When primary pulmonary hypertension (PPH) was first described in the medical literature, it was characterized from a cardiac catheterization on a young woman who had an elevated pulmonary arterial pressure of unknown origin which, after the intravenous administration of acetylcholine, promptly fell. The sentinel description of this phenomenon led to the acceptance of PPH as a medical entity in which inappropriate pulmonary vasoconstriction was a central feature. Since then many series of patients with PPH (now referred to as idiopathic pulmonary arterial hypertension [IPAH]) have been published which document a variable ability to respond to acute vasodilator challenge. Although, the approach to therapy has emphasized the initial classification of responder or nonresponder, most patients demonstrate only a small decrease in pulmonary pressure (PAP) in response to vasodilators. However, vasodilators are widely prescribed in patients who are nonresponders, based on clinical trials that established the response to a 6-minute walk (6 MW) test as the primary end point. The consistent improvement in 6 MW reflects the complexity of exercise intolerance, which may be strongly influenced not only by cardiopulmonary factors, but by peripheral factors such as the muscle ergoreflex.

Who is a Responder?

In the current era, patients with PAH who undergo acute vasoreactivity testing at the time of diagnosis are classified as responders or nonresponders based on the change in PAP from select agents. The definition of a responder has changed many times, the most recent being a fall in the mean PAP of at least 10 mm Hg to a level below 40 mm Hg without any fall in cardiac output. However, the response is in reality a continuum, and not an all or none phenomenon. It is notable that in 2 large series of patients who were deemed acute responders, the characteristic of those who had near perfect survival on calcium blockers (CCB) for up to 18 years had an acute fall in mean PAP of 39% and an acute fall in pulmonary vascular resistance (PVR) of 50%. It is remarkable how similar the experiences from the 2 series are, supporting the validity of the observations.

The majority of patients with IPAH are nonresponders. Although this implies lack of vasoreactivity, this is clearly not the case. In an observational study of patients with IPAH who were monitored with a pulmonary artery catheter over 6 hours without an intervention, considerable variability was noted in the PAP (±8%) and PVR (±13%), suggesting that changing vasomotor tone is common in these patients. In the 2 series on long-term calcium blocker therapy, the nonresponders also had an acute fall in mean PAP and PVR, but of a lesser magnitude than the responder group. In one series, the fall in PAP was 8%, and fall in PVR was 17%. Thus, the characterization of a patient as a nonresponder actually means a minimal response, not lack of response. Although there has never been a direct correlation between the amount of vasoreactivity with the severity of the vascular disease, one early study demonstrated that there was a qualitative relationship between the 2, suggesting that the degree of intimal proliferation and fibrosis may be one reason for the blunted vasomotor responsiveness. In the National Institutes of Health Registry on PPH, a summary of the acute effects of vasodilator challenge in these patients also supports that a limited degree of vasoreactivity is a predictable feature of PPH, and that none of the vasodilators tested were either superior to another or selective for the pulmonary circulation. In the Registry experience, the average acute fall in mean PAP from vasodilators was around 5%. The most current research on IPAH supports the concept that inappropriate proliferation of the endothelium and media of the pulmonary vasculature underlies the increase in pulmonary arterial pressure, not persistent, intense vasoconstriction.

Vasodilator Therapies

Vasodilators have become the mainstay of therapy for PAH since 1996. Although published guidelines advocate their use in all PAH patients, these recommendations are counterintuitive for several reasons. Understandably, patients who qualify as responders are given calcium blockers in high doses with the expectation that the reduction in PAP achieved acutely will be reproduced over the long term. In contrast,
patients who are nonresponders are recommended to receive a different class of vasodilator with the implication that these other vasodilators have some unique properties that will render them effective in minimally vasoreactive patients. Another conundrum is the extrapolation of vasodilator therapies to the entire classification of category 1 PAH patients, which implies a similarity of vascular pathology and pathobiology of each subgroup which is not the case. Thus, it has been recommended that these therapies are equally indicated for IPAH which may arise from inappropriate smooth muscle hypertrophy, scleroderma associated PH which may arise from autoimmune and inflammatory reactions in the pulmonary vasculature, and congenital heart disease associated with intracardiac shunting which may arise from high pulmonary blood flow and sheer stress in the endothelium, as the randomized controlled trials have chosen the 6 MW test as the primary end point to support drug efficacy.

