Heart failure (HF) is the most common cause of pulmonary hypertension (PH). Elevated left heart filling pressures, whether from systolic dysfunction, diastolic dysfunction, or valvular heart disease, can result in elevated pulmonary artery pressures.1 The proportion of HF patients who also have PH varies depending on the subset of patients, but remains invariably high. In 1992, Abramson et al2 reported that 26% of their cardiomyopathy cohort had a systolic pulmonary artery (PA) pressure of 40 mm Hg or higher. In 2001, Ghio et al3 found PH in more than 60% of their patients with moderate or severe HF and left ventricular (LV) dysfunction. In 2009, Lam et al4 presented the Mayo Clinic cohort of HF patients with preserved systolic function, more than 80% of which had PH.

However, although the literature is abundant on the much less common primary pulmonary arterial hypertension, it is relatively scarce on PH in HF, or type 2 PH by the World Health Organization classification. This review will focus on PH in HF.

Definitions

PH is usually defined as a chronic elevation of a mean PA pressure above 25 mm Hg, measured invasively by a PA catheter.5 By echocardiography, PA systolic pressure is commonly estimated from the velocity of tricuspid regurgitation. PH is considered mild if the PA systolic pressure is 35 to 45 mm Hg, moderate if it is 46 to 60 mm Hg, and severe if it is greater than 60 mm Hg.6 The driving pressure across the pulmonary circulation, or the difference of mean PA pressure and pulmonary capillary wedge pressure, is referred to as the transpulmonary gradient (TPG).

Pulmonary vascular resistance (PVR) is derived by dividing the difference of mean PA pressure and left atrial pressure (pulmonary capillary wedge pressure) by the cardiac output. PVR index is used to correct PVR for body size and to avoid underestimation of PH in obesity.

The key feature differentiating PA hypertension and PH resulting from HF is elevated pulmonary capillary wedge pressure, which is present in HF and absent in pulmonary arterial hypertension. The latest diagnostic algorithm is presented by Hoeper et al (Fig. 1).7

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Pathophysiology

In HF, there are 2 major components of PH: hydrostatic and vasoreactive (Fig. 2). Hydrostatic, or the passive component, reflects the backward transmission of elevated LV end-diastolic pressure. Therefore, PA systolic pressure correlates tightly with pulmonary capillary wedge pressure and is roughly twice the wedge pressure. The reactive component represents vasoconstriction and remodeling of pulmonary vasculature.

Normally, the pulmonary vasculature is characterized by low pressure, low resistance, and high distensibility. It can accommodate a significant increase in blood flow with a minimal elevation of PA pressure. When this compensatory capacity is exceeded, PA pressure increases at first on exertion and then at rest. The right ventricle is very sensitive to changes in afterload. With chronic elevation in afterload, the right ventricle begins to fail. Excessive sympathetic adrenergic stimulation as well as activation of the endothelin and renin-angiotensin-aldosterone system contributes to the pathophysiology of right ventricular failure. Right ventricular dilatation results in a leftward shift of the septum causing a change in LV geometry, decrease in LV distensibility, and thus contributing to the low cardiac output state. The measured severity of PH depends, in part, on the performance of the right ventricle. Right ventricular failure as a result of cardiomyopathy, infarct, or ischemia may occur at pulmonary pressures lower than 45 to 50 mm Hg; severe PH may never develop, despite an increase in PVR. An acute increase in pulmonary vascular tone can also result in right ventricular failure as is seen in heart transplant recipients with PH and thus there is the necessity to decrease PA pressure both before and after heart transplant.

Structural changes occur at the capillary level including swelling of the pulmonary capillary endothelial cells, thickening of the basal lamina, and proliferation of reticular and elastic fibrils. These structural changes contribute toward
increasing PVR, decreasing permeability of the vascular bed, and ultimately lower the possibility of development of pulmonary edema and increase the likelihood of right ventricular failure. These changes are mostly reversible if there is a successful reduction in cardiac filling pressures, although the reversal may take several months.\textsuperscript{14}

**Factors Determining PH**

Although related to LV failure, PH in the context of HF does not seem to correlate with the severity of LV systolic dysfunction. On the contrary, it depends on the elevation of filling pressure echocardiographically determined by severity of diastolic dysfunction.\textsuperscript{15–18}

The E wave deceleration rate, E/A ratio,\textsuperscript{15,19} and ratio of E/E′ have been shown to reflect end-diastolic pressure more accurately than other echocardiographic parameters.\textsuperscript{20} According to the results of various studies, the restrictive filling pattern,\textsuperscript{21} the E wave deceleration rate, and the degree of mitral regurgitation were the strongest independent predictors of PH.\textsuperscript{15} A reduction in PA systolic pressure during therapy is determined, to the great extent, by wedge pressure reduction.\textsuperscript{21} Moreover, the reversibility of PH was apparent only in those patients who exhibited improvement of diastolic dysfunction from the restrictive or pseudonormal to impaired relaxation pattern likely representing improvement in filling pressures.

