAP/PCWP was associated with increasing median right atrial area (23, 26, 29 cm², respectively; P<0.005), RV area in diastole (21, 27, 27 cm², respectively; P<0.005), and pulmonary vascular resistance (2.4, 2.9, 3.6 woods units, respectively; P=0.003), and lower RV stroke work index (8.6, 8.4, 5.5 g·m/m² per beat, respectively; P<0.001). RAP/PCWP ratio was associated with death or hospitalization within 6 months (hazard ratio, 1.16 [1, 1.4]; P<0.05).

Conclusions—Increased RAP/PCWP ratio was associated with higher pulmonary vascular resistance, reduced RV function (manifest as a larger right atrium and ventricle and lower RV stroke work index), and an increased risk of adverse outcomes in patients with advanced heart failure. (Circ Heart Fail. 2013;6:264-270.)

Key Words: heart failure ■ hemodynamics ■ pulmonary hypertension ■ renal function ■ right ventricle

Elevated right ventricular and left ventricular filling pressures contribute to many of the symptoms of patients with advanced heart failure. In both systolic and diastolic heart failure, right ventricular filling pressure, ie, right atrial pressure (RAP) is significantly correlated to left ventricular filling pressure, ie, pulmonary capillary wedge pressure (PCWP). This relationship is robust enough such that estimation of the PCWP is often based on assessment of the jugular venous pressure in patients with heart failure. Furthermore, the relationship of the RAP and PCWP has been shown to be stable during a 14-year time period (1993–2007) in the Cardiac Transplant Research Database (CTRD), a registry of patients with advanced heart failure undergoing cardiac transplantation. However, in a sizeable minority of patients with heart failure (25%–30%), the RAP and PCWP are not tightly coupled. The basis of the variability in the relationship of right- to left-sided ventricular filling pressures (which can be expressed as the RAP/PCWP ratio) is not well understood. In addition, whether the RAP/PCWP ratio is associated with outcome in the broader advanced heart failure population, as it is in patients undergoing left ventricular assist device implantation or cardiac transplantation, has not previously been assessed to our knowledge. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, in which patients with advanced heart failure underwent careful hemodynamic and echocardiographic assessment, as well as longitudinal follow-up, afforded an excellent opportunity to define further the physiological basis and prognostic use of the RAP/PCWP ratio in this patient population.

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Methods
ESCAPE Trial
The ESCAPE trial assessed the effectiveness of right heart catheterization in hospitalized patients with severe symptomatic heart failure. Patients had to have left ventricular ejection fraction ≤30%, 3 months of symptoms despite ACE-inhibitor and diuretic therapy, a systolic blood pressure ≤125 mm Hg, and at least 1 sign and 1 symptom of congestion. Of the 433 patients randomly assigned, 215 were assigned to the pulmonary artery (PA) catheter arm. The trial was conducted in the United States and Canada between 2000 and 2003 at 26 sites. The primary results of the trial have been published. The protocols were approved at each site, and written informed consent was obtained from all patients before randomization. This analysis was conducted with a public release of the ESCAPE database.

Right Heart Catheterization and Hemodynamic Classification
The sites participating in ESCAPE were selected for known expertise in invasive monitoring and clinical management of patients with heart failure. Paper printouts were used for hemodynamic measurements. Cardiac output was measured by thermodilution in triplicate. In this analysis, we assessed both the initial hemodynamics and the final hemodynamics at right heart catheter removal. The average length of time the right heart catheter was in place was 1.9 days. We excluded 3 patients attributable to measurements that were extreme outliers possibly because of erroneous data entry: 2 with baseline RAPs of 71 and 85 mm Hg, respectively, and 1 with PCWP of 0 mm Hg. Subjects were classified into tertiles of the RAP/PCWP ratio: 0.27 to 0.40 (tertile 1); 0.41 to 0.61 (tertile 2); and 0.62 to 1.21 (tertile 3).

Echocardiography
Details of components of the echocardiographic examination in ESCAPE have been published. In brief, echocardiograms were performed within 24 hours of right heart catheterization. Echocardiograms were analyzed at the core center at the University of Texas Southwestern Medical Center. Measurements were performed offline by a single sonographer or physician in accordance with the criteria of the American Society of Echocardiography and were made in triplicate and averaged. Measurements were obtained from the apical 4-chamber view (right atrial area, right ventricular [RV] area at end-diastole and end-systole, left atrial area, mitral regurgitant color jet area, and left ventricular end-diastolic and end-systolic volumes by Simpson method of discs) and subcostal view (inferior vena cava size in inspiration and expiration). Derived measures included left ventricular ejection fraction, RV fractional shortening ([RV area diastole–RV area systole]/RV area diastole), and the ratio of the mitral regurgitant color jet area/the left atrial area.

