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Plasma tissue inhibitor of matrix metalloproteinase-1 (TIMP-1): an independent predictor of poor response to cardiac resynchronization therapy

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Aims Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) play a role in left ventricular structural remodelling. The aim of our study was to analyse MMP-2 and TIMP-1 levels as predictors of poor response to cardiac resynchronization therapy (CRT).

Methods and results A cohort of 42 CRT patients from our centre was prospectively evaluated at baseline and after 12-month follow-up. MMP-2 and TIMP-1 assays were performed prior to CRT implant. Cardiac resynchronization therapy responders were defined as patients who survived, were not transplanted, and increased their basal 6 min walking distance test (6MWDT) by $\geq$10% or improved their NYHA functional class. Overall, 25 patients (60%) were classed as responders. At 12-month follow-up, six patients (14.2%) had died and one (2.4%) patient had been transplanted. Compared with responders, non-responders had higher levels of TIMP-1 (277 ± 59 vs. 216 ± 46 ng/mL, $P = 0.001$), MMP-2 (325 ± 115 vs. 258 ± 56 ng/mL, $P = 0.02$), and creatinine (1.76 ± 0.8 vs. 1.25 ± 0.3 mg/dL, $P = 0.01$). In a multivariate analysis, TIMP-1 was the only independent predictor of non-response to CRT [OR 0.97, 95% (CI 0.96–0.99) $P = 0.005$]. TIMP-1$\geq$248 ng/mL predicted non-response with 71% sensitivity and 72% specificity.

Conclusion TIMP-1 is an independent predictor of non-response in patients treated with CRT.

Keywords Resynchronization therapy • Matrix metalloproteinase • Tissue inhibitor of matrix metalloproteinase • Heart failure

Introduction

Cardiac resynchronization therapy (CRT) is considered a class I indication in patients with stable heart failure, NYHA functional class III-IV, ejection fraction (EF) $\leq$35%, and wide QRS $>$120 ms.[1] However, the percentage of patients who do not respond to CRT is about 30%.

Left ventricular (LV) remodelling plays an important role in the progression of heart failure.[2,3] Degradation of the myocardial extracellular matrix contributes to LV remodelling[4,5] and the proteolytic enzyme system responsible for the degradation is matrix metalloproteinases (MMPs).[6,7] This enzyme system is controlled by a group of endogenous proteins called tissue inhibitors of MMPs (TIMPs). Some studies have reported an increase in

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circulating levels of certain MMPs and TIMPs in patients with advanced heart failure.[8] Moreover, increased levels of TIMP-1 and MMP-2 are associated with poor prognosis in these patients.[9,10]

The first objective of our study was to determine whether basal MMP-2 and TIMP-1 levels could predict response to CRT. A second objective was to compare the levels of MMP-2 and TIMP-1 in coronary sinus (CS) vs. peripheral blood samples in patients with chronic heart failure.

Methods

This was a prospective single centre study approved by the Human Research Committee at the Hospital Clinic in Barcelona.

A 1 year cohort of patients who received a CRT device in our centre was included in the study. Inclusion criteria: (i) stable chronic heart failure (NYHA class $\geq$III) despite optimal drug therapy; (ii) LV EF $\leq$35%; (iii) QRS width $>$120 ms. In addition, patients with an EF $\leq$35% and an indication for cardiac pacing were also included in the study, independent of their basal NYHA functional class.

Exclusion criteria

Patients with recent acute coronary syndrome, neoplasia, thyroid disorder, or chronic liver, neuromuscular, or collagen disease, as well as those with infection or surgery in the 6 months prior to the implant, were excluded.

Measures of clinical outcome

All patients underwent a 12-lead electrocardiogram, echocardiogram, and clinical evaluation prior to implant and at 6- and 12-month follow-up. Heart failure symptoms, functional capacity, and quality of life were assessed by NYHA functional class, the 6 min walking distance test (6MWDT), and the Minnesota Living With Heart Failure test (QoL), respectively. Pharmacological treatment was also recorded.

Two-dimensional echocardiography was performed with the patient in left lateral decubitus position, using a commercially available system (Vingmed Vivid-7, Milwaukee, WI, USA) equipped with a 3.5 MHz probe. Standard M-mode and two-dimensional images were acquired at a depth of 16 cm and stored in cine-loop format of three consecutive beats. Left ventricular volumes and EF were calculated by Simpson's rule from the two- and four-chamber apical views. The presence of mitral regurgitation was assessed systematically. Colour Doppler echocardiography was performed in all views after optimizing gain and Nyquist limit. The severity of valvular regurgitation was determined on a qualitative scale according to the ACC/AHA guidelines for the management of patients with valvular heart disease: mild (grade 1), moderate (grade 2), and severe (grades 3–4).

