Tissue inhibitor of metalloproteinases levels in patients with chronic heart failure: An independent predictor of mortality

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Abstract

Background: Matrix metalloproteinases (MMP) and their tissue inhibitors (TIMP) are involved in cardiac remodelling. The prognostic utility of TIMP is unknown in chronic heart failure (CHF).

Aims: We investigated the association of plasma levels of soluble MMP-9 and TIMP-1 with clinical, laboratory and echocardiographic parameters and estimated their prognostic value in the prediction of all-cause death.

Methods: MMP-9, TIMP-1, tumour necrosis factor-α, and amino-terminal pro-brain natriuretic peptide were measured in 249 consecutively enrolled CHF patients and 74 healthy individuals.

Results: After adjustment for age, sex and creatinine, levels of TIMP-1 (1640 vs. 735 ng/ml, \( P < 0.001 \)) but not MMP-9 were elevated in CHF patients compared to controls. During a median follow-up period of 2.5 years, 66 patients (27%) died. In multivariable Cox regression models TIMP-1 but not MMP-9 emerged as an independent predictor of all-cause death (hazard ratio per tertile, 3.5; 95% confidence interval \([CI]\), 2.2–5.1). In addition to the full set of univariately predictive clinical and serological markers, information on TIMP-1 significantly increased the area under the receiver operating characteristic curve from 0.77 (95% CI, 0.71–0.84) to 0.87 (95% CI, 0.82–0.92).

Conclusion: In stable CHF patients, TIMP-1 but not MMP-9 is of independent and incremental value regarding the prediction of all-cause death.

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Keywords: Heart failure; Matrix metalloproteinase; Tissue inhibitor of metalloproteinases; Prognosis

1. Introduction

The myocardial extracellular matrix is a highly dynamic structure, responsive to biological and mechanical stimuli and subject to continuous reconstruction [1]. Collagen accumulation in the myocardium is characteristic of pathologic hypertrophy and heart failure. Matrix turnover is regulated, amongst others, by the matrix metalloproteinases (MMPs), a family of enzymes capable of cleaving components of the extracellular matrix such as collagen or elastin. Elevated MMP-9 plasma levels are associated with increased LV diastolic dimensions and increased wall thickness in man [2]. MMP-9 plasma levels predict the degree of myocardial remodelling and progression to heart failure after myocardial infarction [3–7]. Various MMPs were also found to be elevated in non-ischaemic cardiomyopathy [8–10], and MMP-1 levels are associated with an adverse prognosis in heart failure [11].

The MMPs are inhibited by tissue inhibitors of metalloproteinases (TIMPs). TIMPs prevent uncontrolled collagen degradation but may activate growth factors and inhibit angiogenesis and apoptosis [1]. Targeted deletion of TIMP-1 adversely affected cardiac remodelling following myocardial
infarction [12]. In patients with established or suspected coronary artery disease, TIMP-1 levels were independently predictive of all-cause mortality, cardiac mortality, and myocardial infarction risk [13,14]. TIMP-1 was associated with severity of diastolic compromise [15] and left ventricular mass [16], and was elevated in hypertrophic cardiomyopathy [17]. Elevated levels of TIMP-1 have been consistently reported in chronic heart failure (CHF) regardless of the underlying cause or the type of left ventricular dysfunction [8,11,15,18,19], and a level >1200 ng/ml was indicative of heart failure [20]. However, the available information regarding the prognostic utility of TIMP-1 in heart failure is controversial. TIMP-1 was not predictive of remodelling [19], and TIMP-1 levels and outcome in heart failure were not associated in two smaller studies [8,11].

Prognosis in the individual patient with CHF is uncertain, but it is important to identify patients for advanced therapy like devices or transplantation. Additional prognostic parameters are therefore urgently needed. In addition, identification of a prognostic impact of collagen metabolism may give a hint to pathophysiology. We therefore tested the hypothesis that MMP-9 and TIMP-1 would independently predict all-cause mortality risk in a large cohort of unselected CHF patients. Further, we estimated their incremental prognostic value compared with clinical, laboratory and echocardiographic information.

