TIMPs, MMPs and cardiovascular disease

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This editorial refers to "Relations of plasma total TIMP-1 levels to cardiovascular risk factors and echocardiographic measures: the Framingham heart study" by J. Sundström et al. on page 1509

The matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that cleave the extracellular matrix and have been shown to be regulated by a class of proteins called the tissue inhibitors of metalloproteinases (TIMPs). Several studies have shown that extracellular matrix degradation by MMPs, specifically MMP-9, is involved in the pathogenesis of a wide spectrum of cardiovascular disorders, including atherosclerosis, restenosis, cardiomyopathy, congestive heart failure, myocardial infarction, and aortic aneurysm.1,2 This is not surprising since all remodelling, i.e., change in left ventricular geometry and myocardial architecture is associated with a change in the collagen matrix. That both MMPs and TIMPs have recently become fashionable research toys in cardiovascular medicine is documented by the simple fact that a Medline search on June 28, 2004 with the key words "metalloproteinase" and "cardiovascular" revealed 2864 hits, of which more than half (1544) were published within the past five years.

Data from the Framingham cohort have challenged the cardiovascular community for more than half a century.3 The report in the present issue of the Journal is no exception.4 The authors provide the first community-based investigation relating plasma TIMP-1 to cardiovascular risk factors and echocardiographic measures. Plasma TIMP-1 was directly related to the Framingham Risk Score, and inversely related to LV systolic function. The present paper has to be viewed in light of the recently published data from the same group on a plasma MMP.5 In this twin study the authors documented that plasma MMP-9 levels were associated with increased LV diastolic dimensions and wall thickness, and concluded that plasma MMP-9 levels may be a marker for cardiac extracellular matrix degradation.

Of considerable interest is a comparison of the two studies from the same cohort. With regard to echo indices of LV remodelling, there was no modification of the effect of TIMP-1 by gender, whereas there were striking sex differences of MMP-9 with LV remodelling — the relations being significant in men only. Both TIMP-1 and MMP-9 were related to wall thickness and chamber diameter although the relations of TIMP-1 became non-significant upon adjustment for risk factors. With regard to risk factors, MMP-9 and TIMP-1 both correlated with at least one risk factor, namely, anti-hypertensive therapy. Additionally, plasma TIMP-1 was higher in men than women, correlated with age, body mass index, total/HDL cholesterol ratio, smoking and diabetes. MMP-9 also was related to smoking and diabetes, although the relations were attenuated in multivariate models. Of course, some of these differences could be due simply to the fact that in the MMP-9 study less statistical power was achieved because of the smaller sample size and also because MMP-9 had to be dichotomized since it was not detectable in 80% of individuals. In contrast, the present study with TIMP-1 was 60% larger which obviously increased statistical power perhaps allowing less close relations of TIMP to cardiovascular risk factors to become significant. However, the differences in relation to LV remodelling within TIMP-1 and MMP-9 could also reflect true biological differences. Total TIMP-1 measures TIMP-1 complexed to a variety of MMPs and clearly, therefore, would capture a wide spectrum of MMP/TIMP interactions. In contrast, total MMP-9 is only a measurement of one MMP complexed with TIMP-1 and with other TIMPs. In order to throw some light on this puzzle, free TIMP-1, free MMP-9 and other free MMPs, such as MMP-1, MMP-2 would have to be measured which may allow us to learn more about the relationship of MMP-9 and TIMP-1 to LV remodelling.

Since cardiac fibrosis is a major determinant of LV
systolic function and TIMP-1 must be considered as a marker of fibrosis, at least to some extent, its stronger relation to LV fibre shortening is not surprising. Conceivably, MMP-9, since it is known to break collagen struts, may be more closely related to LV dilatation without necessarily affecting systolic function to the same extent.

Some of the limitations of the present paper need to be emphasized: clearly, this is a cross-sectional study that has been performed within the Framingham cohort which is an ongoing longitudinal study. Therefore, it is impossible to establish a temporal connection between TIMP-1 and LV remodelling or between TIMP-1 and other cardiovascular risk factors. This simply brings up the chicken/egg argument, i.e., it isn’t clear whether LV remodelling caused the elevation in TIMP-1 level or, in turn, whether the elevated TIMP-1 level promoted the change in fractional shortening. The same chicken and egg argument also holds true with regard to TIMP-1 and to its relationship to other cardiovascular risk factors. However, a critical analysis of the biochemical role of TIMP-1 would suggest that elevated levels promote cardiac and vascular remodelling. Ever since Folkow’s pioneering observation,6 numerous studies have documented that vascular remodelling, indeed, raises blood pressure. Blood pressure, therefore, may well be another (apart from LV structure) link between TIMP-1 and the coronary heart disease Framingham Risk Factor Score.

Finally, an interesting vignette of this provocative study is that plasma TIMP-1 (but not MMP-9) was inversely related to alcohol intake. If TIMP-1 does indeed turn out to be a marker of cardiovascular fibrosis, the intriguing possibility arises of alcohol intake (in moderation) having anti-fibrotic properties, and that part of alcohol’s well known favourable cardiovascular effect may be related to this mechanism. However, since excessive alcohol intake gives rise to dilated cardiomyopathy, a disorder possibly associated with elevated TIMP-1 levels, the relationship between TIMP-1 and alcohol intake may well turn out to be U-shaped. Clearly, these fascinating features should be explored in further studies.

References