Hemodynamic Determinants of Dyspnea Improvement in Acute Decompensated Heart Failure

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Background—Dyspnea relief constitutes a major treatment goal and a key measure of treatment efficacy in decompensated heart failure. However, there are no data with regard to the relationship between hemodynamic measurements during treatment and dyspnea improvement.

Methods and Results—We studied 233 patients assigned to right heart catheterization in the Vasodilation in the Management of Acute Congestive Heart Failure trial. Dyspnea (assessed using a 7-point Likert scale) and hemodynamic parameters were measured simultaneously at 15 and 30 minutes and 1, 2, 3, 6, and 24 hours. Dyspnea relief was defined as moderate or marked improvement. There was a time-dependent association between the reductions in pulmonary capillary wedge pressure (PCWP; 25.4, 24.6, 24.0, 23.5, 23.4, 21.5, and 19.9 mm Hg) and the percentage of patients achieving dyspnea relief (17.7%, 24.6%, 32.2%, 36.2%, 37.8%, 47.4%, and 66.1%, in the respective time points). Multivariable logistic generalized estimating equations modeling demonstrated that reductions of both PCWP and mean pulmonary artery pressure were independently associated with dyspnea relief. Compared with the highest PCWP quartile, the adjusted odds ratios for dyspnea relief were 0.92 (95% confidence interval [CI], 0.67–1.29), 1.07 (95% CI, 0.75–1.55), and 1.80 (95% CI, 1.22–2.65) in the third, second, and first PCWP quartiles, respectively (P \text{ trend}<0.0001). Compared with the highest mean pulmonary artery pressure quartile, the adjusted odds ratios for dyspnea relief were 2.0 (95% CI, 1.41–2.82), 2.23 (95% CI, 1.52–3.27), and 2.98 (95% CI, 1.91–4.66) in the third, second, and first mean pulmonary artery pressure quartiles, respectively (P \text{ trend}<0.0001).

Conclusions—A clinically significant improvement in dyspnea is associated with a reduction in both PCWP and mean pulmonary artery pressure. (Circ Heart Fail. 2013;6:53-60.)

Key Words: acute heart failure ■ dyspnea ■ pulmonary capillary wedge pressure ■ pulmonary hypertension

In the acute care setting, dyspnea is the most commonly reported symptom among patients with worsening heart failure and is the principal cause of hospitalization for patients with acute decompensated heart failure (ADHF). Dyspnea is one of the most important standards by which efficacy of therapy is ascertained and is a major end point in clinical trials of investigational agents for the management of patients with ADHF. A number of studies and position articles emphasize the importance of achieving rapid improvement in dyspnea. Recent studies have shown that many patients have only partial relief of dyspnea and congestion during admission, even when guideline-recommended therapies are fully implemented. In addition, persistent dyspnea is associated with higher risk for mortality. There are no clinical characteristics or laboratory measurements (including B-type natriuretic peptide levels) that are reliably associated with dyspnea relief.

The expectation for the improvement of dyspnea with current vasodilator and diuretic therapy is based on the assumption that reductions in filling pressures are likely to translate into a reduction in pulmonary venous congestion, leading to symptomatic benefit. However, there are no data with regard to changes in specific hemodynamic parameters during treatment of ADHF and their relation to dyspnea improvement. Hence, the relationship between dyspnea and objective hemodynamic measures remains unclear.

In the present study, we sought to determine the hemodynamic profile associated with a clinically significant improvement in dyspnea among patients admitted for ADHF. To this aim, we used hemodynamic measurements obtained in patients who were enrolled in the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial. The VMAC hemodynamic substudy included simultaneous assessments of hemodynamic parameters and dyspnea and provided an opportunity to examine the relationship between...
changes in hemodynamic variables and dyspnea improvement in the setting of ADHF.

Methods

The study population included patients enrolled in the VMAC study, a randomized, multicenter trial comparing the hemodynamic and clinical effects of nesiritide (human B-type natriuretic peptide) to nitroglycerin in patients with decompensated congestive heart failure for whom in-patient parenteral vasoactive therapy was considered appropriate. Patients were recruited into the study between October 1999 and July 2000.14

Patients were included if they had dyspnea at rest attributed to decompensated heart failure that was severe enough to require hospitalization and intravenous therapy. One of the inclusion criteria of the VMAC trial was evidence of heart disease, rather than pulmonary disease, as the primary etiology for the dyspnea. A cardiac etiology for dyspnea was established by jugular venous distention, paroxysmal nocturnal dyspnea or 2-pillow orthopnea, chest x-ray film with findings indicative of heart failure and by estimated or measured elevation of cardiac filling pressures (pulmonary capillary wedge pressure [PCWP] ≥20 mm Hg in catheterized patients). Exclusion criteria were systolic blood pressure <90 mm Hg, cardiogenic shock or volume depletion, any condition that would contraindicate an intravenous vasodilator, mechanical ventilation, and anticipated survival of <30 to 35 days.

