Pulmonary Hypertension and Right Ventricular Function in Advanced Heart Failure

Pulmonary hypertension (PH), resulting from a combination of elevated left ventricular (LV) filling pressures, reactive pulmonary arterial vasoconstriction, and pulmonary vascular remodeling, is a common effect of primary left-sided heart failure (HF) irrespective of LV ejection fraction (LVEF) and presence of valvular disease.1,2 Chronic exposure of the right ventricle to elevated afterload, and often to elevated preload as a result of right ventricular (RV) dilation and functional tricuspid regurgitation, leads to RV systolic dysfunction. The presence of PH is associated with worse outcomes in patients with HF, regardless of LVEF and stage of HF,3,4 and prognosis is further aggravated by RV dysfunction.5,6

In patients with advanced HF, severe systolic LV dysfunction is often accompanied by PH, with or without RV dysfunction. This combination poses a number of dilemmas to clinicians in terms of diagnostic and therapeutic approaches and influences decision making for these patients. In this review, we focus on epidemiologic and clinical aspects of secondary PH and RV dysfunction in patients with advanced HF.

Pathophysiology

Patients with chronic LV dysfunction may develop both “passive” and “reactive” secondary PH. Increased LV filling pressures, irrespective of LVEF,7 lead to pulmonary venous hypertension and post-capillary PH. This passive component of PH is largely reversible with normalization of LV filling pressures. However, sustained and excessive exposure to pulmonary venous hypertension, ubiquitous among patients with advanced HF, leads to functional and structural changes in the pulmonary vasculature, initially in the capillaries and later in the arterioles and arteries.8 Endothelial dysfunction is a predominant factor for the impaired pulmonary vascular smooth muscle relaxation, which, in turn, has an integral role in mediating the functional alterations of the pulmonary vasculature. The endothelium-mediated local control of vascular tone is primarily based on a balanced release of nitric oxide and endothelin (ET) 1, and pulmonary vascular resistance (PVR) is critically sensitive to an imbalance of these two opposing systems.9,10 Over time, histological changes in the pulmonary vasculature occur, similar to those observed in patients with primary PH.8,11 Reactive increase in pulmonary arterial tone and eventually intrinsic arterial remodeling lead to a superimposed, precapillary component of PH.1,8 Figure 1 describes the pathophysiologic changes leading to PH. However, the degree of change in vessel structure and PVR in response to venous hypertension varies widely among patients with HF.5

Changes in the pulmonary vasculature and the accompanying increase in RV afterload force the right ventricle, which is normally coupled with a low-impedance, highly distensible vascular system,12 to activate complex adaptive mechanisms. The initial response of the right ventricle is hypertrophy, which, however, decreases RV subendocardial
perfusion. The long-standing pressure overload eventually leads to dilation of the right ventricle, causing it to assume a more spherical shape. The dilated right ventricle initially preserves its output through the Frank-Starling mechanism; however, progressive dilatation increases wall stress, leading to functional tricuspid regurgitation due to altered geometry of the tricuspid annulus, and shifts the septum leftwards, compressing the left ventricle and impairing global ventricular function through ventricular interdependence.

Occurrence of RV dysfunction is an indication of worsening HF for several reasons. The compromised RV output facilitates edema formation by raising the right atrial pressure. In addition, a vicious circle of increased pulmonary vasculature resistance occurs because of the interstitial fluid accumulation, which can further increase the resistance. RV dysfunction also impairs atrial distention and release of atrial natriuretic peptides, increases renal venous pressure, with a consequent reduction in the pressure that drives filtration through the kidney, which, in turn, impairs renal sodium excretion and can trigger positive feedback loops that might hasten HF evolution towards refractoriness.

