doi: 10.1111/j.1751-7133.2011.00234.x

REVIEW PAPER

Pulmonary Hypertension and Right Ventricular Function in Advanced Heart Failure

Pulmonary hypertension (PH) and right ventricular (RV) dysfunction are frequently encountered in patients with advanced heart failure (HF). 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 treatment or even to long-term unloading after left ventricular assist device (LVAD) implantation is a favorable prognostic sign for both medically treated patients and heart transplant candidates. Although patients with severe PH secondary to HF have not derived benefit from pulmonary arterial hypertension therapies thus far, agents that modulate the cyclic guanosine monophosphate pathway, including phosphodiesterase 5A inhibitors, hold promise and are being actively investigated in advanced HF. Therapies that lead to reduction in left-sided pressures, including cardiac resynchronization and LVAD placement, also 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 patients with advanced HF. Congest Heart Fail. *2011;17:189–198.* ©*2011 Wiley Periodicals, Inc.*

Andreas P. Kalogeropoulos, MD;[1,2] J. David Vega, MD;[2] Andrew L. Smith, MD;[3] Vasiliki V. Georgiopoulou, MD[1,3]
From the Emory Clinical Cardiovascular Research Institute,[1] the Division of Cardiothoracic Surgery,[2] and the Center for Heart Failure Therapy and Transplantation, Emory University, Atlanta, GA[3]

Address for correspondence:
Vasiliki V. Georgiopoulou, MD, Emory Clinical Cardiovascular Research Institute, 1462 Clifton Road NE, Suite 535A, Atlanta, GA 30322
E-mail: vgeorgi@emory.edu

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.[8]

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

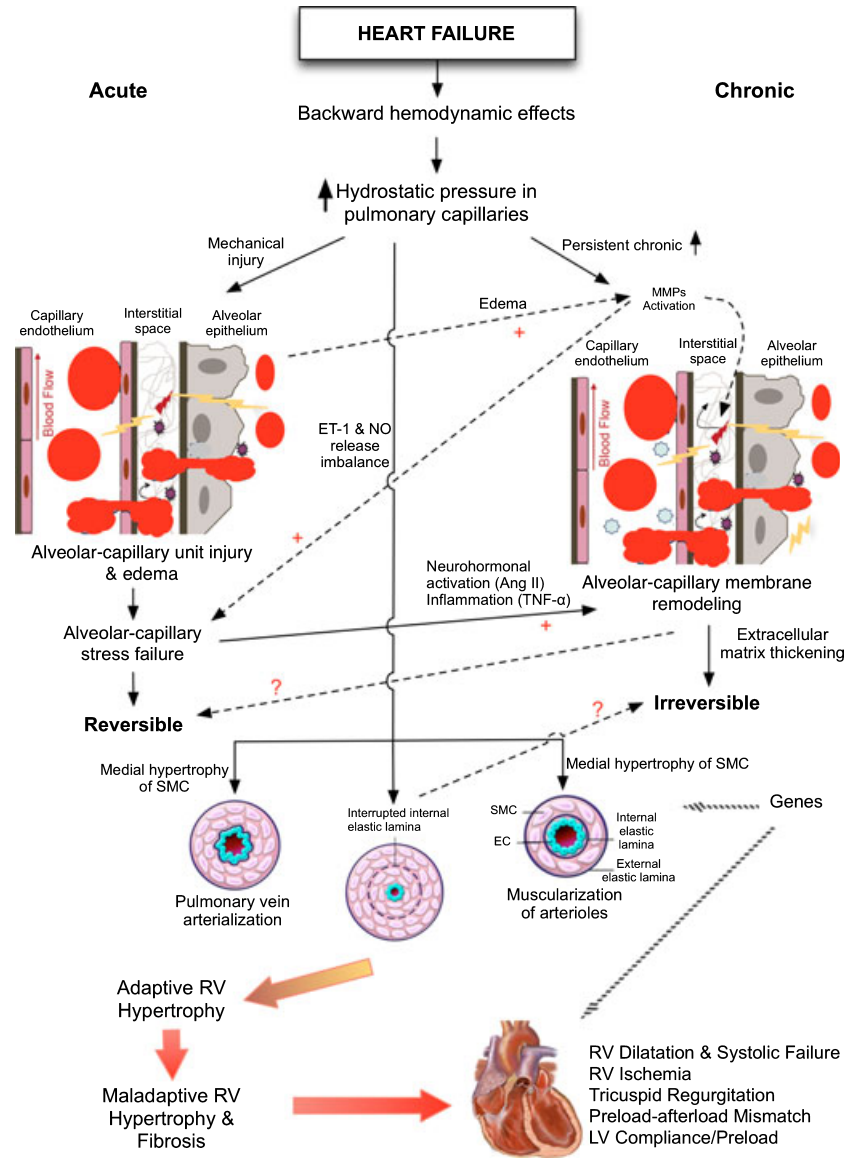

Figure 1. Pathophysiology of pulmonary hypertension and right ventricular failure in left-sided heart disease. Elevation of hydrostatic pressure causes injury to the alveolar-capillary barrier in the acute phase (alveolar-capillary stress failure), whereas excessive and persistent elevated pressure in the chronic phase triggers an adaptive process involving microcirculation and alveolar wall alterations. Edema activates metalloproteinases (MMPs), causing degradation of matrix proteoglycans and alteration in the composition of unit membrane, which, in turn, causes increased endothelial membrane fluidity. Acute stress failure is reversible; however, when the elevated pressure is chronic, the alveolar-capillary membrane undergoes a remodeling process with excessive collagen deposition, augmented by locally produced hormones and inflammatory markers. Increased capillary pressure promotes hypertrophy and fibrotic changes in pulmonary arteries and veins with medial hypertrophy and disruption of the elastic lamina. Genetic factors influence these pulmonary vascular structural changes, while the imbalance of endothelin-1 (ET-1) and nitric oxide (NO) release is also an important component. When the excessive afterload is long-standing, the right ventricle dilates. Once the mechanisms of contractile reserve are exhausted, systemic pressure begins to fall, accompanied by irreversible decrease in right ventricular function. Ang II indicates angiotensin II; EC: endothelial cell; SMC: smooth muscle cells; TNF-α: tumor necrosis factor α.

