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Changes in Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of MMPs Plasma Profiles in Stress-Induced Cardiomyopathy

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Abstract

Background—Transient changes in the composition of the myocardial extracellular matrix may contribute to the ventricular systolic dysfunction in Stress-induced cardiomyopathy (SIC). We examined the changes in plasma matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) that occur early after the clinical presentation of SIC.

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Methods and Results—Ten patients with SIC were enrolled. Plasma concentrations of the six major MMPs (MMP-1,-2,-3,-7,-8,-9) and all 4 tissue inhibitors of MMPs (TIMP-1,-2,-3,-4) were analyzed and compared with data from fifteen control subjects. Within 24 hours of the clinical presentation, SIC patients had lower MMP-1 levels (0.41 ± 0.13 vs 0.70 ± 0.13 pg/mL, $p = 0.048$) and MMP-8 levels (1.61 ± 0.34 vs 4.84 ± 1.38 pg/mL, $p = 0.001$) and higher TIMP-4 levels (3.06 ± 0.40 vs 2.16 ± 0.18 pg/mL, $p = 0.05$) compared to control. Seven of nine SIC patients had elevated LV end-diastolic pressures, and all had normal LV end-diastolic dimensions and volumes.

Conclusion—Patients afflicted with SIC had MMPs and TIMPs profiles similar to those described in hypertensive heart disease and diastolic heart failure and different than the profiles following myocardial infarction. Our findings uncovered a unique biomolecular profile in SIC during the first 24 hours of presentation.

Keywords

Metalloproteinases; Cardiomyopathy; Stress; Stress-induced cardiomyopathy

Introduction

Stress-induced cardiomyopathy (SIC), or Takotsubo cardiomyopathy, is a transient systolic dysfunction of the apical and mid segments of the left ventricle in the absence of obstructive coronary artery disease.

SIC is now recognized worldwide as a distinct clinical entity.^{1–6} It typically occurs in postmenopausal women,⁷ who present with clinical, electrocardiographic and laboratory findings indistinguishable from those of Acute Coronary Syndrome, usually following an emotional or physically stressful event. Left ventriculography most commonly reveals akinesis, hypokinesis or dyskinesis of the left ventricular mid segment with or without apical involvement. Coronary angiography shows no evidence of obstructive coronary artery disease to account for the clinical presentation.⁸ With supportive measures and perhaps standard heart failure therapy, most patients achieve resolution of symptoms with recovery of left ventricular function in 1–4 weeks.⁸ However, this benign course can be complicated in some by dysrhythmias, pulmonary edema, cardiogenic shock and death.^{9–10}

Several lines of evidence suggest that excess catecholamines plays a prominent role in the pathogenesis of SIC.^{4,11} Among the leading postulated mechanisms are catecholamine-induced coronary artery spasm^{2–3} and catecholamine-induced direct myocardial injury.^{11–13} Needless to say, the biomolecular mechanisms involved in the stress-induced myocardial dysfunction have not been fully elucidated.

The extra-cellular matrix (ECM) provides a structural scaffold for cells to differentiate, grow and migrate.^{14–16} Matrix metalloproteinases (MMPs) are enzymes involved in ECM turnover. Based on their substrate specificity for various ECM components, MMPs are divided into different classes: collagenases (MMPs 1,8 and 13), gelatinases (MMPs 2 and 9), stromelysins (MMPs 3 and 10) and matrilysins (MMPs 7,11 and 26).¹⁵ Tissue inhibitors of metalloproteinases (TIMPs) block the action and inhibit the activity of MMPs.¹⁶ Under normal conditions, the balanced interaction between MMPs and TIMPs allows for a normal turnover and maintenance of all body tissues including the myocardium. MMPs and TIMPs are involved in several cardiovascular disease processes including atherosclerosis plaque rupture,^{17,18} acute myocardial infarction,¹⁹ LV aneurysm formation and rupture,²⁰ LV remodeling following pressure and/or volume overload,^{21–27} and age-dependent changes in left ventricular structure.²⁸

Several studies have now demonstrated that unique plasma signatures of MMPs and TIMPs arise in patients with different etiologies of heart failure, and in some cases have been associated with clinical progression of disease.^{29–32} Thus, the present study tested the hypothesis that the presentation of SIC would result in a significant change in MMP and TIMP plasma profiles.

