Matrix metalloproteinases and their tissue inhibitors in heart failure

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INTRODUCTION

Homeostasis of the extracellular matrix (ECM) is maintained by a balanced interaction between matrix metalloproteinases (MMPs) which degrade the ECM proteins and their inhibitors, the tissue inhibitor of matrix metalloproteinases (TIMPs).

MATRIX METALLOPROTEINASES (MMPs)

Action of MMPs

MMPs are the predominant enzymes responsible for the degradation of ECM proteins. MMPs are Cu2+- and Zn2+-activated proteases that are synthethised as inactive zymogens (pro-MMPs) which are activated by the removal of the amino-terminal propeptide by autoproteolysis or by another MMP or serine protease. The following MMPs which are involved in myocardial remodeling, are identified up till now: MMP-1 (interstitial collagenase), MMP-13 (collagenase 3), MMP-8 (neutrophil collagenase), MMP-2 (gelatinase A), MMP-9 (gelatinase B), MMP-3 (stromelysin), MMP-7 (matrilysin) and a membrane-type MMP (MMP-14). MMP-1 degrades collagen types I, II, III and basement membrane proteins; MMP-2 and MMP-9 degrade collagen types I, III, IV and V. MMP-8 and MMP-13 act on collagen types I, II and III; MMP-12 on elastin and MMP-14 on fibronectin, laminin-1 and collagen type I.

MMPs as biomarkers in heart failure

In patients with heart failure the serum concentration of MMP-1 is higher, lower or unaltered in comparison with normal human subjects, while the serum concentration of MMP-2 and MMP-9 are elevated or unchanged (TABLE 1). Increased as well as decreased or unchanged levels of MMP-1, MMP-2 and MMP-9 in serum and left ventricle are found in patients with dilated and hypertrophic cardiomyopathy (DCM, HCM)
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Review

The serum MMP-2 levels are correlated with the NYHA functional classes\(^2\). High levels of MMP-2 (>352 ng/ml) independently increase the risk of hospitalization for HF, death or both\(^2\). In moderate HF patients Jordan et al\(^5\) also found an association between the serum MMP-1 concentration and clinical endpoints such as death due any cause, readmission due to HF and heart transplantation.

Prognostic and predictive value of TIMPs in HF

Frantz et al\(^7\) suggested that TIMP-1 is a strong predictor of mortality. They found that patients with a high plasma TIMP-1 level (>1917 ng/ml) have a much higher all-cause mortality than patients with lower TIMP-1 levels (<1390 ng/ml). Jordan et al\(^5\) observed in moderate HF patients that patients with a clinical endpoint such as death due any cause, readmission due to HF and heart transplantation have a higher serum TIMP-1 level. An increase in TIMP-1 and hence a reduced degradation of collagen has a poor prognosis in patients with moderate HF.

For serum TIMP-1 levels, George et al\(^2\) did however not find a predictive value in moderate HF patients, when mortality due to to HF as an endpoint was used..

In patients with an acute myocardial infarction TIMP-1 is a strong predictor for total and cardiovascular mortality\(^8\).

Tissue Inhibitors of Matrix Metalloproteinases (TIMPs)

TIMPS are physiological MMP inhibitors. The human heart contains 4 TIMP types: TIMP-1, TIMP-2, TIMP-3 and TIMP-4 are 21-30 kDa proteins. TIMP-3 is tightly bound to ECM, while TIMP-1, TIMP-2 and TIMP-4 are localized extracellularly in soluble form.

Serum TIMP-1 and heart failure (HF)

The serum concentration of TIMP-1 is higher in patients with HF in comparison with normal persons (TABLE 2) except in one study\(^6\). The serum levels of TIMP-1 and TIMP-2 are also significant higher in patients with dilated and hypertrophic cardiomyopathy\(^11\)\(^-\)\(^13\)\(^,\)\(^15\) and in patients with myocardial infarction (MI)\(^16\)\(^\)\(^-\)\(^18\).