The protocol was performed in conformance with the guidelines established in the Declaration of Helsinki and was approved by the institutional review board of the participating hospitals. Written, informed consent was obtained from each patient.

Hemodynamic Evaluation

In the VMAC trial, the randomization was stratified based on the investigator’s clinical decision, before randomization, to use a right heart catheter to manage decompensated heart failure (catheterized or noncatheterized strata).

According to investigators, their clinical decision to use a right heart catheter was influenced by ≥1 clinical factor in many subjects. The 6 most common reasons for the use of right heart catheter, in order of decreasing frequency, were as follows: (1) uncertain hemodynamics in 204 subjects; (2) suspected low cardiac output in 131 subjects; (3) to optimize outpatient medications in 110 subjects; (4) to evaluate a potential cardiac transplant candidate in 41 subjects; (5) significant renal dysfunction in 40 subjects; and (6) low or unstable blood pressure in 19 subjects.

In the catheterized group, PCWP and pulmonary artery pressures were measured at baseline (before the initiation of study drugs), at 15 and 30 minutes, and at 1, 2, and 3 hours. The cardiac output and mean right atrial pressure were measured at 1 and 3 hours. After 3 hours, PCWP and mean pulmonary artery pressure (mPAP) were obtained in catheterized patients at 6, 9, 12, 24, 36, and 48 hours and when study drug was discontinued (if ≤48 hours).14,15 Total fluid intake and urine output were recorded for the first 24 hours after the start of study drug.

Evaluation of Dyspnea

Dyspnea was measured with the use of a self-reported 7-point categorical Likert scale, ranging from markedly, moderately, or minimally better; no change; or minimally, moderately, or markedly worse as compared with the degree of dyspnea present at the start time of study drug administration.14 Use of Likert scales has been validated for measuring dyspnea in settings other than ADHF and has been used extensively as an end point in clinical trials of patient with ADHF.3,5,16-17

Dyspnea and global clinical evaluations were assessed at 15 and 30 minutes and at 1, 2, and 3 hours after the start of study drug and repeated at 6 and 24 hours.14 For the present analysis, clinically significant relief of dyspnea was defined as a moderate or marked improvement in dyspnea at each time point, as in previous studies.9,11

Statistical Methods

Continuous variables are presented as means±SDs or medians with 25th and 75th percentiles; categorical variables are presented as frequencies and percentages. Baseline characteristics of the groups were compared using unpaired t test or the nonparametric Mann-Whitney U test for continuous variables and by the χ2 statistic for noncontinuous variables (or the Fisher exact test, where appropriate).

Comparisons of hemodynamic measurements within patients were carried out with the Wilcoxon matched–paired rank-sum test. The relationship between 2 continuous variables was tested by Spearman rank correlation.

The association between the clinically significant dyspnea improvement and hemodynamic variables over time was determined by fitting longitudinal logistic regression models implemented with generalized estimating equations with an assumed binomial family distribution, a logistic link function, and an exchangeable structure of the correlation matrix.14 In this framework, the generalized estimating equation model parallels the logistic regression model but also takes into account the correlation among multiple observations (time points of dyspnea evaluation and hemodynamic measurements) per patient. In these models, the dependent variables were the 7 repeated assessments of dyspnea status during the first 24 hours. Results are reported as odds ratios, together with associated 95% confidence intervals.

The following baseline clinical characteristics were considered in the multivariate procedure, age, sex, history of diabetes mellitus, primary etiology of heart failure stratified as ischemic or nonischemic, systolic blood pressure on admission, baseline epidermal growth factor receptor, ejection fraction (dichotomized as above or below 25%), presence of atrial fibrillation, history of implantable cardioverter-debrillator implantation, and vasoactive therapy assignments (nesiritide or nitroglycerin). The following medications were adjusted for as dichotomous variables, indicating the use or nonuse of the medication at study entry, digoxin, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and spironolactone.