Among patients with normal systolic function, Neuman et al\textsuperscript{22} found a significant increase in PA pressure for each step up in diastolic dysfunction grade. The mean PA pressure was 31.1 ± 6 mm Hg for normal diastolic function, 35.6 ± 10.2 mm Hg for grade 1 diastolic dysfunction (impaired relaxation), 38.9 ± 10.6 mm Hg for grade 2 (pseudo normal), and 55.1 ± 11.4 mm Hg for grade 3 (restrictive pattern) (P < .001). Interestingly, pulmonary venous hypertension has been shown to be highly associated with the metabolic syndrome in patients with normal LV systolic function.\textsuperscript{23}

Age strongly predicts PH as well.\textsuperscript{16} PH is highly prevalent among patients with end-stage renal disease on hemodialysis. In 1 study, diastolic dysfunction was present in three fourths of patients with PH and end-stage renal disease. A higher PA pressure correlated with a higher flow through arteriovenous fistula and the brain natriuretic peptide level.\textsuperscript{24}

In exercise, wedge pressure rises in parallel with PA mean pressure; both correlate well with maximal oxygen consumption, unlike resting cardiac index and resting systemic arterial mean pressure, which did not demonstrate correlation with PA pressure.\textsuperscript{25} However, according to other data, ejection fraction, or degree of systolic dysfunction, is a determinant of PH on exercise. LV ejection fraction (P = .03) and mitral effective regurgitant orifice (P = .008) were independently associated with PA systolic pressure. Furthermore, dyspnea on exertion was more pronounced in patients with greater exercise-related increase in PA systolic pressure.\textsuperscript{26}

Compared with patients with idiopathic pulmonary arterial hypertension, patients with pulmonary venous hypertension have been found to have a higher frequency of metabolic syndrome.\textsuperscript{23}

**Clinical Significance**

In patients with HF, PH is a predictor of poor outcome. It is associated with increased short- and long-term mortality\textsuperscript{2,27} in patients with both reduced and preserved LV ejection fraction.\textsuperscript{28} Moreover, it was recently discovered that PH is associated with poor prognosis and high mortality, not only in HF, but also in general population.\textsuperscript{29}

Patients with a higher velocity of tricuspid regurgitation (greater than 2.5 m/s) had a 40% higher mortality rate and a 50% higher rate of HF admissions than those with normal pulmonary pressures.\textsuperscript{2} Shalaby et al\textsuperscript{30} demonstrated that elevated baseline systolic PA pressure in patients who undergo cardiac resynchronization therapy independently predicted all-cause mortality or transplantation and HF admission. A post-resynchronization decrease in pulmonary pressure was an independent positive prognostic marker. In another study, in which more than 1000 patients with cardiomyopathy were followed for an average of 4.4 years, mean PA pressure appeared to be 1 of the most important hemodynamic predictors of death.\textsuperscript{27} In a cohort of 400 patients with known or presumed HF and PH, a Cox proportional-hazards model apportioned a 9% increase in mortality per 5 mm Hg increase in right ventricular systolic pressure.\textsuperscript{28}

PH also impacts the exercise capacity in HF patients. In treadmill exercise testing with hemodynamic monitoring, increased pulmonary vascular resistance was associated with significantly lower peak exercise oxygen consumption (VO\textsubscript{2}) and lower peak exercise cardiac output, suggesting that PH impairs exercise performance in HF.\textsuperscript{31}

**Role of PH in Heart Transplantation**

PH is a risk factor for early postoperative mortality in heart transplantation, mostly from fatal right ventricular failure. According to data from the International Society for Heart and Lung Transplantation registry, approximately 20% of early deaths after cardiac transplantation can be attributed to right ventricular failure.\textsuperscript{32} Several studies have identified increased PVR > 2.5 Woods units (WU), which is present in about 30% of heart transplant candidates, as an important risk factor for early death after transplant. Other groups reported a 2.5-fold increase in 3-month mortality in patients with a PVR > 2.5 and an increase in 3-, 6-, and 12-month mortality with a TPG > 15 mm Hg.\textsuperscript{33–35} Retrospectively studied transplant patients had a 1-year mortality of 5.6% if their PVR and TPG were below these levels and 24.4% if they exceeded these numbers before the transplant.\textsuperscript{35}

These and other observations are reflected in the listing criteria for cardiac transplantation published by the International Society for Heart and Lung Transplantation.
According to them, PA hypertension and elevated PVR should be considered as a relative contraindication to cardiac transplantation when the PVR is >5 WU or the PVR index >6 or the TPG exceeds 16 to 20 mm Hg. If PA systolic pressure exceeds 60 mm Hg in conjunction with any of the preceding 3 variables, the risk of right HF and early death is increased. If the PVR can be reduced to <2.5 with a vasodilator but the systolic blood pressure falls <85 mm Hg, the patient remains at high risk of right HF and mortality after cardiac transplantation.36

The determination of TPG in combination with PVR is a more reliable predictor of early posttransplant survival than PVR alone.37 Butler et al reported that PA systolic pressure and TPG—but not PVR pretransplant—were associated with poor posttransplant survival.38

Interestingly, some investigators did not see the increased risk when performing transplants with PH. Tenderich et al39 could not confirm increased mortality in patients with elevated PVR. In their 83 patients with preoperative PVR ≥5 WU and TPG >15 mm Hg, 30-day mortality and cumulative survival after 1 and 5 years was not different from patients with more favorable from the hemodynamic profile.40 Addonizio et al41 transplanted 33 patients with PVR index ≥6, and 28 of them survived.