Device implantation and programming

Right ventricular leads were positioned at the right ventricular apex. Conventional atrial leads were used in patients in sinus rhythm or paroxysmal atrial fibrillation. The LV electrode was inserted through the CS into a lateral vein whenever possible. Patients in sinus rhythm were programmed in DDD mode; patients with atrial fibrillation were programmed in VVIR mode at 75 bpm. Maximum rate was set at 85% of the theoretical maximum heart rate. Trigger mode was activated when available.

Responder definition

Under a definition reported and validated in previous studies,[11,12] responders were defined as patients who did not suffer cardiovascular death, did not have a heart transplant, and had increased their basal 6 min walking distance test results by $\geq$10% at the 12-month follow-up. In addition, for patients who did not undertake a 6 min walking distance test, the required improvement was at least one NYHA functional class.[13,14] The 6 min walking distance test and NYHA functional class were assessed by an independent observer.

Biochemical analysis

At the time of CRT implant, blood samples from a peripheral vein and the CS were obtained simultaneously. Samples were centrifuged for 15 min at 3000 rpm and 4°C. Serum and plasma samples were stored at −80°C until assay. Serum MMP-2 and plasma TIMP-1 levels (Quantikine R&D Systems, Minneapolis, Minnesota) were assessed using a commercially available sandwich enzyme immunoassay.

Statistical analysis

Data are expressed as mean $\pm$ SD and were compared using Student's *t*-test for paired and unpaired data, as appropriate. Univariate analysis for categorical variables was performed using the chi-square test. Kaplan–Meier estimates were calculated for mortality and differences between groups assessed using Cox proportional hazard models. To adjust for all prognostic factors, a multivariate Cox regression model was fitted with variables predicting non-response to CRT in the univariate analysis. For all tests, a *P*-value $<$0.05 was considered statistically significant. The calculated sample size was 40 patients, with a statistical power of 80% and statistical significance of 0.05.

Results

Of 55 consecutive patients who received a CRT device in our centre during the inclusion period, 42 (76%) were included in the study. The main reasons for exclusion of the 13 (24%) patients were: (i) CS not cannulated (in 3/13 patients, LV lead was implanted by epicardial approach); (ii) consent for blood extraction not signed (6/13), (iii) antecedents of neoplasia or chronic liver disease (4/13).

Baseline characteristics of the 42 patients included in the study are shown in *Table 1*. Nine of the included patients (21%) were in NYHA class II at baseline with a mean LVEF of 25 $\pm$ 7% and were treated with CRT due to severe bradycardia and the need for continuous ventricular pacing. Since it was impossible to perform the 6MWDT in these patients, the response criteria were the lack of cardiovascular events (cardiovascular death or heart transplant) and the improvement in their stable NYHA functional class (previous to the A-V block).

At 12 months after implant, 25/42 patients (60%) were classed as responders and showed significant improvement in functional capacity, with an increase in 6MWDT from 262 $\pm$ 128 to 380 $\pm$ 133 m ($P = 0.01$) and in quality of life from 45 $\pm$ 22 to 28 $\pm$ 20 points ($P = 0.01$). Furthermore, reverse remodelling produced a decrease in LV end diastolic volume from 217 $\pm$ 58 to 195 $\pm$ 67 mL ($P = 0.05$) and LV end-systolic volume from 163 $\pm$ 56 to 136 $\pm$ 53 mL ($P = 0.02$). Left ventricular EF increased from 27 $\pm$ 7 to 33 $\pm$ 7% ($P = 0.01$).

Table 1 Basal characteristics of patients included in the study

$N = 42$	
Age	66 ± 8
Male sex	35 (83.3%)
Creatinine level (mg/dL)	1.4 ± 0.6
Atrial fibrillation	8 (19%)
Ischaemic cardiomyopathy	19 (45.2%)
Ventricular arrhythmia	16 (38%)
ICD	25 (59.5%)
Beta-blockers	27 (64.3%)
ACEIs/ARBs	33 (78.5%)
Aldosterone	20 (47.6%)
NYHA functional class ≥3	33 (78.5%)
6MWDT (m)	232 ± 126
QoL (points)	42 ± 24
LVEDV (mL)	212 ± 66
LVESV (mL)	162 ± 63
LVEF (%)	27 ± 7
Severe mitral regurgitation	5 (12%)
CS MMP-2 (ng/mL)	278 ± 75
CS TIMP-1 (ng/mL)	228 ± 60
Peripheral MMP-2 (ng/mL)	295 ± 70
Peripheral TIMP-1 (ng/mL)	242 ± 61