Variable Definitions
Creatinine clearance was estimated by the Modification of Diet in Renal Disease equation. Transpulmonary gradient was calculated as the difference between mean PA and PCWP. Pulmonary vascular resistance (PVR) was calculated as transpulmonary gradient/cardiac output. RV stroke work index was calculated as follows: (cardiac index/heart rate)×(mean PA pressure−mean RAP)×13.6. Pulmonary compliance was calculated as stroke volume/(PA systolic pressure−PA diastolic pressure).

Statistics
Data are presented as median (interquartile range) or number (percent). To compare characteristics across ordinal, increasing tertiles of baseline RAP/PCWP, we used the Cochran–Armitage trend test for categorical variables and the Jonckheere–Terpstra trend test for continuous data. The χ² statistic was used to assess any overall racial significance. Spearman correlation coefficients were calculated between baseline RAP/PCWP and other invasively measured hemodynamics. Outcome analysis was with the primary outcome of ESCAPE, number of days alive outside the hospital at 180 days post randomization. In a secondary analysis, we used overall mortality as an outcome. Patients who underwent left ventricular assist device or transplant were treated as dead in 1 analysis and were censored in another analysis. For the outcomes analysis, we excluded patients who were lost to follow-up (N=5). After observing no trends with time for the Schoenfeld residuals, Cox proportional hazards models were used to assess hazard ratios for a 1 SD increase in the RAP/PCWP ratio in both unadjusted and adjusted analyses. For the adjusted analyses, model 1 adjusted for 6-minute walk, blood urea nitrogen (BUN), and systolic blood pressure. Model 2 adjusted for the covariates in model 1 with the addition of PCWP. Two-sided probability values were used in all statistical analysis with a probability value <0.05 considered statistically significant. All statistical analyses were performed using SAS software (v. 9.2; SAS Institute, Inc, Cary, NC).

Results
The distribution of the RAP/PCWP ratio is shown (Figure 1). The median (interquartile range) was 0.50 (0.37, 0.68). The RAP was significantly correlated with the PCWP (r=0.59; P=0.001). The RAP/PCWP ratio measured on the initial hemodynamics was significantly correlated to that measured at the time of right heart catheter removal (r=0.49; P<0.001). Of subjects with baseline RAP/PCWP tertile 1, 12% had shifted to RAP/PCWP tertile 3 when hemodynamics were reassessed before right heart catheterization removal. Similarly, 11% of subjects with baseline RAP/PCWP tertile 3 shifted to final RAP/PCWP tertile 1 (Table 1).

Relationship of Baseline Characteristics and Renal Function to RAP/PCWP Ratio
Baseline characteristics are shown by tertile of RAP/PCWP (Table 2). Increasing RAP/PCWP was associated with impaired renal function as evidenced by a higher baseline creatinine and BUN and a lower creatinine clearance. Increasing RAP/PCWP was also associated with the maximum in-hospital BUN (28, 33, 40 mg/dL), discharge BUN (25, 34, 35 mg/dL), and discharge creatinine (1.2, 1.5, 1.6 mg/dL), respectively (P<0.005 for all). Increasing RAP/PCWP was also associated with signs of right-sided heart failure including elevated jugular venous pressure, ascites, and peripheral edema. In
contrast, there was no association of elevated RAP/PCWP with orthopnea and other clinical predictors associated with worse outcomes such as New York Heart Association class and systolic blood pressure.