The following hemodynamic variables were also considered in the multivariable analysis, PCWP, mPAP, right atrial pressure, cardiac output, cardiac index, and systemic vascular resistance. Because of the potential nonlinear relationship between continuous hemodynamic variables and the likelihood of dyspnea relief, the relationships between hemodynamic variables and dyspnea relief were also assessed with the use of restricted cubic spline transformations with 5 knots at values based on the Harrell recommended percentiles.19,20 Spline functions were used to flexibly model the relation between hemodynamic measurements (as continuous variables) and dyspnea relief, avoiding the need for previous specification of the risk function or the location of a threshold exposure value. When a nonlinear relationship was discovered, hemodynamic variables were divided into quartiles and included in the model as categorical variables.

Differences were considered statistically significant at the 2-sided P<0.05 level. All of the statistical analyses were performed using the STATA statistical software version 11.0 (College Station, TX).

Results

Of the total 489 randomized and treated patients, 246 were in the catheterized stratum. Complete evaluations of early dyspnea changes were obtained in 233 of these patients. Thirteen patients were excluded because they did not have full data on dyspnea relief.

At 24 hours, none of the patients reported marked worsening of dyspnea; 1 patient (0.4%) reported moderate worsening of dyspnea, 2 patients (0.9%) reported mild worsening, and 29 patients (12.4%) reported no change in dyspnea. Forty-seven (20.2%), 74 (31.8%), and 80 (34.3%) patients reported mild, moderate, and marked improvement in dyspnea at 24 hours as compared with baseline. Overall, at 24 hours, clinically significant dyspnea relief occurred in 154 patients (66.1%). No difference in dyspnea reduction occurred between the catheterized and not catheterized strata (66.1% versus 69.6%; P=0.41).

Baseline characteristics of patients with and without dyspnea relief are presented in Table 1. Patients without dyspnea relief had a lower mean blood pressure and were
Hemodynamic measurements in patients with and without dyspnea relief at baseline and at 24 hours are shown in Table 2. There was no significant difference between the 2 groups with regard to baseline hemodynamic measurements. Both groups had reductions in PCWP and mPAP and an increase in cardiac index. However, at 24 hours, PCWP and mPAP were significantly lower in patients with dyspnea relief as compared with patients without dyspnea relief (Table 2). There was a moderate correlation between PCWP and mPAP ($r=0.68$; $P<0.0001$).

Figure 1 demonstrates a time-dependent association between the reductions in PCWP and the percentage of patients achieving clinically significant dyspnea relief, reflecting the increasing number of patients with normal or near normal PCWP. When cubic spline regression was used to explore unadjusted nonlinear relationships between hemodynamic variables and

Table 1. Baseline Characteristics of Patients With and Without Dyspnea Relief at 24 Hours

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n=233)</th>
<th>Dyspnea Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=79)</td>
<td>Yes (n=154)</td>
</tr>
<tr>
<td></td>
<td>$P$ Value</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>Age, y</td>
<td>60±14</td>
<td>61±14</td>
</tr>
<tr>
<td>Female sex</td>
<td>60 (26)</td>
<td>42 (27)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29±11</td>
<td>29±7</td>
</tr>
<tr>
<td>Ischemic etiology of heart failure</td>
<td>126 (54)</td>
<td>85 (55)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>25±13</td>
<td>25±12</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>108 (46)</td>
<td>73 (47)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>81 (35)</td>
<td>51 (33)</td>
</tr>
<tr>
<td>AICD implantation</td>
<td>71 (31)</td>
<td>49 (32)</td>
</tr>
<tr>
<td>Baseline heart rate, beats/min</td>
<td>84±15</td>
<td>84 (16)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>118±20</td>
<td>120±20</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>83±14</td>
<td>85±15</td>
</tr>
<tr>
<td>Baseline creatinine, mg/dL</td>
<td>1.4 (1.0–1.9)</td>
<td>1.4 (1.0–1.9)</td>
</tr>
<tr>
<td>Estimated GFR, mL/min per 1.73 m²</td>
<td>51 (35–74)</td>
<td>52 (34–74)</td>
</tr>
<tr>
<td>Randomized to nesiritide</td>
<td>174 (75)</td>
<td>113 (73)</td>
</tr>
<tr>
<td>Cardiac medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>112 (48)</td>
<td>72 (47)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>156 (67)</td>
<td>110 (71)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>17 (7)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>46 (20)</td>
<td>30 (20)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>67 (29)</td>
<td>45 (29)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>29 (12)</td>
<td>19 (12)</td>
</tr>
</tbody>
</table>

GFR indicates glomerular filtration rate; and ACE, angiotensin-converting enzyme. Values are presented as n (%), mean±SD, or as median (interquartile range).

