Left Ventricular Dysfunction With Pulmonary Hypertension
Part 2: Prognosis, Noninvasive Evaluation, Treatment, and Future Research

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Pulmonary hypertension (PH) secondary to left-sided heart disease (Group 2 PH) is a frequent complication of heart failure (HF) that worsens exercise capacity, risk for hospitalization, and survival independent of left-ventricular ejection fraction (LVEF) or stage of HF. Increased pulmonary artery pressure (PAP) in patients with HF often represents a combination of increased left-sided filling pressures (passive component) and elevated pulmonary vascular resistance (PVR) attributable to functional and structural abnormalities of the pulmonary vascular bed (reactive component). The latter may be reversible with standard HF treatment in the earlier stages, when remodeling of the pulmonary vasculature has not set in, and abnormalities in pulmonary arterial tone are the major driver for elevated PVR. However, chronic exposure to elevated pulmonary capillary wedge pressure (PCWP) may lead to permanent changes in the pulmonary arterial bed (irreversible or fixed PH). Considerefing that a number of drug classes have successfully modified the natural history of pulmonary arterial hypertension (Group 1 PH) and demonstrated that intervention is possible even after pulmonary vascular remodeling has occurred, Group 2 PH is a natural target for screening and potential intervention in patients with HF.

In the second part of this 2-part review, we discuss the prognostic impact of PH in HF, the contemporary diagnostic and evaluation approaches, the current evidence from clinical studies in Group 2 PH, the challenges of appropriate patient selection in clinical trials, and potential ways to overcome these challenges in trial designs.

Prognostic Significance of PH in HF

Echocardiographic Studies

Studies using either right heart catheterization (RHC) or echocardiography for determination of PAP have consistently shown that PH considerably worsens prognosis in HF. Abramson et al reported that tricuspid regurgitation jet velocity >2.5 m/s was associated with 3.4 times higher mortality in 108 patients with dilated cardiomyopathy followed for up to 28 months; hospitalization rate for HF was also 3 times higher in these patients. In more recent studies, estimated right-ventricular systolic pressure (RVSP) has been used to evaluate the presence of PH. Although variable RVSP cutoff points have been used to define PH in these studies, higher RVSP has been consistently associated with higher mortality and hospitalization rates. Of note, in a study of cardiac resynchronization therapy recipients, higher RVSP at baseline was associated with worse survival, but patients with reductions in RVSP on follow-up had better outcomes. The importance of elevated-PAP postcardiac resynchronization therapy has also been reported by other groups.

Invasive Studies

Studies with RHC in chronic HF have mostly included patients with severe systolic dysfunction and advanced HF. Among 377 patients referred for transplant evaluation, 51.3% of those with mean PAP (mPAP) >20 mm Hg died or were transplanted urgently compared with 13.5% of those with mPAP ≤20 mm Hg. In that study, right-ventricular dysfunction further increased risk in patients with PH. In a landmark study on 1134 patients with newly diagnosed cardiomyopathy, mortality sharply increased when PVR exceeded 3 Wood units (WU). In a study with serial RHC data, baseline PH predicted mortality and decompensation of HF, and worsening mPAP over time further increased risk. In a large series of HF patients without any specific LVEF inclusion criteria, mortality was 2-fold higher in patients with PH versus those without. When PH (mPAP ≥25 mm Hg) was further classified into passive (PVR ≤2.5 WU) versus reactive (PVR >2.5 WU), reactive PH was associated with more pronounced risk. Regardless of method of PH determination (echocardiography or RHC), right-ventricular dysfunction worsens outcomes further.