6MWDT, 6 min walking distance test; QoL: quality of life test (Minnesota); ICD, internal cardioverter defibrillator; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end systolic volume; LVEF, left ventricular ejection fraction; MMP-2, matrix metalloproteinase-2; TIMP-1, tissue inhibitor matrix metalloproteinase-1; CS, coronary sinus; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Serum MMP-2 and plasma TIMP-1 levels

Peripheral MMP-2 and TIMP-1 levels were higher than the CS levels obtained (295 ± 70 vs. 278 ± 75 ng/mL ($P = 0.008$) and 242 ± 61 vs. 228 ± 60 ng/mL, respectively). A good correlation was observed between CS and peripheral blood samples (*Figure 1*). Furthermore, TIMP-1 and MMP-2 levels were similar, independent of the underlying aetiology of heart failure (*Figure 2*).

Predictors of non-response to cardiac resynchronization therapy

Creatinine levels, CS, and peripheral TIMP-1 and MMP-2 levels were higher in patients that did not respond to CRT (*Table 2*). After adjusting for baseline covariables in the Cox regression analysis, TIMP-1 was the only independent predictor of non-response to CRT (OR 0.97, 95% CI 0.96–0.99). A peripheral TIMP-1 cut-off value of 248 ng/mL yielded the best sensitivity and specificity results for non-response to CRT (OR 6.8, 95% CI (1.5–31) for TIMP-1 ≥ 248 ng/mL) (*Figure 3*).

TIMP-1, MMP-2, and left ventricular reverse remodelling

TIMP-1 levels were higher in those patients without significant LV reverse remodelling (LVESV reduction ≥10%), whereas there were no differences in MMP-2 levels between the patient groups (*Table 3*).

Correlation between clinical response and left ventricular reverse remodelling

Seventeen of the 25 clinical responders (68%) had significant LV reverse remodelling (LVESV reduction ≥10%).

Cardiovascular mortality and heart transplant

At 12-month follow-up, 6/42 (14.2%) patients had died, 4 (9.5%) due to end-stage heart failure and 2 (4.7%) due to sudden death; 1 patient was transplanted due to poor response to CRT.

Patients who died tended to have larger LV dimensions, lower LV EF, worse basal NYHA functional class, and higher creatinine, peripheral, and CS TIMP-1 levels (*Table 4*).

After adjusting for baseline covariables in the Cox regression analysis, TIMP-1 level was a predictor of non-response to CRT [OR 0.97, 95% CI (0.96–0.99) $P = 0.005$]. Cardiovascular death was higher in the 19 patients with TIMP-1 levels ≥248 ng/mL than in the remaining 23 patients: 5/19 (26.3%) vs. 1/23 (4.3%) (log-rank test 4.77, $P < 0.03$).

Discussion

Structural LV remodelling, a common event in the progression of heart failure, causes progressive dilatation of the left ventricle and pump dysfunction.[15,16] Matrix metalloproteinases have been directly implicated in tissue remodelling because they degrade extracellular proteins.[17]

The main findings of our study are: TIMP-1 and MMP-2 levels are positively associated with a lower probability of response to CRT; TIMP-1 is an independent predictor of non-response to CRT; TIMP-1 and MMP-2 levels are higher in peripheral blood samples compared with CS samples.

MMP-2 and TIMP-1 levels positively correlated with poor response to cardiac resynchronization therapy

In our study, patients with higher TIMP-1 or MMP-2 levels, whether in CS or in peripheral blood samples, had a poor clinical response to CRT. However, after multivariate analysis, TIMP-1 was the only independent predictor of non-response to CRT.

Our study showed higher serum MMP-2 levels in patients who did not respond to CRT when compared with responders. Therefore, MMP-2 was a marker of poor prognosis in terms of clinical response to CRT. In contrast with our results, Hessel *et al.*[18] did not find any difference in baseline MMP-2 level between patients who responded and those who did not respond to CRT. This discrepancy may be explained by differences in the study design, the use of reverse remodelling rather than clinical response as the criterion for response to CRT, and the fact that no patients died or were transplanted during follow-up in that study.

