



## Editorial

### Pulmonary Venous Hypertension- An On Going Quest for Treatment: Is PDE5 Inhibition the Right Solution?

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Pulmonary venous hypertension is pulmonary hypertension resulting from elevated left sided filling pressures. This may result from chronic elevation of left atrial pressures from heart failure; either heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF) or from valvular heart disease. This is classified as Group 2 pulmonary hypertension in the Dana point classification [1]. Pulmonary hypertension due to left heart disease is defined as mean pulmonary arterial pressure (mPAP) greater than or equal to 25 mm Hg, pulmonary capillary wedge pressure (PCWP) of greater than or equal to 15 mm Hg and pulmonary vascular resistance (PVR) greater than 3WU. Chronic elevation of left ventricular end diastolic pressures will result in increased left atrial pressures, initially causing passive congestion and rise in pulmonary venous pressures and resulting pulmonary arterial hypertension. This usually reverses readily with diuresis and lowering the left atrial pressures. Transpulmonary gradient (TPG = mPAP – PCWP) is normal at this stage. Continued elevation in PCWP may result in pulmonary vasoconstriction and reactive pulmonary hypertension where the TPG is greater than 12 mm HG and pulmonary vascular resistance (PVR) is greater than 3WU. This reactive pulmonary hypertension responds to diuresis and pulmonary vasodilation with agents such as nipride, nesiritide, inhaled nitric oxide or milrinone. Over time, the passive congestion and vasoconstriction causes pulmonary vascular remodeling resulting in abnormalities of elastic fibres, smooth muscle proliferation and endothelial proliferation causing pulmonary arterial remodeling and resulting obliterative arteriopathy which is in part mediated by endothelin and is histologically indistinguishable from pulmonary arterial hypertension [2] Table 1.

#### Epidemiology

Pulmonary hypertension is very common in patients with left sided heart disease. Prevalence of this may be as high as 60% in patients with HFrEF and 70% in those with HFpEF [3]. Pulmonary hypertension in these patients has shown to independently correlate with outcomes. In a study by Kjaergaard et al. a 9% increase in mortality with every 5 mm Hg rise in RV systolic pressure was shown in patients with heart failure [4].

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#### Treatment

Various therapies that are used in PAH were tested in this cohort of patients including endothelin receptor blockade, prostaglandins and prostacyclin infusion. None of these therapies have shown promise. Some studies have shown increased mortality. Phosphodiesterase 5 (PDE5) inhibitors have been the most promising agents thus far. PDE5 plays a major role in hydrolyzing cGMP. cGMP is the second messenger for the nitric oxide (NO) pathway. It plays a central role in mediating NO and natriuretic peptide action. PDE5 is found in the vascular smooth muscle, pulmonary and systemic vasculature. Small amounts are found in normal heart but the expression of PDE5 and PDE5 mRNA is increased significantly in hypertrophied right ventricle.

PDE5 inhibition may play a beneficial role in pulmonary venous hypertension through three different mechanisms [5,6]:

- i) Protein kinase G (PKG) mediated smooth muscle relaxation resulting in pulmonary vasodilation.
- ii) cGMP in turn increases cAMP levels resulting in protein kinase A (PKA) mediated calcium influx and increased right ventricular contractility.
- iii) Bcl-2, mitochondrial  $K_{ATP}$  and Rho kinase mediated cardioprotection, reduction in apoptosis and cardiac hypertrophy.

#### Pulmonary vasodilation

Endothelial dependent nitric oxide (eNOS) diffuses to the smooth muscle cells where it triggers soluble guanylate cyclase, which generates cGMP. cGMP acts as a second messenger and in turn activates PKG. PKG lowers intracellular calcium inhibiting voltage gated calcium channels and increasing calcium uptake by sarcoplasmic reticulum via phospholamban [7]. Reduced intracellular calcium results in smooth muscle relaxation. PKG inhibits the Rho A/ROCK pathway leading to activation of myosin light chain phosphatase, which also causes smooth muscle relaxation and vasodilation [8].

