Conclusions—Reactive PH is common among patients with acute decompensated heart failure after initial diuretic and factors are not fully understood.3,5

severity of PH in HF is highly variable, and contributing pulmonary venous pressure. However, the development and ventricular filling pressure results in a “passive” increase in pulmonary venous pressure.1,3

transpulmonary pressure gradient that is superimposed on the pulmonary vascular resistance (PVR) with an increased pulmonary artery pressure and PVR predict higher risk mortality in Patients With Acute Decompensated Heart Failure

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Conclusions—Reactive PH is common among patients with acute decompensated heart failure after initial diuretic and vasodilator therapy. The adverse outcome associated with PH is predominantly due to increased mortality rates in the subgroup of patients with reactive PH. (Circ Heart Fail. 2011;4:644-650.)

Key Words: heart failure ■ pulmonary hypertension ■ pulmonary vascular resistance ■ prognosis

Pulmonary hypertension (PH) is a well-established complication of chronic heart failure (HF).1-4 In patients with chronic left ventricular dysfunction, an elevation in left ventricular filling pressure results in a “passive” increase in pulmonary venous pressure. However, the development and severity of PH in HF is highly variable, and contributing factors are not fully understood.3,5

Clinical Perspective on p 650

Editorial see p 541

With longstanding severe HF, some patients with chronically elevated pulmonary capillary wedge pressures (PCWP) may have development of pulmonary vascular disease with vasoconstriction and remodeling of the pulmonary arterial bed. This “reactive” form of PH manifests as increased pulmonary vascular resistance (PVR) with an increased transpulmonary pressure gradient that is superimposed on the pulmonary venous pressure.1,3

In patients with left ventricular systolic dysfunction, elevated pulmonary artery pressure and PVR predict higher risk for morbidity and mortality.5,6 Furthermore, increased PVR is associated with reduced exercise capacity,3 which contributes to dyspnea on exertion. However, few data are available on the prognostic implications of pulmonary arterial hypertension superimposed on pulmonary venous hypertension in the setting of acute decompensated heart failure (ADHF).

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Methods

Patients

The study population included patients enrolled in the VMAC study: a randomized, multicenter trial comparing the hemodynamic and

Relationship Between Reactive Pulmonary Hypertension and Mortality in Patients With Acute Decompensated Heart Failure

Doron Aronson, MD; Amnon Eitan, MD; Robert Dragu, MD; Andrew J. Burger, MD

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clinical effects of nesiritide (human B-type natriuretic peptide) with nitroglycerin in patients with decompensated congestive HF for whom inpatient parenteral vasoactive therapy was considered appropriate.7 Patients were recruited into the study between October 1999 and July 2000.

Patients were included if they had dyspnea at rest caused by decompensated HF 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 radiograph with findings indicative of HF, and estimated or measured elevation of cardiac filling pressures (PCWP $\geq$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 vasoillator, 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 on the basis of the investigator’s clinical decision, before randomization, to use a right heart catheter to manage decompensated congestive HF (“catheterized” or “noncatheterized” strata).7 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 (RAP) 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).7

Calculations and Derived Indices
Hemodynamic measurements were used to calculate the cardiac index, mPAP, PVR, transpulmonary gradient (TPG), stroke volume index (SVI), and right ventricular stroke work index (RVSWI) as defined by SVI$\times$(mPAP–RAP)/0.136.6

Definitions of PH Categories
In patients with severe HF, information from implanted chronic ambulatory monitoring devices has demonstrated a gradual increase in PCWP and in pulmonary pressures before the clinical decompensation, followed by a reduction toward baseline with acute therapy.9,10 Granted that a postcapillary component also contributes to pulmonary pressures in patients with reactive PH, the term “reactive PH” was used to denote the presence of a superimposed precapillary component of PH caused by pulmonary arterial vasoinconstriction and/or vascular remodeling. Because the reactive form of PH may be either permanent or reversible with alleviation of the high downstream pressure,1 the hemodynamic classification of patients was performed using the final (posttreatment) hemodynamic measurements as follows: (1) no PH (mPAP $\leq$25 mm Hg in the final hemodynamic assessment), (2) passive or postcapillary PH (mPAP $>$25 mm Hg, PCWP $>$15 mm Hg, and PVR $\leq$3 Wood units), and (3) reactive PH (mPAP $>$25 mm Hg, PCWP $>$15 mm Hg, and PVR $>$3 Wood units).2,11

Additional confirmatory analyses were performed in which the distinction between passive and reactive PH was based on the TPG.12 Passive PH was defined as mPAP $>$25, PCWP $>$15 mm Hg, and TPG $\leq$12 mm Hg; reactive PH was defined as mPAP $>$25, PCWP $>$15 mm Hg, and TPG $>$12 mm Hg.