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[12]; however, progressive dilatation increases wall stress, leads 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.[12]

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.[8]

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.[13] Currently, PH is defined invasively as mean PAP $\geq$25 mm Hg at rest.[14] The typical hemodynamic findings in PH secondary to left-sided heart disease (group 2 PH[15]) are an elevated pulmonary capillary wedge pressure (PCWP) >15 mm Hg with a transpulmonary gradient (TPG), ie, the difference between mean PAP and PCWP $\leq$12 mm Hg.[13,14] 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.[1,14] 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.[13] In

many patients with HF, the active component of PH is readily reversed by vasodilators.[1] 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.[1] Although delayed reversibility over time after left ventricular assist device (LVAD) implantation or heart transplantation (HT) has been reported,[16,17] PH not readily responding to pharmacologic testing is generally attributable to structural remodeling ("fixed" PH).[1] Based on data from HT registries, a persistent PVR $\geq$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.[18–20]

Although echocardiography is the modality of choice for detection of PH,[14] 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.[13,20] 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.[13] 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.[21] 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.[22] 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.[23,24]

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 $\geq$50 mm Hg and either TPG is $\geq$15 WU or PVR is >3 WU while maintaining a systolic blood pressure >85 mm Hg (level of evidence: C).[20] 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,[25,26] nonselective vasodilators,[27] adenosine,[28] prostaglandins,[29–32] and phosphodiesterase type-5A (PDE-5A) inhibitors,[33] there are currently no data to support the superiority of a specific testing agent or strategy over others.[14,20,33,34]

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.[35] 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.[36] 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.[37–44] The recent statement on RV function by the American Society of Echocardiography suggests a cutoff point of 35% for RV fractional area change and 10 cm/s for tricuspid s′ to indicate RV systolic dysfunction.[45]

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.[46,47] Consequently, LV filling pressures and degree of mitral regurgitation play a major role in the induction of PH.[7] 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.[48] The severity of PH parallels that of mitral regurgitation in patients with advanced HF (Figure 2).[49] Genetic predisposition may also play a role in the development

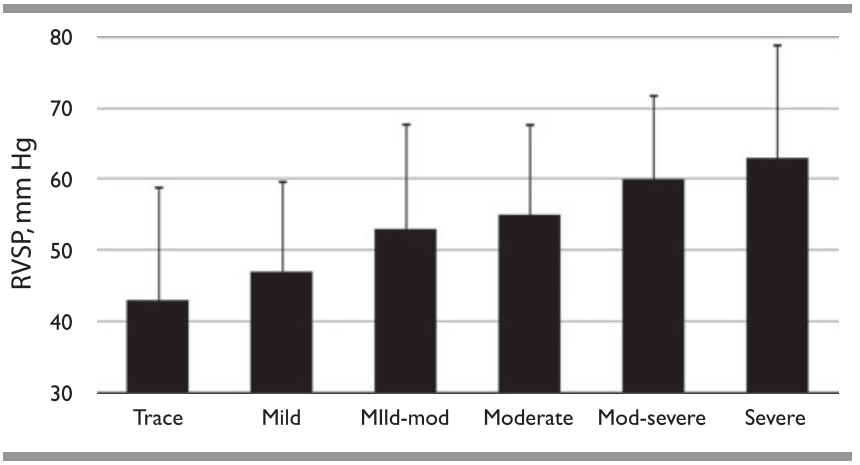

Figure 2. Severity of pulmonary hypertension across mitral regurgitation grades. RVSP indicates right ventricular systolic pressure. Data from Patel and colleagues.[49]

of PH in patients with HF and LV systolic dysfunction.[50]

Beyond the direct effect of increased PAP on RV systolic function,[51] the severity of RV systolic dysfunction strongly parallels that of the left ventricle in patients with severe systolic HF.[52] Also, diastolic dysfunction and severe tricuspid regurgitation further aggravate RV dysfunction.[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.[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.[7] Prevalence increases with disease progression.[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[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%),[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.[56] In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial (NYHA IV, LVEF ≤ 0%, systolic blood pressure ≤125 mm Hg),[2] PH defined as mean PAP ≥25 mm Hg at rest, PCWP >15 mm Hg, and PVR ≥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.[18] Thus, in advanced HF populations, the prevalence of PH requiring evaluation for fixed PH (PVR ≥2.5) is approximately 40% to 50%.

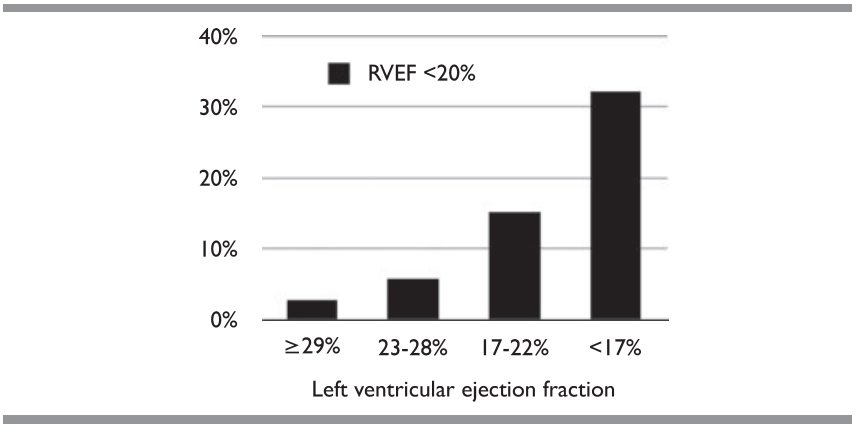

Figure 4. Severe right ventricular dysfunction (right ventricular ejection fraction [RVEF] <20%) according to left ventricular ejection fraction in advanced heart failure patients. Data from Desai and colleagues.[52]