Table 2. Hemodynamic Measurements in Patients With and Without Dyspnea Relief

<table>
<thead>
<tr>
<th>Hemodynamic Variables</th>
<th>Baseline Measurements, Dyspnea Relief</th>
<th>24-h Measurements, Dyspnea Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=79)</td>
<td>Yes (n=154)</td>
</tr>
<tr>
<td></td>
<td>$P$ Value</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>15±8</td>
<td>14±6</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>29±6</td>
<td>27±6</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.3±1.7</td>
<td>4.4±1.6</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>2.2±0.8</td>
<td>2.2±0.8</td>
</tr>
<tr>
<td>Stroke volume index, mL/m²</td>
<td>27±6</td>
<td>27±10</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyne-s/cm²</td>
<td>1369±580</td>
<td>1463±608</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>40±9</td>
<td>38±8</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, WU</td>
<td>3.1±2.3</td>
<td>2.9±2.2</td>
</tr>
<tr>
<td>Transpulmonary gradient, mm Hg</td>
<td>11±6</td>
<td>11±6</td>
</tr>
</tbody>
</table>

Within group changes (baseline vs 24 h). WU indicates Wood units.

*P<0.05.
†P<0.01.
‡P<0.001.
In a univariable analysis, the only nonhemodynamic variable associated with dyspnea relief was the use of angiotensin-converting enzyme inhibitors. In multivariable analyses, only PCWP and mPAP (analyzed either as absolute or as change from baseline) were independent determinants of greater likelihood of dyspnea relief. See the online-only Data Supplement for a model in which baseline PCWP and mPAP were forced into model 2.

To further demonstrate the importance of both PCWP and mPAP reduction, the patients were categorized into 4 groups based on whether PCWP and mPAP were above or below median values. Figure 3 shows that the likelihood of achieving dyspnea relief was higher when both PCWP and mPAP were below median than when only PCWP or mPAP were below median.

The amount of fluids removed during the first 24 hours was not significantly associated with dyspnea relief ($P=0.52$). In addition, a poor correlation was demonstrated between the amount of fluid removed during the first 24 hours and the magnitude of PCWP reduction during the same time ($r=0.06; P=0.35$).

**Discussion**

Based on invasive hemodynamic measurements, the results of the current study indicate that the short-term improvement of dyspnea during therapy with vasodilators and diuretics depends on 2 hemodynamic variables, PCWP and mPAP. Both the absolute level and the magnitude of reduction determine the likelihood of dyspnea improvement. Improvements of other hemodynamic variables, such as cardiac index and systemic vascular resistance, were not associated with dyspnea relief.

Alleviation of dyspnea has been a key measure of efficacy for vasodilator therapy in recent ADHF trials. $^{3,4}$ Dyspnea is also important for the clinician and constitutes a major treatment goal in ADHF. However, although few clinical variables have been associated with dyspnea relief,$^{9,10}$ the hemodynamic determinants of dyspnea improvement in the setting of ADHF have not been reported previously.

Recent studies have shown that rapid relief of dyspnea is frequently not achieved in ADHF patients. In recent ADHF trials, moderately or marked improvement in dyspnea was frequently not achieved in ADHF patients. In recent ADHF trials, moderately or marked improvement in dyspnea was achieved in only 25% to 65% of patients within 24 hours.$^{9,10,12,13}$ These studies demonstrate that contemporary ADHF therapy is suboptimal not only with respect to outcomes,$^{21}$ but also with respect to symptom relief.$^{22}$ Therefore, it is important to understand the reasons for the failure to improve dyspnea.

The present study demonstrates a clear time dependency of dyspnea relief that is strongly related to the hemodynamic response over time. Only a minority of patients achieved a meaningful reduction in PCWP and mPAP within several hours after initiation of therapy. Thus, the failure to achieve early dyspnea relief in a large proportion of patients, as demonstrated in recent studies,$^{6-13}$ is likely related, at least in part, to the failure to achieve a meaningful reduction in PCWP and mPAP within a short time frame.