High Variability in MMP/TIMP Expression

The expression of MMPs differs strongly in the various cardiomyopathies. For the expression of TIMPs is the nature of the underlying cause of the cardiac disease less important. Cardiac remodeling is also a dynamic process and the MMP/TIMP activity is also fluctuating in this process. The method for the determination of MMPs/TIMPs in the aforementioned studies is also important. The MMPs/TIMPs levels are assayed by histology and immunohistochemistry in biopsy samples and by enzyme-linked immunoabsorbent as-

### TABLE 1: MMPs in patients with heart failure (HF)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Studied Condition</th>
<th>Main Findings for:</th>
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<tbody>
<tr>
<td>BARTON et al(^1)</td>
<td>HF</td>
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</tr>
<tr>
<td></td>
<td>detiorated</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>end-stage</td>
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<tr>
<td>GEORGE et al(^2)</td>
<td>CHF</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>(EF 38±1.4%)</td>
<td>↑</td>
</tr>
<tr>
<td>LOPEZ et al(^3)</td>
<td>diast HF (EF&gt;50%)</td>
<td>=</td>
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<tr>
<td></td>
<td>syst HF (EF&lt;50%)</td>
<td>↑</td>
</tr>
<tr>
<td>ALLA et al(^4)</td>
<td>HF (EF&lt;35%)</td>
<td>↓</td>
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<tr>
<td>JORDAN et al(^5)</td>
<td>CHF</td>
<td>↓</td>
</tr>
<tr>
<td>MARTOS et al(^6)</td>
<td>diast HF (EF&lt;50%)</td>
<td>=</td>
</tr>
<tr>
<td>FRANTZ et al(^7)</td>
<td>CHF (EF 36-55%)</td>
<td>=</td>
</tr>
<tr>
<td>GONZALEZ et al(^8)</td>
<td>HYP = HF</td>
<td>↑</td>
</tr>
<tr>
<td>ZILE et al(^9)</td>
<td>diast HF (EF&lt;55%)</td>
<td>↑</td>
</tr>
<tr>
<td>KRAMER et al(^10)</td>
<td>HF rats</td>
<td>↑</td>
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</tbody>
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↑Increase = unaltered CHF: congestive heart failure
diast: diastolic
eysystolic EF: ejection fraction
HYP: hypertension

### TABLE 2: Serum TIMP-1 in patients with heart failure (HF)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Studied Condition</th>
<th>Main Findings for TIMP-1</th>
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<tbody>
<tr>
<td>LINDSAY et al(^19)</td>
<td>HF</td>
<td>↑</td>
</tr>
<tr>
<td>TIMMS et al(^20)</td>
<td>HYP + HF</td>
<td>↑</td>
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<tr>
<td>BARTON et al(^1)</td>
<td>HF</td>
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<tr>
<td>GEORGE et al(^2)</td>
<td>HF</td>
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<tr>
<td>JORDAN et al(^5)</td>
<td>HF</td>
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<tr>
<td>MARTOS et al(^6)</td>
<td>diast HF</td>
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<tr>
<td>KRAMER et al(^10)</td>
<td>HF</td>
<td>↑</td>
</tr>
<tr>
<td>FRANTZ et al(^7)</td>
<td>HF</td>
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<tr>
<td>BIOLO et al(^21)</td>
<td>HF</td>
<td>↑</td>
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<tr>
<td>GONZALEZ et al(^8)</td>
<td>HYP + HF</td>
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<tr>
<td>ZILE et al(^9)</td>
<td>diast HF</td>
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↑Increase = unaltered diast: diastolic HYP: hypertension
says in serum and/or plasma. These assays however do not discriminate between pro-MMPs, active MMPs and MMP-TIMP complexes. Only in the study of Lombardi et al.\cite{12} a discrimination is made between active and free MMP-1. In patients with HCM they found increased levels of active MMP-2, active MMP-9 and total TIMP-1, while free MMP-1 and active MMP-1 were unaltered. Another way of measuring the MMP activity is to determine the MMP/TIMP ratio.

