Pulmonary Hypertension Out of Proportion to Left Heart Disease

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Classically, the term pulmonary hypertension (PH) refers to a resting mean pulmonary pressure greater than 25 mmHg. There are many different etiologies of PH, but by and large, the most common cause is pulmonary venous hypertension (PVH). This particular form of PH occurs in the setting of elevated left sided filling pressure. The main causes of PVH are listed in **Table 1**. Typically, in this form of PH, the degree of elevation in pulmonary artery pressure is concordant with the degree of elevation in left atrial pressure. Identification of this form of PH is important because treatment with selective pulmonary vasodilators typically reserved for use in pulmonary arterial hypertension (PAH) may be potentially harmful. However, some patients have a severely elevated PA pressure with only modestly elevated left-sided filling pressure. This class of patient often causes much confusion for treating physicians because of the uncertainty of whether or not these patients would benefit or be harmed by PAH-selective therapy. It is the aim of this paper to provide an insightful and helpful review of PH related to left heart disease, with specific emphasis on the patient with pulmonary hypertension "out-of-proportion" to the degree of elevation in left-sided pressure.

The differentiation of PAH from PVH can be quite difficult. Some conditions predisposing to this form of PH are quite obvious, such as mitral valve disease or left ventricular (LV) systolic dysfunction. However, other causes like diastolic dysfunction or early restrictive cardiomyopathy are more difficult to diagnose noninvasively. PAH requires a high index of suspicion and the appropriate diagnostic tests. Physical examination can be nonspecific and even normal in some of these patients. Echocardiography can be misleading, as only the right ventricular systolic pressure is routinely estimated. More importantly, echocardiography can not measure left-sided filling pressure, but only comment on abnormal left ventricle filling patterns, which can be markedly abnormal even in the face of normal filling pressure in advanced PH.[1] It is for these reasons, that it is imperative for patients suspected to have pulmonary hypertension to undergo invasive measurement of the PA and wedge pressures.

The results obtained from right heart catheterization alone is usually enough to confirm the diagnosis of PAH.

Table 1. Main Causes of Pulmonary Venous Hypertension.

Heart failure
• Systolic dysfunction
• Diastolic dysfunction, including restrictive cardiomyopathy
Mitral valve disease
• Mitral stenosis
• Mitral regurgitation
Aortic valve disease
• Aortic stenosis
• Aortic regurgitation
Cor triatriatum

Occasionally, however, it is quite difficult to obtain accurate pulmonary capillary wedge pressure (PCWP) in patients with severe PH, due to the significant dilatation of the proximal pulmonary arteries, rapid pruning of distal branches, tricuspid insufficiency and dilatation of the right heart chambers. **Figure 1** shows how the PCWP was erroneously measured twice (panel A and B) before a correct PCWP (panel C) was obtained in a patient with PAH. If there are any doubts regarding the accuracy of the pressure obtained, then a correct positioning could be verify by measuring the oxygen saturation in blood obtained in the "wedge position." However, even this method could be inaccurate in cases of "over-wedging", like example A of **Figure 1**. If the right heart catheterization is nondiagnostic, then a left heart catheterization should be done to accurately measure the left ventricular end-diastolic pressure (LVEDP). We strongly believe that an accurate LVEDP can only be measured with a multihole pigtail catheter placed in the body of the left ventricle, as a single end-hole catheter only measures the pressure in one direction and not the sum of all intraventricular pressures.

Significance of Pulmonary Hypertension in Patients With Left-heart Disease

The presence of significant PH in patients with left heart disease is associated with a poor prognosis in light of its effects on