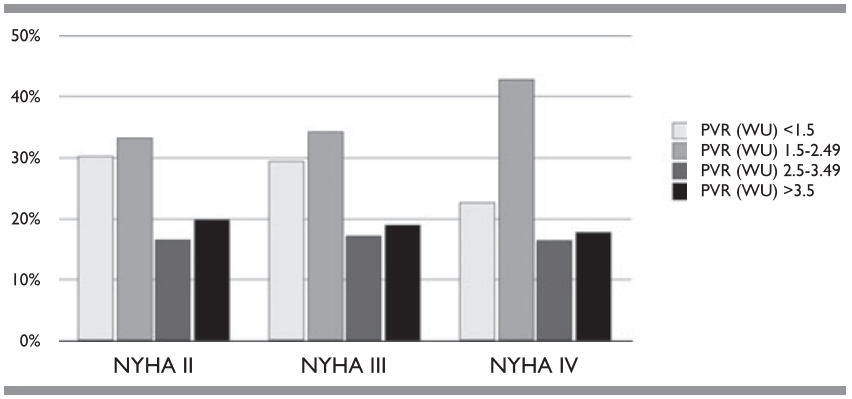

Figure 3. Pulmonary vascular resistance across New York Heart Association (NYHA) classes in referral patients. PVR indicates pulmonary vascular resistance; WU: Wood units. Data from Butler and colleagues.[55]

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.[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 ≤25%, regardless of the measure used (RV fractional area change <45%, tricuspid s′ <11.5 cm/s, or tricuspid annular motion <1.5 cm).[57] However, the definitions used in that study were relaxed relative to current recommendations.[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 ≤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

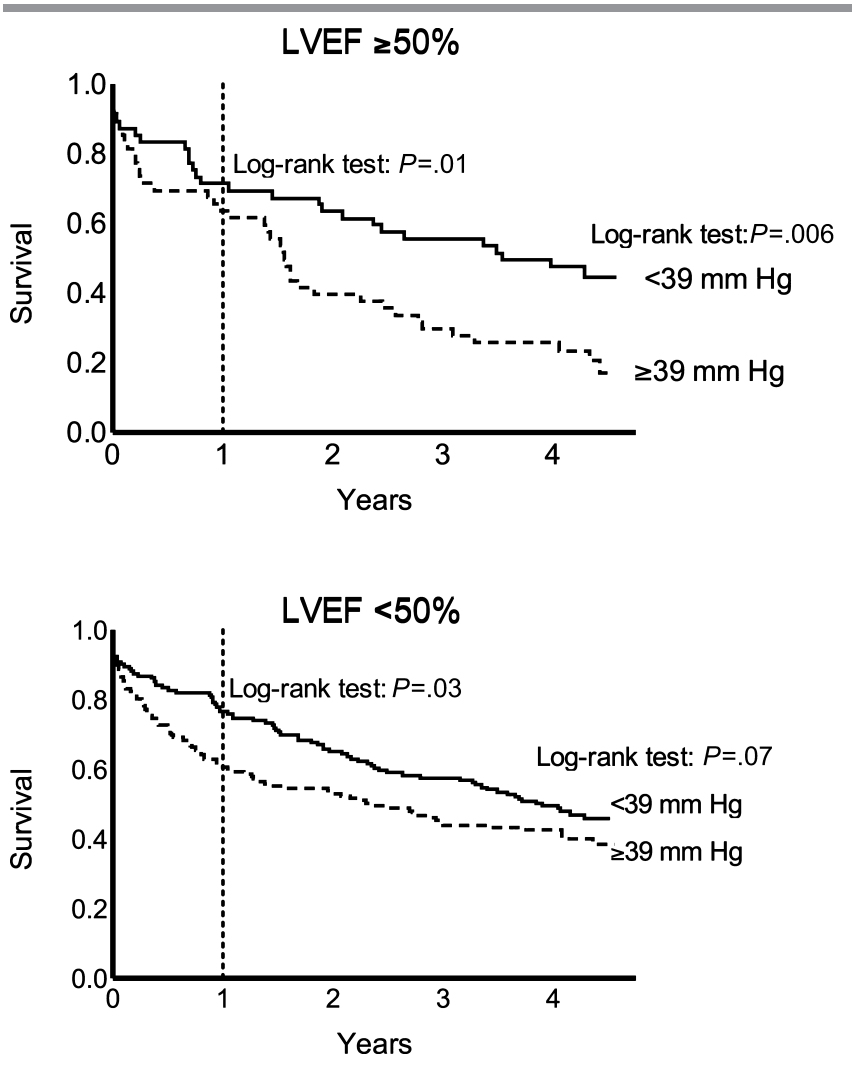

Figure 5. Right ventricular systolic pressure and survival in patients with heart failure with reduced and preserved left ventricular ejection fraction. Reproduced with permission from Kjaergaard and colleagues.[4]

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).[4] 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 $\geq$3 WU. In a series of 196 NYHA III or IV patients (LVEF 27%±9%), PH defined as mean PAP $\geq$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 $\geq$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 HF[65] 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