In contrast to studies in chronic HF, results from RHC data in acute HF are conflicting. Using data from the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, Khush et al reported that reactive PH (mPAP ≥25 mm Hg; PCWP >15 mm Hg, and PVR ≥3 WU), present in 47% of patients at...
enrollment, was not associated with worse 6-month outcomes. In contrast, in the VMAC (Vasodilation in the Management of Acute Congestive) Heart Failure trial,15 a reactive PH profile (using the same definition as in ESCAPE) was associated with higher 6-month mortality (48.3%) compared with passive PH (21.8%) or no PH (8.6%; Figure 1). However, in VMAC, the PH profile was determined using the post-treatment values, potentially reflecting a profile closer to steady-state conditions. Of note, in that study, post-treatment values of hemodynamics parameters classified 50% of patients to a different PH category compared with pretreatment values,16 highlighting the challenges of PH profile determination in patients with HF during the decompensated phase. Table 1 summarizes the studies on prognostic significance of Group 2 PH.

Insights From Continuous Ambulatory Hemodynamic Monitoring
In patients with HF, even mild increases in chronic ambulatory PAP, monitored through wireless implantable devices, are associated with higher rates of hospitalization for HF regardless of LVEF.19–21 In the COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) Study, the likelihood of an HF event increased progressively with higher estimated diastolic PAP (an estimate of LV filling pressure).20 The estimated average diastolic PAP over 6 months among patients who presented with acute HF was 31±8 mmHg versus 26±6 mmHg among those without events. However, the corresponding RVSP estimates were 55±15 and 45±13 mmHg, respectively, potentially indicating the presence of a reactive pulmonary vascular component among patients with events.20 In the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial, a 1-mmHg lower daily average mPAP in the device-guided treatment group compared with the control group over 6 months was accompanied by fewer hospitalizations for HF (32% versus 44%).21

The Role of Echocardiography
RHC is the gold standard for the definitive diagnosis of PH. However, RHC is an invasive procedure and therefore would be better reserved for patients with advanced (Stage D) HF, where decisions on advanced therapies are contingent on the absence of fixed PH. From a clinical trial design perspective, RHC is appropriate for the detailed characterization of hemodynamic response in phase I/IIa trials with novel vasoactive agents. However, noninvasive alternatives for PH screening and evaluation of response to investigational agents are needed for Stage C patients with HF in larger, phase IIb/III clinical trials. Echocardiography is being increasingly used for these purposes. Newer echocardiographic parameters have become available to supplement the traditional RVSP estimates, including estimates of LV filling pressures and PVR to better phenotype these patients.

Feasibility of RVSP Determination
A comprehensive echocardiographic evaluation of the patients with HF should include estimation of RVSP based on the tricuspid regurgitation jet velocity. Potentially, an estimate of right-atrial pressure using the inferior vena cava diameter and its respiratory fluctuation can be added to the transtricuspid gradient to better approximate RVSP. In the absence of pulmonary stenosis, RVSP is an adequate approximation to systolic PAP. The reported feasibility of RVSP determination in patients with chronic HF is highly dependent on the setting. In prospective cohorts, focusing on right-sided hemodynamics, feasibility ranges from 80% to 90% in community HF26,28,29 and to almost 100% in advanced HF.23,24 Feasibility is much lower when RVSP determination is not mandated by protocol or is retrospectively assessed.5,7,8,25 Recently, Nagueh et al26 reported that RVSP determination is feasible in 80% of patients in the acute HF setting.

Validity of RVSP for Assessment of Pulmonary Hypertension
Several studies have investigated the validity of echocardiographic RVSP estimates in patients with HF using RHC values as the gold standard. As expected, most data come from patients with advanced systolic HF. In 70 patients with systolic HF, a concordance correlation coefficient of 0.88 between RHC and RVSP values was reported, with ±20 mmHg 95% limits of agreement and no bias.27 Narrower limits of agreement (<10 mmHg) and clinically relevant correlation between RHC and RVSP (r=0.82–0.97) have been consistently reported in Stage D HF populations.24,28,29 Nagueh et al26 have reported that echocardiographic RVSP determinations correlate well (r=0.83) with invasive estimates in acute HF, with ±15 mmHg limits of agreement. Importantly, echocardiography identified patients with invasive systolic PAP >35 mmHg with 94% sensitivity and 90% specificity.26 A recent analysis from the ESCAPE trial suggested that the accuracy of echocardiographic RVSP estimates in systolic HF might be compromised by right-ventricular systolic dysfunction.30 However, it is important to note that echocardiography in ESCAPE was not protocol driven, and the time differential between RHC and echocardiographic determinations was widely variable.