**Relationship of Invasively Measured Hemodynamics to RAP/PCWP Ratio**

Invasively measured hemodynamics (Table 3) are shown by tertile RAP/PCWP. Increasing RAP/PCWP was associated with a higher RAP but was not associated with PCWP. Subjects with a higher RAP/PCWP also had a higher transpulmonary gradient and PVR than those with a lower RAP/PCWP. Cardiac index and RV stroke work index were lower in those with higher RAP/PCWP. In correlation analysis, RAP/PCWP ratio correlated significantly with RAP ($r=0.78$; $P<0.001$), transpulmonary gradient ($r=0.24$; $P=0.001$), PVR ($r=0.23$; $P=0.002$), cardiac index ($r=-0.15$; $P<0.05$), and RV stroke work index ($r=-0.43$; $P<0.001$), but not PCWP ($r=0.01$; $P=0.9$). In a subgroup analysis restricted to subjects with a PCWP $\geq 22$ mm Hg, similar associations of RAP/PCWP ratio with invasively measured hemodynamics were found, including increasing PVR among those with increasing RAP/PCWP: 2.4 (tertile 1); 3 (tertile 2); 4.3 Wood units (tertile 3); $P<0.001$ (other data not shown). There was no difference in administration of milrinone ($P=0.75$), nitroprusside ($P=0.15$), or dobutamine ($P=0.6$) among tertiles RAP/PCWP.

**Relationship of Echocardiographic Parameters to RAP/PCWP Ratio**

Echocardiographic parameters are shown among tertile RAP/PCWP at baseline (Figure 2). Subjects with a higher RAP/PCWP ratio had echocardiographic markers of RV dysfunction, including a larger right atrial area, RV area in both systole and diastole, and a larger inferior vena cava both in inspiration and expiration. There was no significant association of RAP/PCWP ratio with RV fractional shortening (0.25 [0.2, 0.3] tertile 1; 0.2 [0.13, 0.29] tertile 2; 0.21 [0.15, 0.28] tertile 3; $P=0.2$). There was also no significant association of the RAP/PCWP ratio with left atrial area, tricuspid regurgitation velocity, left ventricular end-diastolic or end-systolic volume, left ventricular ejection fraction, or ratio of mitral regurgitation/left atrial area ($P\geq0.2$ for all; data not shown).

**Relationship of RAP/PCWP Ratio and Outcome**

The association of the baseline and final RAP/PCWP with 6-month outcome (Table 4) is shown. In the whole cohort, increasing baseline RAP/PCWP was associated with death or hospitalization (days) in a model adjusted for 6-minute walk, systolic blood pressure, BUN, and PCWP. The correlation between RAP/PCWP and PCWP was statistically insignificant, and thus multicollinearity was not an issue.

### Table 1. Relationship of the Baseline to Final RAP/PCWP Tertile

<table>
<thead>
<tr>
<th>Baseline RAP/PCWP Tertile</th>
<th>Final RAP/PCWP Tertile</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T1 27 (54%) 17 (34%) 6 (12%)</td>
</tr>
<tr>
<td>T2</td>
<td>T2 16 (34%) 15 (32%) 16 (34%)</td>
</tr>
<tr>
<td>T3</td>
<td>T3 5 (11%) 16 (35%) 25 (54%)</td>
</tr>
</tbody>
</table>

Data are presented as number (% of subjects within baseline RAP/PCWP tertile who were within denoted final RAP/PCWP tertile). PCWP indicates pulmonary capillary wedge pressure; and RAP, right atrial pressure.