Statistical Analysis
Continuous variables are presented as mean$\pm$SD or medians with 25th and 75th percentiles; categorical variables are presented as frequencies and percentages. Baseline characteristics of the groups were compared, using ANOVA for continuous variables and by the $\chi^2$ statistic for noncontinuous variables (or the Fisher exact test where appropriate). When continuous data were not normally distributed or had unequal variance, groups were compared with the nonparametric 1-way ANOVA (Kruskal-Wallis test).

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. Correlation coefficients were compared after Fisher’s $z$ transformation. Analysis of covariance with interaction terms was used to compare the slopes of the relation for 2 continuous variables between groups.

A multivariable logistic regression model was used to determine variables that were independently associated with reactive PH (versus no reactive PH). Clinical and hemodynamic variables (using the baseline hemodynamic measurements) were considered in the multivariable process.

Event-free survival was estimated by the Kaplan-Meier method, and curves were compared with the log-rank test. Univariable and multivariable Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for various hemodynamic and clinical variables. To avoid assuming linearity, hemodynamic variables were divided into tertiles and included in the model as categorical variables.

The following baseline clinical characteristics were considered in the multivariate procedure: age, sex, history of diabetes mellitus, primary etiology of HF stratified as ischemic or nonischemic, systolic blood pressure on admission, baseline estimated glomerular filtration rate, ejection fraction (dichotomized as above or below 25%), presence of atrial fibrillation, and history of implantable cardioverter-defibrillator implantation. The following medications were adjusted for as dichotomous variables, indicating the use or nonuse of the medication at study entry: digoxin, $\beta$-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and spironolactone. We also adjusted for vasoactive therapy assignments (nesiritide or nitroglycerin). Each variable was tested univariately and then retested after adjustments for other possible confounders in the Cox model. Variables with $P$ $<$0.10 in the univariate Cox regression analysis were used in the multivariable Cox model. Backward selection was performed by means of the likelihood ratio test, with a $P$ $>$0.10 value being the criterion to remain in the model. Model discrimination was tested by $c$-statistics (analogous to the area under the receiver-operating characteristic curve), calculated according to the method of Harrell.13

To determine which of the hemodynamic parameters were the best predictors of death, nested models were compared by using $\chi^2$ likelihood ratio tests to determine whether Cox proportional hazards models that included the posttreatment PH categories and other hemodynamic data provided significantly better fit than did the models that were limited to posttreatment PH categories, and vice versa. In addition, comparison of nonnested models that included either posttreatment PH categories or other hemodynamic variables was performed by calculating Akaike information criterion, which is a statistical estimate of the trade-off between the likelihood of a model against its complexity, with a lower value indicating a better model.14,15

Differences were considered statistically significant at the 2-sided $P$ $<$0.05 level. All statistical analyses were performed using the SPSS statistical software (Version 17.0) and STATA version 11.0 (College Station, TX).

Results
Of the total 489 randomly assigned and treated patients, 246 were in the catheterized stratum. Four patients were excluded because of missing hemodynamic data. In the remaining 242 patients, baseline mPAP was elevated in 240 patients (99.0%), and reactive PH was present in 97 patients (40.0%).

In the whole study population, hemodynamic changes in response to vasodilator and diuretic therapy from baseline to PA catheter removal included significant reductions in RAP (15±7 versus 11±6 mm Hg, $P$ $<$0.0001), PCWP (28±6...
versus 20±7 mm Hg, P<0.0001), SVR (1444±608 versus 1247±456 dyne·s/cm5, P<0.0001), and mPAP (38±8 versus 32±9, P<0.0001), with concomitant increases in cardiac output (4.3±1.6 versus 4.6±1.5 L/min, P=0.002), cardiac index (2.2±0.7 versus 2.3±0.7 L/min/m2, P=0.003), and SVI (27±10 versus 29±10 mL/m2, P<0.0001).

The changes in the classification of PH with diuretic and vasodilator therapy are depicted in Table 1. Using the final hemodynamic measurements, 58 patients were classified as normal mPAP, 124 with passive PH, and 60 with reactive PH.

