Determinants of the transition to heart failure or of phenotypes of heart failure in salt-sensitive hypertension

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Summary

Systolic heart failure (SHF) is associated with systolic dysfunction and left ventricular (LV) dilatation, and diastolic heart failure (DHF) is not. We developed models of SHF and DHF in Dahl salt-sensitive rats. This study aimed to investigate determinants of the transition to heart failure or of phenotypes of heart failure in salt-sensitive hypertension, and to get insights into new therapeutic strategy for each type of heart failure.

We used Dahl salt-sensitive rats fed high salt diet since 7 weeks as DHF model and since 8 weeks as SHF model. Those fed a normal chow served as control. In the both models, gene expression of collagens was enhanced. That of MMP-2 and MMP-9 was enhanced in the DHF rats, and the enhancement was greater in the SHF rats. The gelatin zymography demonstrated that there was no difference in the MMP-2 activity between the DHF and SHF rats, and that the MMP-9 activity was higher in the SHF rats than in the DHF rats. In the SHF rats, increases in mRNA levels of MMP-2 and MMP-9 preceded LV dilatation. The administration of angiotensin-converting-enzyme inhibitor (ACEI) at a subdepressor dose inhibited their gene expression and prevented LV dilatation and the transition to overt heart failure.

The current study suggests that MMP-9 and MMP-2 work in concert to induce SHF with LV dilatation in salt-sensitive hypertension. The ACEI-induced attenuation of LV dilatation was likely provided through the suppression of MMPs' expression. Prognosis of patients with heart failure is still poor even under the treatment with ACEI. This study suggests that MMPs, particularly MMP-9, are a therapeutic target in SHF to further improve the prognosis. The promotion of collagen production may precede the enhancement of MMP-9 gene expression, leading to rapid accumulation of extracellular matrix and the transition to overt DHF. The inhibition of collagen production may be a therapeutic target of DHF.