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SERIES "ADVANCES IN PATHOBIOLOGY, DIAGNOSIS, AND TREATMENT OF PULMONARY HYPERTENSION"
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Haemodynamic evaluation of pulmonary hypertension

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ABSTRACT: Pulmonary hypertension is characterised by the chronic elevation of pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) leading to right ventricular enlargement and hypertrophy. Pulmonary hypertension may result from respiratory and cardiac diseases, the most severe forms occurring in thromboembolic and primary pulmonary hypertension.

Pulmonary hypertension is most often defined as a mean PAP >25 mmHg at rest or >30 mmHg during exercise, the pressure being measured invasively with a pulmonary artery catheter. Doppler echocardiography allows serial, noninvasive follow-up of PAPs and right heart function. When the adaptive mechanisms of right ventricular dilatation and hypertrophy cannot compensate for the haemodynamic burden, right heart failure occurs and is associated with poor prognosis.

The haemodynamic profile is the major determinant of prognosis. In both primary and secondary pulmonary hypertension, special attention must be paid to the assessment of pulmonary vascular resistance index (PVRI), right heart function and pulmonary vasodilatory reserve.

Recent studies have stressed the prognostic values of exercise capacity (6-min walk test), right atrial pressure, stroke index and vasodilator challenge responses, as well as an interest in new imaging techniques and natriuretic peptide determinations. Overall, careful haemodynamic evaluation may optimise new diagnostic and therapeutic strategies in pulmonary hypertension.
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The normal adult pulmonary vascular bed is a low-pressure, low-resistance, highly distensible system, and is capable of accommodating large increases in blood flow with minimal elevations of PAP. Pulmonary hypertension (PH) is characterised by the chronic elevation of PAP and PVR leading to right ventricular enlargement and hypertrophy [1–8]. At first, PAP is normal at rest but rises abnormally high with exercise. In more evolved stages, PH occurs at rest (fig. 1). When the adaptive mechanisms of right ventricular dilatation and hypertrophy cannot compensate for the haemodynamic burden, right heart failure occurs and is associated with poor prognosis. PH may result from respiratory and cardiac diseases, the most severe forms occurring in thromboembolic PH and primary PH. The World Health Organization (WHO) has recently proposed a revised diagnostic classification (table 1) [1].

PH is most often defined as a mean PAP >25 mmHg at rest or >30 mmHg during exercise, the PAP being measured invasively with a pulmonary artery (PA) catheter. However, there is no clear consensus as to what level of PAP constitutes PH [1–8]. Proposed upper normal values for mean PAP range 18–25 mmHg at rest. Other definitions of PH have been used, which either include a systolic PAP >30 mmHg, or rely on the level of PVR. During exercise, a mean PAP threshold >30 mmHg may apply in healthy older subjects. Doppler echocardiography allows the noninvasive assessment of PAP, and systolic PAP is most commonly used. Proposed upper normal values range 40–50 mmHg at rest, which correspond to a tricuspid regurgitant velocity of 3.0–3.5 $m \cdot s^{-1}$ [1]. However, Doppler-derived PAP critically depends upon age, body mass index (BMI) and right atrial pressure (RAP).

PH may be identified during testing of symptomatic patients, during screening of patients at risk (table 1), or it may be discovered incidentally [1–8]. PH is a rare condition and its symptoms are nonspecific, which