### Table 2. Baseline Characteristics by Baseline Ratio of RAP to PCWP

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Ethnicity: white</th>
<th>Men</th>
<th>Ischemic etiology</th>
<th>Idiopathic etiology</th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
<th>NYHA class IV</th>
<th>JVP $\geq8$ cm</th>
<th>Ascites $\geq$ moderate</th>
<th>Peripheral edema $\geq2+$</th>
<th>Orthopnea $\geq2$ pillows</th>
<th>Systolic blood pressure, mm Hg</th>
<th>Heart rate, beats per minute</th>
<th>Body mass index, kg/m$^2$</th>
<th>Creatinine, mg/dL</th>
<th>CrCl, mL/min</th>
<th>BUN, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>57 [47, 63]</td>
<td>35 (56%)</td>
<td>42 (67%)</td>
<td>35 (56%)</td>
<td>21 (33%)</td>
<td>32 (51%)</td>
<td>14 (24%)</td>
<td>60 (95%)</td>
<td>47 (77%)</td>
<td>1 (2%)</td>
<td>9 (14%)</td>
<td>54 (86%)</td>
<td>111 [97, 120]</td>
<td>81 [71, 91]</td>
<td>25 [22, 30]</td>
<td>1.3 [0.9, 1.6]</td>
<td>62 [41, 91]</td>
<td>26 [16, 33]</td>
</tr>
<tr>
<td>58 [50, 66]</td>
<td>39 (63%)</td>
<td>48 (77%)</td>
<td>31 (50%)</td>
<td>22 (36%)</td>
<td>28 (45%)</td>
<td>25 (40%)</td>
<td>54 (87%)</td>
<td>59 (98%)</td>
<td>11 (18%)</td>
<td>28 (45%)</td>
<td>50 (81%)</td>
<td>108 [98, 116]</td>
<td>79 [67, 91]</td>
<td>27 [24, 32]</td>
<td>1.5 [1, 1.6]</td>
<td>52 [44, 67]</td>
<td>33 [22, 51]</td>
</tr>
<tr>
<td>59 [48, 70]</td>
<td>36 (57%)</td>
<td>49 (78%)</td>
<td>33 (52%)</td>
<td>23 (37%)</td>
<td>32 (51%)</td>
<td>22 (36%)</td>
<td>55 (87%)</td>
<td>59 (97%)</td>
<td>16 (25%)</td>
<td>39 (62%)</td>
<td>51 (82%)</td>
<td>109 [98, 120]</td>
<td>81 [69, 91]</td>
<td>29 [24, 35]</td>
<td>1.5 [1.2, 2]</td>
<td>52 [37, 68]</td>
<td>30 [22, 49]</td>
</tr>
</tbody>
</table>

$P$ indicates blood urea nitrogen; JVP, jugular venous pressure; and NYHA, New York Heart Association.
In the subgroup of subjects who had elevated PCWP (≥22 mm Hg), increasing baseline RAP/PCWP was associated with death or hospitalization (days) both in univariate and multivariable analysis. In analyses in which the final RAP/PCWP ratio was substituted for the baseline RAP/PCWP, qualitatively similar associations with outcome were noted. In our secondary analysis using 6-month mortality as the outcome, the event rate in increasing baseline RAP/PCWP was 16% (tertile 1), 21% (tertile 2), and 29% (tertile 3); P=0.09.

Table 3. Association of Baseline RAP to PCWP Ratio With Invasively Measured Hemodynamics

<table>
<thead>
<tr>
<th>Tertile RAP/PCWP</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>6 [4, 8]</td>
<td>14 [11, 17]</td>
<td>20 [13, 23]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>23 [18, 30]</td>
<td>25 [22, 32]</td>
<td>24 [19, 30]</td>
<td>0.7</td>
</tr>
<tr>
<td>Pulmonary artery systolic, mm Hg</td>
<td>50 [40, 60]</td>
<td>58 [50, 70]</td>
<td>52 [42, 67]</td>
<td>0.08</td>
</tr>
<tr>
<td>Pulmonary artery diastolic, mm Hg</td>
<td>24 [18, 29]</td>
<td>29 [25, 36]</td>
<td>25 [20, 35]</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>42 [33, 49]</td>
<td>49 [42, 56]</td>
<td>45 [35, 57]</td>
<td>0.049</td>
</tr>
<tr>
<td>Transpulmonary gradient, mm Hg</td>
<td>9 [7, 12]</td>
<td>12 [8, 15]</td>
<td>13 [9, 17]</td>
<td>0.001</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, WU</td>
<td>2.4 [1.8, 3.4]</td>
<td>2.9 [2.4, 4.1]</td>
<td>3.6 [4.2, 4.7]</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.9 [3.4, 4.5]</td>
<td>3.9 [3.2, 4.6]</td>
<td>3.3 [2.8, 4.6]</td>
<td>0.2</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.1 [1.7, 2.3]</td>
<td>1.9 [1.7, 2.3]</td>
<td>1.8 [1.5, 2.2]</td>
<td>0.049</td>
</tr>
<tr>
<td>Mixed venous saturation, %</td>
<td>60 [44, 67]</td>
<td>54 [41, 62]</td>
<td>51 [46, 63]</td>
<td>0.45</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>47 [39, 56]</td>
<td>54 [41, 62]</td>
<td>51 [46, 63]</td>
<td>44 [33, 60]</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyne - s · cm⁻¹</td>
<td>1387 [1042, 1664]</td>
<td>1310 [1089, 1597]</td>
<td>1322 [848, 1987]</td>
<td>0.9</td>
</tr>
<tr>
<td>Right ventricular stroke work index, g · m/m² per beat</td>
<td>8.6 [6.9, 12]</td>
<td>8.4 [6.1, 11]</td>
<td>8.5 [4.7, 6]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulmonary arterial compliance, mL/mm Hg</td>
<td>1.83 [1.3, 2.58]</td>
<td>1.61 [1.3, 2.47]</td>
<td>1.65 [1.14, 2.27]</td>
<td>0.25</td>
</tr>
</tbody>
</table>

PCWP indicates pulmonary capillary wedge pressure; and RAP, right atrial pressure.