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) survival[16]; 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.[40,43,44] Assessment of RV mechanics by strain echocardiography also holds promise as a prognostic and follow-up tool in advanced HF.[76] Notably, a positive response of the right ventricle to vasodilators predicts a favorable outcome in patients with advanced HF and PH and in patients admitted for decompensated systolic HF.[51,76]

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 ET-1 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

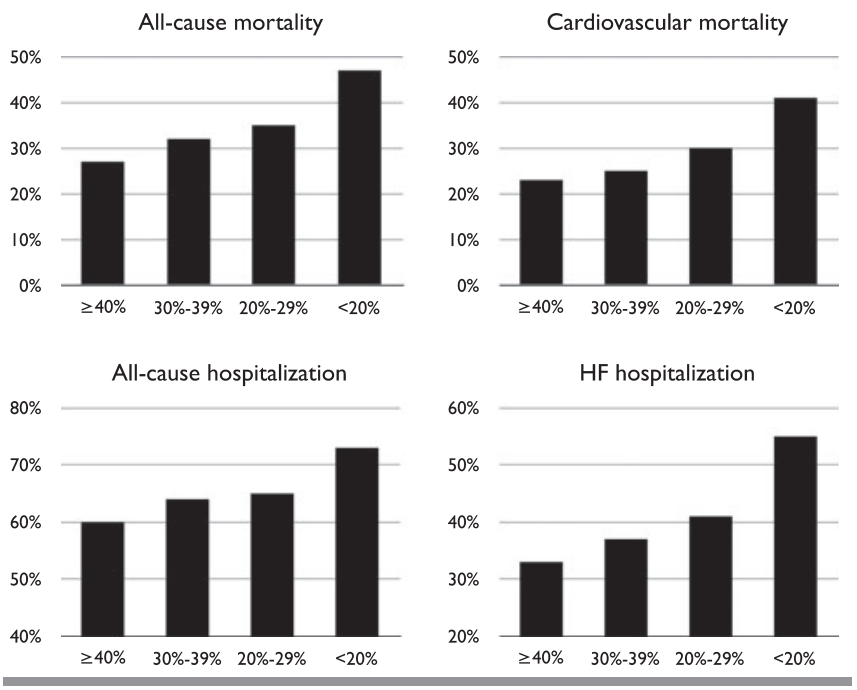

Figure 6. Baseline right ventricular ejection fraction (LVEF) and outcomes in the Beta-Blocker Evaluation of Survival Trial during 24 months of follow-up. HF indicates heart failure. Data from Meyer and colleagues.[6]

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.[93] 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 pulsative[112] and continuous-flow[114] 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[113] 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[118] and the prospective Surgical Treatment for Ischemic Heart Failure (STICH) trial failed to show benefit with SVR.[119] 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.[120] 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'-cytidine phosphate pathway, such as PDE-5A

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.

Acknowledgment and disclosure: *None.*

References

1 Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. *Circulation.* 2000;102(14):1718–1723.

2 Khush KK, Tasissa G, Butler J, et al., ESCAPE Investigators. Effect of pulmonary hypertension on clinical outcomes in advanced heart failure: analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) database. *Am Heart J.* 2009; 157(6):1026–1034.

3 Cappola TP, Felker GM, Kao WH, et al. Pulmonary hypertension and risk of death in cardiomyopathy: patients with myocarditis are at higher risk. *Circulation.* 2002; 105(14):1663–1668.

4 Kjaergaard J, Akkan D, Iversen KK, et al. Prognostic importance of pulmonary hypertension in patients with heart failure. *Am J Cardiol.* 2007;99(8):1146–1150.

5 Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol.* 2001;37(1):183–188.

6 Meyer P, Filippatos GS, Ahmed MI, et al. Effects of right ventricular ejection fraction on outcomes in chronic systolic heart failure. *Circulation.* 2010;121(2):252–258.

7 Damy T, Goode KM, Kallvikbacka-Bennett A, et al. Determinants and prognostic value of pulmonary arterial pressure in patients with chronic heart failure. *Eur Heart J.* 2010;31(18):2280–2290.

8 Guazzi M, Arena R. Pulmonary hypertension with left-sided heart disease. *Nat Rev Cardiol.* 2010;7(11):648–659.

9 Ooi H, Colucci WS, Givertz MM. Endothelin mediates increased pulmonary vascular tone in patients with heart failure: demonstration by direct intrapulmonary infusion of sitaxsentan. *Circulation.* 2002;106(13):1618–1621.

10 Cooper CJ, Jevnikar FW, Walsh T, et al. The influence of basal nitric oxide activity on pulmonary vascular resistance in patients with congestive heart failure. *Am J Cardiol.* 1998;82(5):609–614.

11 Delgado JF, Conde E, Sánchez V, et al. Pulmonary vascular remodeling in pulmonary hypertension due to chronic heart failure. *Eur J Heart Fail.* 2005;7(6):1011–1016.

12 Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part I: anatomy, physiology, aging, and functional assessment of the right ventricle. *Circulation.* 2008;117(11):1436–1448.

13 Hoeper MM. Definition, classification, and epidemiology of pulmonary arterial hypertension. *Semin Respir Crit Care Med.* 2009; 30(4):369–375.

14 Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2009; 30(20):2493–2537.

15 Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2009;54(1 Suppl):S43–S54.

16 Goland S, Czer LS, Kass RM, et al. Preexisting pulmonary hypertension in patients with end-stage heart failure: impact on clinical outcome and hemodynamic follow-up after orthotopic heart transplantation. *J Heart Lung Transplant.* 2007;26(4):312–318.

17 Mikus E, Stepanenko A, Krabatsch T, et al. Left ventricular assist device or heart transplantation: impact of transpulmonary gradient and pulmonary vascular resistance on decision making. *Eur J Cardiothorac Surg.* 2011;39(3):310–316.