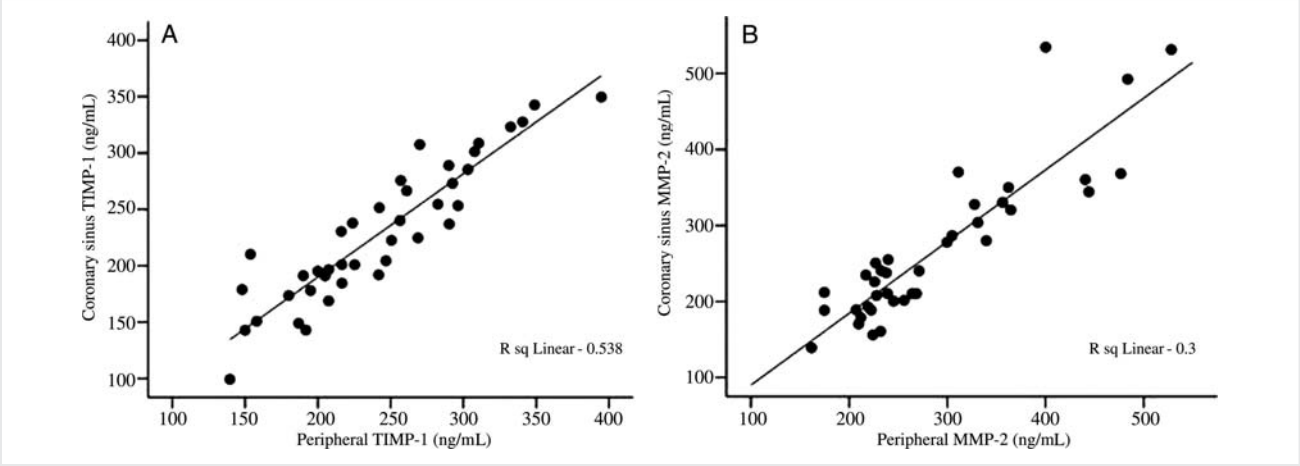

Figure 1 Correlation between coronary sinus and peripheral vein samples for plasma tissue inhibitor of matrix metalloproteinase-1 concentrations (*A*); and serum matrix metalloproteinase-2 concentrations (*B*).

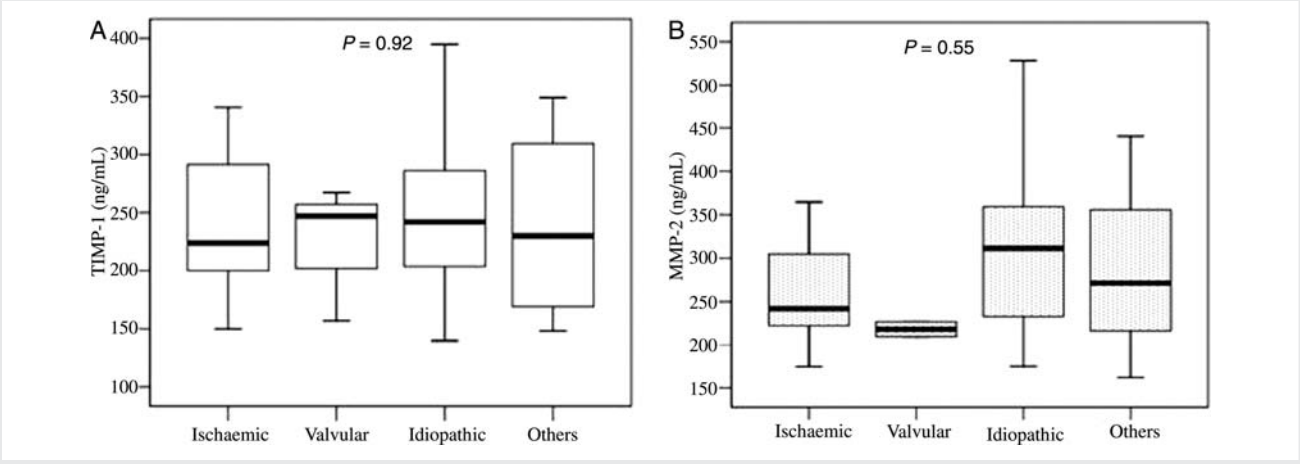

Figure 2 Comparison of plasma tissue inhibitor of matrix metalloproteinase-1 levels (*A*) and serum matrix metalloproteinase-2 levels (*B*) according to the aetiology of heart failure.