Although the need for noninvasive alternatives to invasive estimation of PH is higher in the community setting, most validation data for echocardiographic RVSP estimates
come from referral populations, whereas data on community HF are lacking. However, the clinical validity of RVSP estimates in the community setting is supported by strong prognostic information.

Therefore, it may be acceptable to select Stage C patients with HF for clinical trials on Group 2 PH on the basis of echocardiographic evidence of PH, considering the projected risk associated with elevated echocardiographic RVSP.

### Table 1. Prognostic Significance of Pulmonary Hypertension in Patients With Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Method</th>
<th>Follow-up</th>
<th>Threshold</th>
<th>Outcome</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abramson 1992</td>
<td>108</td>
<td>Dilated CMP; mean LVEF 17.2%</td>
<td>Echo</td>
<td>28 mo (max)</td>
<td>Tricuspid regurgitation jet velocity &gt;2.5 m/s</td>
<td>Mortality 57% vs 17%; RR 3.4</td>
<td>Combined</td>
</tr>
<tr>
<td>Ohio 2001</td>
<td>377</td>
<td>Tx evaluation; LVEF 21.8±6.7%</td>
<td>RHC</td>
<td>17±9 mo</td>
<td>Continuous mPAP</td>
<td>Mortality or urgent Tx</td>
<td>aHR 1.10 per 5 mm Hg (95% CI, 1.00 to 1.21)</td>
</tr>
<tr>
<td>Cappola 2002</td>
<td>1134</td>
<td>New-onset CMP; LVEF: N/A</td>
<td>RHC</td>
<td>4.4 y (average)</td>
<td>PVR &gt;3.0 WU (vs PVR &lt;2.5 WU)</td>
<td>Mortality</td>
<td>aHR 1.86 to 2.04 (depending on PVR level)</td>
</tr>
<tr>
<td>Grigioni 2006</td>
<td>196</td>
<td>NYHA class III-IV; LVEF 27%±9%</td>
<td>RHC</td>
<td>24±20 mo</td>
<td>mPAP &gt;25 mm Hg</td>
<td>Mortality plus acute HF</td>
<td>Adjusted RR 2.30 (95% CI, 1.42 to 3.73)</td>
</tr>
<tr>
<td>Shalaby 2006</td>
<td>270</td>
<td>CRT recipients; LVEF 22.6±9.7%</td>
<td>Echo</td>
<td>19.4±9.0 mo</td>
<td>RVSP ≥45 mm Hg (vs RVSP &lt;30 mm Hg)</td>
<td>Mortality 34% vs 12%; aHR 2.62</td>
<td>(95% CI, 1.07 to 6.41)</td>
</tr>
<tr>
<td>Szwejkowski 2012</td>
<td>1612</td>
<td>LVSD, loop diuretics, and measured RVSP</td>