Methods

Study Population

Ten patients admitted to the Ross Heart Hospital with the clinical presentation of acute coronary syndrome between May 2010 and April 2011 and who met the proposed Mayo criteria⁸ for SIC were enrolled in the study. The protocol was approved by Institutional Review Board and informed consent was obtained prior to obtaining a blood sample from each subject.

Demographic data, clinical characteristics, left ventriculography and coronary angiography, echocardiography and/or cardiac magnetic resonance imaging, and a peripheral blood sample for plasma were obtained on each SIC patient. These studies were performed within 24 hours of arrival in the Emergency Department.

Hypertension was defined as a blood pressure consistently above 140/90mmHg or current treatment with antihypertensive medications. Hyperlipidemia was defined as total cholesterol above 200 mg/dL or current treatment with lipid-lowering agents. Diabetes and chronic obstructive pulmonary disease were considered present based on previous diagnoses by other health-care providers. Stressors were defined as a physical challenge or illness or an emotional event occurring up to 4 weeks preceding the index event. ST segment elevation was defined as deviation more than 1mm higher than baseline in 2 or more contiguous leads. T-wave inversion was defined if present in 2 or more contiguous leads and represented a change from a previous electrocardiogram recording.

Left heart catheterization with coronary angiography was performed in all SIC patients. Echocardiography was performed in eight and cardiac magnetic resonance imaging in six of the SIC patients; all SIC patients had one or the other and four had both imaging modalities. The coronary angiograms, left ventriculograms, echocardiography and cardiac magnetic resonance imaging were reviewed by two cardiologists who agreed that the findings were consistent with the diagnosis of SIC. Normal limits and ranges for LV end-diastolic dimensions (< 5.3 cm) and volumes (96–174 ml) were based on the American Society of Echocardiography guidelines for chamber quantification³³ and a key study of normal ventricular dimensions by cardiac magnetic resonance imaging.³⁴

MMPs and TIMPs Measurement/Analysis

Systemic venous blood samples (10 mL) were obtained with the subjects in a resting, supine position for a minimum of 30 minutes. All samples were placed in chilled EDTA tubes, centrifuged, and plasma stored at –70°C until assay. At the time of assay, plasma samples were allowed to thaw on ice, and subjected to multiplex suspension arrays for MMP (LMP000, R&D Systems) and TIMP (LKT003, R&D Systems) measurements in which all samples could be measured simultaneously for multiple MMPs and TIMPs, thereby minimizing inter-assay variability. The multiplex array was previously validated and calibrated using internal controls for each measured MMP and TIMP.^{35,36} Major classes of MMPs: gelatinases (MMP-2 and MMP-9), collagenase (MMP-1 and 8), stromelysin (MMP-3), and matrilysin (MMP-7); and all 4 tissue inhibitors of MMPs (TIMP-1, -2, -3, -4) were examined. The relative fluorescence obtained for each distinct MMP and TIMP (Bio-Plex 200, BioRad Laboratories) was converted to an absolute concentration using calibration

curves generated from known concentrations of recombinant standards. Average sensitivities for MMPs and TIMPs were 5 pg/mL with a coefficient of variation for these assays of 15% or less. Readings from all samples were within the targeted dynamic range defined by the standards. For the purposes of referent normal comparisons, plasma was collected from 15 age and gender matched referent control subjects.

Statistical Analysis

Absolute MMP and TIMP values for the referent normal and SIC patients were first analyzed using the non-parametric Kruskal-Wallis test. Following which, the SIC MMP and TIMP values were determined as a function of referent normal values and expressed as a percent. Significant differences from this analysis were examined using a t-statistic. The statistical procedures were performed using STATA (STATA Intercooled V 8.0. College Station, TX). Values were reported as the mean $\pm$ standard error of the mean (SEM) where p values <0.05 were considered statistically significant. Results from all of these statistical analyses are listed in Table 3 and Figure 1.

