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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