

Is it Necessary to Define New Hemodynamic Indexes of Pulmonary Hypertension?

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Idiopathic pulmonary hypertension is a syndrome characterized by dyspnea, fatigue, chest pain, syncope, and an increase in pulmonary vascular resistance with no identifiable cause. In most cases it can course asymptotically for years, increasing vascular resistance and remodeling the vascular tree.

Pulmonary hypertension is often found in other disorders which present the same symptomatology, pathology and response to treatment as the idiopathic form. These disorders are associated with collagen disease, congenital cardiopathy with left-right shunts, anorexigen use or human immunodeficiency virus (HIV) carrier status. Following the Evian Meeting,¹ these types of pulmonary hypertension have been grouped, along with the idiopathic form, under the heading of pulmonary artery hypertension (PAH). The conclusions from this meeting were presented recently at the 3rd World Symposium on Pulmonary Hypertension, held in Venice in June 2003.

Pulmonary hypertension is diagnosed when mean pulmonary artery pressure is more than 25 mm Hg at rest or higher than 30 mm Hg during exercise. Symptoms appear when mean pulmonary artery pressure exceeds 30–40 mm Hg. Above this figure, cardiac output begins to decrease progressively. However, in daily clinical practice effort tolerance or heart failure symptoms are not associated with the hemodynamic severity of PAH.

Thus, new hemodynamic definitions of PAH are needed to help us understand this discrepancy. These definitions should include pressure-volume curves, analysis of the beat-to-beat curve or detailed analysis of pulmonary vascular resistance after pulmonary ar-

tery occlusion.²⁻⁵ This should translate into more sensitive noninvasive diagnostic procedures enabling the detection of the disease in its early stages. However, given that the main determinant of mortality is cardiac output and its response to treatment, ventricular function should be quantified more precisely, and in particular, indexes of contractility should be developed which are independent of afterload. The most promising approach to this may be Doppler tissue imaging or magnetic resonance imaging (MRI).

The evaluation of impedance in the pulmonary vascular bed, obtained by measuring the acceleration index, may yield additional information on right ventricular function. Impedance parameters may better reflect right ventricular afterload and yield better hemodynamic information than that derived from pressure and flow measurements. During heart catheterization, impedance can be appropriately evaluated with high fidelity pressure and velocity multisensor transducers.¹

Recently, there have been great advances in our understanding of the biopathology of PAH. Whatever the cause of the progressive increase in pulmonary vascular resistance, different mechanisms combine to perpetuate disease progression. According to a unified theory, the current pathophysiological state is determined by a dynamic interaction of risk factors, genetic predisposition, and vascular lesions with endothelial dysfunction of the muscular layer and adventitia—each of which can react with circulating blood elements.

Smooth muscle hypertrophy in the medial layer of the pulmonary arteries, together with the reduction in pulmonary vascular resistance obtained with vasodilators, led Wood to propose the «vasoconstrictor» hypothesis to explain the pathogenesis and pathophysiology of idiopathic PAH. Wood suggested that the onset involved an active vasoconstriction component of the small-caliber pulmonary muscle arteries and arterioles. This process was also the main determinant of hemodynamic characteristics and the course of PAH. Recently, dysfunction in the K⁺ (K⁺c) channels in the smooth muscle cells of the pulmonary arteries was identified in patients with idiopathic PAH. This ano-

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maly consists of membrane depolarization, increased cytosolic Ca^{2+} and activation of the contractile apparatus with vasoconstriction.⁶ The fact that this alteration has not been detected in patients with secondary PAH is of interest.

Serotonin is a substance that induces the contraction and proliferation of pulmonary artery smooth muscle cells. The main reserves of serotonin are found in platelets, and its circulating levels are normally very low. Plasma concentrations of serotonin are higher in patients with idiopathic PAH than in healthy persons. These plasma values are also higher in patients using anorexigens.

