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**PULMONARY
HYPERTENSION
ARISING FROM
LEFT HEART DISEASE
CAUSES
INTRAPULMONARY
VENOUS**

ARTERIALIZATION IN RATS

To the Editor:

We read with great interest the recently published article by Fujimoto and colleagues.¹ The article described a rat model of pulmonary hypertension (PH). PH related to left ventricular dysfunction represents by far the most common form of PH.² This area of study is important and has not been adequately evaluated, making this article timely and relevant. We would like to add several additional points that we believe will increase the readership's understanding of this emerging topic.

First and foremost, Fujimoto and colleagues¹ did not describe the pathophysiologic mechanisms of PH development in their model. In our opinion, this is of fundamental importance, because it differs from other known PH models. Left atrial (LA) stenosis in the rat causes LA stiffness and reduced LA compliance. This results in impaired LA contractility featuring changes in LA diastolic and systolic parameters. Sequentially, the elevation of the left-sided filling pressure and pulmonary arterial pressure causes congestion of the venous circulation. This induced congestion then results in the disruption of the alveolar-capillary barrier, promoting fluid filtration, which in turn permits leakage of molecules into the alveolar lumen. Because of the direct elevation in afterload, the right ventricle (RV) begins to fail. In the neurohormonal axis, the adrenergic stimulation and activation of the endothelin and renin-angiotensin-aldosterone system contribute to the increase in pulmonary vascular resistance.

Fujimoto and colleagues¹ rightly noted that, despite the importance of the venous circuit, few data are available

on lung's venous pathobiologic changes. Recent research studies have confirmed that the arteries and veins share similarities in the degree of vascular remodeling. In addition, it was also demonstrated that the structural "arterialization" of pulmonary veins in left heart failure is evident.

Because rat models are increasingly being used in PH studies, many of these studies have demonstrated that echocardiographic parameters, such as pulmonary artery acceleration time, RV area, RV thickness, and RV dimensions, are inversely correlated with severity of PH.³ Unfortunately, in their study Fujimoto and colleagues¹ used only echocardiographic parameters of left ventricular dysfunction. Moreover, it appears that this study was developmental in nature, with the goal of achieving PH, and this should have been discussed. PH is defined by a mean pulmonary artery pressure greater than 25 mm Hg. In clinical practice, pulmonary arterial catheterization is mandatory to confirm the presence of PH. It is a major concern from our point of view that pulmonary arterial catheterization was not performed in this study.

We agree with Fujimoto and colleagues¹ that the study and development of PH in left heart failure is very relevant, especially establishing the changes in pulmonary venous remodeling with distinct molecular markers. We acknowledge, as do Fujimoto and colleagues,¹ that these key markers remain elusive in the context of these models. To their credit, Fujimoto and colleagues¹ evaluated messenger RNA expression of numerous genes and found that the expressions of genes for transforming growth factor β 1 and endothelin 1 were significantly increased. Unfortunately, they did not check the expression of the SMAD family signaling proteins for transforming growth factor β 1, which are prime contributors to RV fibrosis.⁴ Nevertheless, these and other findings presented in this article will help to further understanding of the PH related to left heart disease.

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ELUSIVE MECHANISMS RESPONSIBLE FOR PULMONARY HYPERTENSION

Reply to the Editor:

We appreciate Katz and colleagues' letter to the Editor regarding our study of a rat model for pulmonary hypertension as a result of left heart disease.¹ We are in complete agreement with their comments. Despite the clinical importance of pulmonary hypertension as a result of left heart disease, the pathophysiologic mechanisms of pulmonary hypertension as a result of left heart disease have not been sufficiently clarified, even in our article, as was pointed out. Katz and colleagues importantly suggested that the elevation of the left-sided filling and pulmonary venous pressures induce pulmonary congestion and the disruption of the alveolar-capillary barrier, which differs significantly from the pathophysiology of pulmonary arterial hypertension. In our original article, we established an animal model as a first step. We believe that our model should be used further in future studies, by us and by other groups, to increase understanding of this disorder.

Katz and colleagues also pointed out the critical issue regarding the measurement of pulmonary arterial pressure, which we were unable to evaluate in our study. Although we had attempted to measure pulmonary arterial pressure directly with 1.9F Rodent PV Catheters (Transonic Systems Inc, Ithaca, NY), we were unsuccessful because of bleeding. We therefore evaluated the pulmonary hypertension by assessing the ratio of the right ventricular systolic pressure to the left ventricular systolic pressure. Furthermore, as Katz and colleagues pointed out, right ventricular parameters measured by echocardiography are alternate options for evaluating pulmonary hypertension. We identified this shortcoming in the description of limitations in the Discussion section of our article, and we believe that measuring pulmonary arterial pressure in rats with a thinner catheter, such as a 1.0F Millar Mikro-Tip Pressure Catheter (Millar, Inc, Houston, Tex) will be the next challenging task for us to undertake in a future study.

In DNA microarray pathway analysis, 5 genes (*Smad4*, *Hipk2*, *Ctnnb1*, *Cdkn2b*, and *Adam9*) related to the transforming growth factor β signaling pathway were 4 times higher in the group that underwent operation. In addition, *Hipk2* and *Ctnnb1*, which are known to be SMAD protein signal transduction factors, were also increased in the group that underwent operation (see

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Supplemental Table 2 in our original article). We appreciate Katz and colleagues' indication of the importance of transforming growth factor β and SMAD signaling pathways.

We again express our sincere appreciation to Katz and colleagues for taking the time to submit a letter to the Editor regarding our article. Such interaction and airing of other viewpoints strengthens the original submission, and we are grateful for their efforts.

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NOT A CINDERELLA STORY

Reply to the Editor:

Pulmonary hypertension that is secondary to left heart disease is one of the most common pulmonary hypertension types and also one of the most challenging to treat.^{1,2} This type itself is not uniform and can be related to systolic or diastolic dysfunction, valvular obstructive lesions, or pulmonary venous disease (although the last can arguably be classified under pulmonary arterial hypertension type).^{1,2} In addition, there are variations within this type that are associated with timing of development of the left heart lesion (eg, in utero, infancy, older) and speed of progression of the left heart disease (acute vs chronic). Because of the heterogeneity of this disorder and the relatively small yet important number of affected patients, many efforts to understand the pathophysiology of this disease and to develop innovative therapeutic strategies have relied on translational research with animal models.²

In a recent issue of the *Journal*, Fujimoto and colleagues³ from Japan reported their creation of an animal model of pulmonary hypertension in laboratory rats. Through a left