2. Patients and methods

2.1. Study population and study design

Between 06/2002 and 12/2003, the Würzburg Heart Failure Registry prospectively collected information on 1054 CHF patients presenting consecutively at one of the two cardiology hospitals at Würzburg University. For the current analysis, the first 250 patients were selected. Adult outpatients and inpatients were eligible if they gave written informed consent. Two groups of patients were eligible. First, patients with systolic CHF defined as echocardiographic left ventricular (LV) ejection fraction \( \geq 45\% \), and with typical CHF signs and symptoms (at least one of the following: raised jugular venous pressure, peripheral oedema, third heart sound, pulmonary congestion at clinical examination or chest X-ray) responsive to CHF therapy. Second, patients with abnormal LV diastolic filling characteristics, but preserved systolic function (LV ejection fraction (EF) \( \geq 45\% \)), were also eligible [21]. All patients underwent a detailed clinical examination. LVEF was calculated following standard recommendations according to Simpson’s method. Information on medical history and medication was documented, and anthropometric measurements were performed in a standardised manner.

Seventy five healthy controls of similar age groups were selected from relatives of the hospital staff. Only subjects who were free from any medication were eligible.

All participants signed informed consent forms. The study was approved by the Ethics Committee of the Medical Faculty of Würzburg University and conformed with the principles outlined in the Declaration of Helsinki. Blood samples from one patient and one healthy subject were not available for analysis due to storage failure. Hence, results are reported for 249 patients and 74 controls. Death from any cause was ascertained for CHF patients (100% complete) in August 2005 by contacting the patient’s general practitioner to obtain certificates of death or by consulting hospital notes.

2.2. TIMP-1, MMP-9, TNF-α and other laboratory measurements

Venous blood samples were drawn from participants after recompensation between 08:00 and 11:00 h. Samples were centrifuged and plasma and serum stored at 70° until assayed. Plasma TIMP-1 (Amersham, Germany), MMP-9 and tumour necrosis factor (TNF)-α (R&D Systems, Abingdon, UK) were measured in duplicate according to the manufacturer’s protocol using commercially available assays. The TIMP-1 assay recognise total human TIMP-1, i.e. free TIMP-1 and that complexed with MMPs. The test fully crossreacts with TIMP-1 in complexes with MMP-1, MMP-3, MMP-2, MMP-9 and proMMP-9. It does not crossreact with MMP-2. Linearity is given from 3.1 to 50 ng/ml. Samples with higher concentrations were diluted to achieve exact values. TIMP-1 plasma samples are stable for at least 3 years when adequately frozen (personal communication with Amersham). The MMP-9 assay recognises natural human MMP-9. No cross-reactivity is observed with all MMPs tested. Linearity is given over a 1:16 range. All samples were diluted accordingly. The minimum detectable MMP-9 concentration is <0.156 ng/ml. Plasma MMP-9 is stable over a long time [22]. All other serum and plasma parameters including amino-terminal pro-brain natriuretic peptide (NT-proBNP) were measured as part of routine clinical testing in the central laboratory of the Würzburg University Hospital.

2.3. Data analysis

Normally distributed variables are reported with mean (standard deviation) and skewed variables with median (interquartile range). Group comparisons between patients and healthy controls were made using the independent \( t \)-test, Mann-Whitney \( U \)-test and \( \chi^2 \)-test as appropriate. Univariable associations of clinical variables with markers of collagen turnover and inflammation were investigated using linear regression models. Natural logarithmic transformation was used for skewed variables. Trends in covariate-adjusted means across categories of respective markers were examined by ANCOVA. Stepwise multiple linear regression (backward likelihood ratio) was used to investigate the relation of selected variables with the dependent variable. Age and sex were forced into all multivariable regression models. Statistical interactions were examined by introducing the respective product-term in the model. In tables describing multivariable regression models, back-transformed values are given to ease
with 95% confidence interval (CI). To estimate the prognostic capacity of TIMP-1, receiver operating characteristic (ROC) curves were constructed and compared [23]. Differences in the discriminative value between models were estimated by differences in the area under the ROC curve, taking into account the correlation between models as they were based on the same cases [24]. Statistical analysis was performed using SPSS 14.0.1.