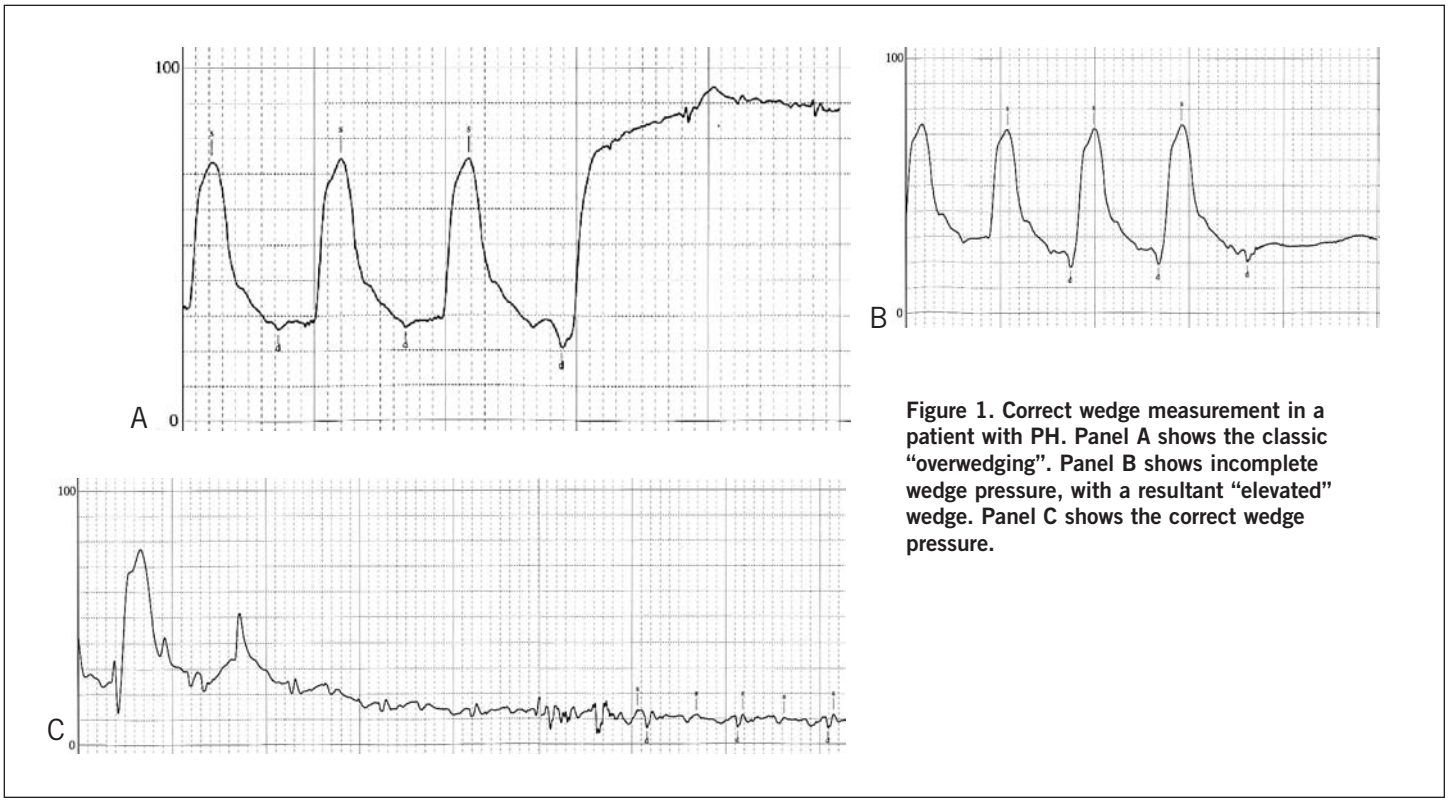

Figure 1. Correct wedge measurement in a patient with PH. Panel A shows the classic "overwedging". Panel B shows incomplete wedge pressure, with a resultant "elevated" wedge. Panel C shows the correct wedge pressure.

the right ventricular (RV) function. Irregardless of the etiology of left heart disease, a reduced LVEF is a powerful predictor of death in patients with heart failure; however, its prognostic value loses strength when applied to patients with advanced heart failure.[1] A number of studies have provided evidence that the RVEF, either directly measured (by radionuclide angiography or rapid response thermodilution) or indirectly estimated (by echocardiography), is an independent prognostic factor in patients with moderate to severe heart failure.[2-6] Pulmonary hypertension frequently complicates heart failure and is generally considered "per se" an indicator of poor prognosis.[7, 8]