Figure 2. Association of echocardiographic measures of right ventricular dysfunction with RAP/PCWP ratio (tertiles). A, Right atrial area; B, right ventricular area (diastole); C, right ventricular area (systole); D, inferior vena cava size (IVC) (expiration); E, inferior vena cava size (inspiration). Data are presented as box-and-whisker plots. RAP/PCWP ratios were Tertile 1 (T1): 0.27 to 0.4; Tertile 2 (T2): 0.41 to 0.61; Tertile 3 (T3): 0.62 to 1.21. *P<0.005 †P<0.01. PCWP indicates pulmonary capillary wedge pressure; and RAP, right atrial pressure.
Table 4. Association of the RAP/PCWP Ratio With Death or Hospitalization (Days) at 6 Months

<table>
<thead>
<tr>
<th></th>
<th>Whole Cohort*</th>
<th>Subgroup PCWP ≥22 mm Hg*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transplant/LVAD</td>
<td>Transplant/LVAD</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI) P</td>
<td>Count as Dead</td>
</tr>
<tr>
<td>Baseline RAP/PCWP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.1 (0.97, 1.3) 0.14</td>
<td>1.12 (0.97, 1.3) 0.14</td>
</tr>
<tr>
<td>Adjusted model 1</td>
<td>1.13 (0.97, 1.3) 0.12</td>
<td>1.14 (0.99, 1.3) 0.08</td>
</tr>
<tr>
<td>Adjusted model 2</td>
<td>1.16 (1.1, 1.4) &lt;0.05</td>
<td>1.19 (1.02, 1.4) 0.03</td>
</tr>
<tr>
<td>Final RAP/PCWP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.2 (1.1, 1.5) 0.001</td>
<td>1.3 (1.1, 1.5) 0.009</td>
</tr>
<tr>
<td>Adjusted model 1</td>
<td>1.17 (0.99, 1.3) 0.07</td>
<td>1.17 (0.99, 1.4) 0.07</td>
</tr>
<tr>
<td>Adjusted model 2</td>
<td>1.19 (0.99, 1.4) 0.06</td>
<td>1.19 (0.99, 1.4) 0.06</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; LVAD, left ventricular assist device; HR, hazard ratio; PCWP, pulmonary capillary wedge pressure; and RAP, right atrial pressure.

*Whole cohort: N=183 for baseline RAP/PCWP; N=137 for final RAP/PCWP. Subgroup PCWP ≥22 mm Hg: N=137 for baseline RAP/PCWP; N=35 for final RAP/PCWP.

Model 1 adjusted for 6-minute walk, blood urea nitrogen (BUN), systolic blood pressure.

Model 2 adjusted for 6-minute walk, BUN, systolic blood pressure, PCWP.

HRs in whole cohort shown are for unit ratio change (1 SD) baseline RAP/PCWP, 0.235; for final RAP/PCWP, 0.306. HRs for subgroup PCWP ≥22 mm Hg are for unit ratio change (1 SD) baseline RAP/PCWP, 0.235; for final RAP/PCWP, 0.26.

Discussion

Although right ventricular and left ventricular filling pressures are significantly correlated in patients with advanced heart failure, there is a large distribution of the RAP/PCWP ratio. The basis for the variability of this trait (RAP/PCWP ratio) is not well understood, nor is its prognostic use. In the ESCAPE trial, which enrolled patients with advanced heart failure selected for signs and symptoms of congestion, most of whom had elevated PCWPs, increasing RAP/PCWP ratio resulted from increasing RAP. Subjects with a low RAP/PCWP ratio had better RV function as assessed by several echocardiographic measures (including smaller right atrial and RV area) and by the RV stroke work index, whereas those with a higher RAP/PCWP ratio had a higher PVR. Additionally, an elevated RAP/PCWP ratio was associated with a lower cardiac index and impaired renal function at baseline and with a worse outcome at 6 months.