**Classification and Diagnosis of PH in Patients With HF**

Although there is no globally accepted hemodynamic definition of PH, it is widely accepted that the upper level of normal for mean pulmonary artery pressure (PAP) is 20 mm Hg. Currently, PH is defined invasively as mean PAP/C21 25 mm Hg at rest. The typical hemodynamic findings in PH secondary to left-sided heart disease (group 2 PH) are an elevated pulmonary capillary wedge pressure (PCWP) >15 mm Hg with a transpulmonary gradient (TPG), ie, the difference between mean PAP and PCWP/C20 12 mm Hg. A subset of patients with HF, however, develop PH “out of proportion” to the degree of LV dysfunction. In these patients, an elevated TPG >12 mm Hg is superimposed on pulmonary venous pressure, suggesting intrinsic changes in the pulmonary circulation. This form of PH is referred to as either “active” or “reactive” PH to differentiate from “passive” PH, where elevated PAP can be solely attributed to elevated PCWP. In
many patients with HF, the active component of PH is readily reversed by vasodilators. However, in patients with advanced HF, chronic venous hypertension frequently leads to frank pulmonary vascular remodeling with abnormalities of the elastic fibers, intimal fibrosis, and medial hypertrophy that result in increased vascular stiffness and reduced vasodilator responsiveness. PH not readily responding to pharmacologic testing is generally attributable to structural remodeling (“fixed” PH). Based on data from HT registries, a persistent PVR >2.5 Wood Units (WU) after testing or PVR that is only feasible to lower to <2.5 WU at the expense of systemic hypotension (systolic blood pressure <85 mm Hg) is considered indicative of fixed PH and is associated with worse outcomes after HT.

Although echocardiography is the modality of choice for detection of PH, diagnosis of PH should be based on right heart catheterization (RHC) in patients with advanced HF because of the prognostic and decision-making implications associated with the degree and reversibility of PH. Echocardiography tends to overestimate PAP, especially when pressures are normal or only mildly elevated. Thus, estimated systolic PAP between 35 mm Hg and 45 mm Hg by echocardiography (corresponding to peak tricuspid regurgitant velocity between 2.5 m/s and 3.0 m/s) should be interpreted with caution. On the other hand, echocardiography can rule out PH. A recent study demonstrated that systolic PAP <45 mm Hg by echocardiography confidently excludes PH in HT candidates. Also, with the exception of patients with borderline PVR, noninvasive assessment by echocardiography may reduce the number of serial RHC procedures in patients awaiting HT. Echocardiography also provides information on RV function and tricuspid regurgitation in these patients and is thus a necessary complement for the evaluation of patients with PH.

Reversibility of PH after pharmacologic maneuvering has important prognostic and decision-making implications. The International Society for Heart and Lung Transplantation recommends that a vasodilator challenge should be administered to HT candidates when the systolic PAP is ≥50 mm Hg and either TPG is ≥15 WU or PVR is >3 WU while maintaining a systolic blood pressure >85 mm Hg (level of evidence: C). However, there is no consensus regarding the optimal agent and protocol for reversibility testing. Although various agents have been used over the past 20 years, including inotropic agents, nonselective vasodilators, adenosine, prostaglandins, and phosphodiesterase type-5A (PDE-5A) inhibitors, there are currently no data to support the superiority of a specific testing agent or strategy over others.

Assessment of RV Systolic Function in Patients With HF

In contrast to PH, definitions of abnormal RV function are practically arbitrary and no consensus exists. The complex geometry of the right ventricle complicates quantification of RV function by echocardiography, the most commonly used modality in practice. Hence, RV function is mostly qualitatively assessed. Several echocardiographic indices of RV dysfunction in patients with HF have been proposed; however, most are underutilized in practice and are not consistently used in decision-making. Among the various echocardiographic measures of RV systolic function proposed in the literature, we recommend use of the RV fractional area change and the systolic velocity (s’) of the tricuspid annulus by tissue Doppler. These measures are easy to obtain and reproducible and have been validated in patients with HF.

Epidemiology of PH and RV Dysfunction in Advanced HF

Determinants of PH and RV Dysfunction. The severity of PH in left-sided heart disease is a function of cumulative exposure to pulmonary venous hypertension regardless of LV systolic function or HF stage. Consequently, LV filling pressures and degree of mitral regurgitation play a major role in the induction of PH. Chronic elevation of LV filling pressures is reflected in left atrial enlargement, which is a strong correlate of systolic PAP in patients with LV systolic dysfunction. The severity of PH parallels that of mitral regurgitation in patients with advanced HF (Figure 2). Genetic predisposition may also play a role in the development of PH.