Demographic and clinical characteristics of the patients according to PH classification are shown in Table 2. Patients with PH were more likely to have a history of atrial fibrillation and a trend toward lower ejection fraction. They presented with lower blood pressure and reduced renal function. They were more likely to receive digoxin and less likely to be treated with β-blockers.

A moderate, direct correlation was found between the reduction in PCWP during vasoactive therapy and the reduction in mPAP (r=0.46, P<0.0005 in patients without PH; r=0.48, P<0.0001 in patients with passive PH; and r=0.47, P=0.0005 in patients with reactive PH). There was no significant difference between the correlation coefficients (P=0.85), and the slopes of these relations did not differ statistically between groups by analysis of covariance (P=0.22), suggesting that a rapidly reversible “passive” component of PH was present in all 3 groups (Figure 1).

Table 1. PH Categories: Baseline and Final (Posttreatment) Hemodynamic Measurements (n=242)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline</th>
<th>No PH</th>
<th>Passive PH</th>
<th>Reactive PH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Final (Posttreatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No PH (n=2)</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Passive PH (n=143)</td>
<td>44 (31)</td>
<td>80 (56)</td>
<td>19 (13)</td>
</tr>
<tr>
<td></td>
<td>Reactive PH (n=97)</td>
<td>13 (13)</td>
<td>43 (45)</td>
<td>41 (42)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>58</td>
<td>124</td>
<td>60</td>
</tr>
</tbody>
</table>

Data are n (%).

Table 2. Baseline Characteristics According to Posttreatment PH Category

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n=242)</th>
<th>PAP ≤25 mm Hg</th>
<th>No PH (n=58)</th>
<th>Passive PH (n=124)</th>
<th>Reactive PH (n=60)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±14</td>
<td>60±14</td>
<td>61±15</td>
<td>60±12</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>58 (24)</td>
<td>19 (33)</td>
<td>25 (20)</td>
<td>14 (23)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29±10</td>
<td>28±6</td>
<td>29±7</td>
<td>29±7</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Ischemic etiology of HF</td>
<td>131 (54)</td>
<td>29 (50)</td>
<td>55 (44)</td>
<td>28 (47)</td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>25±13</td>
<td>28±12</td>
<td>24±13</td>
<td>23±12</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>114 (47)</td>
<td>23 (40)</td>
<td>56 (45)</td>
<td>35 (58)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>83 (34)</td>
<td>13 (22)</td>
<td>52 (42)</td>
<td>18 (30)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>AICD Implantation</td>
<td>71 (29)</td>
<td>15 (26)</td>
<td>37 (30)</td>
<td>19 (32)</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Baseline heart rate, beats/min</td>
<td>83±15</td>
<td>81±17</td>
<td>84±15</td>
<td>84±13</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>118±20</td>
<td>126±22</td>
<td>116±19</td>
<td>115±20</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Baseline creatinine, mg/dL</td>
<td>1.5 [1.1–1.9]</td>
<td>1.2 [0.9–1.5]</td>
<td>1.5 [1.1–2.0]</td>
<td>1.5 [1.1–2.0]</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Estimated GFR, mL/min per 1.73 m²</td>
<td>54 [37–78]</td>
<td>62 [47–81]</td>
<td>49 [33–71]</td>
<td>49 [33–68]</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Randomly assigned to nesiritide</td>
<td>184 (76)</td>
<td>45 (78)</td>
<td>70 (33)</td>
<td>82 (68)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Cardiac medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>116 (48)</td>
<td>19 (33)</td>
<td>61 (49)</td>
<td>36 (60)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>163 (67)</td>
<td>37 (64)</td>
<td>63 (69)</td>
<td>66 (68)</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Angiotensin-ll receptor blockers</td>
<td>17 (7)</td>
<td>5 (9)</td>
<td>7 (8)</td>
<td>5 (5)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>49 (20)</td>
<td>20 (35)</td>
<td>20 (16)</td>
<td>9 (15)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>68 (28)</td>
<td>11 (19)</td>
<td>41 (33)</td>
<td>16 (27)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>29 (12)</td>
<td>8 (14)</td>
<td>13 (11)</td>
<td>8 (13)</td>
<td>0.76</td>
<td></td>
</tr>
</tbody>
</table>

AICD indicates automatic implantable cardioverter-defibrillator; GFR, glomerular filtration rate; and ACE, angiotensin-converting enzyme.

