Hypertensive heart disease (HHD) is characterized by myocardial remodeling not only in the left ventricle but also the left atrium and right ventricle. Clinically it is characterized by intact systolic function and diastolic dysfunction, which make up the major cause of congestive heart failure in the elderly, also termed “heart failure with preserved ejection fraction.” Hypertension is the major determinant for developing heart failure with preserved ejection fraction. As reviewed recently by Diez and Frohlich, most findings in hypertensive animals and patients demonstrate that HHD also results from pathological structural remodeling of the myocardium in response to a number of hemodynamic and nonhemodynamic factors altered in hypertension.

HHD is histologically characterized by left ventricular hypertrophy, cardiac inflammation, and fibrosis. The histological characteristics of inflammation and fibrosis extend from the perivascular space into the interstitial tissue. The mismatch of excessive myocyte hypertrophy and disproportionate myocardial fibrosis leads to increased myocardial stiffness and impaired diastolic function in patients with chronic hypertension and heart failure with preserved ejection fraction.

The activation of the renin-angiotensin (Ang) system (RAS) plays an important pathophysiological role in HHD and the development of myocardial inflammation and fibrosis. This is supported by the findings that blockade of the RAS, either with Ang-converting enzyme inhibitors or its type 1 receptor blockers, significantly improves cardiac function and regresses cardiac remodeling in patients with hypertension. These protective effects were already observed less than low-dose RAS inhibition without a significant reduction of elevated blood pressures.

Understanding the components of remodeling has led to advances in therapeutic strategies. Currently available medications have been used to counteract the compensatory mechanism of postinfarction ventricular remodeling and, consequently, to reduce morbidity and mortality. In some instances, these strategies have improved left ventricular morphology and function in HHD. However, in clinical settings, a convincing or powerful antifibrotic strategy is lacking.

Inflammation as an Early Event in Hypertensive Disease

Various authors have demonstrated that local inflammation and macrophage infiltration are early key events for reactive myocardial fibrosis, especially perivascular fibrosis, in experimental models of Ang II–mediated HHD. Also, it has been shown that Ang II supports leukocyte transmigration via Ang II type 1 receptor–dependent, but arterial pressure–independent, mechanisms. Infiltrated macrophages are known to produce a variety of cytokines and growth factors, which, in turn, amplify the inflammatory process and activate tissue fibrosis. Monocyte chemotactant protein 1 plays a central role by mediating macrophage accumulation, inducing myocardial fibrosis in pressure-overloaded hearts through a transforming growth factor (TGF)-β-mediated process.

In particular, the TGF-β/Smad3 pathway is of interest because of its regulatory effects on the inflammatory response. This pathway suppresses cytokine and chemokine expression in immune and endothelial cells and reduces neutrophil and macrophage chemotaxis. In the context of ventricular remodeling, another interesting aspect of the TGF-β/Smad3 pathway is the regulation of fibroblast activity. In general, TGF-β inhibits fibroblast proliferation. However, it induces phenotypic changes in fibroblasts to increase production of extracellular matrix proteins. A growing body of evidence suggests involvement of the TGF-β/Smad3 pathway in both induction and resolution of the inflammatory response. Smad3-null animals showed decreased local infiltration of monocytes in skin excisional wounds and had reduced cutaneous inflammation after exposure to ionizing radiation. Furthermore, Smad3−/− monocytes exhibited a blunted chemotactic response to TGF-β.

Bujak et al investigated the effects of Smad3 gene disruption on myocardial infarct healing and the pathogenesis of cardiac remodeling. Interstitial fibrosis was markedly reduced. Compared with wild-type animals, Smad3−/− mice exhibited decreased dilative remodeling and attenuated diastolic dysfunction, whereas infarct size was comparable between both groups. They suggested that decreased fibrotic remodeling in infarcted Smad3-null hearts may be attributable to abrogation of the profibrotic TGF-β responses.

Divakaran et al investigated the role of Smad3 deletion in a model of pressure-induced hypertrophy induced by aortic constriction. Loss of Smad3 signaling resulted in a significant 60% decrease in myocardial fibrosis. Using microRNA mi-
croarray, they showed that microRNAs were differentially expressed in Smad3$^{-/-}$ mice, and, of 10 candidate microRNAs, 2 were sufficient to decrease collagen gene expression in isolated cardiac fibroblasts. Surprisingly, the mortality of Smad3$^{-/-}$ mice and the cardiac hypertrophy (primarily the size of the myocytes) after pressure overload were significantly increased, also indicating deleterious effects after Smad3 deletion in this specific model and supporting the hypothesis that the TGF-β/Smad3 pathway mediates profibrotic and antihypertrophic signals in the heart.

In the present issue of Hypertension, Huang et al identified Smad3 as a critical mediator of Ang II–mediated cardiac inflammation and fibrosis. They demonstrated that Ang II–induced cardiac inflammation, particularly perivascular inflammation, increase in LV mass, and the development of cardiac fibrosis was inhibited in Smad3$^{-/-}$ mice infused with Ang II. The authors present findings that Smad3$^{-/-}$ mice were protected against Ang II–mediated cardiac fibrosis and inflammation. These findings suggest that targeting Smad3 may be a novel therapeutic strategy for prevention of inflammation and fibrosis in HHD (Figure). This is in accordance with the studies in myocardial infarction presented by Bujak et al recently, where Smad3$^{-/-}$ mice demonstrated less interstitial fibrosis in the noninfarcted myocardium and improved cardiac function. However, the recent observation by Divakaran et al indicate that inhibition/deletion of Smad3 might not only be beneficial. Whether this is a specific problem of the studied model (aortic constriction in Smad3$^{-/-}$ mice) is not clear. Additional studies investigating these negative effects of Smad3 deletion are needed.

Nevertheless, the present findings further strengthen the central role of the TGF-β/Smad3 pathway in the regulation of cardiac fibrosis and inflammation leading to HHD and cardiac remodeling. Smad3 is clearly an interesting target for novel therapeutic strategies, especially preventing the deleterious effects of progressing fibrosis in the myocardium.

**Sources of Funding**
The work of K.G. is supported by the Zukunftsfond Berlin/Investitionsbank Berlin Brandenburg, project number 10142873.

**Disclosures**
None.

**References**
Is Smad3 the Key to Inflammation and Fibrosis in Hypertensive Heart Disease?
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_Hypertension_. 2010;55:1088-1089; originally published online March 15, 2010;
doi: 10.1161/HYPERTENSIONAHA.110.150466

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/55/5/1088

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