<td>Echo</td>
<td>2.8±2.5 y</td>
<td>RVSP ≥52 mm Hg (vs &lt;33 mm Hg)</td>
<td>Mortality</td>
<td>60.7% vs 47.4%; aHR 1.50</td>
</tr>
<tr>
<td>Lam 2009</td>
<td>244</td>
<td>In-patients and out-patients; LVEF ≥50%</td>
<td>Echo</td>
<td>2.4±1.2 y</td>
<td>Continuous RVSP</td>
<td>Mortality aHR 1.20 per 10 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Tatebe 2012</td>
<td>676</td>
<td>HF patients NYHA II–IV referred for RHC</td>
<td>RHC</td>
<td>2.6 y (median)</td>
<td>mPAP ≥25 mm Hg</td>
<td>Mortality 29.1% (PH) vs 15.3% (no PH)</td>
<td>24.0% (passive PH)</td>
</tr>
<tr>
<td>Bursi 2012</td>
<td>1049</td>
<td>Community in-patients and out-patients with HF</td>
<td>Echo</td>
<td>2.7±1.9 y</td>
<td>Triletes RVSP (&lt;41, 41–54, &gt;54 mm Hg)</td>
<td>Mortality T2 vs T1: aHR 1.45</td>
<td>(95% CI, 1.13 to 1.85)</td>
</tr>
<tr>
<td>Damy 2010</td>
<td>413</td>
<td>270 with LVEF ≤45%</td>
<td>Echo</td>
<td>66 (56–74) mo</td>
<td>Q4 vs Q1–Q3 RVSP</td>
<td>Mortality NT-proBNP–adjusted HR, 1.46 (95% CI, 1.07 to 1.98)</td>
<td></td>
</tr>
<tr>
<td>Kjaergaard 2007</td>
<td>388</td>
<td>Admitted for HF; LVEF 33 (23–50) %</td>
<td>Echo</td>
<td>2.8 yr</td>
<td>Continuous RVSP</td>
<td>Mortality HR per 5 mm Hg 1.09</td>
<td>(95% CI, 1.04 to 1.14)</td>
</tr>
<tr>
<td>Khush 2009</td>
<td>171</td>
<td>Clinical trial; SBP ≤125 mm Hg; LVEF ≤30%</td>
<td>RHC</td>
<td>6 mo</td>
<td>mPAP ≥25 mm Hg; PVR ≥3 WU</td>
<td>Mortality No difference</td>
<td>No difference</td>
</tr>
<tr>
<td>Aronson 2011</td>
<td>242</td>
<td>Clinical trial; LVEF 25±13%</td>
<td>RHC</td>
<td>6 mo</td>
<td>mPAP &gt;25 mm Hg</td>
<td>Mortality Reactive PH: 48.3%; Passive PH: 21.8%; No PH: 8.6%</td>
<td>aHR 1.7 (95% CI, 0.6 to 4.5)</td>
</tr>
<tr>
<td>Tatebe 2012</td>
<td>676</td>
<td>HF patients NYHA II–IV referred for RHC</td>
<td>RHC</td>
<td>2.6 y (median)</td>
<td>mPAP ≥25 mm Hg</td>
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<td>1049</td>
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<td>(95% CI, 1.13 to 1.85)</td>
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</table>

