What Is the Prognostic Significance of Pulmonary Hypertension in Heart Failure?

Neal A. Chatterjee, MD; Gregory D. Lewis, MD

Increased left ventricular filling pressure is a hallmark of heart failure (HF) caused by left ventricular dysfunction (LVD). Within the closed hemodynamic system, increased LV filling pressure results in elevated pressures in the left atrium and pulmonary venous vasculature. When pulmonary hypertension (PH, defined by mean pulmonary artery pressure [mPAP] >25 mm Hg) is associated with an abnormally elevated pulmonary capillary wedge pressure (PCWP >15 mm Hg) or left ventricular end-diastolic pressure (LVEDP >18 mm Hg), it has been variably termed World Health Organization (WHO) Group 2 PH, pulmonary venous hypertension, inefficient ventilation, and increased mortality. Precapillary pulmonary arterial contribution to PH, reflected by an increase in transpulmonary gradient (TPG, defined as TPG/cardiac output), has been termed “mixed PH,” given both precapillary and postcapillary contributions (Table). The observed proportional increase in pressures after “tailored therapy” has been shown to persistently predict mortality in ADHF in other studies.20 In this issue of Circulation: Heart Failure, Aronson and colleagues18 shed light on the prognostic implications of PH subtypes in HF by means of a subgroup analysis of the VasoDilation in the Management of Acute Congestive Heart Failure (VMAC) trial. The VMAC trial compared the hemodynamic effects of nesiritide (a human B-type natriuretic peptide) versus nitroglycerin, in combination with diuretics, in acute decompensated HF (ADHF). The 242 patients included in the subgroup analysis (age, 61±14 years; LVEF, 25±13%) were assigned, at the discretion of the investigators, to a catheterization-based strategy in which intracardiac filling pressures were measured at baseline and then serially over 48 hours or until therapy was stopped. Subgroup definitions of PH were based on posttreatment hemodynamics and included (1) a “no PH” subgroup (mPAP <25 mm Hg), (2) “passive PH” (defined as mPAP >25 mm Hg, PCWP >15 mm Hg, PVR <3 WU), and (3) “reactive PH” (defined as mPAP >25 mm Hg, PCWP >15 mm Hg, PVR >3 WU). The use of the term “reactive PH” in this study is nonstandard, in that it describes a population with persistent “fixed” PH despite lowering of left-sided pressures. Elevations in PVR are highly variable in patients with LV systolic dysfunction (LVSD) and have been unrelated to LV ejection fraction (LVEF) in previous studies. Elevated PVR in LVSD has been associated with reduced exercise capacity, inefficient ventilation, and increased mortality in some studies but not others. Studies to date examining the prognostic impact of PH in HF have been performed in heterogeneous populations, using variable definitions of PH, with nonuniform ascertainment of precapillary and postcapillary contributions (Table). The availability of serial hemodynamic measurements and complete 6-month patient follow-up in this carefully selected HF population permitted robust analysis of the relationship between hemodynamic measurements and short-term outcomes. The investigators are to be commended for dissecting the precapillary and postcapillary components of elevated PAP in ADHF, based on gold-standard, catheter-based measurements. The observed 2-fold higher mortality rate in patients with “reactive PH” compared with “passive PH,” despite similarities between these 2 PH groups in age, HF etiology, LVEF, presenting systolic blood pressure, baseline creatinine, and treatment-induced reduction in PCWP, highlights the important contribution of precapillary PH in the clinical trajectory of patients with ADHF. There are, nonetheless, some caveats to consider when interpreting the identified prognostic implications of PH subtype in the study by Aronson and colleagues. First, an elevated PCWP after “tailored therapy” has been shown to independently predict mortality in ADHF in other studies.
Therefore, by mandating posttreatment PCWP elevation (ie, >15 mm Hg) in the definition of the 2 PH groups, this study may have inflated the prognostic significance of both PH subgroups relative to non-PH controls. To this point, PCWP was a predictor of mortality in univariate analysis. Second, nesiritide was used to treat ADHF in the majority of subjects in this study. The recently negative report from the ASCEND-HF investigators, finding no mortality and limited symptomatic benefit to nesiritide in ADHF, may limit the clinical utility of identifying nesiritide-refractory precapillary PH. Hemodynamic responses to nesiritide are not necessarily generalizable to PH classification, based on acute vasoreactivity testing with selective pulmonary vasodilators, or othervasodilators used to treat ADHF. Furthermore, for patients with “reactive PH” in this study, natriuretic peptide resistance within the pulmonary vasculature may have reflected a systemic state of natriuretic peptide resistance, which has been associated with higher mortality in New York Heart Association class III/IV HF.