Hypertensive pulmonary vascular disease is characterized by an abnormal growth of the vascular endothelium and proliferation of smooth muscle cells which, with time, lead to vessel thickening and cell destruction. Current therapeutic trends include attempts not only to reduce the vasomotor tone of the pulmonary vessels, but also to inhibit these abnormal events, and thus control pathological remodeling.

One of the main limitations to investigating this disorder more thoroughly is the lack of suitable animal models. The model of hypoxia in rodents more closely replicates altitude sickness PAH or chronic obstructive pulmonary disease, and the rat monocrotaline model most resembles acute respiratory distress with pulmonary hypertension. The model closest to the concept of PAH outlined at the Evian Meeting is that of the young pig, but here hypertrophy develops only in the medial layer. This model will need years of observation before the more advanced histological lesions (e.g. plexiform lesions) can be traced.

In this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA, Grignola et al⁷ present an interesting and appropriately designed experimental study based on sound methodology. These authors seek to characterize the buffering function of the pulmonary artery *in vivo*, and to determine the role of vascular smooth muscle (VSM) activation in pulmonary artery wall elasticity.

They conclude that the experimentally produced modifications in the changes in elasticity of the pulmonary artery, when acute and moderate PAH are induced, differ depending on whether or not the muscular layer is activated. In contrast, when the increase in pulmonary artery pressure involves activation of the vascular smooth muscle layer (active PAH), a beneficial effect appears in the arterial mechanics. This pre-

vents increases in wall stiffness of the pulmonary artery and maintains the global buffering capacity of the pulmonary artery system. As the authors note, the role of vascular smooth muscle in the different clinical categories of PAH should be defined.

The only limitation of this study is that the model is applicable to acute PAH situations and therefore cannot be extrapolated to chronic hypertensive vascular disease. Nevertheless, the study is important because of the potential clinical benefits that may arise from these findings.

This interesting study suggests that pharmacological action on the vascular smooth muscle in the early stages of hypertensive vascular disease helps to modify its natural course. The findings may also be useful to test the effect of different drugs on the elasticity and stiffness of the pulmonary artery in situations of PAH induced or exacerbated by exercise.

It remains to be seen how long it will take to translate these findings into the clinical management of patients with PAH. Nevertheless, this experimental study is a call to clinicians who manage this serious disease to support and collaborate with basic research efforts.

REFERENCES

1. Rich S, editor. Primary pulmonary hypertension: executive summary from the World Symposium-Primary Pulmonary Hypertension 1998. World Health Organization. Disponible en: www.who.int/ncd/cvd/pph.html
2. Kafi AS, Melot C, Vachiéry LJ, Brimiouille S, Naeije R. Partitioning of pulmonary vascular resistance in primary pulmonary hypertension. *J Am Coll Cardiol* 1998;31:1372-6.
3. Castelain V, Chemla D, Humbert M, Sitbon O, Simonneau G, Lecarpentier Y, et al. Pulmonary artery pressure-flow relations after prostacyclin in primary pulmonary hypertension. *Am J Respir Crit Care Med* 2002;165:338-40.
4. Nakayama Y, Sugimachi M, Nakanishi N, Takaki H, Okano Y, Satoh T, et al. Noninvasive differential diagnosis between chronic pulmonary thromboembolism and primary pulmonary hypertension by means of Doppler ultrasound measurement. *J Am Coll Cardiol* 1998;31:1367-71.
5. Chemla D, Castelain V, Herve P, Lecarpentier Y, Brimiouille S. Hemodynamic evaluation of pulmonary hypertension. *Eur Respir J* 2002;20:1314-31.
6. Galié N, Manes A, Branzi A. Características biopatológicas de la hipertensión arterial pulmonar. *Rev Esp Cardiol Supl* 2002;2:C9-14.
7. Grignola JC, Bia D, Ginés F, Armentano RL. Hipertensión pulmonar aguda: rol protector de la activación del músculo liso vascular. *Rev Esp Cardiol* 2003;56: 1077-84.