TIMP-1 as an independent predictor of non-response in patients treated with cardiac resynchronization therapy

Our study demonstrated an association between plasma TIMP-1 concentration and lack of response to CRT. Furthermore, after adjusting for relevant prognostic variables in a multivariate analysis, plasma TIMP-1 level was the only independent predictor of non-response to CRT.

In our series, higher TIMP-1 levels were related with a poor response to CRT more accurately than LV dimensions, LV EF, ischaemic aetiology, and paced QRS width, all of which have been previously identified as predictors of response.[11,14]

As was described by Frantz *et al.*,[19] our study also showed that TIMP-1 levels were higher in those patients who died when compared with survivors. But due to the small number of events, this information has to be treated with caution.

In contrast to our data, Garcia Bolao *et al.*,[20] did not find any statistical difference in serum TIMP-l levels between responders and non-responders to CRT, although TIMP-1 levels tended to be higher in the non-responder group (563.8 ± 345.7 vs. 437.5 ± 136.5 ng/mL, $P = 0.135$). The difference in the methods used in the two studies to determine TIMP-1 concentration could explain this discrepancy; previous studies[21,22] have shown that the TIMP-1 concentration differs in serum and in plasma.

It is known that TIMP-1 does more than inhibit MMPs in patients with chronic heart failure.[23] In chronic inflammatory states, TIMP-1 levels increase much more than do MMP levels, promoting collagen formation[24] and myocardial fibrosis.[25,26] Our observations suggest that patients with higher TIMP-1 levels have more myocardial fibrosis, which could negatively affect the response to CRT.

If our results can be confirmed in larger studies, TIMP-1 could be used to achieve better selection of candidates for CRT and to reduce the percentage of patients who obtain a poor response to CRT.

Table 2 Univariate analysis: predictors of non-response to cardiac resynchronization therapy

	Responders (25)	Non responders (17)	*P*-value
Age	67 ± 9	66 ± 7	0.78
Creatinine level (mg/dL)	1.25 ± 0.3	1.76 ± 0.8	0.01*
Atrial fibrillation	6 (24%)	3 (17.6%)	0.47
Ischaemic cardiomyopathy	10 (40%)	10 (59%)	0.31
Ventricular arrhythmia	10 (40%)	6 (24%)	0.8
ICD	16 (64%)	10 (59%)	0.57
Beta-blockers	18 (68%)	11 (65%)	0.82
ACEIs–ARBs	20 (80%)	14 (82%)	0.83
Aldosterone	12 (48%)	9 (53%)	0.65
NYHA functional class IV	2 (8%)	3 (17.6%)	0.38
Basal 6MWDT	248 ± 133	212 ± 117	0.4
QoL test	36 ± 21	48 ± 26	0.45
Post-stimulation QRS width	142 ± 14	147 ± 24	0.18
LVEDV (mL)	218 ± 61	211 ± 80	0.76
LVESV (mL)	162 ± 74	167 ± 60	0.83
LVEF	27 ± 6	25 ± 8	0.37
Severe mitral regurgitation	4 (16%)	1 (6%)	0.32
CS TIMP-1 (ng/mL)	205 ± 51	260 ± 60	0.003*
CS MMP-2 (ng/mL)	239 ± 78	312 ± 70	0.05*
Peripheral TIMP-1 (ng/mL)	216 ± 50	277 ± 59	0.001*
Peripheral MMP-2 (ng/mL)	258 ± 56	325 ± 116	0.02*

ICD, internal cardioverter defibrillator; 6MWDT, 6 min walking distance test; QoL, quality of life test (Minnesota); LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; CS, coronary sinus; MMP-2, matrix metalloproteinase-2; TIMP-1, tissue inhibitor matrix metalloproteinase-1; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.
*$P < 0.05$ responders vs. non-responders.

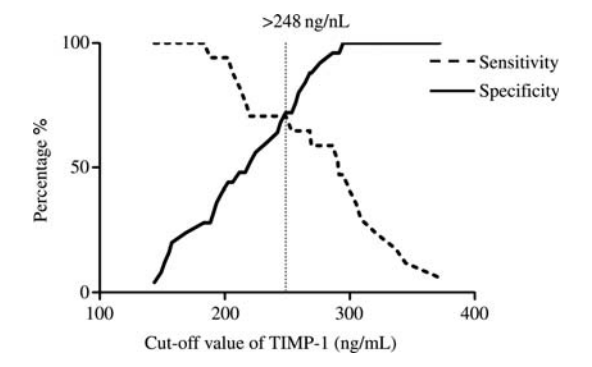

Figure 3 Receiver-operating characteristic curve of TIMP-1 for determining lack of response to cardiac resynchronization therapy.