After heart transplantation, 80% of survivors normalize their PVR at 1 year,42–44 indicating that even “fixed” PH reverses eventually with adequate blood flow and normal filling pressures. Similar favorable changes occur in LV assist device (LVAD) recipients.

**Reversibility Tests**

PH is considered reversible if PVR can decrease to ≤2.5 WU with pharmacological testing, which is commonly done as a part of the transplant evaluation process in an attempt to predict and improve outcomes. Patients with reactive PH can be considered suitable for orthotopic cardiac transplantation.

Different factors influence the reversibility of PH, which is less reversible in patients with ischemic versus nonischemic cardiomyopathy and in ex-smokers versus nonsmokers.45 Reversibility of PH translates into improved 30-day survival rate after heart transplantation, but does not entirely eliminate the risk. Pharmacological tests to predict the reversibility of PH do not always reflect the posttransplant response. Cardiopulmonary bypass and intraoperative blood products may lead to further increase in PVR, which might explain why even patients with “reversible” PH still have a markedly higher mortality compared with patients with normal PVR.34

According to Costard-Jackie et al,46 candidates for transplant with a PVR >2.5 WU had a 3-month posttransplant mortality rate of 17.9% versus 6.9% in patients with PVR ≤2.5 WU. However, if their PVR could be reduced to ≤2.5 WU with nitroprusside without a significant drop in systemic blood pressure, their 3-month mortality after the transplant was only 3.8%, as opposed to 40.6% in those who did not respond to nitroprusside and 27.5% in those who responded but with a drop in systolic blood pressure to below 85 mm Hg. After these data were published in 1992, it became a common practice to conduct acute pharmacological testing in patients with HF and PH before heart transplant.

Historically, sodium nitroprusside was used as a challenge in the acute setting. Intravenous nitroprusside therapy is begun with a dose of approximately 1 mcg kg min and titrated until (1) PVR decreases to below 2.0 Wood units, (2) PA systolic pressure decreases to below 50 mm Hg, or (3) mean blood pressure decreases to below 65 mm Hg.34

Currently, multiple other agents are used for PH reversibility testing. Table 1 has medications and doses used for this purpose. It is difficult to say which agents are better than others because direct comparison of all of them in a randomized manner was never done. To a great extent, the choice of an agent depends on the experience of a particular center.

An intravenous bolus of 0.1 mg of nitroglycerin can be followed by increasing doses according to the criteria used for nitroprusside.47 An intravenous bolus of milrinone followed by continuous infusion can be used acutely and continued for a prolonged time.48,49

Among patients participating in the study by Pamboukian et al,40 none of those who responded to milrinone in pretransplant testing died after the transplant. Milrinone was also tested as a nebulizer.50

Inhaled nitric oxide (NO) is a potent, rapidly acting, and selective pulmonary vasodilator that causes pulmonary vasodilatation with minimal systemic effects, thereby reducing TPG and PVR.51,52 Compared with nitroprusside, NO does not drop systemic pressure, although it can sometimes cause an elevation in pulmonary capillary wedge pressure.53

Intravenous dipyridamole augments and prolongs the pulmonary vasodilator effects of inhaled NO in congestive HF patients with severe PH; when administered in combination with NO inhalation, it can identify PH reversibility in potential cardiac transplant recipients in whom no pulmonary vasodilator response to inhalation of NO alone is observed.54

Prostaglandins are also used for PH reversibility testing with good results. Prostacyclin is infused at a starting dose of 1 to 2 ng kg min and increased until a decrease in systolic arterial blood pressure, increase in heart rate, or side effects such as nausea and headache. Haraldsson and colleagues55 described a good selective dose-dependent decrease in PVR and TPG with inhaled prostacyclin with no effects on systemic circulation. It effectively improves pulmonary hemodynamics, with an almost 50% reduction in PVR (P = .0003) and a doubling of PA compliance (P < .0001), reflecting improvement in pulmonary vascular tone. Furthermore, it produces a positive inotropic effect.56 Intravenous prostaglandin E1 have also safely and successfully lowered PVR and TPG in 99% of patients without any significant side effects.57 In the Muenster experience, all patients with PH experienced a successful reduction in PVR by using prostaglandin E1 or prostacyclin; their 30-day and 10-year survival rates after orthotopic cardiac transplantation were similar to patients without PH.58
Some evidence suggests that prostaglandins may be more effective than other agents in the acute reversal of PH. Prostacyclin, compared with sodium nitroprusside, induced a greater increase in cardiac output and decrease in systemic and pulmonary vascular resistances as well as lesser decrease in cardiac filling pressures.\(^\text{59}\) Inhaled prostacyclin effectively reversed PH in patients resistant to sodium nitroprusside,\(^\text{60}\) and caused a significantly greater reduction in PA pressure and an increase in cardiac output than inhaled NO.\(^\text{61,62}\) Other data have indicated that patients unresponsive to NO may be responsive to prostaglandin E1 and vice versa.\(^\text{63}\)

Murali et al.\(^\text{64}\) compared nitroglycerin and nitroprusside to prostaglandin E1, dobutamine, and enoximone. All of the drugs significantly increased cardiac output and decreased PVR. In addition, all of the drugs except dobutamine significantly lowered PA pressure and wedge pressure. However, prostaglandin E1 was the only drug that significantly lowered TPG. The magnitude of decline in PVR and TPG was greatest with prostaglandin E1.