**aHR** indicates adjusted hazard ratio; CI, confidence interval; CMP, cardiomyopathy; CRT, cardiac resynchronization therapy; HF, heart failure; HR, hazard ratio; LVEF, left-ventricular ejection fraction; LVSD, left-ventricular systolic dysfunction; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RR, risk ratio; RVSP, right-ventricular systolic pressure; SBP, systolic blood pressure; TR, tricuspid regurgitation; Tx, transplantation; and WU, Wood units.

*Follow-up for the entire cohort of 2100 patients (measured and unmeasured RVSP).
Assessment of PVR with Echocardiography

Direct transportation of the RHC formula (difference between mPAP and PCWP divided by the cardiac output) for echocardiographic estimation of PVR has been proposed, but application in practice has been limited, mainly because of the uncertainty introduced by PCWP and cardiac output estimation. Similarly, approaches based on Doppler-derived intervals have been proposed, but adoption has been limited. Abbas et al have introduced an estimate of PVR based on the ratio of tricuspid regurgitation jet velocity to right-ventricular outflow tract velocity–time integral (Figure 2), with good correlation to invasive estimates ($r = 0.93$) and $\pm 0.8$ WU 95% limits of agreement. A tricuspid regurgitation jet velocity/velocity–time integral ratio of $\geq 0.175$ had 77% sensitivity and 81% specificity to determine PVR > 2 WU. This approach and variations thereof have been validated in liver transplant candidates, in patients with pulmonary arterial hypertension, in a mixed non-HF PH population, and in congenital heart disease. Encouraging results have also been obtained in pediatric and postoperative populations. A common theme among these studies is that the tricuspid regurgitation jet velocity/velocity–time integral ratio has a high sensitivity and negative predictive value to detect elevated PVR (> 1.5–2.0 WU), but actual correlation with invasive PVR worsens as PVR increases. Thus, noninvasive PVR estimates are best reserved as a screening tool to exclude high PVR. More recently, Dahiya et al reported that correction of noninvasive PVR for LV filling pressures using the E/e′ ratio improved correlation with invasive PVR in a large non-HF PH population. In this study, corrected noninvasive PVR was a reliable surrogate of invasive PVR during 12 months of follow-up after initiation of pulmonary vasoactive treatment. It is important to note, however, that noninvasive methods for PVR assessment have not been validated in HF populations.

### Table 2. Long-term, Placebo-Controlled Studies in Patients With Heart Failure and Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Duration</th>
<th>Population</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis 2007</td>
<td>Sildenafil (25 to 75 mg TID)</td>
<td>12 wk</td>
<td>NYHA class II–IV, LVEF &lt;40%, mPAP &gt;25 mmHg</td>
<td>34</td>
<td>Sildenafil increased peak VO$_2$ and cardiac output and reduced PVR with exercise; no effect on PCWP, blood pressure, or heart rate; improved 6-MWT distance and reduced HF admissions; higher incidence of headache</td>
</tr>
<tr>
<td>Kaluski 2008</td>
<td>Bosentan (8–125 mg BID)</td>
<td>20 wk</td>
<td>NYHA class IIIb–IV, LVEF &lt;35%, RVSP ≥40 mm Hg (echo), supine SBP ≥100 mm Hg</td>
<td>94</td>
<td>No difference from baseline to week 20 in RVSP (0.1±11.5 mm Hg, P=0.97) or other echocardiographic parameter; more SAEs in the bosentan arm</td>
</tr>
<tr>
<td>Guazzi 2011</td>
<td>Sildenafil (50 mg TID)</td>
<td>1 yr</td>
<td>LVEF ≥50%, RVSP ≥40 mm Hg (echo)</td>
<td>44</td>
<td>Sildenafil reduced mean PAP by 42.0±13.0%, improved right-ventricular function, and reduced right-atrial pressure by 54.0±7.2% and PCWP by 15.7±3.1%</td>
</tr>
<tr>
<td>Guazzi 2012</td>
<td>Sildenafil (50 mg TID)</td>
<td>1 yr</td>
<td>LVEF &lt;45%, mean PAP 25-35 mm Hg</td>
<td>32</td>
<td>Sildenafil increased peak VO$_2$ and exercise ventilation efficiency, and decreased PCWP, mean PAP, and pulmonary vascular resistance</td>
</tr>
</tbody>
</table>

HF indicates heart failure; LVEF, left-ventricular ejection fraction; mPAP, mean pulmonary artery pressure; MWT, minute walking test; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RVSP, right-ventricular systolic pressure; SAE, serious adverse event; and SBP, systolic blood pressure.

Figure 2. Estimation of pulmonary vascular resistance (PVR) by echocardiography. In this patient with advanced heart failure, the peak pressure gradient through the tricuspid valve was 48 mm Hg (left). By adding 15 mm Hg for right atrial pressure, based on <50% collapsibility of the inferior vena cava (not shown), pulmonary artery systolic pressure was estimated at 63 mm Hg. Based on a tricuspid regurgitation jet velocity (TRV) of 3.46 m/s (left) and a time-velocity integral of the right ventricular outflow tract (TVIRVOT) of 7.6 cm (right), PVR was estimated at TRV/(TVIRVOT×10+0.16=3.46/7.6×10+0.16=4.7 Wood units, suggesting the presence of a moderate-to-severe reactive component. On right heart catheterization, PVR was estimated at 4.9 Wood units.
Treatment of PH in HF