3. Results

3.1. Patient characteristics

The detailed characteristics of the CHF cohort are listed in Table 1. Mean age of control subjects was 47±17 years, 48 were female, and the mean body mass index (BMI) was 25.6±3.3 (all $P<0.01$ compared to patients). Biochemical parameters are shown in Table 2. Levels of MMP-9 were similar in patients and controls, between sexes and across NYHA classes (detailed data not shown). Levels of TIMP-1, TIMP-1/MMP-9 ratio, TNF-α and NT-proBNP were markedly elevated in CHF (Table 2). These differences persisted after adjustment for age, sex, and creatinine (all $P<0.001$, respectively). In the CHF patients, TIMP-1 levels were lower in men compared to women [1510 (1200–2011) vs. 1770 (1411–2317) ng/ml; $P=0.018$] but there was no difference in the healthy controls [756 (657–868) vs. 733 (601–856) ng/ml; $P=0.403$]. A close association of TIMP-1 levels with age was apparent after adjustment for sex in healthy subjects and patients (Fig. 1). TIMP-1 levels were similar in CHF patients with both, impaired and preserved LV systolic function and were closely associated with NYHA class (Fig. 2). Further, TIMP-1 was closely related to NT-proBNP ($R^2=0.59$) and TNF-α ($R^2=0.59$) in both patients and controls ($P<0.001$, respectively). By contrast, no such correlation was present between MMP-9 levels and NT-proBNP, NYHA class, and TNF-α levels. TIMP-1 levels were lower among patients receiving statins ($P=0.014$) whereas statin treatment did not affect levels of TNF-α and MMP-9 ($P>0.2$, respectively).

### Table 1
Characteristics of chronic heart failure patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>n=249</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.3 (13.2)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>77 (31)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.3 (4.9)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>127 (22)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>73 (13)</td>
</tr>
<tr>
<td>Heart rate, 1/min</td>
<td>73 (17)</td>
</tr>
<tr>
<td>Ischaemic aetiology, n (%)</td>
<td>107 (43)</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td>35 (14)/94 (38)</td>
</tr>
<tr>
<td>I/II</td>
<td>98 (39)/22 (9)</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter, mm</td>
<td>60 (11)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>44 (36–55)</td>
</tr>
<tr>
<td>Systolic heart failure *, n (%)</td>
<td>147 (59)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>61 (25)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>77 (31)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>145 (58)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>40 (16)</td>
</tr>
<tr>
<td>Anaemia **, n (%)</td>
<td>70 (28)</td>
</tr>
<tr>
<td>Peripheral oedema, n (%)</td>
<td>96 (39)</td>
</tr>
<tr>
<td>Jugular distension, n (%)</td>
<td>27 (11)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB, n (%)</td>
<td>201 (81)</td>
</tr>
<tr>
<td>Beta blocker, n (%)</td>
<td>166 (67)</td>
</tr>
<tr>
<td>Diuretic, n (%)</td>
<td>207 (83)</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>89 (36)</td>
</tr>
<tr>
<td>Antiplatelet therapy or warfarin</td>
<td>193 (77)</td>
</tr>
</tbody>
</table>

Values are mean (SD), median (IQR) or n (%), according to the nature of the data.

NYHA, New York Heart Association; ACE, angiotensin converting enzyme; ARB, angiotensin-1 receptor blocking agent.

* Systolic dysfunction: ejection fraction <45%.