In a retrospective comparison of vasopressors (dobutamine, dopamine, or combination of both) with vasodilators (nitroglycerin, sodium nitroprusside) and prostacyclin, no significant difference in the magnitude of decrease of PA pressure, TPG, or PVR, although cardiac output increased more with prostacyclin. Similar proportion of patients (45% to 50%) demonstrated reversibility of PH with each intervention.\(^\text{65}\)

Recently, oral sildenafil has been used to assess for reversibility of PH, reducing PA pressure in a dose-dependent fashion without significant change in mean pulmonary capillary wedge pressure, cardiac output, systemic vascular resistances, or mean blood pressure.\(^\text{66,67}\) It provided an even stronger effect when used in combination with inhaled NO.\(^\text{54}\)

In a randomized comparison of intravenous milrinone and intravenous sildenafil, milrinone produced greater decrease in mean PA pressure and wedge pressure, as well as increase in heart rate. The reductions in systemic and pulmonary vascular resistance were similar.\(^\text{68}\)

When an acute vasodilator challenge is unsuccessful, hospitalization with continuous inotropes or vasodilators and hemodynamic monitoring may be required. PVR may normalize in days or weeks; it almost always eventually normalizes with LVADs.\(^\text{42}\)

### Treatment

PH resulting from LV failure can be improved using medications that improve LV function. LV unloading results in decreased PA pressure, which in turn leads to favorable effects on systemic circulation. β-blockers that normally do not directly change pulmonary pressure may reverse PH, which was considered fixed after post-nitroprusside, because of the improved LV function.\(^\text{69}\) Cardiac resynchronization therapy increases cardiac output and decreases pulmonary capillary wedge pressure, thereby partially reversing hemodynamic abnormalities that lead to secondary PH in many HF patients—sometimes to the point that they become eligible for cardiac transplantation.\(^\text{70}\) Many treatment options available for pulmonary arterial hypertension have been tested in PH secondary to HF, some of them successfully. Clinical studies in HF population assessing agents used in treatment of pulmonary arterial hypertension are summarized in Table 2. Studies in which patients were exposed to a single dose of a drug are not included in Table 2.

<table>
<thead>
<tr>
<th>Pharmacologic Agents Used for Testing of Reversibility of PH</th>
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<tbody>
<tr>
<td><strong>Agent</strong></td>
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</tr>
<tr>
<td>Milrinone</td>
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<tr>
<td>Enoximone</td>
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<tr>
<td>Dobutamine</td>
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<tr>
<td>Sodium nitroprusside</td>
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<td>Prostaglandin E1</td>
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<td>Prostaglandin E1</td>
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<td>Sildenafil</td>
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<tr>
<td>Nitroglycerin</td>
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<tr>
<td>Dipyridamole</td>
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<td>Nesiritide</td>
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</table>