Table 3 Correlation between MMP-2 and TIMP-1 levels and presence of left ventricular reverse remodelling (LVESV reduction ≥10%) at 12-month follow-up

	LVESV ≥10% (23)	LVESV <10% (19)	*P*-value
CS TIMP-1 (ng/mL)	192 ± 47	258 ± 55	0.001*
Peripheral TIMP-1 (ng/mL)	208 ± 46	267 ± 60	0.001*
CS MMP-2 (ng/mL)	230 ± 55	307 ± 100	0.08
Peripheral MMP-2 (ng/mL)	267 ± 63	299 ± 100	0.32

CS, coronary sinus; MMP-2, matrix metalloproteinase-2; TIMP-1, tissue inhibitor matrix metalloproteinase-1; LVESV ≥ 10%, left ventricular end-systolic volume reduction ≥10%, no death and no transplant; LVESV < 10%, left ventricular end-systolic volume reduction less than 10% or death or heart transplant.
*$P < 0.05$.

Higher peripheral MMP-2 and TIMP-1 levels compared to coronary sinus samples

While many studies have described high peripheral circulating MMP-2 and TIMP -1 levels in patients with heart failure,[8–10,27] to our knowledge this is the first to correlate peripheral and CS MMP-2 and TIMP-1 levels in patients with stable but chronic heart failure.

We found a good correlation between MMP-2 and TIMP-1 samples obtained from the CS and from a peripheral vein. However, peripheral samples had higher concentrations than the CS samples, suggesting that MMP-2 and TIMP-1 were not synthesized only in the heart. Although numerous extra-cardiac factors, including infection, neoplasm, recent surgical intervention, as well as chronic liver, neuromuscular, and collagen diseases, could increase MMP and TIMP levels, these factors do not explain the higher peripheral MMP-2 and TIMP-1 concentration in our study because we specifically excluded patients who fulfilled any of these criteria.

Patients with other cardiovascular risk factors, such as diabetes, dyslipidaemia, and hypertension, also have higher TIMP-1 levels when compared with healthy subjects.[28,29] The existence of these factors in most of our patients may explain the difference between the peripheral and CS TIMP-1 levels.

Based on data obtained in our study, we can conclude that MMP-2 and TIMP-1 levels in patients with chronic heart failure are not exclusively markers of cardiac matrix restructuring. It is possible that MMP-2 and TIMP-1 levels in these patients reflected a greater systemic involvement.

Study limitation

No cardiac biopsies were performed in our patients to assess the degree of myocardial fibrosis. However, other studies[25,26] have

Table 4 Univariate analysis: predictors of cardiovascular mortality

	Survivors (36)	Deaths (6)	*P*-value
Age	66 ± 8	67 ± 8	0.72
Creatinine level (mg/dL)	1.3 ± 0.5	1.8 ± 0.9	0.06
Atrial fibrillation	7 (19%)	1 (17%)	0.87
Ischaemic cardiomyopathy	15 (42%)	4 (68%)	0.25
Ventricular arrhythmia	16 (44%)	1 (17%)	0.33
ICD	23 (64%)	2(33%)	0.16
Beta-blockers	24 (67%)	4 (68%)	0.96
ACEIs–ARBs	30 (83%)	4 (68%)	0.35
Aldosterone	17 (47%)	4 (68%)	0.34
NYHA functional class IV	3 (8%)	2 (33%)	0.08
Basal 6MWDT	240 ± 124	193 ± 128	0.41
QoL test	40 ± 23	54 ± 27	0.17
Post-stimulation QRS width	143 ± 19	145 ± 12	0.81
LVEDV (mL)	210 ± 57	224 ± 60	0.63
LVESV (mL)	159 ± 55	176 ± 80	0.55
LVEF (%)	27 ± 6	25 ± 9	0.52
Severe mitral regurgitation	5 (14%)	0 (0%)	0.33
CS TIMP-1 (ng/mL)	221 ± 58	272 ± 62	0.05*
CS MMP-2 (ng/mL)	268 ± 103	327 ± 130	0.28
Peripheral TIMP-1 (ng/mL)	231 ± 55	298 ± 66	0.01*
Peripheral MMP-2 (ng/mL)	284 ± 91	311 ± 106	0.52

ICD, internal cardioverter defibrillator; 6MWDT, 6 min walking distance test; QoL, quality of life test (Minnesota); LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; CS, coronary sinus; MMP-2, matrix metalloproteinase-2; TIMP-1, tissue inhibitor matrix metalloproteinase-1; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiontensin receptor blockers.
*$P < 0.05$ survivors vs. deaths from cardiovascular aetiology.

already correlated TIMP-1 levels with the degree of myocardial fibrosis.

