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EDITORIAL COMMENT

The Forgotten Left Ventricle in Right Ventricular Pressure Overload*

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In this issue of the *Journal*, Hardziyenka et al. (1) report that in patients with chronic pulmonary hypertension and right ventricular (RV) failure, there is a decrease in left ventricular (LV) mass that is reversible and associated with a marked decrease in RV end-diastolic volume and an improvement in RV function after pulmonary endarterectomy. To gain further insight into this finding, they also studied rats with monocrotaline (MCT)-induced RV pressure overload and failure, and found a similar reduction in LV mass. This translational study suggests a load-dependent decrease in LV mass that is most likely mediated by decreases in both diastolic and systolic loading of the LV through a mechanism of ventricular interdependence (Fig. 1). This report provides important information regarding the effects of

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chronic pressure overload and RV dilation and failure on LV structure and function. It is of interest that in the human and animal model, the LV is affected only in the presence of RV dilation and failure, whereas mild RV pressure overload in the absence of RV failure does not affect LV structure and function. Further, the effects on LV wall thickness are limited to the free wall, whereas the septum follows RV pressure loading. These results suggest that LV abnormalities are purely a result of loading conditions in patients with chronic thromboembolic pulmonary hypertension.

In the rat study of the current investigation (1), there is an impressive decrease in α-myosin heavy chain and sarcoplasmic reticulum calcium ATPase-2 (SERCA2) mRNA in the LV of the MCT-treated hearts by in situ hybridization. This is also consistent with the studies of Depre et al. (2), who demonstrate a similar decrease in these LV markers in the heterotopically transplanted rat heart into an isogenic recipient. In response to the decrease in energy demand, they also report a decrease in glucose transporter-4 and carnitine palmitoyl transferase, which increase significantly when the transplanted hearts are reloaded in a working perfusion model. Taken together, these results are consistent with a pure load-induced mechanism. However, it is of interest that Voekel's laboratory recently reported the difference in effects of purely mechanical RV pressure overload of pulmonary artery banding versus the more systemic effects of a combined vascular endothelial growth factor receptor blocker (SU5416) and hypoxia in rats (3,4). For a similar increase in RV pressure, pulmonary banding induces less RV hypertrophy without failure in comparison to an angioproliferative pulmonary hypertension, which results in a greater amount of RV hypertrophy and RV failure, myocardial apoptosis, fibrosis, a decreased RV capillary density, and a decreased vascular endothelial growth factor mRNA and protein expression. The authors speculate that the diffuse structural disease of the pulmonary circulation secretes more cytokines, neurohormones, and other activated immune cells that can infiltrate the RV as well as the LV. Thus, many of the findings in the LV in the presence of RV dilation and failure may not be related to pure load alone but may also be a result of systemic factors released with the pulmonary vasculopathy. Indeed, MCT, a pyrrolizidine alkaloid derived from *Crotalaria spectabilis*, also causes a pulmonary vascular syndrome in rats characterized by proliferative pulmonary vasculitis (5). The rapid decline in body weight of the rats 1 week after MCT injections in the current investigation suggests a more systemic effect than simply RV pressure overload alone.

In the clinical study of patients with pulmonary endarterectomy (1), there is a significant improvement in LV mass index, LV filling, and LV stroke volume index in the patients who manifested RV failure at the time of pulmonary endarterectomy. In other studies of a systemic pulmonary vasculopathy in the rat, the RV failure correlated with the extent and severity of the pulmonary lesions (5). It is of interest that in the patients without RV failure at the time of surgery, there are no significant differences in LV mass and function versus normals, and there are no changes after endarterectomy, albeit in a small number of patients. If one assumes that the extent of the pulmonary vasculopathy relates to the severity of pulmonary systolic pressure elevation, the question still remains to what extent LV structural and functional abnormalities are related to increased RV load alone and/or systemic factors released from the lungs. Patients with a presumably more simple thromboembolic disease suggest less extensive lung parenchymal disease and thus less systemic release of deleterious cytokines and neuro-

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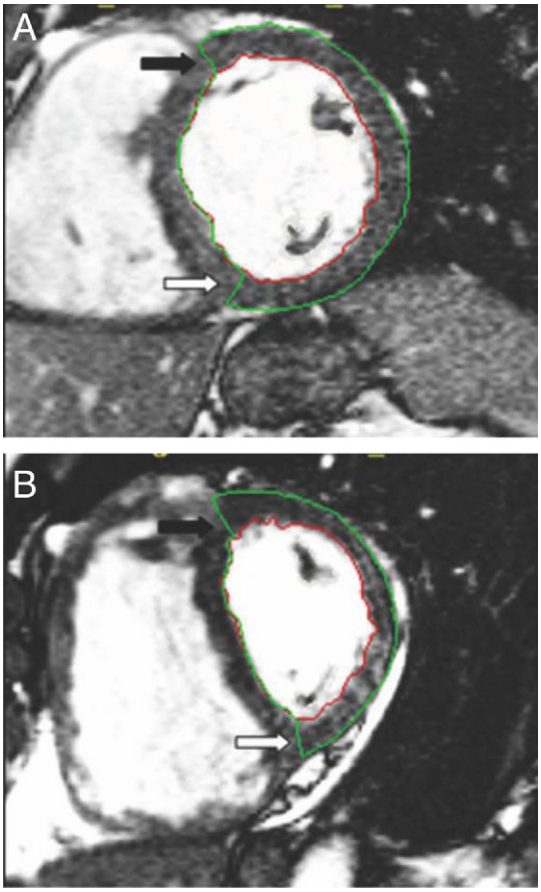

Figure 1 **Short-Axis Images of the Heart at End-Diastole**

In selected short-axis images of the heart at end-diastole from the current study, the RV end-diastolic area is increased in right ventricular (RV) pressure overload at the expense of the left ventricular (LV) end-diastolic area **(B)**. By the Laplace relationship:

$$\text{wall stress} = P \times r/h$$

where P = pressure, r = radius, and h = wall thickness, RV wall stress is increased whereas LV wall stress is decreased in the RV pressure overloaded heart **(B)** compared with normal **(A)**. The true distending pressure of the LV (intracavitary minus intrapericardial pressure) is most likely decreased because of an increase in intrapericardial pressure. This further decreases the true diastolic load on the LV, especially the LV free wall, where wall thickness is decreased in pressure overloaded RV **(B)** compared in the normal heart **(A)**.

hormonal factors. Nevertheless, the findings in the current investigation provide important insights into the mechanisms of ventricular interdependence on regional LV structure and global function in the setting of RV dilation and failure due to chronic pressure overload. The return of LV function after relief of RV pressure overload is consistent with other animal studies demonstrating reversible LV dysfunction in moving from relatively unloaded to loading conditions (6,7). Future clinical studies should include a more extensive evaluation of circulatory inflammatory biomarkers in addition to the BNP employed in the current investigation. This may provide important predictors of the reversibility of LV dysfunction.

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Key Words: atrophy ■ pulmonary hypertension ■ right ventricular failure.