

Matrix metalloproteinase and heart failure: is it time to move from research to clinical laboratories?

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This editorial refers to 'Plasma matrix metalloproteinase-9 and left ventricular remodelling after acute myocardial infarction in man: a prospective cohort study'[†] by D. Kelly *et al.*, on page 711

In basic science research laboratories dedicated to heart failure, several substances have been studied as candidate markers of the disease's severity, as target of therapy and as indicators of therapeutic success. Many potential biological markers have emerged and are now under research, among which, markers of myocyte injury (e.g. troponins), markers of inflammation (e.g. tumour necrosis factor α , IL-6), markers of oxidative stress (e.g. urinary 8-iso-prostaglandin F₂), markers of sodium pump activity (e.g. cardiotonic steroids), and a separate group of peptides associated with heart failure.¹ However, at present, only natriuretic peptides, in particular, B-type natriuretic peptide, has an established clinical impact. Several reasons account for the frequent failure for substances under research to reach clinical laboratories including the multifactorial causes of heart failure and its progression, the capability/willingness of the manufacturing companies to push, costs and cultural background.

Matrix metalloproteinases (MMPs) have a strategic role in the regulation of extracellular collagen matrix turnover, a slow process (t_{1/2} around 25 days) which, in the heart, is crucial for keeping the most efficient shape of the ventricles. Cardiac repair after a myocardial infarction is a highly complex process that involves temporarily overlapping phases which comprehend inflammation, new tissue formation, and tissue remodelling.² MMPs are present in the myocardium, are capable of degrading all the matrix components of the heart, and are the driving force behind myocardial matrix remodelling which is responsible for the progressive worsening of the pump function.³ Considering that the remodelling phenomenon represents an independent adverse prognostic factor affecting mortality and progression of heart failure, it would make complete sense to

correlate the degree of disruption of the extracellular matrix and its turnover with the circulating levels of MMPs. Accordingly, there is a strong rationale to use MMPs as the substances to follow and to foresee ventricular remodelling, and possibly, to understand if a specific treatment is efficient in the single patient. For example, the efficacy of beta-blockers or ACE-inhibitors in the prevention of post-myocardial infarction ventricular remodelling. Furthermore, it has been proposed that antagonists of MMPs might be used to prevent ventricular remodelling.

The real picture, however, is much more complicated and unlikely to provide us with the above reported hopes, at least in the near future. Indeed, left ventricle regional remodelling is a continuous process that lasts for months to years after the injury, and which will, eventually, lead to the development of heart failure.⁴ Moreover, post-myocardial infarction healing is regulated by haemodynamic forces, sympathetic activation, inflammation, new vessel formation, and not only by extracellular matrix turnover.²

The MMPs family, comprising more than 20 members, has been categorized into subfamilies or classes that originally were predicated on similarities in proteolytic substrates,⁵ and include collagenases, such as MMP-1 and MMP-13, stromelysins, as MMP-3, gelatinases, as MMP-2 and MMP-9, and membrane-type MMPs. This substrate-based classification of MMPs turned out to be useful in the past. However, as more is known about the enzymatic activities and substrates, its usefulness becomes less clear because the substrate profile of the enzymes is often more gradual than absolute.

Indeed, MMPs have a different origin and temporal activation after myocardial infarction and are regulated by a number of bioactive signalling molecules which are operative during cardiac remodelling, such as renin-angiotensin-aldosterone system, endothelin-1, neurohormones, cytokines/chemokines, osteopontin, transforming growth factor- β , oxidative stress, integrin-mechanical signalling.⁶ It should be pointed out that the intracellular transduction pathways and activation of transcription factors are integrated and work in a dynamic state within the myocardium. Whether and to what extent a single, or multiple pathways play a dominant role in MMP induction is dependent upon the initiating disease.⁶ Furthermore, identification of high or low plasma levels of MMPs may not correspond to tissue MMPs levels which, furthermore, might be spatially and

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temporarily dishomogenous. So that it is not possible to report the role of MMPs in left ventricular remodelling as a simple cause effect relationship, but it is a still poorly understood complex interplay between various substances, their specific action, and inhibitory control.

A unique temporal and spatial profile of MMPs and of their inhibitors has been determined essentially through the use of myocardial infarction animal models. During the early phase of wound healing, activated MMPs degrade the pre-existing extracellular matrix, disrupting the fibrillar collagen network and allowing inflammatory cells to migrate into the infarct area to remove necrotic myocytes.⁷ Despite their possible beneficial effects in post-myocardial infarction healing, activation of MMPs may also promote detrimental actions. MMP-9 and MMP-2 activity increases in a time-dependent manner and is temporally related to cardiac rupture after myocardial infarction in mice.⁸ This deleterious effect of MMPs may be the result of an inappropriate degradation of myocardial extracellular matrix components and disruption of the myocyte-matrix interface network, causing myocyte misalignment and slippage. The latter may cause, besides cardiac rupture, left ventricular dilatation and dysfunction. Finally, MMPs are likely to have, in chronic heart failure patients, a role in the fibrotic degeneration of other organs such as peripheral muscles, kidneys, and lungs.

Kelly *et al.*⁹ examined in humans, after acute myocardial infarction, the temporal profiles of plasma MMP-2 and MMP-9, and their relationship with echocardiographic parameters of left ventricle function and remodelling. The investigators show that higher peak levels of plasma MMP-9 were associated with greater impairment of left ventricular function during the index admission, while higher plateau levels of MMP-9 in the days following myocardial infarction were associated with less remodelling, and relative preservation of ventricular function. These observations are relevant and are in favour of a different role for MMP-2 vs. MMP-9. Indeed, Kelly *et al.*'s⁹ findings, when considered with previous experimental data, suggest that, in addition to contributing to adverse left ventricle remodelling, MMP-9 activity may also be important to wound healing after myocardial infarction. Unfortunately, as frequently in the clinical setting, the correlations are statistically relevant but poor, making difficult to predict a large-scale clinical application of these results. Furthermore, because of the unequal gender distribution, the present study could not address whether the early change in MMP-9 was associated with gender-specific adverse ventricular

remodelling in the later post-infarct periods. Finally, this study offers other clinical implications, in particular, for the potential therapeutic use of MMP inhibition. Several studies demonstrate that modulating MMP activity represents a potential therapeutic target in the context of left ventricle remodelling and myocardial infarction. However, long-term inhibition of all MMP species might interfere with normal tissue remodelling processes and give rise to undesirable systemic effects, thus limiting clinical utility.¹⁰ In conclusion, additional studies are needed to understand the physiology behind MMP and post-infarct ventricular remodelling. We, however, cannot foresee a scenario with a large-scale clinical use of MMPs either as early markers of development of ventricle remodelling or as target of therapy and indicators of therapeutical success.

Conflict of interest: none declared.

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