Our study was designed to determine whether basal TIMP-1 and MMP-2 levels differed between responders and non-responders to CRT. Due to the small number of patients included in our study, larger studies will be necessary to definitively establish a cut-off TIMP-1 level for optimal sensitivity and specificity to determine the probability for lack of response to CRT.

Like most other CRT studies, the follow-up at which response was assessed in our study was limited to the first 12 months after the implant.

Conclusions

TIMP-1 was an independent predictor of non-response in patients treated with CRT. TIMP-1 and MMP-2 were higher in patients who did not respond to CRT. Peripheral MMP-2 and TIMP-1 levels are higher than levels obtained from the CS in patients with chronic heart failure.

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References

1. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, Linde C, Morgado FB, Oto A, Sutton R, Trusz-Gluza M, European Society of Cardiology; European Heart Rhythm Association. Guidelines for cardiac pacing and cardiac resynchronization therapy. *Europace* 2007;**9**:958–998.
2. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. *J Am Coll Cardiol* 2000;**35**:569–582.
3. Cohn JN, Johnson GR, Shabetai R, Loeb H, Tristani F, Rector T, Smith R, Fletcher R *et al.* Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias and plasma norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993;**87**(Suppl. VI):VI5–VI16.
4. Weber KT, Pick R, Janicki JS, Gadodia G, Lakier JB. Inadequate collagen tethers in dilated cardiopathy. *Am Heart J* 1988;**116**:1641–1646.
5. Gunja-Smith Z, Morales AR, Romanelli R, Woessner JF Jr. Remodeling of human myocardial collagen in idiopathic dilated cardiomyopathy. Role of metalloproteinases and pyridinoline cross-links. *Am J Pathol* 1996;**184**:1639–1648.
6. Woessner JF. Matrix metalloproteinases and their inhibitors in connective tissue remodeling. *FASEB J* 1991;**5**:2145–2154.
7. Birkedal-Hansen H, Moore WG, Bodden MK, Windsor LJ, Birkedal-Hansen B, DeCarlo A, Engler JA. Matrix metalloproteinases: a review. *Crit Rev Oral Biol Med* 1993;**4**:197–250.
8. Wilson EM, Gunasinghe HR, Coker ML, Sprunger P, Lee-Jackson D, Bozkurt B, Deswal A, Mann DL, Spinale FG. Plasma matrix metalloproteinase and Inhibitors Profiles in Patients with Heart failure. *J Card Fail* 2002;**8**:390–397.
9. Jordán A, Roldán V, García M, Monmeneu J, de Burgos FG, Lip GY, Marín F. Matrix metalloproteinase -1 and its inhibitor, TIMP-1, in systolic heart failure: Relation to functional data and prognosis. *J Intern Med* 2007;**262**:385–392.
10. George J, Patal S, Wexler D, Roth A, Sheps D, Keren G. Circulating matrix metalloproteinase-2 but not matrix metalloproteinase-3, matrix metalloproteinase-9 or tissue inhibitor of metalloproteinase-1 predicts outcome in patients with congestive heart failure. *Am Heart J* 2005;**150**:484–487.
11. Díaz-Infante E, Mont L, Leal J, García-Bolao I, Fernández-Lozano I, Hernández-Madrid A, Pérez-Castellano N, Sitges M, Pavón-Jiménez R, Barba J, Cavero MA, Moya JL, Pérez-Isla L, Brugada J, SCARS Investigators. Predictors of lack of response to resynchronization therapy. *Am J Cardiol* 2005;**95**:1436–1440.
12. Vidal B, Sitges M, Marigliano A, Díaz-Infante E, Azqueta M, Tamborero D, Macías A, Roig E, Brugada J, Paré C, Mont L. Relation of response to cardiac resynchronization therapy to left ventricular reverse remodeling. *Am J Cardiol* 2006;**97**:876–881.
13. Molhoek SG, Bax JJ, Bleeker GB, Boersma E, van Erven L, Steendijk P, van der Wall EE, Schalij MJ. Comparison of response to cardiac resynchronization therapy in patients with sinus rhythm vs. chronic atrial fibrillation. *Am J Cardiol* 2004;**94**:1506–1509.
14. Lecoq G, Leclercq C, Leray E, Crocq C, Alonso C, de Place C, Mabo P, Daubert C. Clinical and electrocardiographic predictors of a positive response to cardiac resynchronization therapy in advance heart failure. *Eur Heart J* 2005;**26**:1094–1100.
15. Manolio TA, Baughman KL, Rodeheffer R, Pearson TA, Bristow JD, Michels VV, Abelmann WH, Harlan WR. Prevalence and etiology of idiopathic dilated cardiomyopathy (summary of a National Heart, Lung, and Blood Institute workshop). *Am J Cardiol* 1992;**69**:1458–1466.
16. Seward JB, Tajik AJ. Primary cardiomyopathies: classification, pathophysiology, clinical recognition and management. *Cardiovasc Clin* 1980;**10**:199–230.