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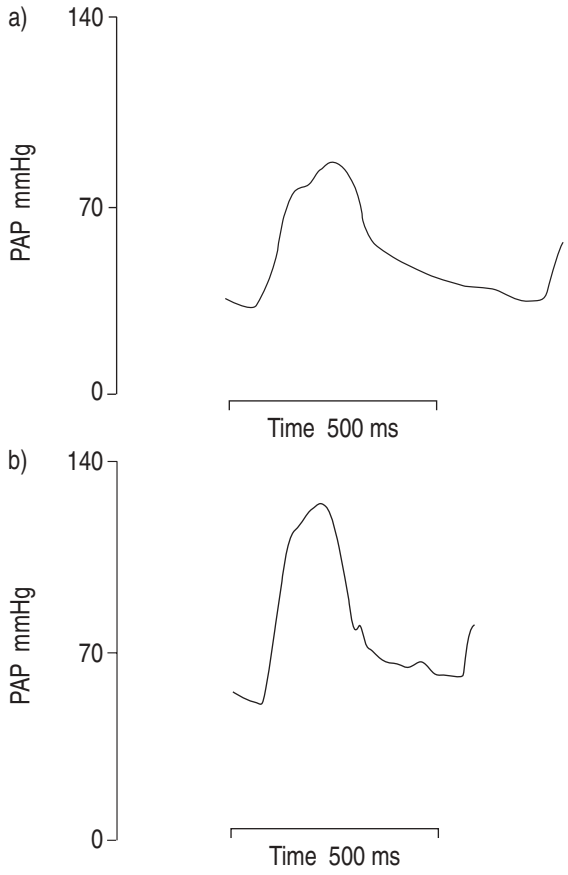

Fig. 1.–Typical pulmonary artery curve tracing a) at rest and b) during exercise (workload 45 W) in a patient with primary pulmonary hypertension. The noise is minimal with the use of a high-fidelity pressure-measuring catheter. PAP: pulmonary artery pressure.

explains why the diagnosis may be delayed. In the National Institutes of Health (NIH) primary PH registry, the mean interval from onset of symptoms to diagnosis was 2 yrs [7]. The most common presenting symptom is dyspnoea, followed by fatigue, syncope or near syncope and chest pain. The clinical presentation of PH critically depends upon its cause, but it is not within the scope of the present review to detail this point. The general diagnostic approach includes physical examination, exercise capacity testing (6-min walk test), chest radiograph, electrocardiography, laboratory tests (blood tests, arterial blood gases, pulmonary function tests), noninvasive cardiac and pulmonary imaging and cardiac catheterisation [1–8]. Cardiac catheterisation allows for the precise establishment of the diagnosis and the type of PH, the severity of the disease, the consequences on right heart function, and the amount of pulmonary vasodilatation in reserve. Echocardiography is especially valuable in the serial assessment of PAP and right and left heart function.

The early initiation of treatments at a time when dynamic or reversible pathogenic mechanisms are present may increase the likelihood of a successful treatment outcome [1]. A screening transthoracic echocardiogram is therefore recommended in asymptomatic patients with scleroderma or liver disease/portal hypertension evaluated for liver transplantation, and in asymptomatic subjects with a family history of primary PH (first degree relatives). Recent studies have identified mutations in the genes which encode for receptor members of the transforming growth factor-β family in familial (and sporadic) primary PH, and in PH associated with hereditary haemorrhagic telangiectasia, and this provides promising perspectives to genetic testing in PH [9].

Table 1.–World Health Organization diagnostic classification

Pulmonary arterial hypertension
Primary pulmonary hypertension
Sporadic
Familial
Related to:
Collagen vascular disease
Congenital systemic to pulmonary shunts
Portal hypertension
HIV infection
Drugs/toxins
Anorexigens
Other
Persistent pulmonary hypertension of the newborn
Other
Pulmonary venous hypertension
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Extrinsic compression of central pulmonary veins
Fibrosing mediastinitis
Adenopathy/tumours
Pulmonary veno-occlusive disease
Other
Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Neonatal lung disease
Alveolar-capillary dysplasia
Other
Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Obstruction of distal pulmonary arteries
Pulmonary embolism (thrombus, tumour, ova and/or parasites, foreign material)
In situ *thrombosis*
Sickle cell disease
Pulmonary hypertension due to disorders directly affecting the pulmonary vasculature
Inflammatory
Schistosomiasis
Sarcoidosis
Other
Pulmonary capillary haemangiomatosis

Although this clinical classification is primarily concerned with causes and thus prevention and treatment, the classification is in keeping with the pathological characterisation of pulmonary hypertensive states; Pulmonary hypertension (PH) that results from identifiable causes (secondary PH) is far more common than pulmonary hypertension with no apparent cause (primary PH); HIV: human immunodeficiency virus.