Figure 2. Severity of pulmonary hypertension across mitral regurgitation grades. RVSP indicates right ventricular systolic pressure. Data from Patel and colleagues.
of PH in patients with HF and LV systolic dysfunction.\textsuperscript{50}

Beyond the direct effect of increased PAP on RV systolic function,\textsuperscript{51} the severity of RV systolic dysfunction strongly parallels that of the left ventricle in patients with severe systolic HF.\textsuperscript{52} Also, diastolic dysfunction and severe tricuspid regurgitation further aggravate RV dysfunction.\textsuperscript{53} Finally, the etiology of HF affects RV function. Because the underlying cardiomyopathic process often involves both ventricles in patients with primary nonischemic cardiomyopathies, a reduced RVEF is more frequently encountered among patients with nonischemic etiology of LV systolic dysfunction, independent of PH and LV status.\textsuperscript{54}

**Prevalence of PH.** The prevalence of PH in patients with HF depends on the population studied, the chronicity of disease, and the definition used. In a recent study of 1380 newly diagnosed, unselected HF patients in the United Kingdom, only 7% had PH by echocardiography using a definition of PASP $> 45$ mm Hg.\textsuperscript{7} Prevalence increases with disease progression.\textsuperscript{5} In 379 consecutive outpatients (New York Heart Association [NYHA] class II or III, LVEF $< 35$%), PH by RHC was present in 62.3% of patients,\textsuperscript{5} however, a more relaxed definition of PH was used (mean PAP $> 20$ mm Hg), underscoring the impact of population and definition on PH prevalence.

In advanced HF, the hemodynamic measure used to define PH (PAP vs PVR) affects prevalence estimates. In 320 patients with severe LV systolic dysfunction (LVEF 23%±9%),\textsuperscript{55} PVR was normal ($< 1.5$ WU) in 28% of the patients, mildly elevated (1.5 WU to 2.49 WU) in 36%, moderately elevated (2.5 WU–3.49 WU) in 17%, and severely elevated (3.5 WU) in 19%. Although PVR was not associated with NYHA class in that study, 35% to 40% of patients in NYHA class III and IV had moderately or severely elevated PVR ($> 2.5$ WU), as shown in Figure 3. Similarly, PH defined as PVR $> 2.5$ WU was present in 71 of 172 patients (41.3%) in a pre-transplant HF population a median of 2.7 months before HT.\textsuperscript{56} In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial (NYHA IV, LVEF $\leq 0$%, systolic blood pressure $\leq 125$ mm Hg),\textsuperscript{2} PH defined as mean PAP $> 25$ mm Hg at rest, PCWP $> 15$ mm Hg, and PVR $\geq 3$ WU, was present in 80 of 171 patients (47%). These data are in concordance with an earlier observational study in HT recipients where PVR $> 2.5$ was present in 50.4% of patients.\textsuperscript{15} Thus, in advanced HF populations, the prevalence of PH requiring evaluation for fixed PH (PVR $> 2.5$) is approximately 40% to 50%.

**Prevalence of RV Dysfunction.** The prevalence of RV dysfunction is difficult to assess in advanced HF because there is no universally accepted definition. In a recent series of 120 HF patients in NYHA class III or IV, RV failure defined as RV dilatation or hypokinesis accompanied by clinical manifestations of RV failure was present in 42% of patients.\textsuperscript{53} The impact of method and definition used on the prevalence of RV dysfunction is highlighted in the following two studies. In a recent study from the Mayo Clinic, RV dysfunction by echocardiography was present in $> 80$% of patients with LVEF $\leq 25$%, regardless of the measure used (RV fractional area change $< 45$%, tricuspid s’ $< 11.5$ cm/s, or tricuspid annular motion $< 1.5$ cm).\textsuperscript{57} However, the definitions used in that study were relaxed relative to current recommendations.\textsuperscript{45} In contrast, in a recent analysis from the Beta-Blocker Evaluation of Survival Trial (BEST), which recruited patients with NYHA III or IV symptoms and LVEF $\leq 35$%, severe RV dysfunction defined as a radionuclide ventriculography RVEF $< 20$% was present overall in 13.5% of patients and the distribution of low RVEF was strongly
dependent on the degree of LV systolic dysfunction (Figure 4).52