The RV is a low pressure, high volume pump, allowing blood to flow into a highly compliant pulmonary circulation. The RV is able to accommodate large changes in volume with minimal pressure changes. As the pulmonary pressure rises, the RV dilates and its hemodynamics, contraction and pressure-volume loops are similar to that of the LV. This depends heavily on interventricular interactions which allows the RV to expand and accommodate the additional preload. As the RV loses the capacity to overcome the high vascular resistance, it becomes more dependant on afterload, and the cardiac output declines precipitously. It is this impaired RV function that portends a poor prognosis in patients with PH of any etiology.

Heart Failure

Elevated PA pressure and abnormal RV function are important determinants of both prognosis and exercise capacity in patients with LV dysfunction. Several studies have shown that exercise capacity, as measured by peak VO_2, is more closely associated with RV ejection fraction (EF) than with LVEF.[2, 3] Moreover, the presence of PH in patients with LV dysfunction further impairs exercise performance in patients with heart failure (HF), as the increased PVR results in further reduction of the cardiac output.[4] In addition, RV dysfunction is also an independent predictor of survival, in patients with LV failure[3] especially when PH is present.[5] Ghio points out in his study that patients with a combined high PAP on right heart catheterization and a low RVEF have the worst prognosis and survival among patients with advanced left sided heart failure. In fact these patients have a seven times higher risk of death than those patients with a normal PAP and preserved RVEF, a 4.3 times higher risk than patients with a high PAP/preserved RVEF and 3.3 times higher risk than that of the patients in the normal PAP/low RVEF[5]. Historically, heart transplantation has been contraindicated in patients with fixed PH due to the very high rate of perioperative mortality.[6] In addition, in a small percentage of patients undergoing placement of a LV assist device, the RV fails acutely, due to the elevated PA pressure and pulmonary vascular resistance (PVR), requiring the concomitant placement of a RV assist device.[9,10] As the surgical techniques and aggressive medical management improves, it may be possible to reverse what has been called "fixed" pulmonary hypertension, allowing these patients to be eligible for transplantation[11, 12].

Pulmonary venous hypertension can occur in the setting of LV diastolic dysfunction, or diastolic heart failure.[13,14] However, the incidence of significant of PH in the setting of diastolic dysfunction has not been well characterized or studied. As clinicians, we often struggle to differentiate those patients with true PAH from those who may have some form of diastolic dysfunction with reactive pulmonary hypertension. It has been postulated that in some patients, the pulmonary vasculature undergoes reactive changes due to the chronic elevation of the left ventricular filling pressure,

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resulting in severe pulmonary hypertension. As the pulmonary vascular disease progresses the cardiac output is reduced due to RV dysfunction, decreasing the venous return to the left heart and, eventually, normalizing the LV filling pressure. At the time of presentation and evaluation, these patients may have normal or only mildly elevated left heart filling pressure with significantly elevated pulmonary pressure, being misdiagnosed as PAH.

Mitral Valve Diseases

Mitral stenosis (MS) is an important cause of pulmonary hypertension. In this particular condition, the elevated left-sided filling pressure is at the atrial level, with normal LVEDP. The elevated pulmonary pressure and PVR results in increased RV end-diastolic volume and pressure, as well as secondary tricuspid regurgitation, which may lead to right heart failure and systemic venous congestion. The presence of PH, either at rest or with exercise is an indication for percutaneous or open commisurotomy or replacement of the stenotic mitral valve.[7]

Pulmonary hypertension can also occur in patients with mitral regurgitation (MR). It is not only related to the LV dysfunction that complicates advanced stages of mitral regurgitation, but it is also seen in patients with chronic, isolated mitral regurgitation with normal LV function.[8] The presence of PH in patients with MR is associated with substantial decreases in cardiac output and possibly a poor outcome. As in patients with MS, the presence of PH in patients with MR, either at rest or with exercise, is an indication for mitral valve surgery.[8]

Aortic Valve Diseases

The incidence of PH in the setting of aortic valve stenosis and/or regurgitation is not as common as with mitral valve diseases. It has been described in up to 4-29% of patients with significant aortic stenosis,[15,16] mainly as a result of elevated LVEDP and marked diastolic dysfunction. The perioperative mortality rate of patients with severe aortic stenosis and PH may be as high as 40%.[12] However, without therapy, the prognosis is even worse, with almost all patients dying after 1.5 years.