** Anaemia: haemoglobin <12 g/dl in women, and <13 g/dl in men.

interpretation. The association of tertiles of TIMP-1, MMP-9, TNF-α, and NT-proBNP with all-cause mortality was estimated by Cox proportional hazards regression. Univariable predictive variables (identified by a $P$-value of $<0.05$) were backward eliminated in stepwise multivariable models. Results in prognostic models are expressed as hazard ratio (HR)
3.2. Determinants of TIMP-1

In sex and age adjusted linear regression, strong positive associations with TIMP-1 were observed for NT-proBNP, creatinine, jugular distension, uric acid, NYHA class, diuretic treatment, diabetes, peripheral oedema, and TNF-α (listed in decreasing strength of association). Likewise, strong negative associations were observed for: haemoglobin, sodium, diastolic and systolic blood pressure, left ventricular end-diastolic diameter and volume, total cholesterol, and statin treatment. Table 3 details the result of the multivariable regression analysis. The remaining variables explained 57% of the variance of TIMP-1 in CHF patients (corrected $R^2$). Table 3 also shows the multiplicative changes in TIMP-1 associated with 1 SD change in each estimator. Qualitatively similar results were obtained if analyses were redone using the TIMP-1/MMP-9 ratio.

3.3. Independent prognostic value of TIMP-1

After a median follow-up of 943 days (IQR 268-1117) 66 patients had died (27%). Crude mortality rates in tertiles of TIMP-1 were (from low to high) 6%, 23%, and 71% ($P$ for trend $<$0.0001), and in tertiles of MMP-9 42%, 26%, and 32% ($P$ for trend $=$0.247), respectively. In univariable Cox regression, TIMP-1 was a strong predictor of all-cause mortality risk (HR per tertile, 4.1; 95% CI, 2.7–6.0; $P$ $<$0.0001), whereas MMP-9 was not (HR per tertile, 0.9; 95% CI, 0.7–1.2; $P$=0.482). In multivariable analysis, the adjusted coefficient for TIMP-1 was modestly attenuated (HR, 3.5; 95% CI, 2.2–5.1; $P$=0.0001). Fig. 3 compares the discriminative utility of tertiles of TIMP-1, MMP-9, TNF-α, and NT-proBNP with respective adjustment for the other significant predictors. TIMP-1 and NT-proBNP but not MMP-9 and TNF-α exhibited independent prognostic value.

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Table 3
Regression coefficients from multivariable analysis on determinants of TIMP-1

<table>
<thead>
<tr>
<th></th>
<th>$\beta$</th>
<th>Multiplicative change in TIMP-1</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jugular distension, vs. not</td>
<td>0.48</td>
<td>1.48 (1.19–1.52)</td>
<td>0.0015</td>
</tr>
<tr>
<td>Diabetes, vs. not</td>
<td>0.30</td>
<td>1.30 (1.10–1.50)</td>
<td>0.0035</td>
</tr>
<tr>
<td>NT-proBNP, 1 SD=1228 ng/ml</td>
<td>0.30</td>
<td>1.30 (1.20–1.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum sodium, 1 SD=3.4 mmol/l</td>
<td>0.19</td>
<td>0.81 (0.72–0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Haemoglobin, 1 SD=2.1 g/dl</td>
<td>−0.21</td>
<td>0.79 (0.69–0.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left ventricular end-diastolic volume, 1 SD=47 ml</td>
<td>0.20</td>
<td>1.20 (1.09–1.31)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Uric acid, 1 SD=2.1 mg/dl</td>
<td>0.13</td>
<td>1.13 (1.04–1.22)</td>
<td>0.0050</td>
</tr>
</tbody>
</table>

$\beta$=coefficient of linear regression; an increase of the independent variable by 1 unit is associated with a $\beta$ increase in TIMP-1. Estimates are adjusted for age and sex.