**TIMP-1 IN PATIENTS WITH AN ACUTE MYOCARDIAL INFARCTION**

That TIMP-1 is a predictor of total and cardiovascular mortality is predictable since MI and the subsequent wound healing induce a strong turnover of ECM. Immediately after a MI, the existing ECM structure degrades and this is accompanied by an increased protease activity and by a high probability of LV rupture. Infiltration of inflammatory cells occurs with an early rise of MMP-8 and MMP-9 activity. This leads to proliferation and maturation of fibroblasts which produce more collagen resulting in matrix deposition and scar formation. In the later phase of post-MI remodeling, inefficient support of newly formed ECM within (peri)infarct region leads to LV wall thickening resulting in further infarct expansion, LV dilation and eventually HF. Impaired or insufficient ECM remodeling leads then to LV rupture. Thus, early prevention of adverse ECM remodeling in the infarct and surrounding myocard is critical in the prevention of rupture and the preservation of the cardiac function after a MI.

**INHIBITION OF MMPs AND CARDIAC REMODELING**

In a pig model, a selective inhibitor (PGE-530742) was administered 3 days prior to an induced myocardial infarction and echocardiographic examination at day 10 post-infarction revealed a less increased percentage fractional shortening, when compared to placebo\cite{22}.

In the PREMIER trial (Prevention of Myocardial Infarction Early remodeling)\cite{23} 125 patients with a first ST-segment elevation MI (EF 15-40%) were enrolled 48 ± 24 h after MI and treated with the MMP-inhibitor PG-116800 for 90 days. Changes in LV diastolic volume, LV systolic volume, LV ejection fraction, sphericity index, plus rates of death or reinfarction were not significantly improved with PG-116800. The reason of this unsuccessful outcome is probably the timing of the drug treatment. MMP levels rise within hours of MI, whereas the rise in TIMPs lags by a few days. The initial rise in MMPs is responsible for the degradation of the ECM which is later replaced with scar tissue.

Treatment of mice lacking TIMP-3 with the broad spectrum MMP-inhibitor PD-166793 for 2 days before and 2 days after MI markedly improved post-MI infarct expansion, LV rupture incident, LV dilation and systolic dysfunction in these mice up to 1 week post-MI\cite{24}. Hence, MMP inhibition after 48 h of infarction, such as in the PREMIER trial, is likely unable to block the initial damaging effects of MMPs on the degradation of the ECM. The initial rise in MMPs early after MI is a triggering factor for subsequent LV adverse remodeling, LV rupture and dilated cardiomyopathy. Hence, timing is a critical factor in developing a treatment to maintain ECM integrity post-MI.

**CONCLUSIONS**

Alterations in MMP and TIMP expression are certainly involved in heart failure. However which MMPs or TIMPs are involved and which underlying mechanisms of these alterations are currently not known. TIMP-1 seems however the most promising biomarker in heart failure\cite{25-26}. In a recent meta-analysis of 30 studies in hypertensive patients Marchesi et al.\cite{27} demonstrated that plasma MMP-9 and TIMP-1 levels are higher in hypertensive patients without HF than normotensive controls. Plasma TIMP-1 levels are greater in patients with LV hypertrophy than without, suggesting that TIMP-1 may reflect hypertensive cardiac remodeling\cite{27}. Plasma MMP-2 levels are increased in hypertensive patients with diastolic HF than without, suggesting that MMP-2 may reflect clinical LV dysfunction in hypertension\cite{27}. Marchesi et al.\cite{27} concluded that TIMP-1, MMP-2 and MMP-9 are probably the best biomarkers of cardiovascular remodeling of hypertension.

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**CONFLICT OF INTEREST**

The authors report no conflict of interest.

**REFERENCES**