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Pathophysiology of haemodynamic changes in pulmonary hypertension

Pulmonary artery pressure

The pressure drop across the pulmonary circulation (*i.e.* the driving pressure) is often referred to as the transpulmonary pressure gradient (TPG):

$$\text{TPG} = \text{mean PAP} - \text{downstream pressure} \quad (1)$$

In analogy with the electric Ohm's law, TPG equals PVR times cardiac output [10–13]:

$$\text{mean PAP} - \text{downstream pressure} = \text{PVR} \times \text{cardiac output} \quad (2)$$

The equation can be rewritten as follows:

$$\text{mean PAP} = (\text{PVR} \times \text{cardiac output}) + \text{downstream pressure} \quad (3)$$

The normal pulmonary circulation is a low resistance circuit, with little or no resting vascular tone, and the most important factors influencing mean PAP are hydrostatic pressure, intra-alveolar pressure, left atrial pressure and alveolar gases.

PH is most often defined as a mean PAP >25 mmHg at rest. According to the mechanistic classification [12], increases in mean PAP may be passive (as a result of increased downstream pressure), hyperkinetic (as a result of increased cardiac output through the lungs) or due to increased PVR resulting from changes in the pulmonary circulation itself. Granted that various hypertensive mechanisms can work jointly, two forms of PH have been defined. Postcapillary PH (or pulmonary venous hypertension) is a passive form characterised by an increased downstream pressure $\geqslant$ 15 mmHg and a normal TPG. Precapillary PH (or pulmonary arterial hypertension) is characterised by a normal downstream pressure (<15 mmHg). TPG is increased because of increased cardiac output or increased PVR. Increases in PVR are due to a significant reduction in the area of the distal (mainly resistive) and/or proximal (mainly capacitive) PAs. This classification illustrates the crucial role of cardiac catheterisation in determining not only the mean PAP and cardiac output but also the downstream pressure.

Pulmonary vascular resistance

The PVR is used to characterise PH in a more restricted sense and to quantify abnormalities of the pulmonary vasculature according to the following equation:

$$\text{PVR} = (\text{mean PAP} - \text{downstream pressure}) / \text{cardiac output} \quad (4)$$

PVR is expressed in Wood units=(1 WU=1 mmHg·min·L^{-1}=80 dyne·s·cm^{-5}).

The PVR is mainly related to the geometry of small distal resistive pulmonary arterioles. According to Poiseuille's law, PVR is inversely related to the fourth power of arterial radius. PVR is therefore considered to mainly reflect the functional status of pulmonary vascular endothelium/smooth muscle cell coupled system [10–13]. PVR is also positively related to blood viscosity and may be influenced by changes in perivascular alveolar and pleural pressure.

Pressure is independent of the size of the system, and PAP from various subjects can therefore be compared without the need to take into account potential differences in their body size. Conversely, variables such as volume are proportional to the size of the system. For comparative purposes, the PVRI is therefore defined as the pressure drop across the circuit divided by cardiac index (in WU·m^2 or in mmHg·L^{-1}·min·m^2 or in dyne·s·cm^{-5}·m^2). In patients with high BMI, the use of PVR instead of PVRI has been responsible for significant underestimation of PH, and for the occurrence of haemodynamic and respiratory failure following heart transplantation. The use of PVRI must be recommended in studies evaluating new therapeutic strategies in PH.

Pulmonary arterial hypertension results from three main elements: vascular wall remodelling, thrombosis and vasoconstriction [8]. The increases in PVRI may be fixed and/or potentially reversible. Arterial obstruction, obliteration and remodelling are responsible for the fixed component, while active increases in vascular tone are responsible for the reversible component, which may account for >50% PVRI. The pulmonary vascular tone results from a complex interplay between the pulmonary endothelium, smooth muscle cells, extracellular matrix, and circulating blood cells and blood components. In PH, the dysfunction of pulmonary arterial endothelium plays a key role, whether due to external stimulus (*e.g.* shear stress, shear rate, hypoxia, acidosis) or to the disease process itself (*e.g.* primary PH).