### The Hemodynamic Effects of Vasodilators in Nonresponders

#### Calcium Channel Blockers

The hemodynamic response to calcium channel blockers in PAH among nonresponders consistently shows a small reduction in PAP and PVR, regardless of which CCB is used. Although these studies were conducted before the era of randomized controlled trials for PAH, the clinical effects of these drugs in nonresponders have been associated with an improvement in the symptoms of dyspnea in the majority of patients, as well as an improvement or stabilization of the disease for 3 to 30 months. There is no way to know how these CCBs would fare in an head to head comparison with the more recently approved vasodilators, but their hemodynamic effects are quite similar (mean fall in PAP of 3% to 11%). Their cost, however, is only a small fraction of the approved drugs. The CCBs also affect the systemic and coronary artery circulations, and can have an adverse effect on myocardial contractility and heart rate. For these reasons it has been cautioned that their chronic use in nonreactive patients must document overall clinical improvement which includes hemodynamics and RV function.

#### Endothelin Receptor Antagonists

Endothelin is a potent vasoconstrictor that affects the entire circulatory system. The rationale for the use of endothelin receptor antagonists in PAH includes the demonstration of elevated circulating endothelin levels in these patients, and the generalized increased expression of endothelin in the lungs in patients with PH (including the lung parenchyma, vasculature, and airways). The endothelin receptor antagonists have also been studied in several clinical trials of congestive heart failure for similar reasons. However, in left ventricular (LV) failure, they have repeatedly failed to demonstrate a sustained clinical benefit. Their success in PAH, however, was not predicated on an improvement in either hemodynamics or on long-term outcome. Rather, it was linked to the demonstration of a statistically significant increase in the 6 MW test over 3 to 4 months which was the primary end point in the clinical trials. The hemodynamic effects of these drugs in PAH indicate that they are similar to the CCBs in nonresponders, with a fall in mean PAP of 4% to 10%. The effect of endothelin receptor antagonists on myocardial contractility, which may differ in normal and diseased hearts, remains uncertain.

#### Phosphodiesterase-5 Inhibitors

The rationale for phosphodiesterase-5 inhibitors in PAH is based on the demonstration that they enhance nitric oxide-
mediated vasodilatation in the lung.\textsuperscript{36} Nitric oxide is a potent vasodilator of arterial vessels, but can only be directly administered as an inhaled gas, and its rapid metabolism prevents it from having systemic effects. The phosphodiesterase-5 inhibitor sildenafil has been the most studied in PAH. Because of its long half-life, it is able to increase nitric oxide availability to the systemic and pulmonary circulations. Its initial development was linked to its effect in men with erectile dysfunction.\textsuperscript{57} Like the other vasodilators, it has been associated with a small but significant increase in 6 MW, as well as a fall in mean PAP of 4\% to 10\%.\textsuperscript{21} In distinction to the CCBs and endothelin receptor antagonists however, there is increasing literature that sildenafil may improve RV myocardial contractility in PH associated with left and right ventricular dysfunction.\textsuperscript{38–40}