In this context, a recent consensus article on the assessment of dyspnea in clinical trials recommended hourly assessment of dyspnea for the first 3 hours followed by an assessment at 6 hours and every 6 hours thereafter until 24 hours.$^{17}$ The present results suggest that achieving a sufficient reduction in key
hemodynamic parameters within several hours after initiation of therapy may not be attainable in many patients. For example, a reduction in PCWP and mPAP that would translate into dyspnea improvement may be particularly difficult in patients with extremely elevated initial filling pressures, mitral regurgitation and severe diastolic dysfunction, or diuretic resistance. Thus, dyspnea evaluation at longer time points after initiation of therapy should be considered in future clinical trials.

Dyspnea is one of the principal symptoms of heart failure and is often found with pulmonary hypertension regardless of the underlying cause. In patients with heart failure, pulmonary vascular resistance is an important determinant of exercise capacity, which contributes to dyspnea on exertion. The present study demonstrates that the probability of a clinically significant improvement in dyspnea was highest when both PCWP and mPAP were reduced. Thus, the severity of pulmonary hypertension may also be an important determinant of dyspnea at rest in patients with ADHF. These findings also indicate that pulmonary vascular hemodynamics may have an important role in determining the clinical response to treatment in ADHF.

Previous studies reported a discrepancy between weight loss and symptom improvement or outcome in patients with ADHF. In the Initiation Management Pre-discharge Assessment of Carvedilol Therapy in Heart Failure registry, the degree of weight loss during hospitalization for ADHF was not associated with the degree of improvement in dyspnea at rest. The MEASURE-AHF registry and the PROTECT pilot study also reported that changes in body weight were not related to changes in symptoms. By contrast, in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, reductions in body weight in response to tolvaptan on day 1 were accompanied by significant improvements in patient-assessed dyspnea.

The discordance between early clinical improvement and fluid loss becomes clearer in view of the poor correlation of the later with the reduction in PCWP. There are several potential explanations for this finding. The effect of vasodilator therapy leads to a reduction of PCWP, which is independent of fluid removal. Furthermore, changes in filling pressures may occur independent of fluid loss because of sympathetically mediated changes in venous capacitance that lead to rapid shifts in effective circulatory volume. Finally, even an effective removal of volume at 24 hours may not be sufficient to produce a significant reduction in filling pressures in some patients because of reabsorption of peripheral edema into the vascular space with minimal reduction in intravascular volume.
Although the preset study demonstrates the importance of hemodynamic improvement for dyspnea relief in ADHF, the mechanisms of dyspnea in heart failure and pulmonary hypertension remain incompletely understood. Pulmonary congestion reduces the compliance of the lung and increases the work of breathing. Several studies have demonstrated that the sensation of dyspnea is also related to reduced inspiratory muscle strength. It has also been postulated that vascular distension and interstitial edema may directly stimulate pulmonary vascular nerve endings and result in dyspnea.

Table 3. Unadjusted and Adjusted GEE Logistic Regression Analysis of Determinants of Clinically Significant Dyspnea Relief

