Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Heart Failure

# Chronic Pulmonary Artery Pressure Elevation Is Insufficient to Explain Right Heart Failure

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***Background***—The most important determinant of longevity in pulmonary arterial hypertension is right ventricular (RV) function, but in contrast to experimental work elucidating the pathobiology of left ventricular failure, there is a paucity of data on the cellular and molecular mechanisms of RV failure.

***Methods and Results***—A mechanical animal model of chronic progressive RV pressure overload (pulmonary artery banding, not associated with structural alterations of the lung circulation) was compared with an established model of angioproliferative pulmonary hypertension associated with fatal RV failure. Isolated RV pressure overload induced RV hypertrophy without failure, whereas in the context of angioproliferative pulmonary hypertension, RV failure developed that was associated with myocardial apoptosis, fibrosis, a decreased RV capillary density, and a decreased vascular endothelial growth factor mRNA and protein expression despite increased nuclear stabilization of hypoxia-induced factor-1$\alpha$. Induction of myocardial nuclear factor E2-related factor 2 and heme-oxygenase 1 with a dietary supplement (Protandim) prevented fibrosis and capillary loss and preserved RV function despite continuing pressure overload.

***Conclusion***—These data brought into question the commonly held concept that RV failure associated with pulmonary hypertension is due strictly to the increased RV afterload. **(*Circulation*. 2009;120:1951-1960.)**

**Key Words:** angiogenesis ■ heart failure ■ microcirculation ■ pressure ■ pulmonary heart disease

Pulmonary hypertension and subsequent right heart failure are increasingly being identified as worldwide problems affecting patients with highly prevalent diseases such as schistosomiasis, sickle cell disease, HIV infection, chronic obstructive pulmonary disease, and chronic left heart failure.[1] Right ventricular (RV) function is the most important determinant of longevity in patients with pulmonary arterial hypertension (PAH), a form of pulmonary hypertension characterized by typical vascular lesions in small pulmonary arteries.[2] Pulmonary hypertension and RV failure are strong predictors of mortality in patients with left ventricular (LV) failure[3,4] and chronic obstructive pulmonary disease.[5] The various structural, functional, and developmental differences that exist between the RV and LV caution us to assume that RV failure is mechanistically not different from LV failure.[6]

## Clinical Perspective on p 1960

Because neither a persistent reversal of pulmonary vascular changes nor a lasting reduction of the pulmonary artery pressure can be accomplished in PAH patients by currently available vasodilator therapies, a specific cardioprotective treatment strategy that improves RV function despite elevated RV afterload may improve the quality of life and survival of PAH patients. Clinical observation and experimental evidence suggest that the mechanical stress of an elevated pulmonary artery pressure is not the only reason for PAH-associated RV failure. RV pressure overload associated with pulmonary artery stenosis carries a much better prognosis than PAH.[7] Progressive pulmonary stenosis induced by pulmonary artery banding (PAB) in rats is not associated with RV failure,[8] but animal models of peripheral pulmonary vascular disease are, despite a similar degree of pressure overload.[9] Pressure-independent components of pulmonary vascular disease may contribute to the development of RV failure in PAH. We hypothesize that progressive pressure overload per se is insufficient to explain RV failure in PAH.

Here, we investigate the relevance to PAH-associated RV failure of 2 mechanisms that play a role in pressure overload–induced LV failure: myocardial fibrosis[10] and a decreased myocardial capillary density (microvascular rarefaction).[11]

Received March 23, 2009; accepted September 1, 2009.

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**The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.109.883843/DC1.**

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*Circulation* is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.109.883843