**Prostacyclins**

Justification for the use of epoprostenol in PAH came from a demonstration that there may be an imbalance between the release of thromboxane A2 and prostacyclin in pulmonary hypertension, reflecting platelet activation and an abnormal response of the pulmonary vascular endothelium in patients with IPAH.\textsuperscript{41} The clinical trials of prostacyclins for PAH are rather unique. The randomized controlled trials for intravenous epoprostenol and subcutaneous treprostinil did not establish a target dose for therapy, but allowed the continued up titration as tolerated by the patient over the duration of the trial.\textsuperscript{19,26,42} The change in 6 MW and hemodynamics were similar to the other vasodilator studies (mean fall in PAP of 4\% to 10\%).\textsuperscript{21} In distinction to the CCBs and endothelin receptor antagonists however, there is increasing literature that these therapies work primarily on exercise hemodynamics. And because there are no vasodilator drugs that have specific actions only on the pulmonary circulation, it raises the possibility that their effects on exercise performance could be mediated by changes elsewhere in the circulatory system, such as the peripheral vasculature. Studies have shown salutary effects of the endothelin receptor antagonists on the systemic circulation in patients with hypertension,\textsuperscript{45} Raynaud phenomena\textsuperscript{56} and fingertip ulceration,\textsuperscript{57} and with prostacyclins in chronic limb ischemia\textsuperscript{58} (Table 2).

![Table 2. Nonpulmonary Vascular Effects of Vasodilators Approved for Use in PAH](http://circheartfailure.ahajournals.org/)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effects</th>
</tr>
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<tbody>
<tr>
<td>Bosentan</td>
<td>Increased healing of skin ulcers from cutaneous vasodilatation\textsuperscript{57}</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Improvement in erectile dysfunction\textsuperscript{59} systemic vasodilatation in heart failure\textsuperscript{60}</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>Portal vein vasodilatation\textsuperscript{61}</td>
</tr>
<tr>
<td>Treprostinil</td>
<td>Improvement in limb blood flow in patients with intermittent claudication\textsuperscript{62}</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Treatment of Raynaud syndrome\textsuperscript{56}</td>
</tr>
</tbody>
</table>

identical regardless of which class of drug is studied, which dose is administered, or which group of patients are enrolled. It also has been pointed out that all of the vasodilators approved for PAH have such small direct effects on pulmonary hemodynamics that there may be some other mechanism by which they increase exercise tolerance and improve symptoms.\textsuperscript{52,53} Indeed, it is hard to accept that a 10\% fall in PAP in a patient whose PAP is increased 300\% from normal translates into significant clinical effects. Although one may argue that the resting hemodynamics do not reflect changes in cardiac output with exercise,\textsuperscript{39} there are no data that document that these therapies work primarily on exercise hemodynamics. And because there are no vasodilator drugs that have specific actions only on the pulmonary circulation, it raises the possibility that their effects on exercise performance could be mediated by changes elsewhere in the circulatory system, such as the peripheral vasculature. Studies have shown salutary effects of the endothelin receptor antagonists on the systemic circulation in patients with hypertension,\textsuperscript{45} Raynaud phenomena\textsuperscript{56} and fingertip ulceration,\textsuperscript{57} and with prostacyclins in chronic limb ischemia\textsuperscript{58} (Table 2).

**The Concept of Ergoreflex**

In the past decade there has been an increasing body of evidence to support what has been termed “the muscle hypothesis” in heart failure.\textsuperscript{63} It has been demonstrated that there is an increased ventilatory response to exercise which has been directly linked to metabolic abnormalities in skeletal muscle, termed the ergoreflex.\textsuperscript{5} There is now data that show that ergoreflex activation is closely related to the severity of exercise intolerance in heart failure.\textsuperscript{5} In addition, the skeletal muscle ergoreflex plays a key role in both symptoms and disease progression.\textsuperscript{64} Overactivity of ergoreceptors (afferents sensitive to metabolic products of skeletal muscle work) has been shown to be an important determinant of exercise hyperventilation and reduced exercise capacity. Early studies pointed out that there is a poor correlation between LV function and exercise tolerance.\textsuperscript{65} However, it has been demonstrated that an exercise training program can cause significant improvements in exercise capacity in heart failure associated with reversal of muscle acidosis, improvement in muscle function and consequently a reduction in the stimulus to the ergoreflex.\textsuperscript{66}
Vasodilators and Their Effects on the Ergoreflex