Whether the RAP/PCWP ratio is a stable and reproducible parameter in patients with heart failure is not well known. In the CTRD, there was a significant correlation (r=0.33) of the RAP/PCWP ratio when measured at least 1 day apart (median time, 188 days).4 In the present study, we confirmed this finding in patients with decompenated, advanced heart failure. In the ESCAPE trial, the correlation between ratios of RAP/PCWP measured 1.9 days apart was 0.49 (P<0.001). Additionally, there was relatively little shifting (11%–12% of subjects) between tertiles 1 and 3 from baseline to final hemodynamic assessment. Together, these data suggest that the RAP/PCWP ratio does, in part, reflect an underlying intrinsic trait in patients with advanced heart failure.

The RAP/PCWP ratio can be influenced by changes in either the RAP or the PCWP. In the ESCAPE trial, a high RAP/PCWP occurred on the basis of an elevated RAP rather than a reduced PCWP (Table 3). In addition to a higher measured RAP, subjects in the highest tertile of RAP/PCWP ratio also had clinical findings that provided confirmation of an elevated RAP, including more severe peripheral edema and ascites, and an elevated jugular venous pressure. In contrast, in the CTRD, subjects in the highest quartile of RAP/PCWP ratio not only had the highest RAP but also they had the lowest PCWP.4 This difference is likely attributable to the selection of patients for the ESCAPE trial on the basis of signs and symptoms of congestion.

To our knowledge, only 2 prior studies have attempted to determine characteristics associated with the relationship of the RAP to PCWP in patients with heart failure.4,5 In a cohort of patients with advanced heart failure undergoing cardiac transplant evaluation, female sex was the only characteristic found to be associated with the RAP to PCWP relationship, as assessed by 4 categories based on whether the RAP was ≥10 mm Hg and PCWP ≥22 mm Hg.4 In the present study, female sex was not associated with RAP/PCWP ratio. Also in contrast to the present study, renal dysfunction, PVR, cardiac index, and echocardiographic assessment of RV dysfunction were not significantly different among the 4 hemodynamic profiles in the prior study.5 We postulate that this difference is in part based on the analytic approach used; i.e., a hemodynamic classification based on dichotomous values of RAP and PCWP or via the RAP/PCWP ratio. Nevertheless, both studies demonstrated significant variability in the relationship of right- and left-sided ventricular filling pressures in patients with advanced heart failure.

In the CTRD, increasing quartile of RAP/PCWP was associated with younger age, female sex, etiology of cardiomyopathy other than idiopathic or ischemic, increased number of prior sternotomies, higher PVR, lower CI, and lower creatinine clearance.4 In the present study, age was not associated with the RAP/PCWP ratio. This difference may be attributable to inclusion of a broader range of patients in the CTRD (eg, complex congenital heart disease) than in the ESCAPE trial. In the ESCAPE database, the number of prior sternotomies was significantly different among the 4 hemodynamic profiles in the prior study.5 We postulate that this difference is in part based on the analytic approach used; i.e., a hemodynamic classification based on dichotomous values of RAP and PCWP or via the RAP/PCWP ratio. Nevertheless, both studies demonstrated significant variability in the relationship of right- and left-sided ventricular filling pressures in patients with advanced heart failure.

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Increasingly, it is recognized that systemic venous congestion is an important contributor to the cardiorenal syndrome.\textsuperscript{11,12} In the ESCAPE trial, an elevated RAP previously was shown to be weakly correlated with baseline renal function\textsuperscript{13} consistent with the findings of the present study. Here we show that impaired renal function was prominent when right- and left-sided ventricular filling pressures began to approximate one another. In such subjects, pericardial constraint may lead to exaggerated diastolic ventricular interaction.\textsuperscript{14,15} This pathophysiology may mediate the reduction in cardiac index associated with increasing RAP/PCWP ratio. A disproportionately elevated RAP in relationship to the PCWP may therefore represent one hemodynamic signature of patients with advanced systolic heart failure and cardiorenal syndrome and suggests that consideration of the right–left relationship may be important when choosing therapeutic strategies for treating congestion in heart failure.