The incidence of PH in patients with isolated aortic valve regurgitation is rare, occurring mainly when the LVEDP is already elevated, as a result of the chronic volume overload[17] and it may portend a poor prognosis, even though the data available is rather small and largely anecdotal.[18]

What Is Pulmonary Hypertension Out of Proportion to Elevated Left-sided Pressure?

The primary goal in the initial evaluation of patients with PH is to differentiate PAH from other causes, especially PVH. By definition, patients with PAH should have a low or normal left-sided filling pressure, as measured by the PCWP or LVEDP. A left-sided filling pressure of <15 mmHg has been accepted as the criteria for patients with pulmonary arterial hypertension.[19] As clinicians, we struggle every day with patients who have severely elevated pulmonary pressure with only modest elevation of the left-sided filling pressure. Several different measurements have been used clinically in an attempt to differentiate those patients with some component of pulmonary arterial hypertension in addition to their left sided disease and PVH. Most of the studies are derived from the heart transplant literature, especially the use of the transpulmonary gradient (TPG).

The TPG is calculated as the difference between the mean PA pressure and PCWP measured in mmHg. It is assumed that a TPG of ≤15 mmHg is acceptable for transplantation, as the elevated PA pressure is in direct proportion with the elevated left-sided filling pressure. An elevated TPG is associated with a very high incidence of post-operative right ventricular failure and death.[20] Many studies have shown that a high PVR is also a risk factor for graft failure due to right heart failure early after cardiac transplantation.[9,21] However, the PVR, by using the cardiac output in its equation may be unreliable because of inherent inaccuracies in the measurement of cardiac output by thermodilution, particularly at low cardiac outputs. The TPG, it is argued, is flow-independent and thus may better reflect resistance to flow across the pulmonary bed. In patients being considered for heart transplantation, the acute reactivity of the pulmonary bed is tested in the catheterization laboratory with nitroprusside or nitroglycerin or chronically with aggressive medical management, including the used of inotropic agents and diuretics.[22,23]

Using the TPG and PVR to define a patient with PH out-of-proportion to the left-sided filling pressure works best in patients with only moderately elevated PA pressure. Most of the patients with PVH seen in clinical practice fall into this group. However, there is subgroup of patients (probable 10-20% by our observation) with enough reactive pulmonary vasoconstriction that develop severe PH with only modest increases in the left-sided filling pressure. Interestingly, even in this subgroup, the PA pressure normalizes with normalization of the elevated left-sided filling pressure. It has been shown in multiple studies that in patients with mitral stenosis, for example, when the PCWP is between 20-25 mmHg, the TPG is in excess of 15-20 mmHg, decompression of the left atrium, either surgically or percutaneously, with a concomitant rapid decrease in the LA and PCWP results in a marked decrease in PA pressure, lower TPG and eventually leads to normalization of the pulmonary pressure.[24,25] We have observed similar results in our practice, especially in patients being considered for heart transplantation, after the administration of long-acting nitrates. Interestingly, in some patients with mitral stenosis, the improvement in the pulmonary hemodynamics does not occur immediately, and further therapy is required, at least acutely.[26] In our institution, we considered PH out-of-proportion to left heart disease when the PA pressure is severely elevated (mean PA ≥35-40 mmHg) with only modest elevation in the left heart disease (PCWP or LVEDP ≤22 mmHg) and a TPG ≥18-20 mmHg. It is still unknown why some patients develop severe and/or fixed PH with the same degree of elevated left-sided filling pressure. Hopefully, further studies in the future will be able to answer this question, as it is likely that genetic predisposition may play an important role.

