HEART FAILURE

# Targeting collagen metabolism in preserved systolic function HF

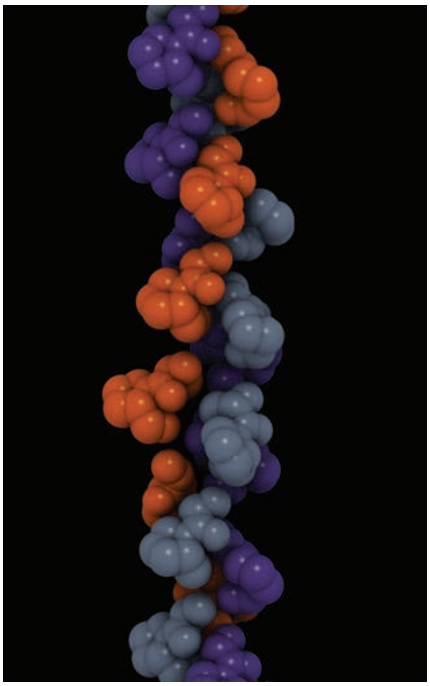
Researchers from Dublin, Ireland have reported that markers of collagen turnover and inflammation are increased among patients with heart failure with preserved systolic function (HFPSF) and that the aldosterone antagonist eplerenone attenuates increases in one such marker, procollagen type III. "There are numerous pathophysiological mechanisms of diastolic heart failure" comments investigator George Mak, "one of the prevailing theories includes fibrosis of the extracellular collagen matrix of the heart."

Previous studies of therapeutic intervention targeted toward collagen metabolism, via the renin–angiotensin–aldosterone system, in patients with HFPSF have proven disappointing. However, "even with ... blockade using angiotensin-converting-enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), aldosterone continues to be produced by several 'escape' mechanisms. Therefore it may be more appropriate to directly inhibit aldosterone itself." says Mak. This approach has already been studied in the setting of hypertensive heart disease, with positive results.

The investigators enrolled 44 patients with a confirmed diagnosis of HFPSF (prior NYHA class IV heart failure or symptoms consistent with heart failure, with evidence of diastolic dysfunction, left ventricular ejection fraction >45%, and B-type natriuretic pepetide level >100 pg/ml). Patients were randomly assigned to standard treatment for heart failure or to eplerenone 25 mg/day (increasing to 50 mg/day after 6 months). Assays for makers of inflammation and collagen metabolism, as well as two-dimensional Doppler echocardiograpy, were performed to determine biochemical and clinical outcomes.

This cohort was typical of patients with heart failure being treated in the 'real-world'; the mean age was 80 years and, at baseline, 64% of patients were already taking ACE inhibitors and 34% were receiving ARBs. Around 91% of those enrolled had hypertension and 27% had diabetes. However, the majority of patients had only mild symptoms of heart failure (NYHA class II).

At the 12-month follow-up assessment, levels of the collagen markers procollagen type I (PINP), procollagen type III (PIIINP), matrix metalloproteinase-2 (MMP-2), and the inflammatory markers interleukin-6 (IL-6) and tumor necrosis factor α, had increased significantly from baseline in the control group. This increase was not evident at 6 months follow-up. Among eplerenone-treated patients, the increase in the levels of PIIINP was attenuated at 12 months. However, there were no differences between the two groups in levels of the other biomarkers or in diastolic function. Levels of IL-6 were correlated with levels of MMP-2 and PIIINP at baseline, and with PINP and PIIINP at 12 months follow-up.





Encouraged by their results, the investigators suggest that aldosterone inhibition could have a therapeutic benefit in diastolic heart failure. A large, multicenter trial (the TOPCAT study) assessing this theory is under way. "Further work on PIIINP needs to be considered" concludes Mak, "as it may eventually become an important prognostic marker in diastolic heart failure."

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**Original article** Mak, G. J. *et al*. Natural history of markers of collagen turnover in patients with early diastolic dysfunction and impact of eplerenone. *J. Am. Coll. Cardiol.* **54**, 1674–1682 (2009)