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Fig. 1. Association between mean (SD) log plasma total TIMP-1 levels and age groups in 249 chronic heart failure patients (closed circles) and 74 healthy controls (open circles), adjusted for sex. $P$ for trend $<$0.0001 and 0.024, respectively. The numbers in the table indicate the proportion of subjects per age group.

Fig. 2. Mean (SD) log-plasma total TIMP-1 levels, adjusted for age and sex, in 74 healthy controls and 249 patients with systolic and non-systolic heart failure (HF; left panel), and TIMP-1 levels, adjusted for sex, in patients according to NYHA class (right panel; black bars indicate women, shaded bars indicate men). $P$ for trend $<$0.001, respectively.
3.4. Incremental prognostic value of TIMP-1

From the complete set of univariable predictors, i.e. age, sex, NYHA class, heart failure aetiology, hypercholesterolaemia, family history of ischaemic heart disease, lung disease, body mass index, blood pressure, heart rate, ejection fraction, haemoglobin, creatinine, and NT-proBNP, an area under the ROC curve of 0.77 (95% CI, 0.71–0.84) was derived. If information on TIMP-1 was added, the area under the ROC curve increased to 0.87 (95% CI, 0.82–0.92; \( P \leq 0.05 \) for comparison between curves).

Fig. 3. Survival plots from multivariable adjusted Cox regression models showing the association of tertiles of each marker with all-cause mortality. Curves were estimated by use of the mean values of covariates. Hazard ratios (HR) and \( P \) values refer to comparison between highest and lowest tertile. TIMP-1: HR, 8.0; 95% CI, 3.4–20.2; \( P \leq 0.001 \); adjusted for age, sex, NYHA class, heart failure aetiology, diabetes, smoking, left ventricular end-diastolic volume, body mass index, NT-proBNP; cut-off values for tertiles were \(<1390, 1391–1917, \geq1917 \text{ ng/ml} \). MMP-9: HR, 1.1; 95% CI, 0.6–1.9; \( P = 0.822 \); adjusted for age, sex, NYHA class, heart failure aetiology; cut-off values for tertiles were \(<48.6, 48.7–89.4, \geq89.4 \text{ ng/ml} \). TNF-\( \alpha \): HR, 1.1; 95% CI, 0.5–2.0; \( P = 0.882 \); adjusted for age, sex, NYHA class, body mass index; cut-off values for tertiles were \(<4.99, 4.99–8.7, \geq8.7 \text{ pg/ml} \). NT-proBNP; HR, 6.4; 95% CI, 2.9–14.3; \( P < 0.001 \); adjusted for age, sex, NYHA class, haemoglobin, creatinine; cut-off values for tertiles were \(<570, 570–2228, \geq2228 \text{ pg/ml} \).

Fig. 4. Left panel: Incremental prognostic value of TIMP-1 values. The dashed line indicates the line of indecision. The grey line indicates the area under the ROC curve (0.77; 95% CI, 0.71–0.84) for a set of clinical and biochemical variables including age, sex, NYHA class, heart failure aetiology, hypercholesterolaemia, positive family history of ischaemic heart disease, lung disease, body mass index, blood pressure, heart rate, ejection fraction, haemoglobin, creatinine, and NT-proBNP, an area under the ROC curve of 0.77 (95% CI, 0.71–0.84) was derived. If information on TIMP-1 was added, the area under the ROC curve increased to 0.87 (95% CI, 0.82–0.92; \( P < 0.05 \) for comparison between curves). For selection mode of variables see Patients and methods. Right panel: Prognostic value of the combined information on TIMP-1 and NT-proBNP (levels split at their median), adjusted for age, sex, and NYHA class. \( P < 0.0001 \) for comparison between extremes.
To assess the combined prognostic value of TIMP-1 and NT-proBNP, both variables were split at the median and the combination of “TIMP-1 low, NT-proBNP low” was defined as referent, i.e. HR 1.00. Patients in the group with “TIMP-1 high, NT-proBNP high” exhibited the highest mortality risk (HR, 16.6; 95% CI, 8.0–19.1; Fig. 4, right panel).

