

Thinking outside the bowl: The recruitment of systemic-to-pulmonary collaterals in chronic and severe pulmonary hypertension as an adaptive mechanism

Dear Editor,

One of the best presentations sent from specific countries to the American College of Cardiology (ACC) Scientific Sessions, is awarded in the category of "Best Abstract" and the award is given to the presenter of that presentation during the Joint Meeting of that specific country and ACC. Last year I have been honored with this award, for being the first name in the presentation of the nation-wide multicenter study "THALES" in the last year's congress of ACC and I received this award on behalf of the investigators of THALES, during the Joint Session of the Turkish and German associations of Cardiology as one of the two owners of "Beast Abstract" award, in a circumstance where the German Association of Cardiology presented a special award to Prof. Eugene Braunwald, as a kind of apology.

This year, our oral presentation on the EUPHRATES study that we conducted in collaboration with Koşuyolu Specialised Training and Research Hospital, which was titled as "The recruitment of systemic-to-pulmonary collaterals in chronic and severe pulmonary hypertension as an adaptive mechanism: Do we treat these collaterals in reality?", has been awarded as the "Best Abstract" in the ACC14 Scientific Sessions. As it happened last year, this year's award was presented to the most voted presentation from Turkey. However, the day before the start of ACC14 meeting, during the Middle East Chapter meeting, it was really a great surprise for us to learn that the same study will be awarded with a second "Best Abstract" award as one out of three most voted presentations from the Middle East countries.

After rushing to get there on time for this last-minute program, this surprising award presented by Prof. Dr. Douglas Zipes will always be an exquisite memory in our mind. Then, during the Joint Session of Asia Pacific Countries and Turkey, we were glad to receive the award that we were formerly informed about, the "Best Abstract" award representing Turkey.

Our presentation represents one of the aspects of a series of studies on pulmonary hypertension (PH), that lasted about 9 years. These studies were grouped under the title of "Evaluation of Pulmonary Hypertension Risk Factors Associated with Survival" (EUPHRATES). This acronym was a reference to the antique name of Firat River. In this study, we examined the formation of the collateral vessels between the major systemic arteries and pulmonary arteries, through the bronchial arteries

(BA) and non bronchial arteries (NBA), in cases of congenital heart disease associated PAH, advanced chronic thromboembolic PH and idiopathic pulmonary hypertension (IPAH), using multislice CT.

Since it was first demonstrated by FRuysch in 1731, the BA circulation remained as a neglected part of the circulation, that transports only 0.5 to 2% of the aortic flow, through the arteries supplying the bronchial walls, lung vessels, nerves and alveolar tissues. However, it was demonstrated that the BA system devel-



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oped before the pulmonary arteries (PAs), during the fetal period and since then, studies using scanning electron microscopy have revealed that the density of systemic to pulmonary artery collaterals may be as incredible as 120 vessel sections per mm² at the level of distal bronchioles (1). Moreover, a link between the BA circulation and one of the branches of PA may result in chronic pulmonary damages and under special circumstances, such as PH, it is possible to develop an adaptive mechanism that transports 25 to 30% of aortic flow to the alveoli, therefore it was also





demonstrated that BA circulation may transform from a supplier into a circulation unit that provides hemodynamic and respiratory contribution. Apart from the comprehensive book of "The Bronchial circulation", published in 1992 by the members of the Da Vinci Society - which was named after Leonardo da Vinci due to his contribution to the knowledge on the anatomy of bronchial arteries- under the leadership of the editor, John Butler, very limited of studies have been dedicated on this subject during the recent years (2). While the untimely death of John Butler prevented the second edition of this unique, classic book, there was an explanation of Fishman, in the preface: "Bronchial circulation reveals similarities to a mother or the Red Cross, we rarely remember them in our good times but they are always there to provide the best support when we need them" (2). Such a wise man that could be rarely encountered nowadays, Fishman's suggestions, which were stated in two distinct articles published in 1961 and 2000, were very important for the inclusions of either these collaterals or the plexiform lesions stated in the Heath-Edwards classifications, into a general frame (3-5).

In the exact way that we believe, Yaginuma et al. (6) defined either collaterals or plexiform lesions and "vein-like dilated vas-

cular structures" within the same model, and stated that while the first ones were macroscopic connections and the second ones were the microscopic connections between the two systems. Our hypothesis suggests that the systemic to pulmonary artery connections which are known to occur in cases of advanced congenital heart diseases related pulmonary hypertension and chronic thromboembolic pulmonary hypertension, as well as in the other of PH group categorized as precapillary PH such as IPAH, may work as a "de facto adaptive and compensatory mechanism". As a matter of fact, in a circumstance of diffuse narrowing and in situ occlusion related to remodelling, thrombosis and permanent vasoconstriction, there is no other pathophysiological solution than this "borrowed by-pass bed" constituted through BA and NBA circulations, for the transport of either aortic arterial blood of the venous blood from proximal part of PA, to the alveoli.

From our standpoint, the actual paradigm on the mechanism of action of the available PAH-specific medications, is based on a stereotype and misses the beneficial role of this collateral system in the treatment of the condition. However, in the dog studies conducted in 1990s, a dose dependent acute reduction

of BA resistance could be induced by prostacyclins selectively infused into BA, while the same phenomenon was not observed in the other BA system of the same animal, into which the prostacyclin was not administered. Furthermore, a similar effect was demonstrated when the prostacyclins were administered into the alveoli via PA or inhalation. Therefore, even then, there was sufficient evidence revealing the importance of the BA system as a treatment target.

In our series, we demonstrated in detail by CT scans that the diffuse collaterals as a vessel system 6 or 7 mm in diameter were formed by BA and NBA circulations along the PA branches, and LIMA,RIMA, phrenic arteries and pleural collaterals were also included in this system, in cases of IPAH, congenital heart diseases related pulmonary hypertension and chronic thromboembolic pulmonary hypertension. These collateral vessels were detected in 61 to 73.5% of the cases and we observed a positive correlation between the mean pulmonary artery pressures and the increases in transpulmonary pressure gradient and pulmonary vascular resistance. Moreover, we also demonstrated that a measurement of diastolic transpulmonary pressure gradient - which is a pretty new parameter- higher than 16 mm Hg, is more likely to be a strong predictor for the formation of these collateral vessels (AUC:0.73, $p<0.0001$). Although our striking examples from all three groups could demonstrate that the collateral vessels originated from BA and NBA might be associated with a relatively benign course on an individual basis, we could not determine any statistically significant survival superiority related to these collateral vessels, in patients on treatment.

In conclusion, we suggest that the collateral vessel formation between the systemic arteries and pulmonary arterial systems intends to maintain the transport of venous or arterial

blood to the alveolar level and is an alternative bypass system, rich in endothelial surface and they may be the main target for the mechanism of action of the current PAH-specific treatments. This approach also suggests that, these vascular structures might be the essential target of the brand new modalities such as gene technologies and PA denervation, in cases of advanced stage PH.

As a last word, I would like to express my endless appreciation for all of my colleagues who are the biggest wealth of my professional life, for the teamwork requiring special effort and skill.

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