**Prognostic Significance and Impact on Clinical Decisions**

**Prognostic Impact of PH in Advanced HF.** More severe PH portends a poorer prognosis in patients with HF regardless of LVEF (Figure 5).5 In patients with severe systolic HF, the presence of PH has been early recognized as an independent predictor of morbidity and mortality regardless of HF etiology.58 In a large series of patients with newly diagnosed cardiomyopathy,3 mean PAP and mean systemic pressure were the strongest predictors of mortality during a mean follow-up of 4.4 years. In that study, the association of PVR with mortality assumed a nonlinear form, with mortality increasing steeply with PVR ≥3 WU. In a series of 196 NYHA III or IV patients (LVEF 27%±9%), PH defined as mean PAP ≥25 mm Hg at rest was associated with a 2.3-fold higher risk of death or HF admission over a mean follow-up of 24 months, after adjustment for clinical and hemodynamic predictors.59 In that study, a ≥30% increase in mean PAP over previous RHC values indicated a subgroup with distinctly higher risk. Interestingly, in the ESCAPE trial, PH was not associated with short-term clinical outcomes.2 However, this was a population with homogeneously poor prognosis due to refractory HF admitted with acute decompensation and, therefore, these data may not apply to outpatients with advanced HF.

Beyond adverse outcomes, PH is also associated with impaired functional capacity. In patients with severe LV systolic dysfunction, increased resting PAP is associated with impaired ventilatory efficiency and exercise capacity, attributed to imbalance of pulmonary vascular tone and alveolar hypoperfusion,60 and increasing PVR correlates with lower peak exercise maximal oxygen uptake.55 Recent data suggest that PH is associated with inspiratory muscle dysfunction and increased ventilatory drive in patients with HF.61

The presence of PH also affects outcomes in special populations with HF and severe systolic dysfunction. In patients who receive cardiac resynchronization therapy (CRT), PH independently predicts mortality or HT and HF admission. Conversely, a decrease in systolic PAP on follow-up is a positive prognostic sign.62 In patients undergoing restrictive mitral annuloplasty for severe functional mitral regurgitation secondary to advanced cardiomyopathy, preoperative PH carries a negative prognostic impact.63 Finally, presence of PH predicts poor event-free survival among patients undergoing palliative cardiomyoplasty.64

**Reversible PH and Post-HT Prognosis.** Reversibility of PH is associated with favorable outcomes in patients with advanced HF65 and positively influences candidacy for HT.20 Fixed PH is a risk factor for mortality both early and late after HT, because the right ventricle may fail when a normal donor heart faces significantly elevated PVR in the post-HT period.66 Mortality increases continuously with increasing PVR and no threshold confidently precludes RV failure, supporting the view that PVR should be considered a relative rather than an absolute contraindication to HT.19,20,56 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

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Figure 5. Right ventricular systolic pressure and survival in patients with heart failure with reduced and preserved left ventricular ejection fraction. Reproduced with permission from Kjaergaard and colleagues.4

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PH and RV function in advanced HF
heart-lung transplant.66,67 On the other hand, if PVR can be reduced to <2.5 WU without hypotension, post-HT outcomes are comparable to patients without PH.18,68 In a series of 410 HT recipients, reversible PH did not negatively affect short- or long-term (5-year) survival6; 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 40 patients with reversible PH was comparable to those without PH (61% vs 63%).69