Values are presented as n (%), mean±SD, or as median (interquartile range).
Table 3. Hemodynamic Measurements According to Posttreatment PH Category

<table>
<thead>
<tr>
<th>Hemodynamic Variables</th>
<th>Baseline Measurements</th>
<th>Posttreatment Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No PH (n=58)</td>
<td>Passive PH (n=124)</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>12±5</td>
<td>16±7</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>26±6</td>
<td>28±6</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.5±1.6</td>
<td>4.5±1.8</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>2.2±0.7</td>
<td>2.2±0.7</td>
</tr>
<tr>
<td>SVI, mL/m²</td>
<td>29±9</td>
<td>27±10</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyne·s/cm²</td>
<td>1526±516</td>
<td>1355±615</td>
</tr>
</tbody>
</table>

Table 3 displays the hemodynamic changes occurring during therapy in the 3 study groups. In patients without PH at the final assessment, the reduction in PCWP was associated with a marked decline in mPAP into the normal range (Table 3). Patients with passive PH also displayed a positive hemodynamic response, although PCWP did not normalize in all patients, and the improvements in mPAP, PVR, and cardiac index were modest (Figure 2). Patients with reactive PH presented with high mPAP, PVR, and TPG values, without any improvement in these parameters and without an increase in cardiac index in response to the reduction in filling pressures (Figure 2).

Predictors of Reactive PH

Multivariable logistic regression identified several variables that were independently associated with reactive PH, including diabetes mellitus (adjusted odds ratio, 2.4; 95% CI, 1.2 to 5.0; P=0.005), left ventricular ejection fraction <25% (adjusted odds ratio, 2.4; 95% CI, 1.2 to 4.6; P=0.02), baseline PCWP (adjusted odds ratio, 1.5 per 5 mm Hg increase; 95% CI, 1.1 to 1.9; P=0.003), and baseline PVR (adjusted odds ratio, 1.4 per 1 Wood unit increase; 95% CI, 1.2 to 1.6; P<0.0001). The c-statistics of the model was 0.76±0.03, indicating moderate discrimination.

Effect of Reactive PH on Mortality

Patients were followed for 6 months after study entry. During follow-up, 61 patients (25.2%) died, with 5 (8.6%), 27 (21.8%), and 29 (48.3%) deaths occurring in patients without PH, patients with passive PH, and patients with reactive PH, respectively. The corresponding Kaplan-Meier survival-free estimates (Figure 3) were 91.4% (95% CI, 84.1 to 98.7), 76.7% (95% CI, 69.1 to 84.3), and 48.3% (95% CI, 35.4 to 61.2).

In a univariable Cox regression model, other hemodynamic variables including PCWP, SVI, mPAP, and PVR were also associated with mortality (Table 4). However, the model-based posttreatment PH categories yielded the lowest Akaike information criterion.

The results of a multivariable Cox proportional hazards model that included posttreatment PH categories and other potential clinical predictors of death are shown in Table 5.
After multivariable adjustments, reactive PH remained an independent predictor of death, with an adjusted hazard ratio of 4.8 as compared with patients without PH (Table 5). Compared with the group of patients with passive PH, the adjusted hazard ratio for 6-month mortality rate was 2.8 (95% CI, 1.7 to 4.7; P=0.0001). Similar results were obtained when passive and reactive PH categories were defined according to the TPG. The adjusted HR for 6-month mortality in patients with reactive PH was 3.9 (95% CI, 1.5 to 10.2; P=0.005) compared with patients without PH and 2.0 (95% CI, 1.2 to 3.4; P=0.01) compared with patients with passive PH.

Log-likelihood ratio tests were used to compare the fit of the Cox models that were based on categories of type of PH (Table 5) in combination with other hemodynamic variables that were associated with mortality (Table 4), and vice versa. Comparing nested models, including PCWP (χ²=2.4, 2 df, P=0.30), SVI (χ²=1.1, 2 df, P=0.59), mPAP (χ²=1.9, 2 df, P=0.38), or PVR (χ²=4.4, 2 df, P=0.11), data did not significantly improve the prediction of the model based on the type of PH for the prediction of 6-month mortality. In contrast, the addition of type of PH data to models based on PCWP (χ²=14.9, 2 df, P=0.0006), SVI (χ²=16.1, 2 df, P=0.0003), mPAP (χ²=13.8, 2 df, P=0.001), or PVR (χ²=16.3, 2 df, P=0.0003) significantly improved the prediction of these models.

