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, postcapillary PH, or "passive PH." This type of PH, which is "out of proportion" to underlying left-sided disease in the setting of normalized volume status, has been termed "mixed PH," given both precapillary and postcapillary contributions to elevated PAP. PH in HF can be simplistically organized along 2 sequential dyads: (1) the presence or absence of a significant precapillary contribution to elevated PAP (ie, mixed PH as opposed to purely passive PH) and (2) if present, the relative fixed (ie, nonreversible with lowering left-sided filling pressures) or reactive (ie, reversible with reduction of left-sided filling pressures) character of the precapillary contribution to PH (Figure).

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).

In this issue of Circulation: Heart Failure, Aronson and colleagues 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. At 6-month follow-up, mortality was significantly higher in the "reactive PH" group (48.3%) compared with the "passive PH" group (21.8%) and "no PH" group (8.6%). The negative prognostic value of "reactive PH" persisted after multivariate adjustment for age, baseline renal function, initial systolic blood pressure, and HF pharmacotherapy.

The findings from Aronson and colleagues are an important addition to the expanding literature regarding the prognostic and functional importance of PH in HF. 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.

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

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_Circ Heart Fail_ is available at [http://circheartfailure.ahajournals.org](http://circheartfailure.ahajournals.org)

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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 other vasodilators 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 WU), was not associated with worsened 6-month survival when compared with patients without mixed PH. The most important difference in these studies was the use of pretreatment hemodynamic measurements in the primary analysis by Khush and colleagues. This is an important distinction, given that approximately 50% of subjects in the Aronson study were reclassified into a different PH subgroup after vasodilator and diuretic treatment. The prognostic value of posttherapy hemodynamics identified by Aronson et al is analogous to previous work illustrating that post--“tailored therapy” PCWP, but not baseline hemodynamic profiles, predicted prognosis in HF. The null prognostic value of baseline hemodynamics in ADHF from ESCAPE, coupled with the significant prognostic implications of posttherapy hemodynamics identified in this study and elsewhere, provides rationale for ascertaining PH burden after attempts to normalize LV filling pressures in ADHF.

**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 HFrEF 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
secondarily 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 approaches in LVSD. By carefully defining HF phenotypes beyond a focus on LV dysfunction, elusive incremental benefit approaches in LVSD. By carefully defining HF phenotypes beyond a focus on LV dysfunction, elusive incremental benefit approaches in LVSD. By carefully defining HF phenotypes beyond a focus on LV dysfunction, elusive incremental benefit approaches in LVSD. By carefully defining HF phenotypes beyond a focus on LV dysfunction, elusive incremental benefit approaches in LVSD. By carefully defining HF phenotypes beyond a focus on LV dysfunction, elusive incremental benefit approaches in LVSD. 

### 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>
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</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Abramson14 (n=108)</td>
<td>Outpatient HFpEF, 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>
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<tr>
<td>Saxon17 (n=528)</td>
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<td>Ghio15 (n=377)</td>
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<tr>
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<tr>
<td>Mancini16 (n=65)</td>
<td>Outpatient HFpEF, NYHA II–IV</td>
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<td>Survivors vs nonsurvivors (8 mo)</td>
<td>NS for rest mPAP; exercise mPAP (P=0.01)</td>
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<tr>
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<td>Outpatient HFpEF, NYHA II–IV</td>
<td>mPAP/Watt &gt;0.25 (with exercise)</td>
<td>Rest, exercise</td>
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</tr>
<tr>
<td>Aronson18 (VMAC, n=242)</td>
<td>Hospitalized ADHF, NYHA II–IV, mean LVEF 25±13%</td>
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<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.

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 HFpEF. 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 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
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 pathways 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.

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None.

References


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