PAH-D, is there a non-invasive way to predict the unpredictable?

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Abstract

Group D PAH-CHD is a problematic increasingly recognized group of patients, in which pulmonary hypertension continues to progress despite the correction of a significant cardiac lesion with pulmonary overflow. Early and non-invasive testing that can predict this subset of patients, prior to correction of their underlying cardiac lesion, is still non-established in practice and under-investigated in literature. Serum markers and angiogenic molecules denoting apoptosis resistance, can be game changer to the standard practice in this context. We hope that this letter can encourage researchers concerned with PAH-CHD to start investigating the diagnostic accuracy and cut-off values of these biomarkers.

Letter to the editor

PAH-D, is there a non-invasive way to predict the unpredictable?

To the Editor:

Types of PAH-CHD and the problematic group D PAH-CHD

Pulmonary arterial hypertension (PAH) is a common complication of congenital heart disease (CHD), with most cases occurring in patients with congenital cardiac shunts.

PAH-CHD is clinically classified into 4 groups; Group A being Eisenmenger, Group B includes patients with severe PAH due to significant shunt lesions with no reversal of the shunt and no cyanosis, Group C includes patients with PAH due to small defects whose clinical picture is found to be comparable to that of IPAH (idiopathic PAH) and lastly, Group D which is PAH following repair of the CHD.[1]

To date, there is no test established that can predict the outcome of pulmonary arterial hypertension, and whether PAH will improve after repair of the shunt lesion, or will possibly persist. [2]

Determining the potential persistence of CHD-PAH after closure of the shunt lesion is of utmost importance, as this shunt lesion, might later serve as a possible vent to the right side of the heart.

The underlying mechanism of CHD-PAH-C and CHD-PAH-D is possibly attributed to the coexistence of IPAH together with shunt lesion. While it is easy to recognize this in Group C; due to the triviality of the associated left to right shunt, it is currently very difficult, if not impossible, to recognize group D, except retrospectively after closure of the left to right shunt. [3]

Lung Pathology in IPAH vs. early reversible PAH-CHD.

Differentiating IPAH from early PAH-CHD warrants the understanding of the lung pathology associated with each of them. In end-stage PAH, regardless of the underlying etiology, the lung tissue is characterized by the occurrence of concentric laminar hypertrophy and plexiform lesions. While isolated, vasoconstriction

or medial hypertrophy driven by increased pulmonary blood flow is generally reversible after cessation of the trigger. [4]

The true identification of reversibility of pulmonary vascular lesions in PAH, is either via hyperoxia test done through invasive cardiac catheterization or by invasive lung biopsy; and it is illogic to perform any of these routinely before closure of a large shunt lesion, to discriminate between PAH-CHD patients who might respond to repair of the CHD and those in whom the PAH will progress even after repair. [5]

Apoptosis sensitive vs. apoptosis resistant endothelium, and the uninvestigated role of serum markers.

The key factor to developing the malignant plexiform lesions is the loss of apoptosis signals leading to excessive and uninterrupted cellular proliferation. It is increasingly established currently that keeping the endothelial cells at a balance between apoptosis and apoptosis resistance is the turning point between reversible CHD-PAH and irreversible CHD-PAH, or in other terms between early CHD-PAH, and other forms of PAH. [6]

Several markers are expressed in the endothelial cells, that can signal this transition from apoptosis-sensitive to apoptosis resistant endothelium. P53, is a pro-apoptotic marker, which increases in PAH-CHD after closure of the shunt and reflects a good prognosis of regression of PAH. While markers such as Bcl-2 (B-cell Lymphoma-2), survivin, were expressed in patients with progressive disease, and reflect this shift from apoptosis sensitivity to apoptosis resistance. [7]

To date, most of the investigations conducted on these markers did not involve human subjects, and those involving human subjects, did not compare IPAH with the different groups of PAH-CHD mentioned above, especially group D.

Hence, we suggest that researchers start case-control studies to study the serum levels of these markers, across different groups of PAH, notably, IPAH and PAH-CHD-B and the problematic PAH-CHD-D.

These markers, though currently expensive, are non-invasive and easier to perform, and can be generalized to practice, when deciding the repair of CHD, to predict patients who will respond poorly to repair and will continue to develop progressive PAH, after cessation of pulmonary overflow.

Conclusion:

Group D PAH-CHD is a problematic increasingly recognized group of patients, in which pulmonary hypertension continues to progress despite the correction of a significant cardiac lesion with pulmonary overflow. Early and non-invasive testing that can predict this subset of patients, prior to correction of their underlying cardiac lesion, is still non-established in practice and under-investigated in literature. Serum markers and angiogenic molecules denoting apoptosis resistance, can be game changer to the standard practice in this context. We hope that this letter can encourage researchers concerned with PAH-CHD to start investigating the diagnostic accuracy and cut-off values of these biomarkers.

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