Is surgical treatment the cure for patients with congenital heart disease?

It has been largely acknowledged that pulmonary vascular disease (PVD) and congenital heart disease (CHD) are closely related. This link has been established for more than a century now, and is based on careful observations and hard scientific work of many outstanding investigators. Much of the current knowledge on the pathobiology of pulmonary hypertension (the clinical and hemodynamic expression of PVD) is based on detailed analysis of lung biopsy specimens collected over decades during surgical repair of congenital cardiac anomalies (or lung tissue obtained at autopsy).[1-4] From isolated medial hypertrophy of pulmonary arteries to complex dilated lesions, necrotizing arteritis, and pulmonary capillary hemangiomatosis, all types of vascular abnormalities known to be present in pulmonary arterial hypertension in general (PAH) and idiopathic pulmonary arterial hypertension (IPAH) have been extensively described in PAH-CHD.

Despite this huge collection of data, translation of knowledge into the development of effective strategies to cure the disease is neither easy nor immediate, in particular since there are many unsolved problems at clinical level and relevant social issues as well. The Eisenmenger syndrome, known as the most advanced form of PAH-CHD, is still relatively prevalent (4-12% in adults with CHD), reflecting a limited access to early repair of the cardiac anomalies, especially in underserved areas of developing countries. In institutions devoted to the treatment of cardiovascular diseases, the Eisenmenger syndrome may appear as the most prevalent etiology of PAH.[5]

Continued progress in understanding genetics and pathobiology may help solving problems at clinical level. For example, there has not been a precise definition of the boundaries between patients who will and those who will not benefit from surgical treatment. We are not talking about the vast majority of pediatric patients with congenital cardiac shunts now assigned to surgery early in life, with no residual elevation of pulmonary vascular resistance (>90% of cases). We are talking about 5-10% of patients, those older at repair, presenting with extra cardiac syndromes, bidirectional shunting across the communications, with periods of systemic oxygen desaturation and without a clinical history of congestive heart failure and/or failure to thrive (PAH-CHD). A false impression of success is frequently based on early postoperative observations, while late postoperative data remain scarce. Indeed, some patients who appear to have a successful repair of their anomalies will present years after surgery with severe PAH. Biomarkers may be considered as important tools for predicting prognosis and long-term outcomes, provided that they can be properly validated for use in clinical practice.[6-9] There have been attempts in this way. Besides, PVD is rapidly progressive when associated with specific anomalies, as is the case of persistent truncus arteriosus, transposition of the great arteries in the presence of a ventricular septal defect, and atrioventricular septal defects (particularly in subjects with Down syndrome). Why that? Common gene families or gene clusters explaining both the cardiac anomaly and the predisposition to PVD? It is noteworthy that the BMP genes, largely associated with sporadic and heritable PAH play an important role in cardiac morphogenesis.[10,11] Isn't this a fascinating field for investigation?

In the era of the so-called new drugs for PAH (prostanoids, endothelin receptor antagonists, drugs acting on the nitric oxide pathway including phosphodiesterase inhibitors, and other molecules acting on receptors and cascades related with cellular proliferation),[12] changes in the paradigm of operability tend to occur very rapidly, as long-term outcomes may be modified by appropriate combinations of medical (drug) therapy and surgical strategies in subjects with mild to moderate PVD. A patient is deemed operable not only if he or she is likely to survive operation, but also, and very importantly, if a substantial improvement of the clinical condition is expected to occur over the long term. In this way, many drugs initially developed to act as "pulmonary vasodilators" have now been demonstrated to have antiproliferative properties. Therefore, from the theoretical point of view, one could expect benefits from these therapies even beyond the limits of the immediate postoperative period.

However, words of warning are needed here. There has not been evidence to support generalized recommendations.[13-15] Well-designed clinical trials are required to demonstrate

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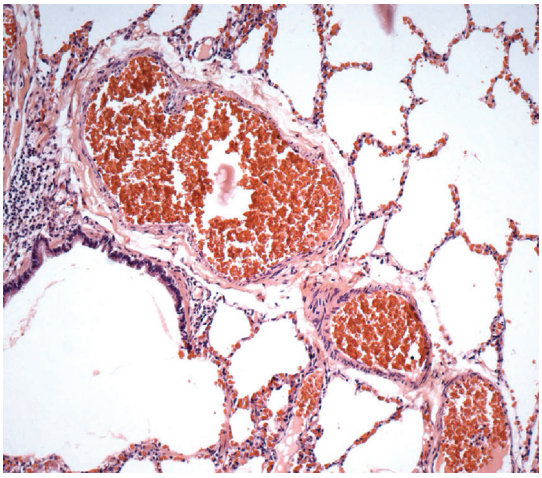

Figure 1: Photomicrography of a lung biopsy taken intra-operatively from a 3-year-old patient with ventricular septal defect. Note the presence of thin-walled arteries at the entrance of the pulmonary acinus. This could lead to the interpretation that there is no structural pulmonary vascular disease. But to the experienced pathologist, the apparent discrepancy between clinical and morphological data besides the knowledge that distal dilatation occur in severe pulmonary vascular disease, may indicate that a search for obstructive lesions is mandatory. In the present case, a plexiform lesion was found in another level of the lung tissue, after semi-seriated sections. Hematoxylin-eosin stain, objective magnification 10×. Courtesy, Professor Vera D. Aiello, Heart Institute, University of São Paulo, Brazil.

the benefits of combining drug therapy and surgery in the setting of PAH-CHD, and the problem must be analyzed in different scenarios: (1) young patients (e.g., below the age of 2 years) with specific defects; (2) presence/absence of associated syndromes; (3) older children; (4) adolescents and adults; and (5) particular conditions in the adulthood as is the case of atrial septal defects. In each tertiary institution, every single patient should be registered and followed-up in a systematic way over the long term.

Translational medicine has an obvious place here. Continued knowledge is needed on the basic mechanisms underlying the progression or regression of pulmonary vascular remodeling in specific subsets of PAH-CHD patients subjected to therapy with the new PAH drugs. Quite surprisingly, however, exactly at the moment of increased needs in terms of understanding basic mechanisms of human PVD, the number of lung biopsies performed in tertiary centers for diagnostic and prognostic purposes decreases worldwide under the statement that "biopsy specimens are not representative of the whole lung." The real problem is probably far beyond that. Not many pathologists are sufficiently familiar with PVD as to describe, understand, and interpret mechanisms beyond the microscopic field (Fig. 1); not many are involved with research and able to use appropriate methodology to persuade the answer of emerging new questions. Therefore, it is time to consider that in selected cases, especially in well-designed studies, adequately processed intraoperative lung biopsies may be crucial to understand the aggressive nature of the disease and define what one can really expect from the emerging new therapies.

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