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Key Words: single ventricle, aortopulmonary collateral, congenital heart disease

EDITORIAL COMMENTARY

Aortopulmonary collaterals: Angiogenesis, or a whole lot more?

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Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Oct 21, 2015; accepted for publication Oct 22, 2015; available ahead of print Nov 24, 2015.

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J Thorac Cardiovasc Surg 2016;151:1135-6
0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2015.10.086>

Favorable pulmonary vascular dynamics is the key element of successful Fontan circulation. Unfortunately, alterations in the pulmonary vascular tree are not uncommon in children who have complex congenital heart disease. Aortopulmonary collaterals (APC), which divert oxygenated blood from the systemic circulation back to the lungs, are the most commonly acquired pulmonary vascular abnormalities. Several investigators have attempted to identify the physiologic stimuli for the formation and progression of APC. As the field of molecular biology has matured, additional efforts have been made to define the molecular basis for the formation of APC.

Along those lines, this article by Sandeep and colleagues¹ seeks to correlate the serum level of angiogenic factors with angiogenic activity in vitro, and APC formation in vivo.

Aortopulmonary collaterals to the left lung, pre-Fontan.

Central Message

Angiogenic factors do not fully explain aortopulmonary collateral formation in complex congenital heart disease.

See Article page 1126.

Although factor concentration in the serum differed significantly between the 2 groups of patients studied, it was poorly correlated with the extent of APC. Despite this negative result, the authors should be congratulated for pursuing what many investigators would have regarded as too simplistic a hypothesis.

One of the major drawbacks of the study is that the 2 groups being compared were made up of a heterogeneous cohort of patients, including some single-ventricle patients post-Fontan, who most likely were not cyanotic, whereas other patients in the control group had considerable periods of cyanosis earlier in their lives. Significant variations were found in arterial and venous levels of the factors studied, both within the same patient, and among patients within the same group.

Such widespread serum levels did not reliably correlate with either endothelial cell sprouting in vitro or APC in vivo. To explain this discrepancy, the authors invoke a theory of phasic changes in angiogenic factor levels. This theory, although attractive, is at best speculative, without any experimental data in their study to support its veracity. The more germane explanation would be that their hypothesis was not sophisticated enough to explain this intricate disease process.

Despite these substantial limitations, the study by Sandeep and colleagues,¹ like any thoughtful work in science, raises more questions than it attempts to answer. Why are the arterial versus venous levels of serum angiogenic factors different in patients with single-ventricle physiology? Is the pulmonary bed itself the source of additional factors; if so, would levels measured in the lungs be more predictive

of clinical findings? Alternatively, is a possible explanation that a real difference exists in a subset of relevant angiogenic factors, but the authors did not pick the correct ones to study? A more global analysis of the blood with RNA sequencing or angiogenesis-specific microarrays would be required on a large number of patient samples to identify novel candidate proteins worthy of pursuit. Or could there be patient-specific factors that determine the extent of APC development under a given milieu of cyanosis and hypoxia? This explanation would require comparing gene expression in patients who have similar physiologic states but dissimilar APC profiles.

The quest to identify serum biomarkers that can be correlated with APC formation, and more importantly, develop novel biological therapies to address them, is laudable. Although the study by Sandeep and colleagues¹ is negative, it challenges researchers in this area to expand their horizons and redefine a more complex paradigm to approach APC formation. Likely, APC has a lot more to it than just angiogenesis.

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