Editorial Comment

Matrix Metalloproteinases in Hypertensive Heart Disease: New Mechanistic Insights

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Hypertensive heart disease (HHD) will soon become the most common cause of heart failure, as the prevalence of hypertension is increasing globally (*1*). Chronic arterial hypertension causes left ventricular hypertrophy (LVH), decreased relaxation rate, and increased stiffness of the myocardium. One of the important pathologic features of hearts from HHD patients is the change in quantity and quality of the extracellular matrix (ECM) in the myocardium. To evaluate this, many researchers have examined the changes in the pattern of specific ECM proteolytic proteins/peptides (matrix metalloproteinases [MMPs]) and their inhibitors (TIMPs) in the sera or myocardium. However, the effects of chronic pressure overload on the MMP/TIMP expression in patients with HHD have not yet been fully investigated.

Previous results regarding the roles of MMPs/TIMPs in HHD have been difficult to interpret due to the simplicity of the animal models compared with HHD patients. In hypertensive Dahl salt-sensitive rats fed a high sodium diet, MMP-2, TIMP-1, and TIMP-2 expression enhances as LVH progresses (*2*). Similarly, MMP-2 activity increases in spontaneous hypertensive rats (*3*). However, these models exhibit an extremely high blood pressure that develops in the short term, and many studies have focused only on the early phase of ECM changes. As it stands, there are only limited data about the effects of long-term pressure overload (as a proxy for human chronic hypertension) on MMP/TIMP expression in HHD animal models.

Studies using genetically modified animals have revealed the importance of the particular MMPs. The MMP-2– or MMP-9–deficient mice are protected from cardiac fibrosis and dysfunction after short-term pressure overload (*4*, *5*). Although the causal relationship between these MMPs and cardiac remodeling might be determined, the roles of other MMPs in HHD remain unclear. This phenomenon is at least partly attributable to the limitations of gelatin zymography, which only shows the activities of gelatinase MMP-2 and MMP-9.

In this issue of *Hypertension Research*, Lin *et al*. report the effects of chronic pressure overload on ECM remodeling in a rat HHD model (*6*). In addition to providing the most complete evaluation of ECM profiles to date, they reveal the early and late effects of chronic hypertension by examining the difference in the profile between young (4 months old) and middle-aged (13–15 months old) rats presenting with hypertension. They used Dahl salt-sensitive rats fed a “low” sodium diet, which develop chronic hypertension and LVH as they age, and found that the mean arterial pressures increased steadily from 120 mmHg to 160 mmHg (*7*).

The most significant finding of this study is that the net effect of chronic hypertension is a loss of collagen and an increase in the cardiac MMP-8 and MMP-14 levels in the late phase. In contrast, the early-phase hypertensive effects and the age-related effects caused similar ECM profiles (*i.e.*, decreased MMPs and increased fibrosis). These observations suggest that the initial MMP decrease might be an adaptive reaction that may occur in the non-hypertensive old myocar-

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dium, while the late increase of the specific MMPs might be associated with the HHD-related abnormal process.

From a clinical perspective, knowledge about the specific MMP/TIMP expression patterns will be useful to develop new biomarkers and therapy for HHD. Epidemiological studies have demonstrated that an increase in the plasma TIMP-1 level (>1,200 ng/mL) suggests the development of diastolic heart failure in patients with HHD (*8*). Other studies have reported that plasma MMP-1 levels significantly correlate with the mean blood pressure in hypertensive patients with LVH (*9*). However, these studies have a limitation in regard to the determination of MMP/TIMP function in HHD patients: the plasma levels do not necessarily reflect the net ECM proteolytic activity that occurs within the myocardium (*10*).

On the other hand, clinical trials have revealed the difficulty in using various MMP inhibitors to prevent remodeling. In a double-blind, prospective placebo-controlled trial entitled "Prevention of Myocardial Infarction (MI) Early Remodeling; PREMIER" (*11*), the selective MMP-1/MMP-7 inhibitor PG11680 was well-tolerated in post-MI patients, but no significant effects were observed with respect to LV remodeling.

Finally, these studies offer valuable lessons in terms of the complexity of translating basic studies into clinical therapeutics and the diversity of the MMP/TIMP system. It is important for the therapeutic application to better understand the actual roles of the system in human HHD. To achieve this, the comprehensive and temporal profiles of MMP/TIMP expression should be further explored in different hypertension models in the future.

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