PO, orally; IV, intravenously.
<table>
<thead>
<tr>
<th>Treatment, Duration</th>
<th>Study Acronym and Characteristics</th>
<th>Patients Population, Duration</th>
<th>PH is an Inclusion Criterion</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan 500 mg twice daily</td>
<td>REACH-1 Double-blind, randomized, placebo controlled</td>
<td>n = 370 NYHA III/IV 26 weeks</td>
<td>No</td>
<td>Terminated early because of liver function test abnormalities</td>
</tr>
<tr>
<td>Bosentan 62.5 mg twice daily for 4 weeks, then 125 mg twice daily</td>
<td>ENABLE Placebo controlled, randomized</td>
<td>n = 1600 NYHA III/IV 1.5 years</td>
<td>No</td>
<td>No improvement with bosentan</td>
</tr>
<tr>
<td>Darusentan varying daily doses: 10 mg, 25 mg, 50 mg, 100 mg, 300 mg or placebo every 3 days</td>
<td>EARTH Placebo controlled, randomized, parallel</td>
<td>n = 642 NYHA II-IV 6 months</td>
<td>No</td>
<td>No change in left ventricular end systolic volume</td>
</tr>
<tr>
<td>Tezosentan 50 mg or 100 mg/hour IV, twice daily</td>
<td>RITZ-5 Placebo controlled, randomized, blinded</td>
<td>n = 84 Acute pulmonary edema 24 hours</td>
<td>No</td>
<td>No change in oxygen saturation</td>
</tr>
<tr>
<td>Bosentan 15 mg, 3 times/day</td>
<td>Not controlled, not randomized</td>
<td>n = 40 NYHA III-IV EF &lt;35% 12 weeks</td>
<td>Yes</td>
<td>No difference in systolic PAP change, cardiac index shift, or any of the other 22 echocardiographic measurements. More patients in the bosentan arm experienced adverse and serious adverse events</td>
</tr>
<tr>
<td>Epoprostenol 4.0 ng.kg.min IV for a total of 24 hours over 3 consecutive days every 3 months</td>
<td>The Flolan International Randomized Survival Trial (FIRST)</td>
<td>n = 471 NYHA III-IV EF &lt;25% 2 years + 30 days’ Follow-up</td>
<td>No</td>
<td>Increased mortality rates and no improvement in quality of life with Flolan</td>
</tr>
<tr>
<td>Prostaglandin E1 10 mg/kg/min IV 36 months’ survival: 72.7% in the PGE1 group and 56% in the control group (NS). The mean EF increased from 25.78% to 32.1% in the PGE1 group and from 23.38% to 26.15 in the control group (P &lt; .001); the NYHA mean class improved from 3.18 to 2.24 in the PGE1 group and from 3.46 to 3.38 in the control group (P &lt; .05). The PA pressure decreased from 57.7 to 40.8 mm Hg (P &lt; .001)</td>
<td>Yes</td>
<td>No change in left ventricular end systolic volume</td>
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<tr>
<td>Prostacyclin continuous IV infusion</td>
<td>Prospective controlled not randomized</td>
<td>n = 33 NYHA III-IV EF &lt;35% 12 weeks</td>
<td>No</td>
<td>Mean PA pressure &gt; 25 mm Hg by catheter</td>
</tr>
<tr>
<td>Sildenafil 25 mg, 3 times/day 6 months</td>
<td>Not controlled, not randomized</td>
<td>n = 40 NYHA III-IV EF &lt;30% 12 weeks</td>
<td>No</td>
<td>Improved heart rate recovery (baseline: 17.5 ± 3.5 beats per minute versus post: 20.6 ± 3.2 beats/min)</td>
</tr>
<tr>
<td>Sildenafil 50 mg twice per day</td>
<td>Prospective, randomized</td>
<td>n = 46 NYHA II-III EF &lt;45% 6 months</td>
<td>No</td>
<td>Reduction of systolic PAP (33.7 to 23.9 mm Hg), decrease in ventilation to CO2 production slope (from 35.5 to 29.8), and breathlessness score (from 23.6 to 17.2)</td>
</tr>
<tr>
<td>Sildenafil 25 to 75 mg orally 3 times daily</td>
<td>Prospective randomized placebo controlled 12 weeks</td>
<td>n = 34 NYHA II-IV EF &lt;40%</td>
<td>Yes</td>
<td>The change in peak VO2 from baseline was greater in the sildenafil group (1.8 ± -0.7 mL x kg(-1) x min(-1)) than in the placebo group (-0.27 mL x kg(-1) x min(-1))</td>
</tr>
</tbody>
</table>
increased in the systemic and pulmonary vasculature and in the kidney. It is partially responsible for natriuretic peptide desensitization in HF, and many effects of phosphodiesterase type 5 inhibition produce effects similar to brain natriuretic peptide infusion.82

Basic studies suggest that phosphodiesterase inhibition has potentially favorable direct myocardial effects that may block adrenergic, hypertrophic, and proapoptotic signaling.73 Sildenafil protects cardiomyocytes against necrosis and apoptosis in the ischemia-reperfusion model,74 and prevents LV dysfunction in the anthracycline-induced cardiomyopathy model.75 In humans, it has been found to enhance endothelial function76 and improve arterial stiffness.77

Sildenafil increases myocardial contractility and reduces LV afterload,78 blunts adrenergic stimulation,79 and improves lung diffusion capacity as well as pulmonary hemodynamics at rest and during exertion. Measurements on right cardiac catheterization have shown that sildenafil acutely reduced resting and exercise pulmonary arterial pressure, systemic vascular resistance, and PVR while increasing the resting and exercise cardiac index (P < .05 for all) without altering mean arterial pressure, heart rate, or pulmonary capillary wedge pressure, thereby acting as a selective pulmonary vasodilator.80 These effects are sustained if sildenafil is used regularly.81 It also reduces fluid transition to the alveolar interstitium.80,82 In addition, sildenafil augmented and prolonged the hemodynamic effects of inhaled NO in patients with HF and PH.83

In exercise, sildenafil improves exercise ventilation efficiency and aerobic performance,84 as well as heart rate recovery after exercise.77 It increases peak VO₂ and decreases ventilatory response to carbon dioxide output during a cardiopulmonary stress test.80,85 Sildenafil’s ability to augment peak VO₂ is directly correlated with baseline resting PVR and indirectly correlated with baseline resting right ventricular ejection fraction.86

Some early concerns about potential arterial oxygen desaturation with sildenafil have yet to be confirmed. Sildenafil is usually well tolerated without desaturation or significant changes in heart rate or blood pressure.87 The only common side effect is flushing.85

Favorable physiologic effects of sildenafil translate into better outcomes in HF patients. A randomized, double-blind, placebo-controlled trial demonstrated that sildenafil in HF patients with severely reduced systolic function decreased PA systolic pressure at 60 minutes and at 4 weeks compared with a placebo.88 Symptomatically, stable HF patients on optimal therapy experienced less breathlessness after adding sildenafil as their systolic PA pressure decreased from 33.7 to 25.2 mm Hg and 23.9 mm Hg (P < .01) in 3 and 6 months, respectively.85 Sildenafil treatment has also been associated with improvement in right ventricular systolic function, 6-minute walk distance, and Minnesota Living with Heart Failure score.86