Blood flow to working skeletal muscles is typically reduced during exercise in heart failure. Studies have demonstrated that prostaglandins, which are potent arterial dilators, serve as counter regulatory mediators to skeletal muscle vasoconstriction in these patients.\(^\text{6}\)\(^\text{7}\)\(^\text{8}\) In addition, studies have linked increased circulating endothelin to exercise intolerance in heart failure. Consequently, it has been proposed that endothelin blockade may be useful to improve exercise capacity in these patients.\(^\text{6}\)\(^\text{8}\) And more recently, it has been shown that the phosphodiesterase-5 inhibitor sildenafil improves ventilatory and aerobic efficiencies in heart failure patients by improving muscle perfusion and endothelial activity.\(^\text{6}\)\(^\text{9}\) What is particularly striking is that these are the same classes of vasodilators that have been shown to increase exercise performance in patients with PAH.

Skeletal Muscle in Patients With PH

It has also been known for many years that the neurohormonal abnormalities in LV failure, an important link in the ergoreflex, are similar in patients with RV failure and PH.\(^\text{7}\)\(^\text{0}\)\(^\text{7}\)\(^\text{1}\)\(^\text{7}\)\(^\text{2}\) Exercise capacity in heart failure can be improved by a therapy that enhances oxygen delivery to the skeletal muscle, whether it be from inotropic agents, vasodilators, or hemoglobin.\(^\text{7}\)\(^\text{3}\) However, before one can extrapolate that vasodilators work via the ergoreflex in patients with PAH, it is necessary to demonstrate that similar skeletal muscle abnormalities exist in these patients. In congestive left ventricular failure, inefficient ventilation is associated with reduced inspiratory muscle strength,\(^\text{7}\)\(^\text{4}\) which is associated with prognosis and can be improved by selective respiratory muscle training. Similar respiratory muscle dysfunction in patients with IPAH has also been reported.\(^\text{6}\)\(^\text{5}\) More recently, Bauer et al studied forearm muscle function in 24 patients with IPAH and found abnormalities that were qualitatively similar to those in patients with LV failure.\(^\text{7}\)\(^\text{5}\) In addition, the reduction in skeletal muscle strength was paralleled by respiratory muscle dysfunction in these patients.\(^\text{7}\)\(^\text{6}\) And further support of this concept comes from a study that has demonstrated a marked improvement in exercise capacity in patients with severe PAH following an exercise rehabilitation program,\(^\text{2}\)\(^\text{7}\) far greater than the effects from vasodilator therapy, but analogous to the observations that have been made in LV failure.\(^\text{7}\)\(^\text{7}\)

Conclusion

Various degrees of vasoactivity exist in virtually all patients with PAH, even if they are considered nonresponders to acute vasodilator challenge. A review of vasodilators used in these patients shows a remarkably similar pulmonary hemodynamic effect in nonvasoreactive patients, irrespective of the drug class. Vasodilators do differ with respect to their potential effects on the myocardium, which may have important implications in the failing myocardium. This requires further study and clarification.

Parenteral prostacyclins also differ in that when administered at high doses they appear to increase contractility which is associated with a more robust increase in exercise tolerance and improvement in symptoms. Whether this effect improves overall survival, as suggested when compared with historical controls, or shortens overall survival, as has been observed in LV failure, has never been tested.

The peripheral vascular effects of vasodilators in PAH have been ignored. However, the literature supports the possibility that these drugs may improve 6 MW primarily via their effects on the ergoreflex and skeletal muscle. It is consistent with exercise data in LV and RV failure and with the classes of drugs that have been developed for the symptomatic relief of dyspnea in patients with PAH. It also would provide an explanation as to how these drugs consistently produce improvements in exercise tolerance, and clinical stabilization, without having much of an impact on the pulmonary hemodynamics. Given the absence of any studies demonstrating direct pulmonary vascular remodeling effects of vasodilators in humans with PAH, this important issue remains unanswered.

Disclosures

None.

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Rich Vasodilators in Pulmonary Hypertension


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