#### Effects on myocardium

Very little if any PDE5 is detected in normal resting heart. Lu et al. was able to demonstrate increased PDE5 expression in

Pulmonary venous hypertension	Hemodynamic characteristics	Diagnostic implication
Passive pulmonary hypertension	PCWP>15 mm Hg, TPG <12 mm Hg, PVR <3WU	Lower PCWP and treat left heart failure or valvular disease to lower mPAP
Reactive pulmonary hypertension	PCWP >15 mmHg, TPG >12 mm Hg, PVR>3WU	Lower PCWP and treat with pulmonary vasodilators to lower the mPAP
Fixed pulmonary hypertension	PCWP >15 mm HG, TPG >12 mm Hg and PVR >3WU	Lowering PCWP and vasodilation does not immediately lower mPAP.

Table 1:

myocardium of patients with heart failure. Increased cyclase tone is necessary for PDE5 expression. Right ventricular hypertrophy from pressure overload and elevated oxidative stress result in increased PDE5 and mRNA expression [9,10]. In this setting PDE5 mediated increased cGMP uses alternate pathway and causes increase in cAMP by inhibiting PDE3. cAMP then acts through PKA and causes increased contractility and hence has beneficial effect in the failing right ventricle which is independent of its pulmonary vasodilatory mechanism.

### Cardioprotection

Tadalafil has been shown in mice model to improve survival in doxorubicin cardiotoxicity. PDE 5 inhibition increases PKG, which causes increases in Bcl-2, which inhibits apoptosis. PKG also opens mitochondrial  $K_{ATP}$  channels which protects against ischemia/reperfusion injury [11,12].

PDE5 inhibition as we now know has multiple mechanisms of action in preclinical trials. In small clinical studies sildenafil had beneficial effects on hemodynamic acutely and showed improvement in functional parameters in short term. Lewis et al. have shown improvement in exercise capacity, increase in peak  $VO_2$ , reduction in PVR, reduction in hospitalizations for heart failure and improvement in Minnesota living with heart failure scores in patients with HFREF and pulmonary venous hypertension [13]. The treatment effect best correlated with baseline resting PVR. This effect was seen over a 12 week period. Guazzi et al. were able to demonstrate benefit with longer follow up. They randomized 46 patients with stable CHF to either sildenafil 50 mg twice a day or placebo and over a six-month period were able to demonstrate reduction in PA systolic pressure, improvement in  $V_E/V_{CO_2}$  slope and increase in brachial artery flow mediated dilatation [14].

Even though the data thus far is promising in this class of medications, long term randomized controlled studies with hard end points is lacking. As with many things in medicine including endothelin receptor antagonists, which showed encouraging results in small preclinical trials with regards to improvement in end points such as exercise capacity and 6 minute walk test although larger studies have shown no significant improvement in clinical outcomes and some evidence of harm [15]. Hence once should interpret this data with caution and await the results of ongoing large scale randomized trials prior to wide spread use of these drugs for this indication.

### Ongoing and upcoming trials

NIH sponsored RELAX trial will investigate the role of PDE5I in patients with HFpEF. 190 patients will be randomized to sildenafil or placebo for 24 weeks. The primary end point is change in exercise capacity as assessed by peak  $VO_2$ . Even though this is the first long term, prospective, multi-center study testing the use of PDE5I in patients with HFpEF, this trial is not assessing hard clinical outcomes such as hospitalizations or mortality. The diagnosis of pulmonary venous hypertension is not necessary to be enrolled in this trial. There are some small studies that suggest that the benefit of PDE5I is seen best in patients with heart failure with evidence of pulmonary

hypertension [13].

PITCH-HF study will evaluate efficacy of long acting PDE5I tadalafil in patients with HFREF. Study patients will need to have an EF <40% and pulmonary hypertension. Over 2000 patients will be enrolled in this study with 2.5 years of follow up. This study has hard end points such as time to hospitalization or mortality. The presence of diastolic dysfunction is not necessary for enrollment. Data by Enriquez-Sarano et al. suggest that pulmonary hypertension is determined predominantly by the presence of diastolic dysfunction and correlates poorly with parameters of systolic dysfunction alone. [16]. The study does require recent decompensation of heart failure or presence of elevated BNP and will hence eliminate stable patients. This will be the first long term study to evaluate benefit of PDE5I in pulmonary venous hypertension with clinically important end points.

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