Correlation coefficient (Pearson's r values) were determined to assess the relationships between the MMPs and TIMPs versus peak troponin, left ventricular end-diastolic pressure and ejection fraction.

Results

Clinical characteristics

The fifteen referent controls were 9 women and 6 men with a mean age of 59 ± 2 years, and a mean body surface area of 1.8 ± 0.1 Kg/m². They had a mean heart rate of 68 ± 2 BPM, a mean systolic blood pressure of 125 ± 2 mmHg, and a mean diastolic blood pressure of 74 ± 1 mmHg. All had a normal ECG, echocardiogram and 6 minute hall walk times. Referent controls had a mean LV EDD of 4.4 ± 0.1 cm, and a mean LV EDV of 88.4 ± 6.6 ml. None of the referent controls had a history of, current evidence for, or were being treated for hypertension, diabetes, hyperlipidemia or any cardiovascular disease.

The clinical characteristics of SIC patients are outlined in table 1. All ten SIC patients met the proposed criteria for the diagnosis of SIC. Women represented 90% of the group. Mean Age was 60.3 years. Hypertension was present in 90% of patients with 50% of patients receiving an angiotensin converting enzyme inhibitor. Chest pain and/or dyspnea were the presenting symptoms in 80% of the study population, and a clearly identified stressor was present in 80%. ST-Segment elevation was present on the index electrocardiogram in 20% of patients, while dynamic T-wave inversion was present in the remaining 80%. Troponin-I elevation was present in all patients with an average peak of 3.316 ng/ml.

The LV end-diastolic dimensions, LV end-diastolic volumes and LV end-diastolic pressures for the SIC patients are presented in table 2. The mean LV end-diastolic dimension on echocardiography was 4.3 ± 0.12 cm and the mean LV end-diastolic volume was 85.4 ± 4.6 ml. The mean LV end-diastolic dimension on cardiac magnetic resonance imaging was 4.7 ± 0.2 cm and the mean LV end-diastolic volume was 137.8 ± 11.3 ml. LV end-diastolic pressure was available in 9 patients and the mean value was 16.9 ± 1.2 mmHg. All SIC patients had normal LV end-diastolic dimensions and volumes. Seven patients had LV end-diastolic pressures above the upper limit of our normal range, specifically 15, 16, 16, 18, 20, 21 and 22 mmHg.

MMP and TIMP profiles

Plasma values for MMP-1, -2, -3, -7, -8, -9 and TIMP-1, -2, -3, -4 in the SIC patients and referent controls are shown in columns 2 and 3 respectively in table 3. MMP-12 and -13 did not reach detectable thresholds in the multiplex suspension array, and therefore were excluded from further analysis.

Columns 4 and 5 of table 3 and figure 1 present the differences between SIC patients and referent controls in MMP and TIMP values for this study. SIC patients had a significant reduction in plasma MMP-1 and MMP-8 compared with the referent control subjects (both $p < 0.05$). MMP-1 was reduced by a relative 40%, MMP-8 was reduced by 60%. The remainder of the MMPs measured (MMP-2, MMP-3, MMP-7 and MMP-9) were not significantly different from the referent control subjects.

SIC patients had a significant increase in plasma TIMP-4 compared with the referent controls ($p < 0.05$). TIMP-4 increased by a relative 40%. The remainder of the TIMPs (TIMP-1, TIMP-2, and TIMP-3) were unchanged compared with the referent control subjects.

Correlation studies were performed between the MMPs and TIMPs versus peak troponin, left ventricular end-diastolic pressure or ejection fraction. The correlation (r values) were in the - 0.57 to 0.58 range (max $r^2=0.34$) with p values >0.2 .

Discussion

The SIC patients in this study had demographic, clinical and laboratory findings similar to those described in previous reports of patients with SIC.¹⁻⁴ The intent of this study was to examine plasma MMPs and TIMPs levels early in the course of SIC, which may provide insight into the underlying molecular mechanisms causing the LV remodeling and the transient nature of the structural and functional changes that occur in SIC.