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>P Value</th>
<th>P Trend</th>
<th>Adjusted (95% CI)</th>
<th>P Value</th>
<th>P Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>1.79 (1.02–3.16)</td>
<td>0.044</td>
<td>—</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (≤19 mm Hg)</td>
<td>2.96 (2.13–4.12)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>1.80 (1.22–2.65)</td>
<td>0.003</td>
<td>0.003</td>
</tr>
<tr>
<td>Q2 (20 to 22 mm Hg)</td>
<td>1.53 (1.10–2.13)</td>
<td>0.01</td>
<td>1.07 (0.75–1.55)</td>
<td>0.70</td>
<td></td>
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</tr>
<tr>
<td>Q3 (23 to 28 mm Hg)</td>
<td>1.19 (0.88–1.61)</td>
<td>0.26</td>
<td>0.92 (0.67–1.29)</td>
<td>0.63</td>
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<td></td>
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<tr>
<td>Q4 (≥29 mm Hg)</td>
<td>1.0 (Referent)</td>
<td>—</td>
<td>1.0 (Referent)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Q1 (≤29 mm Hg)</td>
<td>4.19 (2.85–6.16)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>2.98 (1.91–4.66)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q2 (30 to 34 mm Hg)</td>
<td>2.47 (1.74–3.52)</td>
<td>&lt;0.0001</td>
<td>2.23 (1.52–3.27)</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Q3 (35 to 40 mm Hg)</td>
<td>2.04 (1.46–2.83)</td>
<td>&lt;0.0001</td>
<td>1.99 (1.41–2.82)</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Q4 (≥41 mm Hg)</td>
<td>1.0 (Referent)</td>
<td>—</td>
<td>1.0</td>
<td>—</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>Model 2†</td>
<td></td>
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</tr>
<tr>
<td>ACE inhibitor</td>
<td>1.79 (1.02–3.16)</td>
<td>0.044</td>
<td>—</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ΔPCWP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (≤0 mm Hg)</td>
<td>1.0 (Referent)</td>
<td>—</td>
<td>&lt;0.0001</td>
<td>1.0 (Referent)</td>
<td>—</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q2 (≥1 to –4 mm Hg)</td>
<td>0.98 (0.76–1.27)</td>
<td>0.90</td>
<td>0.94 (0.72–1.23)</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 (≥5 to –8 mm Hg)</td>
<td>1.90 (1.44–2.51)</td>
<td>&lt;0.0001</td>
<td>1.66 (1.23–2.23)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 (≥9 to –9 mm Hg)</td>
<td>2.79 (2.08–3.75)</td>
<td>&lt;0.0001</td>
<td>2.01 (1.43–2.81)</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>ΔmPAP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (≤0 mm Hg)</td>
<td>1.0 (Referent)</td>
<td>—</td>
<td>&lt;0.0001</td>
<td>1.0 (Referent)</td>
<td>—</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q2 (≥1 to –3 mm Hg)</td>
<td>1.53 (1.17–2.02)</td>
<td>0.002</td>
<td>1.51 (1.15–2.00)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 (≥4 to –7 mm Hg)</td>
<td>1.36 (1.01–1.83)</td>
<td>0.04</td>
<td>1.21 (0.89–1.66)</td>
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<tr>
<td>Q4 (≥8 to –9 mm Hg)</td>
<td>3.30 (2.43–4.49)</td>
<td>&lt;0.0001</td>
<td>2.38 (1.68–3.37)</td>
<td>&lt;0.0001</td>
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</tr>
</tbody>
</table>

mPAP indicates mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; ACE, angiotensin-converting enzyme; OR, odds ratio; CI, confidence interval; and GEE, generalized estimating equations.

*GEE logistic model is based on absolute hemodynamic measurements.
†GEE logistic model is based on the changes in hemodynamic parameters compared with baseline.

Figure 3. Dyspnea improvement stratified by the achieved level of pulmonary capillary wedge pressure (PCWP) and mean pulmonary artery pressure (mPAP). Error bars represent 95% confidence intervals. Cutoff values for PCWP and mPAP are based on the median values.
Study Limitations
Our study has some limitations that merit emphasis. Although mPAP is directly measured, PCWP is an indirect measure of left ventricular filling. PCWP may not accurately reflect left-sided filling pressures, especially when proper wedge position is not routinely confirmed by measuring oxygen saturation. Thus, difficulties in obtaining a proper wedge position may have weakened the association between PCWP and dyspnea. No data were available with regard to specific conditions that might have contributed to the lack of hemodynamic response to vasodilators and diuretics (eg, severe mitral regurgitation). In addition, the short-term improvement in dyspnea does not necessarily translate into long-term clinical response.

Conclusions
The present study of acute hemodynamic changes in the setting of ADHF suggests that a meaningful improvement in dyspnea depends on the ability to reduce both PCWP and mPAP. The failure to achieve early dyspnea relief in clinical trials is likely related, at least in part, to the failure to achieve a rapid reduction in these hemodynamic parameters.

Disclosures
None.

References
CLINICAL PERSPECTIVE

Relief of dyspnea constitutes a major treatment goal in acute heart failure and an important end point in clinical trials. However, recent studies have shown that rapid relief of dyspnea is frequently not achieved in patients with decompensated heart failure. Previous studies failed to identify clinical characteristics or laboratory tests that reliably predict dyspnea relief. In the present study we examined the relationship between hemodynamic changes and dyspnea relief (defined as moderate or marked improvement) using frequent measurements of hemodynamic parameters and simultaneous dyspnea assessments in patients with acute heart failure who were treated with vasodilators and diuretics. We observed a clear time dependency of dyspnea relief that was strongly related to the improvement in hemodynamic parameters. Specifically, dyspnea relief depended on 2 hemodynamic variables, pulmonary capillary wedge pressure and mean pulmonary artery pressure. Both the absolute level and the magnitude of reductions of these hemodynamic variables were associated with the likelihood of dyspnea improvement. The likelihood of achieving dyspnea relief was particularly high when both pulmonary capillary wedge pressure and mean pulmonary artery pressure were effectively reduced. These results suggest that the failure to achieve early dyspnea relief in clinical practice and in clinical trials is likely related, at least in part, to the failure to achieve a rapid reduction in these hemodynamic parameters.
Hemodynamic Determinants of Dyspnea Improvement in Acute Decompensated Heart Failure
Amir Solomonica, Andrew J. Burger and Doron Aronson