The epidemiological data suggest that PH could be a natural therapeutic target in patients with HF. However, no adequately powered trials of PH-specific treatment have demonstrated to date that decreasing PAP or PVR improves morbidity and mortality in patients with HF. Despite promising results in acute hemodynamic studies, the experience with prostacyclin analogs and endothelin antagonists in outcome-driven trials in chronic and acute HF has been invariably neutral or negative to date. These results are in contrast to the favorable effects of these pulmonary vasoactive agents in populations with Group 1 PH. However, trials with prostacyclin analogs and endothelin antagonists in HF did not target patients with evidence of concomitant PH, but rather enrolled relatively unselected HF populations on the premise that a more comprehensive neurohormonal blockade would improve outcomes for all patients with HF. Only recently, the focus has shifted to HF patients with concomitant PH, investigating predominantly the effects of phosphodiesterase type 5 (PDE5) inhibitors in HF with and without PH. Long-term sildenafil treatment improved hemodynamics in a single-center trial of patients with preserved ejection fraction and PH. It is important to note, however, that the degree of right-ventricular dysfunction and right heart congestion in this study was higher than that seen in typical heart failure with preserved ejection fraction populations.

Following the paradigm of other pulmonary vasoactive agents, the long-term effects of PDE5 inhibitors were initially tested in unselected HF populations. On the basis of early encouraging experience from short-term use in patients with HF and erectile dysfunction, the favorable effects of these agents on endothelial function, and the favorable effects of these agents on cardiovascular function, LV assist device (LVAD) implantation improves pulmonary hemodynamics in patients not responding to vasodilator treatment. PH candidates with severe PH who received LVAD were in a small retrospective study of HT candidates with PH and PH without PH (61% versus 63%). LVADs improve pulmonary hemodynamics and candidacy for HT. Long-term survival post-HT in these patients was similar to that of HT recipients without PH who either received or did not receive LVAD. However, there are no data directly comparing patients with PH who received versus those who did not receive LVAD. Improvement in hemodynamics has been reported early after LVAD implantation even in severe PH, and this improvement lasts with longer support. A recent study reported that the time frame in which significant reductions in mPAP, PCWP, and PVR of patients with fixed PH occur is within 6 months after LVAD placement with no additional benefit after that period, giving thus reasonable time for HT candidacy decisions. Favorable outcomes were observed after HT in a small series of patients with initially unresponsive PH who regained reversibility of PH after a 12-week treatment with oral sildenafil in a small prospective uncontrolled trial. PH in Heart Transplant Candidates

Fixed PH increases mortality both early and late after heart transplantation (HT), because the right ventricle may fail when a normal donor heart faces significantly elevated PVR in the post-HT period. Mortality increases continuously with increasing PVR, and no threshold confidetly precludes right-ventricular failure, supporting the view that PVR should be considered as a relative rather than an absolute contraindication to HT. However, a resting PVR >5 WU indicates that the patient may not be a good candidate for HT or, alternatively, that they should be offered heterotopic HT or heart-lung transplantation. On the other hand, if PVR can be reduced to <2.5 WU without hypotension, then post-HT outcomes are comparable with patients without PH. In a series of 410 HT recipients, reversible PH did not affect negatively short- or long-term (5-year) survival; however, residual post-HT PH was associated with decreased long-term survival. In another series of 217 patients who received HT, 10-year survival among the 40 patients with reversible PH was comparable with those without PH (61% versus 63%). LVADs improve pulmonary hemodynamics and candidacy for HT. Long-term survival post-HT in these patients was similar to that of HT recipients without PH who either received or did not receive LVAD. However, there are no data directly comparing patients with PH who received versus those who did not receive LVAD. Improvement in hemodynamics has been reported early after LVAD implantation even in severe PH, and this improvement lasts with longer support. A recent study reported that the time frame in which significant reductions in mPAP, PCWP, and PVR of patients with fixed PH occur is within 6 months after LVAD placement with no additional benefit after that period, giving thus reasonable time for HT candidacy decisions.
precondition previously disqualified HT candidates for safe transplantation.