Hypoxia, acidosis, endothelin, nitric oxide, thrombosis, neurohormones

Alveolar hypoxia is a major stimulus leading to pulmonary vasoconstriction either *via* a direct pressor effect or by causing mediators to discharge. Acidosis leads to pulmonary vasoconstriction as well as acting synergistically with hypoxia. Hypoxic vasoconstriction is the main mechanism explaining mild and moderate degrees of PH in patients with chronic obstructive pulmonary disease (COPD), in whom severe chronic long-standing hypoxia is observed. An oxygen tension in arterial blood (P_{a,O_2}) <7.98 kPa (<60 mmHg) and a carbon dioxide tension in arterial blood >5.32 kPa (>40 mmHg) are thought to be accurate thresholds for the development of PH in COPD [14]. A recent study has shown that mean PAP inversely correlated with arterial P_{a,O_2}, forced expiratory volume in one second (%) and single-breath carbon monoxide diffusion capacity (%) and directly correlated with pulmonary wedge pressure in patients with severe emphysema [15]. Surprisingly, all factors but P_{a,O_2} remained significant determinants of mean PAP when multiple regression analysis was used. Although

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methodological explanations may be discussed, this result suggests that factors other than hypoxia are involved in PH of patients with severe emphysema [15]. In COPD patients with mild-to-moderate hypoxia, the progression of PAP is very slow (+0.4 mmHg·yr^{-1}) and only initial values of resting and exercise mean PAP are independently related to the subsequent development of PH [16]. In patients with primary PH or chronic pulmonary thromboembolism, hypocapnia is commonly observed; the P_{a,O_2} may be within normal limits or only slightly decreased at rest, while hypoxaemia is observed with exercise [17, 18]. Right-to-left shunt is the main mechanism of hypoxia in the Eisenmenger syndrome. Severe hypoventilation is associated with hypoxia and may lead to PH, particularly if there is associated acidosis. This may explain the PH observed in the setting of the obesity-hypoventilation Pickwickian syndrome and in a number of muscular disorders [6]. In patients with PH, high resting PAP and PVRI values increase further following exercise or acute hypoxaemia (*e.g.* rapid eye movement (REM) sleep or respiratory failure in patients with COPD). It is important to prevent, diagnose and treat pulmonary infections in PH patients. Altitudes >1500 m must be avoided without supplemental oxygen, and altitudes >3000 m must be discouraged.

The pathogenic role of endogenous endothelin-1 has been stressed, together with impaired synthesis of vasorelaxant nitric oxide, and this may have therapeutic implications [19, 20]. PH is associated with activation of the endothelin system, which has potent vasoconstrictive and mitogen properties. Thrombosis can play a part in the pathophysiology of the disease, as attested to by the platelet activation, disturbances of various steps of the coagulation cascade and abnormal thrombolysis described in PH [21]. Primary or secondary endothelial dysfunction increase the risk of thrombotic events. Dilated right heart chambers, sluggish pulmonary blood flow and sedentary lifestyle also increase this risk. Adrenergic overdrive may precipitate right ventricle (RV) failure and high plasma noradrenaline is associated with increased mortality in patients with primary PH, suggesting that the level of sympathetic activation relates to the severity of the disease [22].

Other precipitating factors

Changes in the rheological blood properties may aggravate PH. Erythrocytosis may be secondary to hypoxia, and is potentially responsible for increased blood viscosity and changes in erythrocyte deformability. PH may be aggravated by increases in cardiac output in the setting of hyperadrenergic states, anaemia and hyperthyroidism. Decreased diastolic time (*e.g.* tachycardia) or the loss of atrial contribution to left ventricle (LV) filling (*e.g.* atrial fibrillation) tend to increase left atrial pressure and thus may also aggravate PH. Finally, permanent PH is self-aggravating, as it favours several local pathological processes, including the remodelling of small distal arteries and the loss of the elastic properties of proximal arteries, thus leading to a vicious circle.