A third issue to consider in interpreting the results by Aronson et al is that the etiology of precapillary PH may not have fully been related to LVSD. Inclusion criteria in the VMAC trial mandated that HF be the primary limiting condition, but there was no information provided regarding the presence of other conditions associated with precapillary PH (eg, chronic obstructive pulmonary disease, thromboembolic disease, or obstructive sleep apnea). As the authors acknowledge, the extent to which these conditions were present in the reactive PH subgroup may represent a confounder in the mortality differences identified. Finally, there was limited information provided about right ventricular (RV) size, shape, and function and degree of tricuspid regurgitation, which is important to consider, given the interactive and compensatory role of the RV in the setting of HF and PH. Previous studies in LVSD have shown the independent prognostic value of RVEF in addition to PAP, further highlighting the important role of the RV pulmonary vascular unit in this population. Despite these limitations, this study clearly advances our understanding of the importance of a fixed burden of precapillary PH in ADHF.

To date, there is only one other study that also examined the prognostic implications of PH subtype in ADHF. In a retrospective analysis of the ESCAPE database, Khush and colleagues defined PH subtypes on the basis of baseline (pretherapy) hemodynamic measurements. They found that “mixed PH,” defined using parameters equivalent to the “reactive PH” subgroup of Aronson et al (ie, mPAP >25 mm Hg, PCWP >15 mm Hg, and PVR >3 Wood units and TPG >15 mm Hg are clearly abnormal).

**Figure.** Diagnostic framework for pulmonary hypertension in heart failure (HF). mPAP indicates mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; and PH, pulmonary hypertension. There are no widely established cut-points to define PVR and transpulmonary gradient (TPG) elevation in HF, but PVR >3 Wood units and TPG >15 mm Hg are clearly abnormal.

**Optimal Timing and Conditions for Characterization of PH in HF**

The findings of Aronson et al highlight the increasingly recognized importance of serial measurements of PAP, particularly before and after provocation or treatment, as the optimal method of characterizing PH in HF. Whether it is the use of posttherapy hemodynamics, exercise provocation, acute vasoreactivity testing with selective pulmonary vasodilators, or continuous PAP measurement with implantable device therapy, there is mounting evidence that serial measurements of PAPs potently predict functional capacity and outcomes in patients with HF (Table). For example, patterns of exercise-induced elevations in PAP in both HFrEF and HfPEF populations have been shown to have diagnostic value as well as both functional and prognostic implications. In addition to exercise, selective pulmonary vasodilators or systemic vasodilators with pulmonary activity may be additional tools in further stratifying PH subtypes.

**PH in HF: Therapeutic Implications and Future Directions**

The dominant therapeutic paradigm for LVSD has focused on the attenuation of aberrant neurohormonal activation and...
secondary LV remodeling. The limited success of several recent efforts focused on further blunting neurohormonal activation, including trials in ADHF, frames the need for novel approaches in LVSD. By carefully defining HF phenotypes beyond a focus on LV dysfunction, elusive incremental benefit in HF pharmacotherapy may be achievable.

PH guidelines caution against adoption of WHO Group 1 pulmonary arterial hypertension (PAH)-specific therapy in group 2 PH, out of concern for causing pulmonary edema as well as lack of supportive evidence from outcomes trials of PAH therapies in HF (eg, epoprostenol and nonsselective endothelin antagonism). However, precapillary PH burden has not been used as an entry criterion in any large-scale trial to date, nor have attempts been made to examine therapeutic responses after optimization of LV filling pressures. Small, short-term studies of the prostacyclin analog iloprost and the phosphodiesterase 5 inhibitor sildenafil have shown favorable hemodynamic responses in LVSD. In a small, randomized, controlled trial from our group, sildenafil increased exercise capacity proportionate to the degree of elevation in baseline PVR, improved quality of life, and reduced HF hospitalizations. These findings suggest deficient cGMP-related signaling in the pulmonary vasculature of HF patients with precapillary PH. More recently, phosphodiesterase 5 inhibition has been shown to reduce PVR after LVAD implantation to facilitate heart transplantation and to markedly reduce PVR without adversely influencing LV filling pressures in HfP-EF. Importantly, acute reductions in PVR pose the risk of increased pulmonary blood flow and subsequent excessive elevation of left-sided filling pressures. This potential risk, and the previously mixed results of careful patient selection, ideally guided by serial measurements of TPG and PCWP, for evaluation of therapies that target precapillary PH in patients with LVSD.

In summary, the important findings by Aronson and colleagues provide a further mandate to increase our understanding of the mechanisms of PH in HF with the eventual