18 Costard-Jäckle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. *J Am Coll Cardiol.* 1992; 19(1):48–54.

19 Costanzo MR, Augustine S, Bourge R, et al. Selection and treatment of candidates for heart transplantation. A statement for health professionals from the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. *Circulation.* 1995; 92(12):3593–3612.

20 Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates – 2006. *J Heart Lung Transplant.* 2006;25(9):1024–1042.

21 Bacal F, de Freitas AF, Moreira LF, et al. Validation of a cutoff value on echo Doppler analysis to replace right heart catheterization during pulmonary hypertension evaluation in heart transplant candidates. *Transplant Proc.* 2010;42(2):535–538.

22 Kuppahally SS, Michaels AD, Tandar A, et al. Can echocardiographic evaluation of cardiopulmonary hemodynamics decrease right heart catheterizations in end-stage heart failure patients awaiting transplantation? *Am J Cardiol.* 2010;106(11):1657–1662.

23 McDonald MA, Ross HJ. Trying to succeed when the right ventricle fails. *Curr Opin Cardiol.* 2009;24(3):239–245.

24 Bhave NM, Ward RP. Echocardiographic assessment and clinical management of tricuspid regurgitation. *Curr Cardiol Rep.* 2011;13(3):258–264.

25 Givertz MM, Hare JM, Loh E, et al. Effect of bolus milrinone on hemodynamic variables and pulmonary vascular resistance in patients with severe left ventricular dysfunction: a rapid test for reversibility of pulmonary hypertension. *J Am Coll Cardiol.* 1996; 28(7):1775–1780.

26 Schulze-Neick I, Luther YC, Ewert P, et al. End-stage heart failure with pulmonary hypertension: levosimendan to evaluate for heart transplantation alone versus combined heart-lung transplantation. *Transplantation.* 2004;78(8):1237–1238.

27 Semigran MJ, Cockrill BA, Kacmarek R, et al. Hemodynamic effects of inhaled nitric oxide in heart failure. *J Am Coll Cardiol.* 1994;24(4):982–988.

28 Haywood GA, Sneddon JF, Bashir Y, et al. Adenosine infusion for the reversal of pulmonary vasoconstriction in biventricular failure. A good test but a poor therapy. *Circulation.* 1992;86(3):896–902.

29 Murali S, Uretsky BF, Reddy PS, et al. Reversibility of pulmonary hypertension in congestive heart failure patients evaluated for cardiac transplantation: comparative effects of various pharmacologic agents. *Am Heart J.* 1991;122(5):1375–1381.

30 Montalescot G, Drobinski G, Meurin P, et al. Effects of prostacyclin on the pulmonary vascular tone and cardiac contractility of patients with pulmonary hypertension secondary to end-stage heart failure. *Am J Cardiol.* 1998;82(6):749–755.

31 Klotz S, Deng MC, Hanafy D, et al. Reversible pulmonary hypertension in heart transplant candidates – pretransplant evaluation and outcome after orthotopic heart transplantation. *Eur J Heart Fail.* 2003;5(5):645–653.

32 Braun S, Schrötter H, Schmeisser A, Strasser RH. Evaluation of pulmonary vascular response to inhaled iloprost in heart transplant candidates with pulmonary venous hypertension. *Int J Cardiol.* 2007;115(1):67–72.

33 Botha P, Parry G, Dark JH, Macgowan GA. Acute hemodynamic effects of intravenous sildenafil citrate in congestive heart failure: comparison of phosphodiesterase type-3 and -5 inhibition. *J Heart Lung Transplant.* 2009;28(7):676–682.

34 Torres Macho J, Delgado Jimenez JF, Sanz Salvo J, et al. Effect of different pharmacologic agents to reverse severe pulmonary hypertension among end-stage heart failure patients. *Transplant Proc.* 2009;41(6): 2477–2479.

35 Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18(12):1440–1463.

36 Matthews JC, Dardas TF, Dorsch MP, Aaronson KD. Right-sided heart failure: diagnosis and treatment strategies. *Curr Treat Options Cardiovasc Med.* 2008;10(4):329–341.

37 Melužín J, Spinarová L, Bakala J, et al. Pulsed Doppler tissue imaging of the velocity of tricuspid annular systolic motion; a new, rapid, and non-invasive method of evaluating right ventricular systolic function. *Eur Heart J.* 2001;22(4):340–348.

38 Zornoff LA, Skali H, Pfeffer MA, et al. Right ventricular dysfunction and risk of heart failure and mortality after myocardial infarction. *J Am Coll Cardiol.* 2002;39(9):1450–1455.

39 Spinarová L, Meluzín J, Toman J, et al. Right ventricular dysfunction in chronic heart failure patients. *Eur J Heart Fail.* 2005;7(4):485–489.

40 Meluzin J, Spinarová L, Hude P, et al. Prognostic importance of various echocardiographic right ventricular functional parameters in patients with symptomatic heart failure. *J Am Soc Echocardiogr.* 2005;18(5):435–444.

41 Dokainish H, Sengupta R, Patel R, Lakkis N. Usefulness of right ventricular tissue Doppler imaging to predict outcome in left ventricular heart failure independent of left ventricular diastolic function. *Am J Cardiol.* 2007; 99(7):961–965.

42 Anavekar NS, Skali H, Bourgoun M, et al. Usefulness of right ventricular fractional area change to predict death, heart failure, and stroke following myocardial infarction (from the VALIANT ECHO Study). *Am J Cardiol.* 2008;101(5):607–612.

43 Damy T, Viallet C, Lairez O, et al. Comparison of four right ventricular systolic echocardiographic parameters to predict adverse outcomes in chronic heart failure. *Eur J Heart Fail.* 2009;11(9):818–824.