The right ventricle in pulmonary hypertension

Right ventricular function

RV has a complex geometry and is characterised by a crescentic shape and a thin wall [23]. The crista supraventricularis divides the RV into inflow and outflow regions. Inflow (sinus), which is located posterior and inferior, has a greater fibre shortening and is the effective flow generator, pumping >85% of the stroke volume. Outflow (conus), which is located anterior and superior, is a resistive and pulsatile conduit with a limited ejection capacity. RV contraction proceeds from the sinus to the conus according to a peristaltic movement. Right ventricular output equals heart rate times stroke volume. For a given stroke volume, RV output increases when heart rate increases (chronotropic reserve). For a given heart rate, RV output increases when RV end-diastolic volume increases (preload reserve) or when RV end-systolic volume decreases. The RV end-systolic volume decrease can be due to increased inotropy (inotropic reserve) or to decreased RV end-systolic pressure. The latter mechanism may be observed in some healthy subjects during exercise (distensibility, recruitment) and in a subgroup of PH patients following vasodilators (pulmonary vasodilatory reserve).

The thin-walled, highly compliant RV can accommodate with high volumes at physiological pressures (*e.g.* exercise), thanks to its marked preload-dependence and RV-LV interdependence [23]. However, the RV is unable to face an acute increase in PVRI, and works inefficiently when confronted with PH [24]. Thus, unlike the LV, the RV performance is markedly afterload-dependent. In PH patients, the use of preload reserve (Frank-Starling′s mechanism) helps preserve RV function. Furthermore, according to Laplace′s law, an increase in afterload can be offset by an increase in RV wall thickness (RV hypertrophy), and this normalises RV wall stress and myocardial oxygen consumption. There is a linear correlation between RV mass and free wall area, indicating that an increase in afterload causes RV enlargement with both dilatation and hypertrophy [25]. Chronic cor pulmonale is defined as dilatation and hypertrophy of the RV secondary to PH caused by diseases of the pulmonary parenchyma and/or pulmonary vascular system between the origins of the main PA and the entry of the pulmonary veins into the left atrium [26, 27].

Right ventricular ejection fraction (RVEF) is much more sensitive to changes in ventricular afterload than LV ejection fraction [28]. The RVEF has been found to augment with exercise in healthy subjects given the decreased PVRI and increased contractility of the RV free wall [29, 30]. In patients with PH, the decreases in RVEF are not indicative of decreased RV contractility but mainly reflect increased afterload [31]. In primary PH studied at rest, cardiac function is characterised by RV systolic overload due to PH and diastolic overload with tricuspid regurgitation (TR), whereas the LV is subject to diastolic underloading and reduced compliance [32, 33]. With exercise, RV systolic performance further declines with a reduction in stroke volume and ejection fraction, and consequently heart

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rate becomes the mechanism by which cardiac output increases.

Right ventricular failure

RV failure may be related to the natural evolution of the disease or to acute exacerbation of PH (*e.g.* following acute hypoxaemia). In both primary PH and thromboembolic PH, the main cause of death is RV failure [1–8]. COPD is the most common pulmonary disease that culminates in RV dysfunction [24, 34]. An autopsy study suggests that cor pulmonale is found in 40% COPD patients [35]. Cor pulmonale is mainly observed in "blue bloaters" who develop a low cardiac output profile and severe hypoxaemia and erythrocytosis resulting in PH. Conversely, "pink puffers" exhibit less severe hypoxaemia, decreased cardiac output and increased arteriovenous oxygen content difference, and cor pulmonale is less likely to develop despite increased PVRI [24]. In a number of COPD patients, peripheral oedema may not always be explained by RV failure, but rather relate to hypercapnia, acidosis and increased sympathetic and renin-angiotensin-aldosterone activities, and the related changes in renal haemodynamics and redistribution of body water [36].