Table. Studies That Tested the Prognostic Significance of Pulmonary Hypertension in Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>HF Population</th>
<th>PH Definition</th>
<th>Measurement Conditions</th>
<th>Comparison and Mean Follow-Up</th>
<th>Hazard Ratio for Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abramson14 (n=108)</td>
<td>Outpatient HfE, NYHA I–IV</td>
<td>TR jet velocity &gt;2.5 m/s</td>
<td>Rest</td>
<td>TR &gt; vs &lt;2.5 m/s (28 mo)</td>
<td>3.35</td>
</tr>
<tr>
<td>Saxon17 (n=528)</td>
<td>Hospitalized HfE, NYHA 3.4±0.6</td>
<td>PAD &gt;19 mm Hg</td>
<td>Rest</td>
<td>PAD &gt; vs &lt;19 mm Hg (12 mo)</td>
<td>2.3</td>
</tr>
<tr>
<td>Ghio13 (n=377)</td>
<td>Outpatient HfE, NYHA II–IV</td>
<td>mPAP &gt;20 mm Hg</td>
<td>Rest</td>
<td>N/A–univariate analysis (17 mo) mPAP</td>
<td>1.1 per 5 mm Hg ↑ mPAP</td>
</tr>
<tr>
<td>Lam2 (n=244)</td>
<td>Outpatient HfPEF</td>
<td>PASP &gt;35 mm Hg</td>
<td>Rest</td>
<td>HFPEF vs HTN without HF (34 mo) mPAP</td>
<td>1.2 per 10 mm Hg ↑ PASP in HfPEF</td>
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</tbody>
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Studies That Tested the Prognostic Value of Elevated Resting Pulmonary Vascular Resistance With Provocation/Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>HF Population</th>
<th>PH Definition</th>
<th>Measurement Conditions</th>
<th>Comparison and Mean Follow-Up</th>
<th>Hazard Ratio for Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cappola4 (n=1134)</td>
<td>Outpatient HfE</td>
<td>PVR &gt;3 WU</td>
<td>Rest</td>
<td>PVR &gt;3 WU vs PVR &lt;2.5 WU (48 mo)</td>
<td>Unadjusted HR 2.3</td>
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<td>Khush7 (ESCAPE, n=171)</td>
<td>Hospitalized ADHF, HfE, NYHA IV</td>
<td>Mixed PH=mPAP &gt;25, W &gt;15, PVR &gt;3 WU</td>
<td>Rest, pretreatment ADHF</td>
<td>Mixed PH no mixed PH (6 mo)</td>
<td>No difference</td>
</tr>
<tr>
<td>Costard-Jack15 (n=293)</td>
<td>Outpatient HfE, transplant referral, NYHA IV</td>
<td>PVR &gt;2.5 WU or PASP &gt;40 mm Hg</td>
<td>Rest, pharmacological response</td>
<td>PVR &gt; vs &lt;2.5 WU and PVR &lt;2.5 WU in response to nitroprusside (yes/no), (3 mo)</td>
<td>1.87 (PVR &gt; or &lt;2.5 WU); 10.1 (response to nitroprusside yes/no)</td>
</tr>
<tr>
<td>Mancini16 (n=65)</td>
<td>Outpatient HfE, NYHA II–IV</td>
<td>mPAP (continuous outcome)</td>
<td>Rest, exercise</td>
<td>Survivors vs nonsurvivors (8 mo)</td>
<td>NS for rest mPAP; exercise mPAP (P&lt;0.01)</td>
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<tr>
<td>Lewis3 (n=60)</td>
<td>Outpatient HfE, NYHA II–IV</td>
<td>mPAP/Watt &gt;0.25 (with exercise)</td>
<td>Rest, exercise</td>
<td>mPAP/Watt &gt; vs &lt;0.25 (96 mo)</td>
<td>2.84</td>
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<tr>
<td>Aronson18 (VMAC, n=242)</td>
<td>Hospitalized ADHF, NYHA II–IV, mean LVEF 25±13%</td>
<td>Reactive PH=mPAP &gt;25, W &gt;15, PVR &gt;3 WU</td>
<td>Rest, posttreatment ADHF</td>
<td>Reactive PH or passive PH vs no PH (3 mo)</td>
<td>Reactive PH 4.8 Passive PH 2.8</td>
</tr>
</tbody>
</table>

HFpEF indicates heart failure with reduced ejection fraction; NYHA, New York Heart Association class; ADHF, acute decompensated heart failure; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation; m/s, meters/second; PAD, pulmonary artery diastolic pressure; mPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressure; W, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; WU, Wood units; NS, not statistically significant.

Top rows: Studies that assessed the prognostic value of elevated PAP, which is an integrative measurement of both left ventricular filling pressure and precapillary PH burden. Middle rows: Studies that specifically focused on the prognostic value of elevated PVR or the precapillary burden of PH in HF. Bottom rows: Studies in which serial hemodynamic evaluations were performed before and after provocation or treatment. Unless otherwise indicated, the hazard ratio for death was statistically significant.
goal of designing therapeutic strategies specifically for this population. Prognostication based on PH-subtypes in HF may be further refined by exercise or other pharmacotherapy interventions and complemented by biochemical signatures, elucidation of permisive genotypes that predispose to mixed PH in HF, and comprehensive evaluation of RV function. Ultimately, large-scale intervention studies, stratified by pre-capillary PH burden, are needed to determine whether PH in HF is a risk marker alone or an appropriate specific target for therapeutic interventions.

Sources of Funding
We gratefully acknowledge support from the National Heart, Lung, and Blood Institute (NIH-K23HL091106 and NIH-U01-HL084877, Dr Lewis), and the Massachusetts General Hospital Heart Failure Innovation Fund (Dr Lewis).

Disclosures
None.

References


**Key Words:** Editorials | heart failure | hemodynamics | pulmonary hypertension
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Circ Heart Fail. 2011;4:541-545
doi: 10.1161/CIRCHEARTFAILURE.111.963785
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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