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Table 2. Major Trials With Pulmonary Vasodilators in Patients With Heart Failure

Study [Ref]	Agent	Condition	N patients randomized	Clinical Improvement	Hemodynamic improvement	Effect on Mortality
FIRST [29]	Epoprostenol	Advanced HF	471	Yes	Yes	Worsen
RITZ-5 [36]	Tezosentan	Pulmonary edema	84	Yes	N/a	N/a
VERITAS [37]	Tezosentan	ADHF	1300	Similar to placebo	+/-	None
REACH-1 [39]	Bosentan	Severe HF	377	Worse than placebo, then similar	N/a	None
ENABLE [40]	Bosentan	Severe HF	1613	Probable worse than placebo	N/a	None

ADHF: Acute decompensated heart failure; HF: heart failure.

Therapy of Pulmonary Hypertension Out of Proportion to Left Heart Disease

There has been a remarkable growth in the therapy for PAH over the last decade. There are now five approved drugs in the United States with several other awaiting FDA approval, for a disease with a grim prognosis, once considered universally fatal in a short period of time. The increased awareness for PAH has resulted in an augmented interest in PH secondary to left-heart disease. This interest has been followed by the use of pulmonary vasodilators for patients with secondary PH. As patients with left heart disease and PH have a worse prognosis than those without, it has been assumed that improving the PA pressure should translate into an improved prognosis and survival. As we will discuss below, there is no correlation in the hemodynamic improvement and overall survival.

The main concern in treating patients with elevated left-sided pressure and PH with pulmonary vasodilators is that by decreasing the PVR, there is an associated increased in the cardiac output and venous return to the left ventricle. If the LV has either significant systolic or diastolic dysfunction, it would not be able to handle this increased venous return. This would trigger further failure by increasing an already elevated left heart filling pressure and result in pulmonary edema, a dread complication in these severely ill patients with a very high mortality rate. This effect is probably worse in patients with a noncompliant LV and significant diastolic dysfunction than in dilated LV with normal filling pressure. Most of the studies done to evaluate the response of pulmonary vasodilators in patients with left heart disease and PH are in patients with advanced HF and systolic dysfunction with secondary PH. There are no studies with the use of pulmonary vasodilators in patients with heart failure due to diastolic dysfunction.

Maximize Therapy for Primary Condition

Before even considering the administration of pulmonary vasodilators to patients with left heart disease, the therapy for the specific condition should be maximized. Mitral valve surgery or valvuloplasty results in a normalization of the pulmonary HTN in some patients with mitral stenosis. Unfortunately, despite the normalization of their left atrial pressures, a proportion of these patients are still left with significant pulmonary hypertension. Whether specific pulmonary arterial vasoremodeling therapy is beneficial in these patients at this point is unknown. The use of PAH drugs in patients with HF has failed to show any improvement in symptoms, or survival (**Table 2**). Maximizing the therapy for HF with approved drugs or assist devices may also result in a normalization of the PA pressure in patients with secondary PH (**Table 3**). Several already approved therapies are effective in these instances, like nitrates and chronic inotropic use.

Prostacyclin Analogues

The acute administration of epoprostenol in patients with HF and secondary PH results in significant reductions in mean PA, PCWP and marked increase cardiac output with a resultant decrement in the SVR and, more importantly, the PVR[27]. These beneficial hemodynamics effects persist with long-term infusions.[28] In contrast to the improved survival seen in patients with PAH, the chronic use of epoprostenol in patients with HF and PH was not associated with a survival benefit. The large-scale Flolan International Randomized Survival Trial (FIRST)[29] randomized 471 patients to epoprostenol infusion or standard care. The trial was terminated early because of strong trend (P = .055) toward a decreased survival in patients treated with epoprostenol. There is still debate regarding the potential explanation for the discouraging results seen in FIRST. It may be due to a direct stimulation of prostacyclin on certain neurohormones, like renin[30] and the sympathetic nervous system.[31] Moreover, therapeutic doses of prostacyclins exert a positive inotropic effect in patients with heart failure, which may explain the increased mortality observed in FIRST[28]. Finally another possible explanation is that a subgroup of patients respond "too well" to the prostacyclin analogues, with marked decrease in the PCWP, which may lead to negative pathophysiologic effects, not measured by the usual hemodynamic parameters[32]. Ilopost is another prostacyclin analog that has been used in patients with HF. It is administered by inhalation, therefore, exerting most of its effect in the pulmonary vasculature and decreasing the potential detrimental systemic effects. However, this effect is probable no different than that observed with nitroglycerin, nitroprusside or nitric oxide.[33] Given these results, we believe that there is a very limited role for the use of epoprostenol or other prostacyclin agonists in the therapy of