When pulmonary arterial impedance is chronically increased, RV function and output are preserved thanks to RV dilation and hypertrophy, increased inotropy and faster heart rate. Both increased impedance and increases in RV size and annulus diameter lead to TR, which further compromise RV function. Decreased RV function is observed when the limits of cardiac reserves are reached or when significant RV-LV interdependence or chronic RV ischaemia are present (fig. 2). The mechanisms for RV ischaemia include increased pressure work leading to increased myocardial oxygen consumption; reduced systemic pressure leading to decreases in the coronary perfusion driving pressure; and higher sensitivity to hypoxia and reduced vasodilatory reserve of the hypertrophied RV [23, 34]. In patients with end-stage RV failure, the maintenance of a sufficiently high systemic pressure is of major importance to prevent RV ischaemia, and this may require high doses of vasoconstrictive agents (*e.g.* noradrenaline).

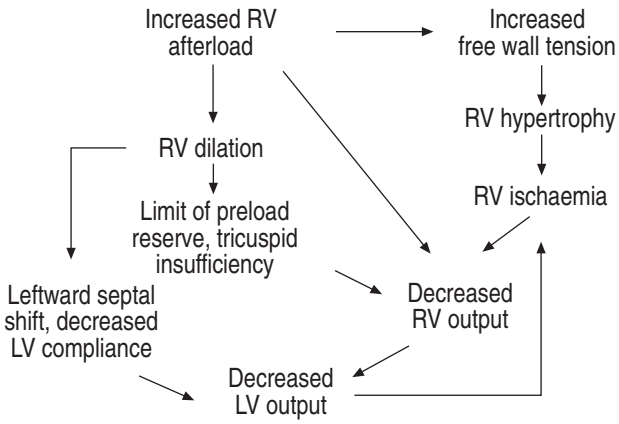

Fig. 2. – Main pathophysiological factors involved in right and left heart failure in patients with pulmonary hypertension. RV: right ventricle; LV: left ventricle.

Numerous factors may precipitate RV failure [23, 24, 34]. Factors related to preload include impaired venous return (*e.g.* mechanical ventilation), decreased preload reserve (*e.g.* hypovolaemia) and mechanical limitation (*e.g.* effusive pericarditis). Factors related to afterload include acute load increases (although pulmonary embolism-related RV failure is observed only for acute systolic pressure >60–70 mmHg), increased pulsatile load (*e.g.* proximal obstruction with markedly increased pulse wave reflections), and factors related to transpulmonary pressure, lung compliance and mechanical ventilation. Major tricuspid valve insufficiency may precipitate RV failure, and the anatomical and functional status of the tricuspid valve has a key role in preserved RV function. Other factors potentially precipitating RV failure are decreased inotropy, RV ischaemia, REM sleep and obstructive sleep apnoea syndrome. The deleterious role of hypoxia and neurohormonal factors has also been demonstrated.

Therapeutic implications

The main goals in the prevention and treatment of RV failure include: 1) reducing RV afterload by decreasing PVRI; 2) limiting pulmonary vasoconstriction (*e.g.* prevention of hypoxaemia); 3) optimising RV preload; and 4) preserving coronary perfusion through maintenance of systemic blood pressure. Other strategies may depend upon the cause of PH (*e.g.* recipient selection for preventing acute RV failure following cardiac transplantation) [37].

Exercise capacity

During exercise, the pulmonary vascular bed of normal subjects shows a minimal rise in PAP despite the doubling or tripling of cardiac output, thanks to the substantial reserve of pulmonary circulation. The fall in PVRI reflects passive distension of compliant small vessels and/or recruitment of additional vessels in the superior portions of the lung [10–13, 38].

According to the New York Heart Association (NYHA) functional classification, symptoms may be caused by ordinary physical activity (Class II), less than ordinary activity (Class III) or may even be present at rest (Class IV) in PH patients [1–8]. Recent guidelines focus on the rational management of patients without any limitation of their physical activity (Class I) [1]. It must be remembered that clinical symptoms poorly correlate with resting mean PAP [39]. The degree of preservation of systolic performance of the RV is the main factor governing the clinical presentation.

In patients with primary PH, impaired cardiac reserve during exercise is reflected in reduced peak O_2 uptake ($V'O_2$) [40, 41]. The NYHA functional class best correlates with % predicted peak $V'O_2$, which

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