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EDITORIAL COMMENT

Are Animal Models in Pulmonary Hypertension Relevant to the Clinical Disease?*

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In this issue of the *Journal,* Aguero et al. (1) demonstrate that the intratracheal delivery of sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a), which attenuates vascular remodeling by altering calcium hemostasis within vascular cells, improved pulmonary hemodynamics and right ventricular function in a large "pre-clinical" model of pulmonary hypertension (PH). Although inhaled delivery of gene therapy has been previously demonstrated to produce modest effects in small animal models of pulmonary artery hypertension (PAH) such as that produced by monocrotaline (2,3), the large animal model used by Aguero et al. (1) provides the opportunity to more fully assess the hemodynamic effects of this approach and to study these effects in a different form of PH. This work also provides insight into 2 fundamental questions that are critical for advancing our approaches to PH in patients: 1) how does the pathophysiology of pulmonary vascular disease in different conditions determine the likelihood of benefit with potential therapies; and 2) how do PAH-targeted therapies exert their vascular effects?

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WHAT TYPE OF HUMAN PH IS THIS MODEL ANALOGOUS TO?

Aguero et al. (1) used a model of post-capillary PH produced by partial interruption of pulmonary venous flow, which is similar to neither PAH nor PH due to left-sided heart disease. The former is characterized by intrinsic and advanced arteriopathy that includes concentric intimal and adventitial proliferation and plexiform lesions, whereas the latter is characterized by an elevated left atrial pressure, mild and potentially reversible arteriopathy (4), and an elevated pre-capillary pressure that is compensatory to maintain the transpulmonary pressure gradient required for intrapulmonary blood flow.

What, then, accounts for the PH in this model, where the pulmonary capillary wedge pressure, an indirect measure of pulmonary venous pressure, is normal? The answer lies in the physiology of the human condition that this model best replicates: pulmonary veno-occlusive disease. The pulmonary capillary wedge pressure is typically normal in pulmonary veno-occlusive disease because the venopathy is patchy, and blood flows to venous channels that are patent and therefore transmit left atrial pressure to the wedged catheter (5). This is likely the case in the animal model used by Aguero et al. (1), in which the increased blood flow through the patent venous system eventually leads to shear stress and intrinsic vascular damage in the small- and medium-sized pulmonary veins. Thus, the pulmonary capillary wedge pressure measured in these studies underestimates the degree of venous hypertension in this model, and the resultant arteriopathy is solely the result of downstream vascular disease. Measurements of transpulmonary gradient and pulmonary vascular resistance, commonly used in the clinical setting to characterize the site and severity of vascular disease, do not accurately reflect the vascular dynamics in this setting.

In left-sided heart disease, targeting the pre-capillary pulmonary vasculature with therapies is, in

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fact, off target, because improvements in pulmonary arterial pressure can only be achieved by reducing pulmonary venous pressure, as the studies by Aguero et al. (1) actually support. However, although their studies suggest that the venopathy is the primary site of action of their inhaled gene therapy, they do not provide histopathology of the veins in sham and treated animals to support this notion. Furthermore, it remains to be determined whether ameliorating the modest degree of venous remodeling that is likely in this model with their approach can result in similar effects in the advanced pre-capillary vasculopathy that is present in PAH. As this model shows, arteriopathy will exist so long as venous pressure is elevated and flow to the left heart is regionally or globally impaired. The clinical trials using PAH-targeted therapies in PH due to left-sided heart disease have failed because these drugs do not affect the elevated venous pressure, the driver of arterial remodeling in this condition.

HOW DO PAH-TARGETED THERAPIES WORK?

It is time to put to rest the concept that PAH-targeted therapies exert their beneficial effects through pulmonary vasodilation, as cited by Aguero et al. (1) in their paper. Although all 14 drugs that have regulatory approval for PAH have vasodilator properties to varying degrees, it is doubtful that this property is responsible for their effects on the pulmonary circulation, for several reasons. First, the histopathology of pulmonary arteries in PAH typically shows evidence of extensive proliferation of all layers of the vessel wall, predominantly of the intima and adventitia—features that are not consistent with a predominant vasoconstrictive process. Second, the vast majority of PAH patients do not respond to inhaled nitric oxide, a potent and pulmonary selective vasodilator, with any reduction in pulmonary artery pressure or pulmonary vascular resistance. Only the handful of PAH patients who respond acutely to nitric oxide acutely may respond to calcium-channel blockers, and most of those lose this response over time (6,7). Third, combination therapy strategies that target multiple pathways involved in the pathogenesis of PAH not only result in greater improvement than monotherapy strategies, but these combination strategies are also not associated with increased signs or symptoms of systemic vasodilation, even in patients with advanced pulmonary vascular disease (8,9). If simple vasoconstriction was the cause of PAH, then monotherapy alone would suffice and the use of multiple nonselective vasodilators would result in untoward systemic effects, as typically occurs when calcium-channel blockers are administered to PAH patients who lack responsiveness to inhaled nitric oxide. Fourth, were these drugs "pulmonary vasodilators," it would seem reasonable to expect that they would be beneficial in PH due to left-sided heart disease by unloading both right and left ventricles, because they are nonselective, pulmonary and systemic vasodilators. Additionally, they might increase venous capacitance and reduce pre-load. Yet, they have consistently failed to demonstrate benefit in clinical trials of this condition. Thus, it is likely that these drugs exert their effects through a combination of vascular antiproliferation and, in some cases, direct effects on cardiac contractility. All of the currently targeted pathogenic pathways—endothelin, nitric oxide, and prostacyclin—are involved in vascular proliferation, and antiproliferative effects have been demonstrated in ex vivo experiments with the drugs targeting these pathways.

In summary, the studies by Aguero et al. (1) provide encouraging data regarding the potential to treat pulmonary vascular diseases with gene therapy targeting pathways responsible for vascular proliferation. However, extrapolation of these findings to any form of human pulmonary vascular disease—conditions in which the physiological and pathogenic mechanisms and severity of vascular remodeling are quite different—will await further studies in more relevant animal models and in carefully performed clinical trials.

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