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Table 3. Recommended Approach to Patients With Pulmonary Hypertension Out of Proportion to Left Heart Disease

Maximize medical management for primary condition • Surgery for valvular heart disease • ACE inhibitors, β-blocker, spironolactone, digoxin for systolic heart failure • Diuretics **to optimize volume status**
Test reactivity with nitrates, nitroprusside, nitric oxide **(transplant candidates)**
Empiric treatment with oral nitrates and/or CCB
Reassess response frequently
Consider placement of LV assist device in patients with systolic dysfunction to chronically unload the LV and decrease the pulmonary venous hypertension
Use of sildenafil or an endothelin antagonist should be avoided until further studies are available

patients with PH secondary to left heart disease; however, this has not been proven.

Endothelin Antagonists

Endothelin-1 levels are elevated in patients with HF and correlated with clinical and hemodynamic measures of severity, as well as with a poor prognosis. Several studies of selective (ET_A) or nonselective (ET_A/ET_B) receptor antagonists in patients with acute and chronic HF have now been completed, all with similar disappointing results.

The short-term administration of tezosentan, a dual endothelin-receptor blocker results in a rapid, dose-dependant improvements in the PA, PCW pressure and cardiac index[34] in patients with advanced HF and class III to IV symptoms. This beneficial hemodynamic effect was again seen in patients hospitalized for acute decompensated HF[35]. Further studies have failed to demonstrate any significant clinical benefit from the use of tezosentan in patients with pulmonary edema[36] over usual therapy, including VERITAS,[37] a large randomized trial that was stopped early due to a lack of effect in the treatment arm.

A small pilot study using oral bosentan, a non-selective endothelin antagonist in patients with HF, demonstrated similar beneficial hemodynamic effects than intravenous agents.[38] A larger pilot study, REACH-1,[39] randomized 377 patients with HF and NYHA class III-IV to receive oral bosentan to goal doses of 500 mg twice daily or placebo (four times the recommended dose for PAH). Bosentan exerted no apparent benefit when all patients were analyzed, but in the subgroup of patients that were treated for at least 26 weeks, there was a significant beneficial treatment effect in favor of bosentan. The results of the large, randomized trial ENABLE,[40] powered to detect mortality differences between bosentan-treated patients and placebo, was similarly disappointing with a lack of survival benefit, and an early risk of worsening HF and hospitalization, as a consequence of fluid retention. The overall interest in the possible beneficial effect of endothelin antagonist in HF has declined significantly lately, and there is the possibility that we may not have any additional trials with these class of agents, at least in patients with systolic HF.

Phosphodiesterase Inhibitors

Sildenafil is a selective phosphodiesterase-5 inhibitor that has been used extensively for the treatment of male erectile dysfunction. It has been recently approved for the use in patients with PAH, given its beneficial hemodynamic and clinical effects and safety profile. A single oral dose of sildenafil in patients with HF and PH results in significant reductions in the mean PA, PCWP, PVR and an increase in the cardiac index, and may even potentiate the effect of nitric oxide.[41] Moreover, sildenafil has been used to test pulmonary reactivity in patients with HF and PH being evaluated for heart transplantation.[42] Sildenafil also appears to improve the exercise capacity in this population.[43] There are also anecdotal reports of improvement in PH in patients with HF awaiting transplantation, including one of our patients with severe LV dysfunction, with a LV assist device and markedly elevated PA pressure and PVR, despite adequate unloading of the LV by the assist device to a PCWP of <12. After 3 months of therapy the PA pressure normalized and the patient was successfully transplanted. Whether the normalization of the PA pressure in this particular case was the effect of the chronic unloading of the LV and therefore resolution of the pulmonary venous pressure, or a direct effect of sildenafil is unknown. However, despite these anecdotal reports, and until further studies are available, the long-term use of sildenafil in patients with PH associated with left heart disease should be discouraged.