**Prognostic Impact of RV Function.** Impairment of RV systolic function, usually assessed through radionuclide ventriculography or echocardiography, has been consistently associated with worse outcomes in patients with advanced HF, independently of LV function.40,70–73 Although increased afterload affects RV function, RVEF provides prognostic information beyond PAP in these patients.5 In the largest study to date evaluating the impact of RV function on outcomes in patients with advanced systolic HF,6 low RVEF was associated with increased mortality and hospitalization rates after adjustment for other prognostic variables (Figure 6). Poor RV function is also associated with reduced exercise capacity and ventilatory inefficiency in advanced HF.70,74,75 Among the various echocardiographic measures of RV systolic function studied in advanced HF, tricuspid annular s’ velocity has been recently shown to be a robust predictor of outcomes in patients with severe systolic HF;6 low RVEF was associated with increased mortality and hospitalization rates after adjustment for other prognostic variables (Figure 6). Poor RV function is also associated with reduced exercise capacity and ventilatory inefficiency in advanced HF.70,74,75

**Treatment of PH in Advanced HF**

Advances in the treatment of PH pertain mainly to pulmonary arterial hypertension (group 1 PH). There is practically no progress for group 2 PH, which is the most prevalent form of PH. Optimal treatment of HF is a necessary first step in management of these patients. Although all recommendations for group 2 PH are level of evidence C,14 optimization of LV filling pressures is of paramount importance. Most conventional therapies for HF reduce PVR. Despite the lack of data, medications proven to be efficacious in pulmonary arterial hypertension management are being used to manage other forms of PH. Although this approach may be justified in carefully selected patients, these medications may be ineffective or even harmful in many cases. Thus, more studies are needed to establish their effectiveness in group 2 PH.

**Endothelin Antagonists.** ET-1 binds to ETA and ETB receptors on vascular smooth-muscle cells, resulting in profound vasoconstriction and cellular proliferation, and circulating ET-1 levels have been correlated with hemodynamics, symptoms, and survival in patients with HF.77,78 However, despite promising preliminary results with ETA-selective and nonselective ET-1 antagonists in patients with severe HF,79–82 larger trials with bosentan and darusentan failed to show benefit.83–86 In advanced HF patients with PH, bosentan did not provide any measurable hemodynamic benefit over placebo and was associated with more adverse events requiring drug discontinuation.87 However, in a retrospective study of advanced HF patients and longstanding PH, patients receiving low-dose bosentan exhibited better survival and a higher proportion of bosentan-treated patients received HT during follow-up.88 In all, current evidence does not support the use of ETA antagonists in advanced HF, and more data for specific patient subgroups are needed.

**Prostaglandins.** Prostaglandin E1 has favorable short-term effects on PVR in HT candidates,29,89 allowing patients to become eligible for HT with good postoperative outcome.31,89,90 However, in the Flolan International Randomized Survival Trial (FIRST), systematic infusions of epoprostenol, a prostacyclin
analogue, increased mortality in patients with advanced HF while no improvement in functional capacity and quality of life was observed.91 Recently, preliminary data suggest that intermittent prostaglandin E1 infusion in patients with advanced HF and PH improves functional status, ventricular contractility, and PAP without increasing mortality.92 Therefore, the use of prostaglandins in select advanced HF populations remains an open question.

**PDE-5A Inhibitors.** Attenuated sensitivity of pulmonary vasculature to endogenous cGMP-dependent vasodilators is increasingly recognized as a key mechanism of PH and release of cGMP is diminished in patients with advanced HF and PH.93 The cGMP-selective phosphodiesterase type-5A (PDE-5A) is abundant in pulmonary tissue. Inhibitors of this enzyme, such as sildenafil, induce marked pulmonary vasodilatory response.94 A single dose of oral sildenafil, alone or combined with other vasodilators, improves resting and exercise hemodynamics in patients with group 2 PH.95,96 Recently, sildenafil has been shown to reduce PVR even in patients exhibiting no response to other vasodilators.95 Several studies evaluating short-term administration of sildenafil (ranging from several weeks to more than 6 months) in HF patients have shown favorable effects on pulmonary hemodynamics, exercise tolerance, and quality of life without serious side effects.97–100 In a small number of advanced HF patients with low systemic pressure, addition of nitrates to sildenafil led to synergistic pulmonary vasodilation without adverse hemodynamic consequences.101 Long-term sildenafil use has been evaluated in patients after LVAD implantation and persistently elevated PVR, exerting favorable effects on mean PAP, PVR, and RV function without deleterious hemodynamic consequences.102,103 Also, long-term sildenafil reduced PVR to acceptable levels and was well tolerated among high-risk HT candidates.104,105 Sildenafil has been shown to be effective as a bridge to prevent rebound PH and prevent or resolve acute RV failure during weaning from intravenous and inhaled pulmonary vasodilators after HT.106,107