44 Bistola V, Parissis JT, Paraskevaidis I, et al. Prognostic value of tissue Doppler right ventricular systolic and diastolic function indexes combined with plasma B-type natriuretic Peptide in patients with advanced heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol.* 2010;105(2):249–254.

45 Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr.* 2010;23(7):685–713. quiz 786-8.

46 Lam CS, Roger VL, Rodeheffer RJ, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol.* 2009; 53(13):1119–1126.

47 Leung CC, Moondra V, Catherwood E, Andrus BW. Prevalence and risk factors of pulmonary hypertension in patients with elevated pulmonary venous pressure and preserved ejection fraction. *Am J Cardiol.* 2010;106(2):284–286.

48 Tumminello G, Lancellotti P, Lempereur M, et al. Determinants of pulmonary artery hypertension at rest and during exercise in patients with heart failure. *Eur Heart J.* 2007;28(5):569–574.

49 Patel JB, Borgeson DD, Barnes ME, et al. Mitral regurgitation in patients with advanced systolic heart failure. *J Card Fail.* 2004;10(4):285–291.

50 Olson TP, Snyder EM, Frantz RP, et al. Repeat length polymorphism of the serotonin transporter gene influences pulmonary artery pressure in heart failure. *Am Heart J.* 2007; 153(3):426–432.

51 Gavazzi A, Ghio S, Scelsi L, et al. Response of the right ventricle to acute pulmonary vasodilation predicts the outcome in patients with advanced heart failure and pulmonary hypertension. *Am Heart J.* 2003;145(2): 310–316.

52 Desai RV, Meyer P, Ahmed MI, et al. Relationship between left and right ventricular ejection fractions in chronic advanced systolic heart failure: insights from the BEST trial. *Eur J Heart Fail.* 2011;13(4):392–397.

53 Berkowitz R, Alhaj E, Manchikalapudi RB, et al. Determinants of right ventricular failure in patients admitted with acute left heart failure. *Congest Heart Fail.* 2010;16(6): 243–248.

54 La Vecchia L, Zanolla L, Varotto L, et al. Reduced right ventricular ejection fraction as a marker for idiopathic dilated cardiomyopathy compared with ischemic left ventricular dysfunction. *Am Heart J.* 2001;142(1):181–189.

55 Butler J, Chomsky DB, Wilson JR. Pulmonary hypertension and exercise intolerance in patients with heart failure. *J Am Coll Cardiol.* 1999;34(6):1802–1806.

56 Chang PP, Longenecker JC, Wang NY, et al. Mild vs severe pulmonary hypertension before heart transplantation: different effects on posttransplantation pulmonary hypertension and mortality. *J Heart Lung Transplant.* 2005;24(8):998–1007.

57 Puwanant S, Priester TC, Mookadam F, et al. Right ventricular function in patients with preserved and reduced ejection fraction heart failure. *Eur J Echocardiogr.* 2009; 10(6):733–737.

58 Abramson SV, Burke JF, Kelly JJ, et al. Pulmonary hypertension predicts mortality and morbidity in patients with dilated cardiomyopathy. *Ann Intern Med.* 1992; 116(11):888–895.

59 Grigioni F, Potena L, Galiè N, et al. Prognostic implications of serial assessments of pulmonary hypertension in severe chronic heart failure. *J Heart Lung Transplant.* 2006; 25(10):1241–1246.

60 Reindl I, Wernecke KD, Opitz C, et al. Impaired ventilatory efficiency in chronic heart failure: possible role of pulmonary vasoconstriction. *Am Heart J.* 1998; 136(5):778–785.

61 Filusch A, Ewert R, Altesellmeier M, et al. Respiratory muscle dysfunction in congestive heart failure-The role of pulmonary hypertension. *Int J Cardiol.* 2010; May 3; [Epub ahead of print].

62 Shalaby A, Voigt A, El-Saed A, Saba S. Usefulness of pulmonary artery pressure by echocardiography to predict outcome in patients receiving cardiac resynchronization therapy heart failure. *Am J Cardiol.* 2008;101(2):238–241.

63 Kainuma S, Taniguchi K, Toda K, et al. Pulmonary hypertension predicts adverse cardiac events after restrictive mitral annuloplasty for severe functional mitral regurgitation. *J Thorac Cardiovasc Surg.* 2011; March 11; [E-pub ahead of print].

64 Moreira LF, Benício A, Bacal F, et al. Determinants of long-term mortality of current palliative surgical treatment for dilated cardiomyopathy. *Eur J Cardiothorac Surg.* 2003;23(5):756–763. discussion 763-4.

65 Levine TB, Levine AB, Goldberg D, et al. Impact of medical therapy on pulmonary hypertension in patients with congestive heart failure awaiting cardiac transplantation. *Am J Cardiol.* 1996;78(4):440–443.

66 Ghio S. Pulmonary hypertension in advanced heart failure. *Herz.* 2005;30(4):311–317.

67 Kittleson MM, Kobashigawa JA. Management of advanced heart failure: the role of heart transplantation. *Circulation.* 2011; 123(14):1569–1574.

68 Drakos SG, Kfoury AG, Gilbert EM, et al. Effect of reversible pulmonary hypertension on outcomes after heart transplantation. *J Heart Lung Transplant.* 2007;26(4):319–323.

69 Klotz S, Wenzelburger F, Stypmann J, et al. Reversible pulmonary hypertension in heart transplant candidates: to transplant or not to transplant. *Ann Thorac Surg.* 2006;82(5): 1770–1773.

70 Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. *J Am Coll Cardiol.* 1995;25(5):1143–1153.

71 Gavazzi A, Berzuini C, Campana C, et al. Value of right ventricular ejection fraction in predicting short-term prognosis of patients with severe chronic heart failure. *J Heart Lung Transplant.* 1997;16(7):774–785.