Treatment of PH and Diastolic Dysfunction

The presence of diastolic heart failure has been known for years. Epidemiologic studies have shown a very high prevalence of up to 50% of all patients diagnosed with heart failure, especially in the elderly population.[44] However, only one randomized trial has been done in patients with diastolic dysfunction, the pre-specified subgroup of the CHARM trial with preserved LVEF.[45] The additional recommendations are based on understanding the physiologic changes that occur in a stiff, noncompliant left ventricle, like control of the heart rate and reduction in the LV volume and pressure with the adequate use of diuretics and nitrates. It is in this population where we worry the most that the inappropriate use with pulmonary vasodilators may decrease the PVR, increasing the cardiac output and therefore the venous return to an already non-compliant LV, increasing even further the pulmonary venous pressure resulting in pulmonary edema. In order to answer this concern, a trial looking at the effect of sitaxsentan, a specific endothelin type A receptor antagonist, in patients with diastolic dysfunction will start later this year. Until the results of the study are available, we should avoid the use of pulmonary vasodilators in patients with documented left heart disease, based on a PCWP or LVEDP ≥16 mmHg.

Conclusions

The most common etiology for elevated pulmonary artery

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pressure is pulmonary venous hypertension. This is most commonly due to LV failure, either systolic or diastolic, but also occurs in the setting of mitral and/or aortic valve disease. The concomitant presence of PH and left heart disease carries a poor prognosis. In some patients, the elevated pulmonary pressure appears to be out-of-proportion to the elevated left-sided filling pressure. The exact reason why some patients have severely a elevated PA pressure in the setting of only modestly elevated left-sided filling pressure is unknown. Pulmonary vasodilators have been tested in patients with elevated left-sided filling pressure, mainly prostacyclin agonists and endothelin antagonists in chronic systolic HF. These trials have failed due to an increase in mortality or worsening HF and hospitalization, possibly due to fluid retention. Despite anecdotal reports of patients improving after the addition of pulmonary vasodilators to their HF regimen, especially with the use of sildenafil in patients waiting for heart transplantation due to severe LV systolic dysfunction, the routine use of these agents should be discouraged. Further studies, using specific endothelin anagonists in diastolic dysfunction are planned, and may be able to answer these concerns. Until then, we recommend maximizing the therapy for the primary condition (HF) as a way of decreasing the elevated PA pressure in patients with left heart disease. ■

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Profile - Jack Reeves, MD

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Dr Reeves served on the board of directors for the Hypoxia Symposium and for the Pulmonary Circulation Foundation. He also served as the Research Director of the former Colorado Altitude Research Institute in 1992.

An accomplished researcher, Dr Reeve authored 11 books and nearly 400 papers or journal articles pertaining to high altitude medicine, pulmonary circulation, pulmonary hypertension, and pulmonary edema.

In another tribute, Benjamin Honigman, MD, Director of the Colorado Center for Altitude Medicine and Physiology, added: "Jack was a brilliant scientist and an exceptional human being. He had the ability to explain complex thoughts in simple terms and get to the heart of an issue with candor, an unassuming manner, and a wonderful sense of humor. He was the inspiration for the development of the altitude center at CU-Health Sciences Center and will be missed in so many ways."

On a personal level, Dr Reeves was generous with his time and talent in helping those in poor countries. He sought out and supported students and young faculty, especially in the former Soviet Union and Asia. He received numerous teaching awards and was the recipient of the Thomas Jefferson Award at the University of Colorado along with countless personal expressions of thanks and appreciation. ■

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