Sildenafil may be effectively used not only for acute hemodynamic testing of PH reversibility, but also for treatment of secondary, irreversible PH in potential heart transplant recipients because it allows patients who may otherwise have been excluded because of PH to be transplanted. In 1 study, 6 patients with PH nonresponsive to nitroprusside were put on oral sildenafil. After 1 month, 3 patients had normalized PVR and TPG and 2 patients became responsive to nitroprusside.89 Moreover, sildenafil appears to not only make patients eligible for heart transplant, but also provide a smooth postoperative course in transplanted patients. Six patients received 50 mg of sildenafil before the transplant, followed by 50 or 25 mg 3 times per day after heart transplantation; good short-term outcomes occurred in 4 of them. Sildenafil treatment was discontinued 10 to 14 days after surgery, using a stepwise dose reduction.90

After LVAD implantation, sildenafil provides additional reduction of PA pressure and facilitates weaning from inhaled NO and inotropes, which can otherwise cause a rebound PH.91 All these small studies provide a good background for future randomized controlled clinical trials in HF population with PH.

Prostaglandins

Prostaglandins are potent vasodilators that have been used in the treatment of primary (arterial) PH. They have multiple effects that seem to benefit HF patients. Available prostaglandins include prostaglandin I₂ (prostacyclin, epoprostenol, Flolan) and prostaglandin E₁. Although the former is a potent systemic vasodilator with consequent deleterious effects on ischemic myocardium, the latter is degraded in the pulmonary vessels and has a systemic effect only at high doses.92,93 Intravenous prostaglandin E₁ reduces atrial natriuretic peptide and norepinephrine while increasing renal perfusion and diuresis.94

Despite their vasoactive properties, prostaglandins did not perform well in the HF setting. The acute effects of intravenous prostacyclin in HF patients include a decrease in pulmonary capillary wedge pressure and PVR and an increase in cardiac index; however, at the same time, they can cause a drop in arterial pressure and systemic vascular resistance, with a subsequent rise in plasma epinephrine, norepinephrine, renin, and aldosterone concentrations.96

Some small nonrandomized trials provided encouraging results with improved hemodynamics and symptoms, showing a trend toward better outcomes through intermittent infusion of prostaglandin E₁.97 Epoprostenol (prostacyclin), added to a maximal conventional treatment—including dobutamine in 30% of patients—resulted in an increase in 6-minute walk distance by 30 meters in 12 weeks when compared with standard treatment only. Long-term outcomes were not studied.98

One case report described a longer successful use of prostaglandins. Intravenous prostacyclin and dobutamine combined with inhaled iloprost given for 21 days stabilized a patient with PH for heart transplantation, which was uncomplicated.99 A direct prospective and randomized
comparison of prostaglandin E1 versus prostacyclin versus low-dose dobutamine in patients awaiting heart transplantation resulted in treatment failure in 13% of patients on prostaglandin E1, 50% on prostacyclin, and 43% on dobutamine ($P < .05$). Intermittent infusion of prostaglandin E1 has been shown to decrease PA pressure in patients with advanced HF. Some data indicate that prostaglandins can benefit short-term management of PH during the early postoperative period after cardiac transplantation. When 9 patients with PH after cardiac surgery or heart transplantation and an elevated PVR treated with inotropic support were given inhaled prostacyclin, a dose-dependent decrease occurred in PVR and TPG (which decreased by 29% and 26%, respectively), right ventricular performance improved, and no changes were evident in systemic vascular resistance. In patients with PH undergoing mitral valve surgery, inhaled iloprost was superior to intravenous nitroglycerin for preventing acute right ventricular failure during weaning from cardiopulmonary bypass. Aerosolized iloprost in a patient after heart transplant with early postoperative right ventricular failure resulted in a decrease of PVR (-23.5%), whereas cardiac index (+24.0%) and mixed venous saturation (+9.0%) increased, without affecting systemic vascular resistance. However, in clinical trials, patients with severe HF and decreased LV ejection fraction randomly assigned to epoprostenol demonstrated a strong trend toward decreased survival, despite improvements in cardiac index and pulmonary capillary wedge pressure. The Flolan International Randomized Survival Trial was prematurely stopped because of increased mortality in the epoprostenol arm. This increased mortality could have resulted from a positive inotropic effect. It is important to realize though that PH was not among inclusion criteria in the Flolan International Randomized Survival Trial. Therefore, treatment with Flolan in this study did not target subset of patients with HF and PH, where the benefit from Flolan could be expected.

**Endothelin-receptor Blockers**

Endothelin, one of the most potent natural vasoconstrictors, plays an important role in the regulation of vascular tone. Vasodilatation is in turn mediated by the release of NO and prostacyclin. Studies in both experimental models and patients suggest that NO-dependent pulmonary vasodilatation (which depends on endothelial functions) is impaired in HF. Production of endothelin-1 is markedly increased in HF, correlating with both prognosis and symptoms. Endothelin-receptor blockage provides hemodynamic benefits in experimental and clinical HF. Endothelin receptor blockage after experimental myocardial infarction also reduced PH and right ventricular hypertrophy. Elevated plasma endothelin levels in patients with HF correlate with PA pressures and PVR. Acute effects of intravenous bosentan in HF have included a reduction in mean arterial and pulmonary pressures, right atrial and wedge pressure, and PVR as well as an increased cardiac and stroke volume index without change in heart rate. Short-term oral therapy has demonstrated that oral bosentan provides similar but enhanced hemodynamic effects: PVR normalized and dyspnea improved. In a multicenter, double-blind, placebo-controlled trial, Givertz et al demonstrated similar hemodynamic responses to sitaxsentan. However, vascular resistance also significantly decreased, which can create problems in HF. And indeed, the outcomes of the use of endothelin antagonists in HF trials thus far have been discouraging.

