# Biomarkers of Extracellular Matrix Turnover

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**KEYWORDS**

• Heart failure • Extracellular matrix • Fibrosis
• Collagen • Biomarkers • Metalloproteinases

The extracellular cardiac matrix (ECCM) plays an important role in the support of myocytes and fibroblasts. Collagen is the principal structural protein, and collagen types 1 and 3 are the most abundant in the myocardium. Collagen type 1 has a poor specificity but represents most cardiac collagen (85%) and confers tensile strength and resistance to stretch and deformation. Type 3 is less abundant but more specific to the heart and confers resilience.[1–3] Fibrillar collagens within the myocardium are substrates for matrix metalloproteinases (MMPs). Among the MMPs, MMP-1 has the highest affinity for fibrillar collagen and preferentially degrades collagen 1 and 3.[3] The net level of MMP-1 activity depends on the relative concentrations of active enzyme and of a family of tissue inhibitors of metalloproteinases (TIMP). MMP-1 and TIMP-1 are coexpressed in cardiac fibroblasts and are regulated to maintain the architecture of the ECCM.[4] Type I C-terminal telopeptide (CITP) is a pyridinoline cross-linked telopeptide produced as a result of the hydrolysis of collagen type 1 fibrils by MMP-1; additionally, it is a marker of collagen type 1 degradation.[5]

The disruption of the equilibrium between the synthesis and degradation of the ECCM results in an excessive accumulation of collagen type 1 and 3 fibers within the myocardium. ECCM remodeling is an essential process in cardiac remodeling, hypertensive cardiac hypertrophy, dilated cardiomyopathy, and postinfarction healing.[5] ECCM turnover is influenced by ischemia, stretch, inflammation, and neurohormonal mediators. Myocardial fibrosis is therefore the consequence of several pathologic processes mediated by mechanical, neurohormonal, and cytokine factors. Cardiac fibrosis, a major determinant of diastolic dysfunction and pumping capacity, results in tissue heterogeneity and anisotropy and provides the structural substrate for dys-synchrony and arrhythmogenicity, thus potentially contributing to the progression of congestive heart failure (HF) and sudden cardiac death. ECCM turnover may be the target of therapeutic agents aimed at preventing or limiting the progression of adverse cardiac remodeling in HF and therefore hospitalization for HF and death due to progressive HF and sudden cardiac death.

## NONINVASIVE ASSESSMENT OF EXTRACELLULAR CARDIAC MATRIX

Given the importance of fibrous tissue in the pathophysiology of myocardial dysfunction and failure, the noninvasive assessment of fibrosis could prove to be a clinically useful tool, particularly given the potential for cardioprotective and cardioreparative pharmacologic strategies.[6] The

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measurement of various serum peptides arising from the metabolism of collagen types 1 and 3 may provide information on the extent of myocardial fibrosis[7] and thus prognosis and clues to appropriate strategies to improve prognosis. Because procollagen type I C-terminal propeptide (PICP), aminoterminal propeptides of type-I procollagen (PINP), and N terminal type III collagen peptide (PIIINP) are released with collagen type 1 or 3 molecules in a stoichiometric manner during collagen biosynthesis, they are important markers of this process (**Fig. 1**).[6,8,9]

Although these markers are not specific to the myocardium, Querejeta and colleagues have shown a correlation between myocardial collagen content and the serum concentration of PICP in patients have hypertension[10] and have demonstrated that serum PICP is secreted by the heart by means of the coronary sinus in patients who have hypertensive heart disease (**Fig. 2**).[11] The procollagen type I N-terminal propeptide (PIP)/CITP ratio, an index of coupling between the synthesis and degradation of collagen type 1, was found to be higher in hypertensive patients who had increased collagen accumulation in myocardial tissue than in those who had normal collagen accumulation.[12] In patients who had dilated cardiomyopathy, Izawa and colleagues showed that both collagen volume fraction and the abundance of collagen type 1 and 3 mRNAs in the left ventricular (LV) myocardium were higher in patients who had an increased serum PICP/CITP ratio than in those who had a lower PIP/CITP ratio. Changes in blood procollagen PIIINP correlate with changes in LV end diastolic volume index in patients from baseline to 1 month after acute myocardial infarction (MI) (**Fig. 3**).[13]

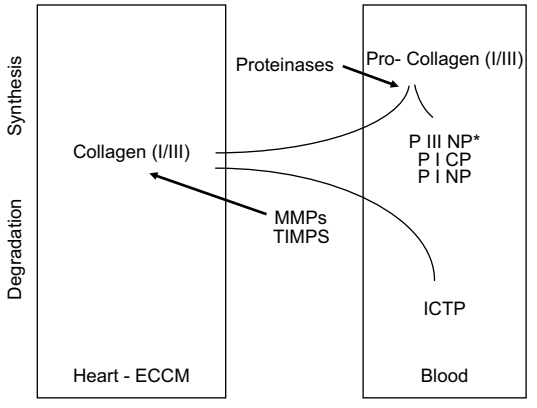


**Fig. 1.** Schematic diagram of extracellular cardiac matrix (ECCM) turnover. ICTP, type I pyridinoline cross-linked C-terminal telopeptide; MMPs, metalloproteinases; PIIINP*, procollagen III N-terminal peptide; P ICP, procollagen I C-terminal peptide; PINP, procollagen I N-terminal peptide; TIMPs, tissue inhibitors of metalloproteinases.

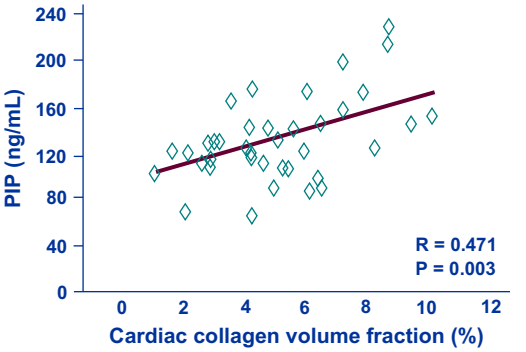


**Fig. 2.** Correlation between myocardial collagen content and the serum concentration of procollagen I C-terminal peptide (PICP) in patients with hypertension. It has been demonstrated that serum PICP is secreted by the heart by means of the coronary sinus in patients with hypertensive heart disease. (*Adapted from* Querejeta R, Varo N, Lopez B, et al. Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. Circulation 2000;101:1729–35; with permission.)

This evidence linking serum ECCM markers to the heart's ECCM content provides a rationale for their use as biomarkers of ECCM remodeling in cardiac disease.[14] MMP-1 and TIMP-1 levels in coronary sinus blood were higher than in

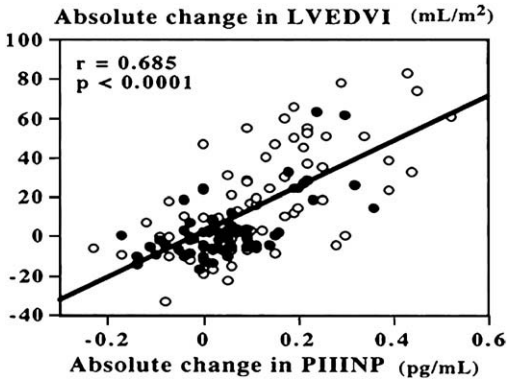


**Fig. 3.** Changes in blood procollagen type III N-terminal peptide (PIIINP) correlate to changes in left ventricular end diastolic volume index (LVEDVI) in patients from baseline to 1 month after acute myocardial infarction. (*From* Hayashi M, Tsutamoto T, Wada A, et al. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents postinfarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. Circulation 2003;107:2559–65; with permission.)