Published in final edited form as:

Ann Intern Med. 2015 January 20; 162(2): 148–149. doi:10.7326/M14-2700.

Vasodilator Responsive Pulmonary Arterial Hypertension: *Evidence for a new disease?*

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Idiopathic pulmonary arterial hypertension (IPAH) is a highly morbid disease characterized by progressive obliteration of the pre-capillary arterioles and a contemporary survival of just over 5 years after diagnosis.(1) A small subset – 5 to 10% – of IPAH patients displays dramatic hemodynamic improvement in response to acute exposure to pulmonary vasodilators such as nitric oxide and epoprostenol. These so-called vasodilator-responsive IPAH patients have an expected survival measured in decades and an excellent response to therapy usually with calcium channel blockers.(2) This disparity in outcomes has fueled speculation for decades that vasodilator responsive and non-responsive PAH may be two distinct diseases.

In modern thinking, IPAH arises from pulmonary vascular remodeling with a potentially small contribution of vasoconstriction. Both the limited improvement in pulmonary vascular resistance with treatment for IPAH and pathologic studies showing vascular remodeling and plexiform lesions support this theory. But does this apply to the sub-set of vasodilator-responsive IPAH? Pathologic studies have been performed in patients with IPAH but none using contemporary criteria to define the vasodilator-responsive subtype. A single pathology study examined the relationship between histologic findings and response to pulmonary vasodilators.(3) At least in part because of the excellent survival in vasodilator responsive IPAH, there have been no pathologic studies that specifically examined how these patients differ from those without a response. The marked drop in mean pulmonary artery pressure and pulmonary vascular resistance with acute vasodilator administration, however, argues against an irreversible pulmonary vascular pathology.

It is rare for research to warrant publication based on findings in a total of two patients. Such work must necessarily demonstrate a new discovery or unveil an aspect of a disease that was previously unknown. In this issue of *Annals*, Langleben et al. accomplish both with respect to vasodilator-responsive IPAH (4). Applying a technique to measure endothelial functional cross-sectional area, Langleben et al. present the most definitive evidence to date that vasodilator responsive PAH is characterized by immediately reversible vasoconstriction (without luminal obstruction) while non-responsive PAH has irreversible vascular

obliteration. They did this by measuring the functional capillary surface area (FCSA) in vasodilator responders and non-responders at baseline and after exposure to epoprostenol infusion. The rationale for the experiment was that if elevated pulmonary vascular resistance and pressure are driven by vasoconstriction, FCSA would increase after exposure to a vasodilator through recruitment of microvasculature. Conversely, if PAH is caused by precapillary microvascular obstruction the vasculature would be unable to recruit additional capillaries, resulting in no change in FCSA. Using a clever technique, FCSA was measured by leveraging the capacity of pulmonary capillary endothelium to metabolize angiotensin; the greater the metabolism of angiotensin, the greater the surface area of the pulmonary vascular bed. The authors used a synthetic substrate known as H-Benzoyl-Phe-Ala-Pro (BPAP), the metabolism of which is highly specific to pulmonary capillary endothelial bound-angiotensin converting enzyme. BPAP metabolism was measured across the pulmonary circulation and FCSA could then be calculated.(5,6)

The combination of baseline hemodynamics and BPAP metabolism in response to vasodilator challenge revealed two distinct phenotypes. Non-responders had worse hemodynamics and lower resting FCSA at baseline compared with responders. In non-responders, cardiac output increased 36% after epoprostenol but BPAP metabolism fell and calculated FCSA remained unchanged. This indicates that augmented flow was not associated with recruitment of additional microvasculature. The responder group, by contrast, exhibited a substantial decrease in mean pulmonary artery pressure and increase in cardiac output. These hemodynamic changes were associated with no change in BPAP metabolism and an increase in FCSA. Therefore, increased flow in the responders was matched by increased exposure to pulmonary capillary endothelial bound-angiotensin converting enzyme in newly recruited microvasculature.

In addition to physiologically proving the hypothesis that vasoconstriction is the primary mediator of pulmonary hypertension in vasodilator responsive PAH, Langleban's work also draws attention to the importance of careful, deep phenotypic studies of common and rare diseases. The clinical observation that some IPAH patients have an excellent response to treatment with calcium channel blockers was made over 20 years ago(7), but what mediates vasodilation in these patients and what is different from those without a response remains unknown. This work is a first step in proving that this sub-phenotype is physiologically different and suggests important next steps. Specifically, the molecular etiology of vasodilator responsive PAH must be studied to define the mechanisms of vasoconstriction in this group and determine if they can be used to improve therapy and outcomes in the much larger non-responsive group. Recent work from our group shows that vasodilator-responsive PAH patients have a different peripheral blood transcriptomic pattern from non-responsive PAH.(8) Whether there is a genetic predisposition for this sub-phenotype or if these types of responses can be identified in other groups of "out of proportion" pulmonary hypertension such as that seen in hypoxia are unknown. Answers to these questions will undoubtedly improve care for all patients with pulmonary hypertension, demonstrating how phenotyping in a rare subset can have impact far beyond those few patients.

The study has important limitations to acknowledge in addition to the small sample size. The authors do not explain why cardiac output increased in non-responders in the absence of

microvascular recruitment. One potential explanation is that epoprostenol increased right ventricular contractility, an observation made in prior studies in PAH patients.⁽⁹⁾ Correlating BPAP metabolism with pathology demonstrating lack of luminal obstruction would be definitive validation of the methodology. Of course, the rarity of the responder group and their excellent survival make pathologic studies difficult in this group.

Overall, this report is an important scientific contribution to our understanding of the pathobiology of IPAH and, as the authors propose, suggests that these two hemodynamic phenotypes may represent two pathologically distinct diseases. This work has addressed the age-old question of what drives the elevation in pressure in IPAH, vascular remodeling or vasoconstriction? The answer is pleasing to both sides of the argument – it depends on the type of IPAH. The task before us is to use this information to improve identification and treatment for the largest group of IPAH, those without a marked response to vasodilators.

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