**Effects of LVAD on PH.** LVAD implantation improves hemodynamics in patients not responding to maximal vasodilatory treatment, suggesting that LVAD may be a treatment strategy for HT candidates with fixed PH.108 In several studies, PVR was significantly reduced and patients became eligible for HT with good post-HT outcomes.109–114 Both pulsatile and continuous-flow LVADs improve pulmonary hemodynamics and candidacy for HT.115 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.111 However, there are no data directly comparing survival in patients with PH who received vs those who did not receive LVAD therapy.115 Improvement in hemodynamics has been reported early after LVAD implantation even in severe PH, and this improvement lasts with longer support.112 A recent study reports that the timeframe in which significant reductions in mean PAP, PCWP, and PVR of patients with fixed PH occur is within 6 months after LVAD placement with no additional benefit after that period, giving reasonable time for HT candidacy decisions.116

**Surgical Therapeutic Interventions in Patients with Fixed PH.** Surgical ventricular reconstruction (SVR) is designed to improve LV remodeling and function in advanced HF through restoration of ventricular geometry. Although SVR is feasible and several studies have shown favorable results,117 none of these were randomized and the prospective Surgical Treatment for Ischemic Heart Failure (STICH) trial failed to show benefit with SVR.118 Severe PH is considered a contraindication to SVR. However, a retrospective study evaluating consecutive patients who underwent SVR showed that hemodynamics in patients with PH improved significantly after the procedure and became similar to those of patients without PH.119 However, survival at 3 years was lower, albeit not statistically significant, in patients with PH.120

**Management of RV Dysfunction in Advanced HF**

There is no specific therapy for RV failure; instead, treatment is based on identifying and correcting the underlying disorders. Appropriate therapy for left-sided heart disease reduces elevated PCWP, PAP, and RV dysfunction; however, limited evidence exists regarding direct effects on RV function. β-Blockers improve both RV and LV ejection fraction in HF patients.121,122 Similarly, in patients with advanced HF and LV dyssynchrony, CRT results in significant reverse LV and RV remodeling after 6 months, accompanied by reductions in PAP and tricuspid regurgitation.123 Despite the lack of evidence supporting their use in RV failure, a combination of loop diuretics, aldosterone antagonists, and thiazides are often used to manage peripheral edema, ascites, and end-organ congestion. These evidence gaps underscore the need to include pulmonary vascular and RV functional parameters in physiologic HF studies.

**Conclusions**

In patients with advanced HF, both PH and RV dysfunction are frequently encountered. Both conditions aggravate prognosis and influence clinical decisions. Echocardiography is the screening tool of choice for pulmonary pressures and RV function, although invasive assessment of PH is necessary when advanced therapies are considered. Reversibility of PH in response to short-term pharmacologic manipulation or even to long-term unloading after LVAD implantation is a favorable prognostic sign both for medically treated patients and for HT candidates. Although patients with severe PH secondary to HF have not derived benefit from primary PH therapies thus far, agents targeting the cyclic-3',5'-cystidine phosphate pathway, such as PDE-5A

**PH and RV function in advanced HF**

July–August 2011 195
inhibitors, are currently actively investigated in these patients. Therapies that improve LV filling pressures, including CRT and LVAD placement, have a favorable effect on pulmonary pressures and RV function. However, no specific medical treatment for RV dysfunction exists to date, highlighting an important gap in the management of advanced HF patients.

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