We hypothesized that since the LV systolic functional changes with SIC resemble those of myocardial infarction following an acute coronary occlusion, the underlying changes in MMPs and TIMPs should be similar and directionally parallel. Contrary to our hypothesis, we found that early in the course of SIC, the collagenases MMP-1 and MMP-8 were significantly decreased and TIMP-4 was significantly increased. This stoichiometric extracellular profile favors the preservation of extracellular collagen structure rather than collagen degradation.

Extracellular changes leading to LV remodeling after myocardial infarction (secondary to coronary artery occlusion) were studied recently, demonstrating an acute rise in plasma MMP-8 and MMP-9 and a significant reduction in TIMP-4 early post infarction.¹⁹ Additionally, the levels of MMP-1, MMP-8 and MMP-9 were increased in atheromatous vulnerable plaques compared to fibrous plaques,^{37,38} and in patients with acute coronary syndromes.^{39,40} This molecular pattern in the interstitial proteases is distinctly different from that seen in our patients, suggesting differences in the underlying pathophysiologic changes in structure and function. Following an acute myocardial infarction, there is a rapid and sustained increase in LV end-diastolic volume;¹⁹ this may be related to the increased protease expression and activity that favor extracellular matrix degradation. By contrast, during SIC, LV end-diastolic volume remains normal, perhaps explained by the decrease in proteases activity. In fact, all patients in this report had normal LV end-diastolic dimensions and volumes. Another control group, namely patients with Acute Coronary Syndrome (ACS), would have been informative.

A number of studies have evaluated changes in the myocardial ECM in hypertensive heart disease and diastolic heart failure. A plasma multibiomarker profile consisting of increased MMP-2 and TIMP-4 and decreased MMP-8 predicted the presence of diastolic heart failure.²⁷ Other studies have demonstrated elevated levels of MMP-2, MMP-9 and TIMP-1 in hypertensive patients with diastolic dysfunction.^{41,42} Moreover, MMP-1, which degrades collagen type-1 and is inhibited by TIMP-1, was found to be reduced in the blood of patients with hypertension.⁴³ Interestingly, this pro-fibrotic MMP/TIMPS profile seen in hypertensive patients with diastolic dysfunction is very similar to the extracellular profile described in our patients. This may suggest a role for transient LV stiffness or a transient pro-fibrotic state as an underlying mechanism for SIC. Indeed, seven of nine patients in this report had LV end-diastolic pressures above normal and in all patients, the pressures resided above 10 mmHg.

Among the postulated mechanisms for SIC, catecholamine-induced coronary artery spasm²⁻³ and/or catecholamine-induced direct myocardial injury¹¹⁻¹³ are the most widely studied. Plasma catecholamine levels were reported to be considerably higher in patients with SIC as compared to patients with acute myocardial infarction.¹¹ In rats, norepinephrine infusion was associated with increased MMP-2 activity and LV hypertrophy.⁴⁴⁻⁴⁶ In addition, isoproterenol infusion was associated with upregulated MMP-1, MMP-2 and MMP-9 activities, in addition to increased myocardial fibrosis and myocardial cross sectional area.^{47,48} Similarly, in humans, MMP-2 and MMP-9 levels were significantly elevated in severe heart failure patients and plasma MMP-2 was positively correlated with noradrenaline levels.⁴⁹ In the same study, exposure of human cardiac fibroblasts to noradrenaline resulted in increased MMP-2 levels. Our findings do not reflect such changes on MMP-2 or MMP-9, at least within 24 hours of clinical presentation of SIC.

Our study has a number of limitations. First, it is a relatively small population of what could turn out to be a more heterogeneous disease. Second, baseline pre-SIC or post-SIC blood samples are not available for comparison. The use of a single measurement in a transient, dynamic disease affecting the complex myocardial ECM may be insufficient. On the other hand, a baseline pre-SIC is not practical or feasible. Third, this study does not provide the direct mechanism for SIC. Nevertheless, this study does provide information on the myocardial cellular responses in SIC, which may then account for the difference in the myocardial behavior and characteristics following SIC, compared to Acute Coronary Syndromes. Lastly, although patients with co-morbidities that could alter the MMP/TIMP levels were excluded, these biomarkers are, at best, surrogates for the regional myocardial matrix changes.