**Pulmonary Pressures From Implanted Devices as a Therapeutic Target**

Recent trials with implanted devices for hemodynamic monitoring demonstrated that goal-directed therapies based on real-time diastolic PAP assessments, as a surrogate of left-sided filling pressures, might reduce HF hospitalizations.\(^{20,21}\) In the COMPASS-HF study,\(^{20}\) the risk for HF events was 1.10 per 6 months, when daily median–estimated diastolic PAP was ≥25 mm Hg at baseline and remained chronically ≥25 mm Hg versus 0.47, when pressures declined to <25 mm Hg for more than half of the days. Patients with low-baseline daily median–estimated diastolic PAP (<25 mm Hg), which increased only after initiation of the ambulatory monitoring to ≥25 mm Hg for the majority of their days, had a high HF event rate during 6 months of 1.10 compared with a rate of only 0.23 in those in whom low-baseline daily median–estimated diastolic PAP remained low at <25 mm Hg.\(^{20}\)

However, the 21% reduction in HF events by the implanted device remained nonsignificant.\(^{11}\) Although the CHAMPION trial was not restricted to HF patients with PH,\(^{21}\) maintenance of less-elevated filling pressures could also represent an appealing target for PAP-active drugs, such as the cGMP-enhancing PDE5 inhibitors or soluble guanylate cyclase stimulators.

**Ongoing Clinical Trials**

Currently, a number of clinical trials in various planning and conduct stages are investigating the effects of PDE5 inhibitors and soluble guanylate cyclase activators in HF patients with or without PH. The recently completed, NIH-funded RELAX (Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People With Diastolic Heart Failure) trial is a double-blind, placebo-controlled phase III trial testing the hypothesis that the PDE5% inhibitor sildenafil will improve exercise capacity after 24 weeks of therapy in patients with heart failure with preserved ejection fraction.\(^{112}\) This trial will also assess the effects of sildenafil on a host of pathophysiological parameters postulated to impact clinical status and exercise performance in heart failure with preserved ejection fraction. Results are awaited in Spring 2013. LEPHT (The Study to Test the Effects of Riociguat in Patients With Pulmonary Hypertension Associated With LV Systolic Dysfunction) trial is a phase Ib, double-blind placebo-controlled trial enrolling patients with LVEF ≤40% and mPAP ≥25 mm Hg at rest.\(^{113}\) Patients on optimized HF therapy received placebo or the soluble guanylate cyclase activator riociguat for 16 weeks with mPAP as the primary efficacy end point; secondary end points include LVEF, exercise capacity, quality of life, and other hemodynamic and echocardiographic measurements. Follow-up was completed in August 2012, and results were announced during the 2012 American Heart Association Scientific Sessions. Riociguat was well tolerated, but no significant reduction in mPAP was observed with any of the 3 doses tested. However (1) cardiac index increased without changes in heart rate or systemic blood pressure, (2) systemic and PVR decreased in parallel, and (3) quality of life improved in patients receiving 2 mg TID riociguat.\(^{114}\) As previously discussed, the phase III PITCH-HF will be the first clinical trial to investigate the effect of PDE5 inhibition on hard outcomes in patients with HF. To accomplish this goal, 2102 patients with HF and reduced LVEF (<40%), New York Heart Association (NYHA) class II–IV symptoms, and either mPAP ≥25 mm Hg at rest or ≥30 mm Hg with exercise or RVSP ≥40 mm Hg at rest will be assigned to receive either the PDE5 inhibitor tadalafil or placebo for an average of 2.5 years. The trial is currently in the planning stages.