4. Discussion

TIMP-1 but not MMP-9 was of independent and incremental value for the prediction of all-cause mortality risk in patients with chronic heart failure. In addition, TIMP-1, but not MMP-9, was associated with heart failure severity as indicated by NYHA class and NT-proBNP, with the biomarker of immune activation TNF-α, the comorbid conditions diabetes and renal failure, and the use of statins.

4.1. Independent and incremental prognostic value of TIMP-1

TIMP-1 emerged as a strong predictor of all-cause death over a 24 month period. Patients in the highest TIMP-1 tertile had an eight-fold increase in mortality risk. This effect was robust against adjustment for potential confounders selected from clinical and biological risk factors/mediators known to be associated with increased mortality risk in heart failure. TIMP-1 exhibited incremental prognostic information when added on top of a summary set of clinical and biochemical CHF descriptors including NT-proBNP. In particular, the combination

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Table 4

<table>
<thead>
<tr>
<th>Author (ref. no.)</th>
<th>N, patients</th>
<th>N, controls</th>
<th>Condition studied</th>
<th>Type of study</th>
<th>Endpoints</th>
<th>Main findings</th>
</tr>
</thead>
</table>
| Jordan A [11]    | 50          | 53          | Systolic dysfunction | Follow-up study (17.5 months) | Composite of all-cause death, readmission for heart failure, cardiac transplant | • Associated with peak oxygen consumption  
• Elevated in congestive heart failure  
• Not independently associated with outcome |
| Martos R [15]    | 32          | 54          | Diastolic dysfunction | Cross-sectional | – | • Elevated in diastolic heart failure  
• Associated with severity of diastolic compromise |
| Ahmed SH [20]    | 50          | 53          | Hypertensive heart disease | Cross-sectional | – | • Level >1200 ng/ml indicative of heart failure |
| Kotlyar E [18]   | 58          | 0           | Systolic dysfunction | Follow-up study (12 months) | LV volumes and ejection fraction (radionuclide ventriculography) | • Elevated in heart failure  
• Not predictive of remodeling |
| Yan AT [19]      | 184         | 0           | Systolic dysfunction | Cross-sectional | – | • Not predictive of remodeling |
| George J [8]     | 88          | 30          | Heart failure of various causes | Follow-up study (24 months) | Composite of all-cause death and readmission for heart failure | • Elevated in heart failure  
• Not predictive of outcome |
| Tziakas DN [7]   | 52          | 0           | Systolic dysfunction | Cross-sectional | – | • Lower in non-ischaemic compared with ischaemic cardiomyopathy  
• Elevated in hypertrophic cardiomyopathy |
| Noji Y [17]      | 28          | 50          | Hypertrophic cardiomyopathy | Cross-sectional | – | • Correlated with left ventricular mass |
| Tayebjee MH [16] | 74          | 34          | Hypertensive heart disease | Cross-sectional | – | • Elevated in heart failure |
| Allieri P [35]   | 51          | 52          | Heart failure of various causes | Cross-sectional | – | • Elevated in heart failure |
| Schwartzkopff B [36] | 43        | 47          | Dilated cardiomyopathy | Cross-sectional | – | • Elevated in heart failure |
| Wilson EM [10]   | 24          | 48 (stable CAD) | Systolic dysfunction | Follow-up study (12 months) | No outcome analysis included | • Elevated in heart failure  
• Similar in patients with ischaemic and non-ischaemic cardiomyopathy  
Elevated in heart failure (stable during follow-up) |
| Present study    | 249         | 74          | Systolic and non-systolic dysfunction; heart failure of any aetiology | Follow-up study (30 months) | All-cause death | • Elevated in heart failure  
• TIMP-1, but not MMP-9, of independent and incremental value for the prediction of mortality risk  
• TIMP-1, but not MMP-9, associated with heart failure severity, NT-proBNP, TNF-α, diabetes, renal failure, use of statins |
of high TIMP-1 and high NT-proBNP levels was associated with a particularly adverse prognosis. One plausible explanation for this additive detrimental effect may be that NT-proBNP mainly reflects deteriorated loading conditions, whereas TIMP-1 mirrors changes in the extracellular matrix in CHF patients.