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doi: 10.1161/CIRCHEARTFAILURE.112.970335

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SUPPLEMENTAL MATERIAL
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<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>P value</th>
<th>P trend</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
<th>P trend</th>
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</thead>
<tbody>
<tr>
<td>Baseline PCWP (mm Hg)</td>
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<tr>
<td>Q1 (&lt;23 mm Hg)</td>
<td>1.0</td>
<td>—</td>
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<td>Q2 (23 to 26 mm Hg)</td>
<td>1.00 (0.60-1.68)</td>
<td>0.99</td>
<td>—</td>
<td>0.87 (0.50-1.51)</td>
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<tr>
<td>Q3 (27 to 31 mm Hg)</td>
<td>1.06 (0.63-1.78)</td>
<td>0.84</td>
<td>—</td>
<td>1.11 (0.61-2.02)</td>
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<tr>
<td>Q4 (&gt;31 mm Hg)</td>
<td>0.78 (0.46-1.32)</td>
<td>0.35</td>
<td>—</td>
<td>0.96 (0.47-1.93)</td>
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<tr>
<td>Baseline mPAP (mm Hg)</td>
<td></td>
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<td>Q1 (&lt;33 mm Hg)</td>
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<td>Q2 (33 to 38 mm Hg)</td>
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<td>0.70 (0.39-1.23)</td>
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<tr>
<td>Q3 (39 to 44 mm Hg)</td>
<td>0.90 (0.54-1.49)</td>
<td>0.69</td>
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<td>0.73 (0.41-1.28)</td>
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<td>Q4 (&gt;44 mm Hg)</td>
<td>0.52 (0.31-0.88)</td>
<td>0.015</td>
<td>—</td>
<td>0.36 (0.17-0.73)</td>
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<tr>
<td>ΔPCWP (mm Hg)</td>
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<tr>
<td>Q1 (≤0 mm Hg)</td>
<td>1.0</td>
<td>—</td>
<td>&lt;0.0001</td>
<td>1.0</td>
<td>—</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q2 (-1 to -4 mm Hg)</td>
<td>0.98 (0.76-1.27)</td>
<td>0.90</td>
<td>—</td>
<td>0.93 (0.71-1.23)</td>
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<tr>
<td>Q3 (-5 to -8 mm Hg)</td>
<td>1.90 (1.44-2.51)</td>
<td>&lt;0.0001</td>
<td>—</td>
<td>1.66 (1.22-2.26)</td>
<td>0.001</td>
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<tr>
<td>Q4 (≥ -9 mm Hg)</td>
<td>2.79 (2.08-3.75)</td>
<td>&lt;0.0001</td>
<td>—</td>
<td>2.06 (1.45-2.94)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>
ΔmPAP (mm Hg)

<table>
<thead>
<tr>
<th>Q1 (&lt;0 mm Hg)</th>
<th>1.0</th>
<th>—</th>
<th>&lt;0.0001</th>
<th>1.0</th>
<th>—</th>
<th>&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q2 (-1 to -3 mm Hg)</td>
<td>1.53 (1.17-2.02)</td>
<td>0.002</td>
<td>1.55 (1.16-2.07)</td>
<td>0.002</td>
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<tr>
<td>Q3 (-4 to -7 mm Hg)</td>
<td>1.36 (1.01-1.83)</td>
<td>0.04</td>
<td>1.28 (0.93-1.76)</td>
<td>0.13</td>
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<tr>
<td>Q4 (≥ -8 mm Hg)</td>
<td>3.30 (2.43-4.49)</td>
<td>&lt;0.0001</td>
<td>2.62 (1.82-3.76)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* GEE logistic model based on the changes in hemodynamic parameters compared with baseline with baseline values forced into the model