Pathophysiology of the pulmonary circulation

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SUMMARY

The pulmonary circulation is a high flow and low pressure circuit, with an average resistance of 1 mmHg.min.L\(^{-1}\) in young adults, increasing to 2.5 mmHg.min.L\(^{-1}\) over 4-6 decades of life. Pulmonary hypertension is defined by a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg. The upper limit of normal of mPAP is 20 mmHg. There is thus a grey zone of mPAP between 20 and 25 mmHg which serves as a safety margin to avoid false positive diagnosis of pulmonary hypertension. A similar safety margin is applied for pulmonary vascular resistance (PVR) with a cut-off value of 3 mmHg.min.L\(^{-1}\) defining pulmonary vascular disease while the upper limit of normal is 1.5 mmHg.min.L\(^{-1}\). The PVR equation

\[ \text{PVR} = \frac{\text{mPAP} - \text{PAWP}}{\text{CO}} \]

where CO is cardiac output and PAWP wedged PAP, rewritten as

\[ \text{mPAP} = \text{PVR} \times \text{CO} + \text{PAWP} \]

has been at the basis of initial classifications of pulmonary hypertension as caused by (1) increased pulmonary blood flow, such as in congenital left-to-right cardiac shunts, but also anemia, hyperthyroidism or liver disease, (2) increased PAWP such as in heart failure with reduced or preserved ejection fraction or valvulopathies, and (3) increased PVR such is in lung diseases, hypoxia, thromboembolic diseases and pulmonary arterial hypertension.

The gold standard method to assess the functional state of the pulmonary circulation is a right heart catheterization with measurements of pulmonary vascular pressures using fluid-filled catheters and pulmonary flow by thermodilution or the Fick principle. These measurements are accurate but may be unprecise. Estimated precisions of right heart catheterization measurements are of -15/+9 mmHg for PAWP, +/- 8 mmHg for PAP and +/- 1 L/min for thermodilution cardiac output. Therefore, single number-derived decisions are not encouraged.

A PAWP is an acceptable estimate of left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) in the absence of mitral stenosis. Pulmonary capillary pressure (PCP) can be calculated from the analysis of a pressure decay curve after pulmonary arterial occlusion, or estimated from an equation initially proposed by Gaar stating that

\[ \text{PCP} = 0.4 \times (\text{mPAP} - \text{PAWP}) + \text{PAWP} \]

As a rule of thumb, PCP is about mid-way between mPAP and PAWP.

The reference pressure for PAP and PAWP is pleural pressure. Thus PAP and PAWP follow pleural pressure swings during exercise and/or in patients with obstructed airways, and become predominantly positive during expiration in case of dynamic hyper-inflation. Thus pulmonary vascular pressure readings are better averaged over several respiratory cycles.
The regional distribution of pulmonary blood flow is mainly determined by the effects of gravity. However, there is an active hypoxic regulation of pulmonary vascular tone, or “hypoxic pulmonary vasoconstriction” (HPV) which diverts blood flow from hypoventilated lung regions and thereby improves gas exchange. Global HPV in hypobaric hypoxia at high altitudes may be a cause of pulmonary hypertension and right heart failure. Pre-natal HPV prevents perfusion of the unventilated foetal lung. There is considerable inter-individual and inter-species variability of post-natal HPV. The clinical relevance of HPV in lung diseases with altered gas exchange is not known.

The pulmonary circulation is remarkably distensible system so that more than 50 % of it has to be obstructed for mPAP only reaching the upper limit of normal of 20 mmHg. A pneumonectomy is not a cause of pulmonary hypertension. A mPAP of 40 mmHg is reached at a normal cardiac output and 70-80 % obstruction of the pulmonary vascular bed. A mPAP ≥ 25 mmHg and a PVR ≥ 3 mmHg.min.L⁻¹ which define pulmonary hypertension on pulmonary vasculopathy are manifestations of advanced disease.

Vascular resistance increases linearly with blood viscosity, which is in turn curvilinearly related to hematocrit following the equation of Whittaker and Winton which states that:

\[ PVR (45\%) = PVR(HCT) \times (1 - \phi )^{1/3} / 0.234 \]

where PVR at a hematocrit of 45 % is equal to PVR at actual hematocrit times an exponential function of it (\(\phi\)). It appears that PVR measured at a hematocrit of 20 % approximately doubles at a normalized hematocrit of 45 %. For example, a PVR of 2 mmHg.min.L⁻¹ in a patient with severe sickle cell anemia becomes 4 mmHg.min.L⁻¹, which is diagnostic of pulmonary vascular disease. On the other hand, a PVR of 5 mmHg.min.L⁻¹ at a hematocrit of 80 % in a patient with chronic mountain sickness comes down to 2.5 mmHg.min.L⁻¹ which excludes a diagnosis of hypoxic pulmonary hypertension. Thus corrections are thus necessary to diagnose pulmonary vascular disease on the basis of a PVR at very low or very high hematocrits.

Increased pulmonary blood flow such as during exercise is associated with a decreased PVR This is explained by resistive vessel distensibility, which is estimated by an \(\alpha\) coefficient in % increase in vessel diameter per mmHg of transmural pressure. The normal value of \(\alpha\) is 1.5 to 2 %/mmHg. While PVR normalized for body size is not different between men and women, \(\alpha\) is higher in pre-menopausal women.

Left atrial pressure is transmitted upstream to pulmonary artery pressure in a less than 1/1 ratio in steady flow conditions, but in a higher than 1/1 ratio in pulsatile flow conditions. Thus the transpulmonary pressure gradient (TPG), or numerator of the PVR equation, increases rapidly above a value of 12 mmHg taken as upper limit of normal when left atrial pressure is higher than 15 mmHg. Furthermore, the TPG increases with increasing cardiac output. The diastolic pulmonary pressure gradient (DPG) is less sensitive to flow and left atrial pressure, and is therefore preferable to the TPG (or PVR) to diagnose pulmonary vascular disease in left heart conditions with increased pulmonary venous pressure. The upper limit of normal of the DPG is 5 mmHg, with a pathological cut-off value of 7 mmHg.

The product of arterial compliance and resistance is near-constant in the pulmonary circulation, while compliance and resistance are not correlated in the systemic circulation. Therefore the pulsatile component of right ventricular (RV) hydraulic load (W), or product of stroke volume (SV) by PAP, is constant and total W (Wtot) as a measure of RV afterload is calculated as

\[ W_{tot} = SV \times mpAP \times 1.23 \]

Another consequence of the constancy of the product of compliance and resistance in the pulmonary circulation is that systolic, diastolic and mean PAP are tightly related, with reliable prediction of mPAP from systolic PAP (sPAP).
mPAP = 0.6 x sPAP + 2 mmHg

Right ventricular systolic function is coupled to the pulmonary circulation with an optimal ratio of end-systolic to arterial elastances of 1.5-2. In this analysis, RV afterload is calculated as a ratio between end-systolic pressure and SV.

REFERENCES