4.2. TIMP-1 and heart failure

The collagen matrix plays a critical role in maintaining the structural alignment of myocytes and, thus, the left ventricular geometry. The collagen matrix is tightly regulated by its degrading enzymes, such as various MMPs and the antagonistic TIMPs. A cause and effect relationship for MMP expression and left ventricular remodelling has been postulated on the basis of studies in transgenic mice or through the use of pharmacologic MMP inhibitors [25,26]. TIMP-1 deficiency exacerbated left ventricular remodelling after experimental myocardial infarction [12]. Data on expression patterns of TIMP-1 in myocardial biopsies of patients with cardiac diseases are inconsistent. Whereas some reports suggested a decrease [27] or no change [28], others observed an increase of TIMP-1 levels [29,30] in heart failure patients. By contrast, all studies investigating TIMP-1 levels from peripheral blood samples observed elevated levels in heart failure (Table 4). In a community based sample of healthy men, higher plasma TIMP-1 levels were associated with increased LV diastolic dimensions and increased wall thickness [2]. TIMP-1 levels correlated with diastolic dysfunction in hypertensive patients [16]. The present study found elevated TIMP-1 levels in patients with CHF regardless of the type of heart failure, i.e. systolic or non-systolic. TIMP-1 levels were associated with the severity of heart failure as indicated by NT-proBNP, NYHA class, jugular distension, peripheral oedema, the use of diuretics, LV end-diastolic dimension and volume, the latter keeping its diagnostic utility also in multivariable analysis (Table 3). In addition, we found a positive association of TIMP-1 plasma levels with inflammatory markers as TNF-α, and lower TIMP-1 levels in patients treated with statins. This is in accordance with in vitro data where TIMP-1 expression was regulated by pro-inflammatory proteins [31], and treatment with 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitors reduced TIMP-1 production [32]. Yet, TIMP-1 levels were still two-fold higher compared with controls. In order to relate TIMP-1 levels to the pathophysiology of CHF, the source of plasma TIMP-1 should be evident. One possibility might be that plasma MMPs/TIMPs represent a spillover from cardiac MMP/TIMP production into the interstitium. Yet, other cells as leukocytes or endothelial cells are capable of MMP and TIMP production as well. Thus, the source of elevated TIMP in heart failure remains unclear and requires further investigation.

4.3. MMP-9 and heart failure

Some smaller studies have reported elevated MMP-9 expression in patients with heart failure [8,10,28,33,34]. By contrast, we and others [8] found that levels of MMP-9 measured from peripheral blood are not different between patients with heart failure and controls, and are not associated with mortality risk. The reasons for these differences are unclear and not explained by variation of severity or aetiology of heart failure, age or sex, between the different studies.

4.4. Limitations

Since this study was cross-sectional, we cannot draw conclusions on a proposed cause and effect relation between MMP-9 and the course of CHF. However, our data do not support a prognostic role for MMP-9 in these patients. Since MMPs constitute a family of enzymes with over 20 different species, our findings cannot be extrapolated to other MMPs. Further, collagen degradation products (e.g., pro-collagen type III N-terminal pro-peptide) were not measured and collagen metabolism in a stricter sense may therefore not be related to TIMPs and MMPs in this study.

In summary, we have demonstrated elevated TIMP-1 serum levels in patients with CHF with both, impaired or preserved LV function. TIMP-1 levels were closely associated with established markers of CHF severity, parameters of systemic inflammation, markers of myocardial remodelling and all-cause mortality.

Acknowledgments

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References