Conclusions

The findings reported uncover a unique profile of serum MMPs and TIMPs in SIC patients 6–24 hours after their clinical presentation.

Acknowledgments

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Figure 1. Percentage change in MMP (matrix metalloproteinase) and TIMP (tissue inhibitor of MMP) levels in patients with Stress-induced cardiomyopathy (SIC) compared with referent controls. The pattern of changes in MMPs and TIMPs suggests a pro-fibrotic profile, one that is clearly different from an acute myocardial infarction. * = $p < 0.05$ versus referent controls.

Table 1

Clinical characteristics of patients with stress-induced cardiomyopathy (n=10)

Demographic		Value
Age		60.3 years
Female		9 (90%)
Hypertension		9 (90%)
Hyperlipidemia		5 (50%)
Diabetes Mellitus		2 (20 %)
Chronic Obstructive Pulmonary Disease		1 (10%)
Tobacco Use	<i>Never</i>	8 (80%)
	<i>Former</i>	2 (20 %)
	<i>Current</i>	0 (0%)
Presenting symptom	<i>Chest pain alone</i>	5(50%)
	<i>Chest pain and dyspnea</i>	3 (30%)
	<i>Dyspnea alone</i>	1 (10%)
	<i>Confusion</i>	1 (10 %)
Stressor	<i>Emotional</i>	8 (80%)
	<i>Physical</i>	0 (0%)
	<i>No stressor</i>	2 (20 %)
Medications on admission	<i>ASA</i>	1 (10 %)
	<i>Beta Blocker</i>	2 (20%)
	<i>ACE-I</i>	5 (50 %)
	<i>Statin</i>	1 (10 %)
Admission Electrocardiogram	<i>ST elevation</i>	2 (20%)
	<i>T-wave inversion</i>	8 (80%)
Elevated Troponin I		10 (100%)

Table 2

LV end-diastolic dimensions, LV end-diastolic volumes and LV end-diastolic pressures of patients with stress-induced cardiomyopathy

Patient	LVEDP (mmHg)	LVED Diameter (cm)		LVED Volume (ml)	
		Echo	MRI	Echo	MRI
A	13	4.4	N/A	68	N/A
B	18	4.7	N/A	86	N/A
C	11	4.8	4.8	106	154
D	20	4.2	4.2	88	101
E	N/A	N/A	5.5	N/A	168
F	21	4.3	N/A	83	N/A
G	16	4.1	4.4	80	114
H	22	3.5	4.6	71	127
I	16	N/A	4.6	N/A	163
J	15	4.7	N/A	101	N/A
Mean ± SEM	16.9± 1.2	4.3±0.12	4.7±0.2	85.4 ± 4.6	137.8 ± 11.3

Table 3

Plasma levels of MMPs and TIMPs in patients with stress induced cardiomyopathy (SIC) versus normal referent controls

Analyte (ng/mL)	Normal (n=15)	SIC (n=10)	* (p-value)	† (p-value)
MMP-1	0.70±0.13	0.41±0.13	0.047	0.048
MMP-2	374.82±35.71	345.82±30.54	0.651	0.37
MMP-3	10.72±1.64	11.35±3.55	0.437	0.86
MMP-7	1.39±0.25	1.23±0.28	0.640	0.58
MMP-8	4.84±1.38	1.61±0.34	0.421	0.001
MMP-9	121.06±13.12	118.41±40.24	0.387	0.95
TIMP-1	106.30±4.40	100.44±6.81	0.506	0.41
TIMP-2	73.67±3.33	78.48±2.78	0.318	0.12
TIMP-3	3.69±0.38	3.51±1.06	0.101	0.87
TIMP-4	2.16±0.18	3.06±0.40	0.035	0.05

* Kruskal Wallis, non-parametric analysis

† % change from referent control