17. Spinale FG. Matrix metalloproteinases. Regulation and dysregulation in the failing heart. *Circ Res* 2002;**90**:520–530.
18. Hessel MH, Bleeker GB, Bax JJ, Henneman MM, den Adel B, Klok M, Schalij MJ, Atsma DE, van der Laarse A. Reverse ventricular remodelling after cardiac resynchronization therapy is associated with a reduction in serum tenascin-C and plasma matrix metalloproteinase-9 levels. *Eur J Heart Fail* 2007;**9**:1058–1063.
19. Frantz S, Störk S, Michels K, Eigenthaler M, Ertl G, Bauersachs J, Angermann CE. Tissue inhibitor of metalloproteinases levels in patients with chronic heart failure: an independent predictor of mortality. *Eur J Heart Fail* 2008;**10**:338–395.
20. Garcia Bolao I, López B, Macias A, Gavira JJ, Azcárate P, Diez J. Impact of collagen type I turnover on the long-term response to cardiac resynchronization therapy. *Eur Heart J* 2008;**29**:898–906.
21. Jung K. A strong note of caution in using matrix metalloproteinase-1 and its inhibitor, TIMP-1 in serum as biomarkers in systolic heart failure. *J intern Med* 2008; (Epub ahead of print).
22. Gerlach RF, Tanus-Santos JE. Matriz Metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in congestive heart failure. *Am Heart J* 2006;**152**:e9.
23. Lovelock JD, Baker AH, Gao F, Dong JF, Bergeron AL, McPheat W, Sivasubramanian N, Mann DL. Heterogeneous effects of Tissue inhibitor of metalloproteinases on cardiac fibroblast. *Am J Physiol Heart Circ Physiol* 2005;**288**: H461–H468.
24. Mann DL. Inflammatory mediators and the failing heart. Past, present, and foreseeable future. *Circ Res* 2002;**91**:988–998.
25. Lindsay M, Maxwell P, Dunn FG. TIMP-1 a marker of left ventricular diastolic dysfunction and fibrosis in hypertension. *Hypertension* 2002;**40**:136–141.
26. Schwartzkopff B, Fassbach M, Pelzer B, Brehm M, Strauer BE. Elevated serum markers of collagen degradation in patients with mild to moderate dilated cardiomyopathy. *Eur J Heart Fail* 2002;**4**:439–444.
27. Tziakas DN, Chalikias GK, Papaioakeim M, Hatzinikolaou EI, Stakos DA, Tentes IK, Papanas N, Kortsaris A, Maltezos E, Hatseras DI. Comparison of levels of Matrix Metalloproteinase -2 and -3 in patients with ischemic cardiomyopathy vs. nonischemic cardiomyopathy. *Am J Cardiol* 2005;**96**:1449–1451.
28. Sundström J, Evans JC, Benjamin EJ, Levy D, Larson MG, Sawyer DB, Siwik DA, Colucci WS, Wilson PW, Vasan RS. Relation of plasma total TIMP-1 levels to cardiovascular risk factors and echocardiographic measures. The Framingham heart study. *Eur Heart J* 2004;**25**:1509–1516.
29. West MJ, Nestel PJ, Kirby AC, Schnabel R, Sullivan D, Simes RJ, Pollicino Ch, Lubos E, Münzel TF, White HD, Tonkin AM, Bickel Ch, Tiret L, Blankerberg S, for the LIPID investigators. The Value of N-terminal fragment of brain natriuretic peptide and Tissue inhibitor of Metalloproteinase-1 levels as predictors of cardiovascular outcome in the LIPID study. *Eur Heart J* 2008; **29**:932–931.