In the randomized, double-blind, placebo-controlled EndothelinA Receptor Antagonist Trial in Heart Failure (ie, EARTH), endothelin blockage with darusentan did not improve cardiac remodeling or clinical symptoms or outcomes in patients with chronic HF. In another multicenter, double-blind, randomized, and placebo-controlled trial comparing bosentan to a placebo in HF patients with PH, no difference emerged in PA pressure and cardiac index—or any of the other 22 echocardiographic measurements obtained. The frequency of adverse events requiring drug discontinuation was higher in the bosentan group. In the Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ie, ENABLE) study, treatment with bosentan increased the risk of worsening HF, necessitating hospitalization. In the Heart Failure ET(A) Receptor Blockade Trial (ie, HEAT), short-term administration of darusentan increased the cardiac index, but did not change pulmonary capillary wedge pressure,
PA pressure, PVR, or right atrial pressure. Systemic vascular resistance decreased significantly, and a trend toward more adverse events (including death and early exacerba-
tion of HF) was also evident.112

Tezosentan, an intravenous short-acting endothelin re-
ceptor antagonist tested in the Value of Endothelin Receptor
Inhibition With Tezosentan in Acute Heart Failure Studies (ie, VERITAS), neither improved dyspnea nor re-
duced the incidences of death or worsening HF.113

Packer et al114 found that bosentan-treated HF patients
had an increased risk of HF during the first month of treat-
ment, but a decreased risk of HF during the fourth, fifth,
and sixth months of therapy when compared with a placebo.
The major noncardiac adverse effects of bosentan included
an increase in hepatic transaminases (in 15.6% of patients)
and a decrease in hemoglobin.

There may be still a place for short-term treatment with
endothelin antagonists in the setting of pretransplant or
early posttransplant PH. Indeed, in 5 of 7 patients consid-
ered ineligible for heart transplantation because of high
PVR (post-nitroprusside infusion), bosentan therapy signif-
ically reduced PVR.115

However, in the only long-term randomized control trial
where PH was in inclusion criterion, patients on bosentan
experienced more serious adverse events than controls.110

Inhaled NO

NO is synthesized endogenously from L-arginine and ox-
gen through a family of 3 NO synthases—all of which
are expressed in the lung—and provides vasorelaxation and
bronchodilation as well as the inhibition of mitochondrial
respiration, inhibition of platelet and leukocyte activation,
and modulation of vascular smooth muscle cell prolifera-
tion.116 Normal basal pulmonary resistance is maintained
in part by continuous local production of NO.117 Drugs
that generate NO, such as nitroglycerin and sodium nitro-
prusside, can dilate the pulmonary vasculature, but they
also cause systemic hypotension.

In 1991, Frostell et al118 described the decrease in PA
pressure with inhaled NO in experimental PH and found
that doses up to 80 parts per million did not alter systemic
blood pressure. In 1999, it was approved by the Food and
Drug Administration for the treatment of hypoxemic infants
with PH.119 Since then, it has been widely used in adult car-
diology as well.

Inhaled NO diffuses rapidly across the alveolar-capillary mem-
brane into the smooth muscle of pulmonary vessels and
provides effects similar to endogenous NO—namely,
vassodilatory, bronchodilatory, anti-inflammatory, and anti-
proliferatory.120 Inhaled NO has facilitated the weaning
of right ventricular assist devices in animal experi-
ments.121 In addition, in cardiopulmonary stress test, NO
has been shown to improve oxygen consumption at the an-
aerobic threshold.122

Inhaled NO in concentrations from 5 to 80 parts per million
has been used for the treatment of PH in HF patients, especially post-ventricular assist device placement and post-
transplant. When inhaled NO was started before the termina-
tion of cardiopulmonary bypass, patients had better 30-day
survival rate and decreased incidence of right ventricular dys-
fuction compared with the historical cohort.123 Their hemo-
dynamics were also better,124–126 and the weaning from
bypass was easier.127 After LVAD implantation, inhaled
NO reduced PA pressure and increased LVAD flow.128

When several drugs (inhaled NO, intravenous prostacy-
clin, prostaglandin E1, and sodium nitroprusside) were com-
pared in posttransplant PH management, cardiac output,
right ventricular end-diastolic volume, and central filling
pressures were highest, whereas systemic and pulmonary
vascular resistance were lowest with prostacyclin. Only in-
haled NO induced a selective decrease in pulmonary vascular
resistance, with no change in systemic vascular resistance.
Cardiac output increased with NO, whereas mean pulmonary
arterial pressure, transpulmonary gradient, and central
venous pressure decreased, had the most pronounced
effect at an inhaled concentration of 20 parts per million.92

Because of its short half-life, NO has to be administered
continuously; even brief interruptions may cause a dangerous
rebound of PH, leading to a decreased cardiac output and sys-
temic hypotension.129 The risk can be minimized by gradu-
ally weaning the concentration of inhaled NO.119 The
downregulation of endogenous NO synthesis or elevated
endothelin-I levels by inhaled NO may be responsible for
this phenomenon.120 Inhaled NO also carries a small risk of
methemoglobinemia, which is rarely an issue in adult popu-
lation. Testing for methemoglobin regularly, Ardehali et al123
and Beck et al127 did not observe any abnormalities even after
4 days of continuous NO. Some authors still advocate routine
methemoglobin checks especially in patients inhaling con-
centrations of 80 parts per million,116 although we did not
find any mentioning of actual occurrence of methemoglo-
binemia in any reviewed papers.