**Future Steps and Study Designs**

There are 2 distinct uses of elevated PAP as a therapeutic target in HF. Acute fluctuations in PAP secondary to increased LV filling pressures and elevated PCWP are a signal of impending acute HF.\(^{19}\) Noninvasive monitoring of these fluctuations can potentially serve as a treatment goal to fine-tune HF therapy and eventually improve outcomes.\(^{21}\) Chronic PAP elevation despite optimal therapy, on the other hand, is more likely to signify a permanent remodeling component in the pulmonary vasculature and a plausible target for long-term treatment in patients with HF. Oral agents with combined pulmonary and systemic vasodilatory activity seem to be promising to this end, and their therapeutic role is being evaluated in ongoing clinical trials.\(^{30,113}\) However, 2 related challenges need to be addressed in the planning stage of such trials: (1) how to identify patients with the most promising benefit versus risk profile and (2) which surrogate markers to use, either as selection criteria to optimize the benefit-risk ratio or as phase II end points.

To address specificity in patient selection, careful characterization of responder profiles would be required as part of dose-finding phase II studies. Because of the complexity of the various hemodynamic profiles in HF with PH, this would require in-depth mechanistic phase II trials, including RHC, echocardiography, and cardiopulmonary exercise testing. These profiles could then identify the appropriate population for long-term, outcome-driven trials to establish clinical benefit. Subsequently, simplified phase III designs would be desirable to ensure feasibility and better representation of the HF population at large.

The issue of surrogate markers and end points poses a challenge for HF clinical trials in general\(^{115}\) and in HF with PH in specific. Hemodynamic (eg, echocardiographic RVSP) and circulating (eg, B-type natriuretic peptide) markers in HF are characterized by short-term dynamic changes under the influence of multiple confounders. Current evidence suggests that functional surrogates (improvement in B-type natriuretic peptide or exercise capacity) do not always match the results of outcome-driven trials.\(^{116}\) On the other hand, although improvement in structural characteristics of the failing heart seems to match long-term outcomes better,\(^{117}\) it is difficult to implement this approach in the case of HF with PH. Effects on LV function may not be apparent in the traditional remodeling time frame (6–12 months), because the target is primarily the pulmonary circulation; and the right ventricle, the primary chamber of interest in PH, is notoriously difficult to quantify echocardiographically outside the research arena. Hence, the
optimal surrogates in this population remain an open question. In this direction, ancillary studies with novel biomarkers (eg, markers of cGMP pathway activity) as part of the ongoing phase III trials might help bridge this gap.

**Conclusion**

Group 2 PH portends worse prognosis and is a plausible therapeutic target in HF. Evaluation of right-sided hemodynamics with RHC is the gold standard for stage D patients and for initial detailed characterization of responses to novel agents in phase I/IIa trials. Echocardiography is a reasonable alternative for screening, enrollment, and response monitoring among the large stage C population for phase IIb/III trials. The initial experience with selective pulmonary vasodilating agents in unselected HF populations has been disappointing. However, shifting the focus to cGMP-enhancing agents, which provide a more balanced vasodilation, and selecting patients on the basis of elevated PAP have yielded promising results in phase II studies. Phase III clinical trials currently underway will answer the fundamental question: does reduction of PVR and PAP on a long-term basis improve outcomes in HF with PH?

**Disclosures**

Dr Gheorghiade has been a consultant for Abbott Laboratories, Astellas, AstraZeneca, Bayer HealthCare AG, CorThera, Cytokinetics, Debiopharm S.A., Errekappa Terapeutici, GlaxoSmithKline, Ikaria, Johnson & Johnson, Medtronic, Pericor Therapeutics, Protein Design Laboratories, Sanofi-Aventis, Sigma Tau, Solvay Pharmaceuticals, Takeda Pharmaceutical, and Trevena Therapeutics. Dr Butler has a relationship with Ono Pharma, Trevira, Bayer, and Amgen. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Key Words: heart failure • outcomes • prognosis • pulmonary hypertension • treatment