The c-statistic of the Cox model that included clinical variables alone was 0.76±0.04. Adding the posttreatment PH categories to the model resulted in an additional significant gain in the c-statistic and thus predictive accuracy of the model (0.81±0.03; P=0.043).

**Discussion**

In the present study, we examined the clinical outcome of passive versus reactive PH in patients hospitalized for ADHF. After diuretic and vasoactive therapy for ≤48 hours, passive PH and reactive PH were present in one-half and one-quarter of patients, respectively. The type of PH was the most powerful hemodynamic predictor of mortality, and the adverse outcome associated with PH was predominantly due to a striking increase of mortality in the subgroup of patients with reactive PH. These results indicate that the type of PH is a critically important determinant of short-term outcome in ADHF.

Elevated left heart filling pressures, whether from systolic dysfunction,4,6 diastolic dysfunction,16 or valvular heart disease,17 can result in elevated PAP. Two hemodynamic profiles have been described in patients with elevated left-sided filling pressures.18 The first hemodynamic pattern involves an elevation in mPAP with only a minimal increase in the TPG, as a reflection of the increase in PAP necessary to overcome the increased downstream resistance. This pattern, termed “passive” or “postcapillary” PH, may represent an appropriate response to elevated, left-sided filling pressures aimed to maintain adequate forward blood flow.

However, a subset of patients will have a reactive component superimposed on the elevated pulmonary venous pressure. Reactive (or precapillary) PH is caused by pulmonary arterial vasoconstriction and vascular remodeling leading to further increase in PAP, especially in cases in which left heart filling pressure is markedly and durably increased.1,2,11,18 Reactive PH frequently results in marked elevations in mPAP beyond that which is necessary to maintain cardiac output.18 It has been suggested that these patients may have a permissive genotype that, when exposed to high pulmonary venous resistance, develops reactive pulmonary hypertension with more severe arterial changes, including neointima forma-
The term “congestive vasculopathy” has been used to describe the morphological changes in the pulmonary vasculature caused by congestion, most commonly found in rheumatic mitral stenosis but also in patients with HF caused by cardiomyopathy.

A reduction in PAP during therapy is determined, to a great extent, by wedge pressure reduction. The reduction of mPAP in response to the fall of PCWP during therapy occurred in patients with passive PH and patients with reactive PH, indicating that a passive component is also present in patients with reactive PH. However, PVR remained disproportionately high, with an elevated TPG in reactive PH. The lack of an acute pulmonary vasodilator response in patients with reactive PH may be attributable to impaired endothelial function or the severe and relatively fixed remodeling in the pulmonary arterial vasculature.

It should be emphasized, however, that lack of PVR decline during short-term vasoactive therapy in the reactive PH group does not indicate permanent elevation of PVR. In patients with severe left heart disease, the magnitude of the fall can be quite variable, with some patients achieving normal hemodynamics within 24 hours and others taking many months to improve. Notwithstanding, the absence of an initial response of PVR to vasodilator and diuretic therapy implies that pulmonary vascular vasoconstriction and remodeling may exist and identifies a subset of patients at very high risk for short-term mortality.

PH and Clinical Outcome

In chronic HF, PH has been associated with poor outcome with either reduced or preserved left ventricular systolic function. There have been surprisingly few data with regard to the prognostic significance of reactive versus passive PH. Using hemodynamic data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, Khush et al reported similar clinical outcomes in patients with and patients without mixed PH at baseline. However, the number of patients with mPAP ≥25 mm Hg and PVR ≥3 Wood units at PA catheter removal was small (n = 29), and some patients were treated with inotropes, which may have additional effects on cardiac index, PCWP, and pulmonary pressures. The clinical profiles of patients with passive PH and patients with reactive PH were similar, with the exception of higher rates of diabetes and atrial fibrillation (which are markers of chronically elevated filling pressures) with reactive PH. Although patients with reactive PH presented with higher PCWP, mPAP and PVR, a substantial overlap of these hemodynamic parameters in patients with passive PH was present. Thus, the presence of reactive PH cannot be easily identified on clinical grounds. Several mechanisms may explain the marked increase in mortality rates in the reactive PH group. In patients with passive PH, vasodilator therapy provided relief in filling pressures that was accompanied by an indirect increase in cardiac index, presumably through a reduction in left ventricular forward impedance and backward valvular regurgitation. By contrast, in patients with reactive PH, the alleviation of increased filling pressures did not result in an improvement of cardiac index. Because RV systolic function is highly sensitive to changes in RV afterload, it is conceivable that the lack of PVR response to vasodilator therapy might worsen RV loading conditions, preventing improvement of cardiac index, and, if sustained, could ultimately lead to a decline in RV systolic performance. Indeed, in patients with persistent elevations of mPAP, mortality is strongly related to RV function. The adverse clinical outcome associated with reactive PH may also be attributed to a more advanced disease state, given the worse hemodynamic profile at baseline.