Another potential side effect of inhaled NO is an increase
in LV filling pressure in patients with HF from an increased
pulmonary venous return to a poorly compliant left ventricle,
resulting in an acute pulmonary edema.53,130 This finding
has not been confirmed by other authors. Thus, Sablotzki et al61
found no increase of pulmonary capillary wedge pressure
during NO inhalation. To the contrary, they observed a falling
trend in wedge pressure with NO inhalation. In their study,
the main disadvantage of NO inhalation was an increase in
PA pressure and PVR in 4 patients (28.6%).

Some success has occurred with inhaled NO as a supple-
ment to other treatments. Of particular interest is the com-
bination of inhaled NO and sildenafil. After the Food and
Drug Administration approved sildenafil for the treatment
of erectile dysfunction, reports of severe and possibly fatal
hypotension in patients taking sildenafil and nitrates led to
changes in drug labeling that warned against the adminis-
tration of nitrates in patients using sildenafil. An expert
panel of the American College of Cardiology/American
Heart Association concluded that concomitant use of sildena-
afil and nitrates should be avoided unless the benefits are
determined to far outweigh the risks. However, Parker et al found that the actual risk is low. In HF patients with PH, when sildenafil did not result in the desired magnitude of pulmonary vasodilation, adding systemic nitrates (oral isosorbide dinitrate) led to a reduction in mean PA pressure of 11 mm Hg, whereas mean systemic arterial pressure decreased by only 3 mm Hg. The ratio of pulmonary vascular resistance to systemic vascular resistance was reduced by 45%, suggesting some pulmonary selectivity of the combination. Treatment with sildenafil and nitrates was continued for 2 to 8 months, with no episodes of marked systemic hypotension, syncope, or lightheadedness.

Inotropes and Vasodilators

Milrinone, a type 3 phosphodiesterase inhibitor with vasodilating and positive inotropic properties, has been shown to lower PVR. Milrinone produces sustained inotropic effect with increase in contractility and cardiac output and venous and pulmonary vasodilation with decrease in right and left heart filling pressures and systemic and PVR without significant change in TPG. In right ventricular failure due to residual PH after the implantation of LVAD, milrinone caused a significant reduction in PVR and an increase in LVAD flow. Inhaled milrinone also can be useful for decrease of PA pressure in the postoperative setting, alone or in combination with prostacyclin. Nesiritide decreases pulmonary capillary wedge pressure and therefore decreases pulmonary pressure. A 31% decrease in wedge pressure was accompanied by 15.6% reduction in mean PA pressure.

LVAD

When pharmacological interventions fail to decrease PVR sufficiently to allow heart transplantation, it can be achieved with LVADs, which reverse many pathological processes in HF, including PH. Unloading the left ventricle alleviates left atrial hypertension and decreases pulmonary capillary wedge pressure, thereby inducing a decline in the PA pressure. In addition, improved cardiac output reduces hypoxia at the tissue level, resulting in less pulmonary vasoconstriction.

Initial anecdotal reports of normalization of “fixed” PH after LVAD support have been replaced by case series, as summarized in the Table 3.

Even in patients with fixed PH, long-term LVAD therapy usually results in normalization of pulmonary pressures within several months, and patients become eligible for transplant, regardless of the type of LVAD used. Pulsatile and nonpulsatile flow devices appear equally effective in PH reduction. Subsequent heart transplantations result in good outcomes.

However, according to some data, LVAD before heart transplant in the presence of PH—although decreasing PVR from 4.3 ± 1.6 to 2.0 ± 0.6WU, $P < .05$—did not provide better long-term outcomes. The 30-day survival rate in patients who received LVADs pretransplant was 82% versus 91% in patients with similar degree of PH who did not receive LVADs; the 4-year survival was 64% and 82%, respectively.

Conclusions

PH is highly prevalent in HF. It is associated with high morbidity and mortality. PA pressure correlates with increased LV end-diastolic pressure and diastolic dysfunction, but not with LV ejection fraction.

Many drugs currently used for pulmonary arterial hypertension are being tested as treatment options for PH in HF. Although the short-term benefit of such therapies is well established in the peritransplant setting, the effects on long-term outcomes are unclear. Randomized clinical trials with endothelin antagonists and prostaglandins did not target HF patients with PH and are therefore inconclusive. Sildenafil appears to be a promising agent based on small studies with surrogate outcomes. Randomized clinical trials designed to elucidate its potential role would be justified.

Pulmonary hypertension in HF may be a potentially important treatment target. Advances in its management could potentially improve the clinical outcomes in heart failure population.

Disclosures

None.

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