72 Karatasakis GT, Karagounis LA, Kalyvas PA, et al. Prognostic significance of echocardiographically estimated right ventricular shortening in advanced heart failure. *Am J Cardiol.* 1998;82(3):329–334.

73 Field ME, Solomon SD, Lewis EF, et al. Right ventricular dysfunction and adverse outcome in patients with advanced heart failure. *J Card Fail.* 2006;12(8):616–620.

74 Lewis GD, Shah RV, Pappagianopolas PP, et al. Determinants of ventilatory efficiency in heart failure: the role of right ventricular performance and pulmonary vascular tone. *Circ Heart Fail.* 2008;1(4):227–233.

75 D'Andrea A, Gravino R, Riegler L, et al. Right ventricular ejection fraction and left ventricular dyssynchrony by 3D echo correlate with functional impairment in patients with dilated cardiomyopathy. *J Card Fail.* 2011;17(4):309–317.

76 Verhaert D, Mullens W, Borowski A, et al. Right ventricular response to intensive medical therapy in advanced decompensated heart failure. *Circ Heart Fail.* 2010; 3(3):340–346.

77 Cody RJ, Haas GJ, Binkley PF, et al. Plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. *Circulation.* 1992; 85(2):504–509.

78 Pacher R, Stanek B, Hülsmann M, et al. Prognostic impact of big endothelin-1 plasma concentrations compared with invasive hemodynamic evaluation in severe heart failure. *J Am Coll Cardiol.* 1996;27(3): 633–641.

79 Sütsch G, Kiowski W, Yan XW, et al. Short-term oral endothelin-receptor antagonist therapy in conventionally treated patients with symptomatic severe chronic heart failure. *Circulation.* 1998;98(21):2262–2268.

80 Spieker LE, Mitrovic V, Noll G, et al. Acute hemodynamic and neurohumoral effects of selective ET(A) receptor blockade in patients with congestive heart failure. ET 003 Investigators. *J Am Coll Cardiol.* 2000;35(7): 1745–1752.

81 Givertz MM, Colucci WS, LeJemtel TH, et al. Acute endothelin A receptor blockade causes selective pulmonary vasodilation in patients with chronic heart failure. *Circulation.* 2000;101(25):2922–2927.

82 Lüscher TF, Enseleit F, Pacher R, et al. Hemodynamic and neurohumoral effects of selective endothelin A (ET(A)) receptor blockade in chronic heart failure: the Heart Failure ET(A) Receptor Blockade Trial (HEAT). *Circulation.* 2002;106(21):2666–2672.

83 Mylona P, Cleland JG. Update of REACH-1 and MERIT-HF clinical trials in heart failure. Cardio.net Editorial Team. *Eur J Heart Fail.* 1999;1(2):197–200.

84 Kalra PR, Moon JC, Coats AJ. Do results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study spell the end for non-selective endothelin antagonism in heart failure? *Int J Cardiol.* 2002;85(2–3):195–197.

85 Anand IS, Wu T. Syndromes of subacute mountain sickness. *High Alt Med Biol.* 2004; 5(2):156–170.

86 Packer M, McMurray J, Massie BM, et al. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. *J Card Fail.* 2005;11(1):12–20.

87 Kaluski E, Cotter G, Leitman M, et al. Clinical and hemodynamic effects of bosentan dose optimization in symptomatic heart failure patients with severe systolic dysfunction, associated with secondary pulmonary hypertension – a multi-center randomized study. *Cardiology*. 2008;109(4):273–280.

88 Hefke T, Zittermann A, Fuchs U, et al. Bosentan effects on hemodynamics and clinical outcome in heart failure patients with pulmonary hypertension awaiting cardiac transplantation*. *Thorac Cardiovasc Surg*. 2011; March 22. [E-pub ahead of print].

89 Pacher R, Stanek B, Hülsmann M, Sinzinger H. Effect of prostaglandin E1 infusion in severe chronic heart failure. *Prostaglandins*. 1997;53(4):221–235.

90 Murali S, Uretsky BF, Armitage JM, et al. Utility of prostaglandin E1 in the pretransplantation evaluation of heart failure patients with significant pulmonary hypertension. *J Heart Lung Transplant*. 1992;11(4 Pt 1):716–723.

91 Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). *Am Heart J*. 1997;134(1):44–54.

92 Serra W, Musiari L, Ardissino D, et al. Benefit of prostaglandin infusion in severe heart failure: preliminary clinical experience of repetitive administration. *Int J Cardiol*. 2011;146(1):e10–e15.

93 Melenovsky V, Al-Hiti H, Kazdova L, et al. Transpulmonary B-type natriuretic peptide uptake and cyclic guanosine monophosphate release in heart failure and pulmonary hypertension: the effects of sildenafil. *J Am Coll Cardiol*. 2009;54(7):595–600.

94 Kass DA, Champion HC, Beavo JA. Phosphodiesterase type 5: expanding roles in cardiovascular regulation. *Circ Res*. 2007;101(11):1084–1095.

95 Lepore JJ, Maroo A, Bigatello LM, et al. Hemodynamic effects of sildenafil in patients with congestive heart failure and pulmonary hypertension: combined administration with inhaled nitric oxide. *Chest*. 2005; 127(5):1647–1653.

96 Lewis GD, Lachmann J, Camuso J, et al. Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. *Circulation*. 2007;115(1):59–66.

97 Lewis GD, Shah R, Shahzad K, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. *Circulation*. 2007;116(14):1555–1562.

98 Guazzi M, Samaja M. The role of PDE5-inhibitors in cardiopulmonary disorders: from basic evidence to clinical development. *Curr Med Chem*. 2007;14(20):2181–2191.