The findings of the present study should aid the interpretation of hemodynamic data in the setting of ADHF. Previous studies have emphasized the reduction of filling pressures in the treatment of ADHF. In the present study, classification of patients according to PH subtypes was a more robust indicator of mortality than filling pressures and other hemodynamic variables. These observations emphasize the importance of reactive PH when trying to define response to therapy and the individual risk of patients with ADHF. Our results also highlight the need for developing novel therapeutic interventions aimed at targeting left-sided PH.

Study Limitations

No data were available with regard to specific conditions that might have contributed to the development of reactive PH such as the severity of mitral regurgitation or other secondary causes of PH such as pulmonary embolism or sleep-disordered breathing. A decrease in left heart filling pressure usually reverses both the passive and vasoreactive components of PH. In patients with severe left heart disease, a progressive decline of pulmonary pressures may be observed over weeks or months. Thus, it is possible that some patients with reactive PH may have been misclassified because of a continued reduction in PVR after the last hemodynamic measurement. Finally, our study lacks direct assessment of RV function, which is highly dependent on the degree of PH.

Conclusion

Reactive PH is common among patients admitted for ADHF after initial diuretic and vasodilator therapy. The adverse outcome associated with PH is predominantly due to increased mortality rates in the subgroup of patients with reactive PH. Persistent elevation of mPAP and PVR after initial treatment for ADHF and reduction of filling pressures represents a hemodynamic profile that identifies a subgroup of patients at a particularly high risk for short-term mortality.

Disclosures

None.

References


Aronson et al Reactive Pulmonary Hypertension in Heart Failure

649
Patients with heart failure (HF) frequently have development of secondary pulmonary hypertension (PH) caused by a “passive” increase in pulmonary venous pressure. With longstanding elevation of left-sided filling pressures, pulmonary vascular disease may develop with vasoconstriction and remodeling of the pulmonary arterial bed. This “reactive” form of PH manifests as increased pulmonary vascular resistance and increased transpulmonary pressure gradient. Patients with HF who have development of secondary PH have reduced exercise capacity and increased mortality rates, but few data are available with regard to the clinical implications of reactive versus passive PH. We analyzed the relationship between the hemodynamic pattern of PH and death in patients with acute decompensated HF. After initial diuretic and vasodilator therapy with a reduction in pulmonary capillary wedge pressure, passive PH and reactive PH were present in one-half and one-quarter of patients, respectively. The type of PH was the most powerful hemodynamic predictor of death. The adverse outcome associated with PH was predominantly due to a striking increase of mortality rates in the subgroup of patients with reactive PH (adjusted hazard ratio, 2.8 for 6-month mortality in reactive PH versus passive PH). These findings are important in the interpretation of hemodynamic data in the setting of HF and the definition of a favorable hemodynamic response to therapy. Our results highlight the risk associated with the development of reactive PH and the need for developing novel therapeutic interventions aimed at targeting left-sided PH.
Relationship Between Reactive Pulmonary Hypertension and Mortality in Patients With Acute Decompensated Heart Failure
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An erratum has been published regarding this article. Please see the attached page for:
/content/5/1/e18.full.pdf
In the article, “Relationship Between Reactive Pulmonary Hypertension and Mortality in Patients With Acute Decompensated Heart Failure” by Aronson et al, which appeared in the September 2011 issue of the journal (Circ Heart Fail. 2011;4:644–650), there were several errors in the second sentence of the Methods and Results section of the Abstract. The sentence should read as follows:

Patients were classified into 3 groups, using the final (posttreatment) hemodynamic measurements: (1) no PH (mean pulmonary artery pressure \( \geq 25 \) mm Hg; (2) passive PH (mean pulmonary artery pressure \( >25 \), pulmonary capillary wedge pressure \( >15 \) mm Hg, and pulmonary vascular resistance \( \leq 3 \) Wood units); and (3) reactive PH (mean pulmonary artery pressure \( >25 \), pulmonary capillary wedge pressure \( >15 \) mm Hg, and pulmonary vascular resistance \( >3 \) Wood units).

The online version of the article has been corrected.

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