The RAP/PCWP ratio also seems to have important relationships to the pulmonary vasculature and the performance of the right ventricle. Increasing RAP/PCWP ratio was found to be a marker for RV failure manifested by an enlarged right atrial area, enlarged RV area (both in systole and diastole), and a lower RV stroke work index. The RAP/PCWP ratio was not associated with left ventricular volumes, ejection fraction, or severity of mitral regurgitation, further emphasizing that this ratio reflected RV performance. The hemodynamic data also suggest that the RAP/PCWP ratio was related to changes in the pulmonary vasculature because increasing RAP/PCWP ratio was associated with a higher PVR, despite a similar PCWP in each tertile. It is well known that there is variability in the increase of the PA pressure and PVR in response to an elevated PCWP in patients with heart failure. The basis of this variability is not yet well understood,\textsuperscript{16} but pulmonary hypertension is now being tested as a therapeutic target in patients with heart failure.\textsuperscript{17} We hypothesize that an exaggerated response in the pulmonary vasculature in response to an elevated PCWP (ie, an increased PVR) is a proximal pathophysiological event, leading to RV dysfunction and subsequently an increased RAP/PCWP ratio. Studies with serial imaging and hemodynamic assessments are needed to test this hypothesis.

Whether the RAP/PCWP ratio is associated with outcome in patients with heart failure has not previously been investigated to our knowledge. A high RAP/PCWP ratio was associated with worse outcomes in patients with advanced heart failure who underwent left ventricular assist device implantation\textsuperscript{4} or transplantation.\textsuperscript{4} An elevated jugular venous pressure, consistent with a high RAP, has been shown to be an independent risk factor for outcome in patients with New York Heart Association class II–III heart failure.\textsuperscript{18} In the ESCAPE trial (Table 4), a high baseline RAP/PCWP ratio was associated with adverse events at 6 months as assessed by the primary outcome of the ESCAPE trial (number of days alive outside the hospital), but not with crude mortality. A lack of association with mortality may represent limited power, given that a higher RAP/PCWP ratio was associated with markers of RV dysfunction and with impaired renal function, both well-known risk factors for adverse outcomes in heart failure.\textsuperscript{19–22} The final RAP/PCWP ratio was similarly associated with the primary ESCAPE outcome. The association of increasing RAP/PCWP ratio with outcome was more consistent in those with a PCWP≥22 mm Hg, highlighting the importance of assessing this ratio in patients who have elevated left-sided ventricular filling pressures. Overall, these findings reinforce the importance of RV function in patients with advanced heart failure.

**Limitations**

This was a retrospective analysis. The associations of RAP/PCWP with death and hospitalization did not reach conventional levels of statistical significance in all models, perhaps, because the overall size of the cohort in ESCAPE who underwent right heart catheterization was relatively small. As such, the prognostic use of the RAP/PCWP ratio needs to be validated in other, larger data sets.

**Conclusions**

In patients with advanced heart failure selected for signs and symptoms of congestion, there was a wide distribution in the RAP/PCWP ratio. A high RAP/PCWP ratio was associated with a high RAP, underlying RV dysfunction in the setting of an elevated PVR, and was an adverse prognostic finding associated with impaired renal function and a worse 6-month outcome.

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**Disclosures**

None.

**References**

Although right ventricular filling pressures often mirror left ventricular filling pressures in patients with heart failure, in a sizeable minority of patients this is not true. The basis of this variability is not well understood. We explored the relationship of the right to left ventricular filling pressure, as measured by the right atrial pressure (RAP)/pulmonary capillary wedge pressure (PCWP) ratio in patients with advanced heart failure who had signs and symptoms of congestion and were enrolled in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial. There was a wide distribution of RAP/PCWP ratios: median (25th, 75th percentile) 0.5 (0.37, 0.68). Increasing RAP/PCWP was associated with markers of right ventricular dysfunction (including increasing right ventricular area by echocardiography and lower right ventricular stroke work index), elevated pulmonary vascular resistance, lower cardiac index, and reduced creatinine clearance. Further, increasing RAP/PCWP was associated with death or hospitalization within 6 months. We conclude that in patients with advanced heart failure selected for signs and symptoms of congestion, the RAP/PCWP ratio is a marker of right ventricular dysfunction in the setting of elevated pulmonary vascular resistance and was an adverse prognostic finding associated with reduced cardiac index, impaired renal function, and a worse 6-month outcome. Clinicians should consider reporting this easily calculated parameter after right heart catheterization.
Relationship of Right- to Left-Sided Ventricular Filling Pressures in Advanced Heart Failure: Insights From the ESCAPE Trial

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