99 Behling A, Rohde LE, Colombo FC, et al. Effects of 5′-phosphodiesterase four-week long inhibition with sildenafil in patients with chronic heart failure: a double-blind, placebo-controlled clinical trial. *J Card Fail*. 2008;14(3):189–197.

100 Guazzi M, Vicenzi M, Arena R, Guazzi MD. PDE5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure: results of a 1-year, prospective, randomized, placebo-controlled study. *Circ Heart Fail*. 2011;4(1):8–17.

101 Stehlik J, Movsesian MA. Combined use of PDE5 inhibitors and nitrates in the treatment of pulmonary arterial hypertension in patients with heart failure. *J Card Fail*. 2009; 15(1):31–34.

102 Klodell CT, Morey TE, Lobato EB, et al. Effect of sildenafil on pulmonary artery pressure, systemic pressure, and nitric oxide utilization in patients with left ventricular assist devices. *Ann Thorac Surg*. 2007;83(1):68–71. discussion 71.

103 Tedford RJ, Hemnes AR, Russell SD, et al. PDE5A inhibitor treatment of persistent pulmonary hypertension after mechanical circulatory support. *Circ Heart Fail*. 2008;1(4): 213–219.

104 Jabbour A, Keogh A, Hayward C, Macdonald P. Chronic sildenafil lowers transpulmonary gradient and improves cardiac output allowing successful heart transplantation. *Eur J Heart Fail*. 2007;9(6–7):674–677.

105 Zakliczynski M, Maruszewski M, Pyka L, et al. Effectiveness and safety of treatment with sildenafil for secondary pulmonary hypertension in heart transplant candidates. *Transplant Proc*. 2007;39(9):2856–2858.

106 Boffini M, Sansone F, Ceresa F, et al. Role of oral sildenafil in the treatment of right ventricular dysfunction after heart transplantation. *Transplant Proc*. 2009;41(4):1353–1356.

107 De Santo LS, Mastroianni C, Romano G, et al. Role of sildenafil in acute posttransplant right ventricular dysfunction: successful experience in 13 consecutive patients. *Transplant Proc*. 2008;40(6):2015–2018.

108 Haddad H, Elabbassi W, Moustafa S, et al. Left ventricular assist devices as bridge to heart transplantation in congestive heart failure with pulmonary hypertension. *ASAIO J*. 2005;51(4):456–460.

109 Martin J, Siegenthaler MP, Friesewinkel O, et al. Implantable left ventricular assist device for treatment of pulmonary hypertension in candidates for orthotopic heart transplantation-a preliminary study. *Eur J Cardiothorac Surg*. 2004;25(6):971–977.

110 Salzberg SP, Lachat ML, von Harbou K, et al. Normalization of high pulmonary vascular resistance with LVAD support in heart transplantation candidates. *Eur J Cardiothorac Surg*. 2005;27(2):222–225.

111 Zimpfer D, Zrunek P, Sandner S, et al. Posttransplant survival after lowering fixed pulmonary hypertension using left ventricular assist devices. *Eur J Cardiothorac Surg*. 2007;31(4):698–702.

112 Nair PK, Kormos RL, Teuteberg JJ, et al. Pulsatile left ventricular assist device support as a bridge to decision in patients with end-stage heart failure complicated by pulmonary hypertension. *J Heart Lung Transplant*. 2010;29(2):201–208.

113 Torre-Amione G, Southard RE, Loebe MM, et al. Reversal of secondary pulmonary hypertension by axial and pulsatile mechanical circulatory support. *J Heart Lung Transplant*. 2010;29(2):195–200.

114 John R, Liao K, Kamdar F, et al. Effects on pre- and posttransplant pulmonary hemodynamics in patients with continuous-flow left ventricular assist devices. *J Thorac Cardiovasc Surg*. 2010;140(2):447–452.

115 Liden H, Haraldsson A, Ricksten SE, et al. Does pretransplant left ventricular assist device therapy improve results after heart transplantation in patients with elevated pulmonary vascular resistance? *Eur J Cardiothorac Surg*. 2009;35(6):1029–1034. discussion 1034-5.

116 Mikus E, Stepanenko A, Krabatsch T, et al. Reversibility of fixed pulmonary hypertension in left ventricular assist device support recipients. *Eur J Cardiothorac Surg*. 2011; Feb 25. [E-pub ahead of print].

117 Athanasuleas CL, Buckberg GD, Stanley AW, et al. Surgical ventricular restoration: the RESTORE Group experience. *Heart Fail Rev*. 2004;9(4):287–297.

118 Subramanian H, Kunadian B, Dunning J. Is it worth performing surgical ventricular restoration in patients with ischemic cardiomyopathy and akinetic but non-aneurysmal segments in the left ventricle? *Interact Cardiovasc Thorac Surg*. 2008;7(4):702–707.

119 Jones RH, Velazquez EJ, Michler RE, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med*. 2009;360(17):1705–1717.

120 Patel ND, Williams JA, Nwakanma LU, et al. Surgical ventricular restoration for advanced congestive heart failure: should pulmonary hypertension be a contraindication? *Ann Thorac Surg*. 2006;82(3):879–888. discussion 888.

121 Tatli E, Kurum T, Aktoz M, Buyuklu M. Effects of carvedilol on right ventricular ejection fraction and cytokines levels in patients with systolic heart failure. *Int J Cardiol*. 2008; 125(2):273–276.

122 Quaife RA, Christian PE, Gilbert EM, et al. Effects of carvedilol on right ventricular function in chronic heart failure. *Am J Cardiol*. 1998;81(2):247–250.

123 Bleeker GB, Schalij MJ, Nihoyannopoulos P, et al. Left ventricular dyssynchrony predicts right ventricular remodeling after cardiac resynchronization therapy. *J Am Coll Cardiol*. 2005;46(12):2264–2269.