Relation Between Connective Tissue Growth Factor and Cardiac Sympathetic Nerve Activity in Heart Failure in DCM Patients

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SUMMARY

Cardiac fibrosis is an important process of myocardial remodeling. Connective tissue growth factor (CTGF) is a cytokine that plays a key role in the occurrence of progressive fibrosis and excessive scarring. CTGF levels are increased in the failing heart. In addition, sympathetic nerve activity is enhanced in the failing heart, and exacerbates heart failure. To clarify the relation between cardiac sympathetic nerve activity and CTGF, we studied 35 (M/F = 28/7 patients) aged 57 ± 15 years with dilated cardiomyopathy (DCM). Cardiac sympathetic nerve activity was estimated from the total defect score (TDS) and from the H/M ratio and washout rate (WR) on I-123-MIBG imaging. Cardiac symptoms (NYHA class), exercise capacity (specific activity scale: SAS), brain natriuretic peptide (BNP), hemodynamics, and CTGF were assessed. There was a significant correlation between the CTGF and WR on I-123-MIBG (r = 0.45, P = 0.008). Also, a higher plasma CTGF level was associated with a lower SAS score (r = 0.51, P = 0.002), but not the TDS, H/M ratio, or BNP concentration. Moreover, a higher NYHA class and pulmonary artery wedge pressure were associated with a higher plasma CTGF level. The plasma CTGF level can be strongly related with cardiac sympathetic nerve activity in heart failure in DCM patients. (Int Heart J 2012; 53: 282-286)

Key words: MIBG imaging, Cardiomyopathy, Exercise capacity

Sympathetic nerve activity is increased in patients with cardiac failure, and prolonged activation of the cardiac sympathetic nerves causes cardiomyocyte injury with the loss of cells and remodeling of the myocardium. Therefore, it seems that the regulation of cardiac sympathetic nerve activity is important for treating heart failure. β-blocker treatment, γ-aminobutyric guanidine (MIBG) scintigraphy is a nuclear medicine technique for assessing cardiac sympathetic nerve function that is employed for investigation of cardiac sympathetic nerve activity under various conditions. 123I-MIBG scintigraphy is clinically useful for evaluating the severity of heart failure, predicting the outcome of β-blocker treatment, and predicting the prognosis.15 Congestive heart failure is associated with structural alteration of the myocardium, which is known as myocardial remodeling.10 Characteristic features of remodeling include cardiac myocyte hypertrophy and the development of myocardial fibrosis.16 Koitabashi, et al have previously demonstrated that connective tissue growth factor (CTGF) acts as a mediator of myocardial remodeling and fibrosis.7 Further, CTGF expression is increased in myocardial samples obtained from patients with cardiomyopathy1 or diastolic heart failure.7 Transforming growth factor-β (TGF-β) has been demonstrated to mediate cardiac fibrosis as well as fibrosis in other organs. In addition, it has been shown that the profibrotic effects of TGF-β are partly mediated through induction of CTGF in various organs.9 Activation of the renin-angiotensin-aldosterone system (RAAS) has been shown to trigger the exacerbation of congestive heart failure and cardiac sympathetic nerve activity.10,11 In addition, CTGF was reported to be produced by the stimulation of angiotensin II.12,13 Therefore, we assumed that the plasma CTGF level is correlated with cardiac sympathetic nerve activity evaluated by 123I-MIBG scintigraphy in patients with dilated cardiomyopathy. We measured the plasma CTGF level in patients with dilated cardiomyopathy and compared CTGF data with the clinical characteristics, echocardiographic parameters of cardiac function, and brain natriuretic peptide (BNP) level and cardiac sympathetic nerve activity evaluated by 123I-MIBG scintigraphy.

METHODS

Patients: Patients with left ventricular (LV) dysfunction who were suspected of having dilated cardiomyopathy (DCM) underwent cardiac catheterization with a Swan-Ganz catheter, coronary angiography, left ventriculography, and myocardial biopsy. Patients with normal coronary arteries and decreased LV ejection fraction under 45% were diagnosed as DCM based on the myocardial biopsy findings. We excluded ischemic car-

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Received for publication December 26, 2011.

Revised and accepted June 14, 2012.
diomyopathy, valvular heart disease, and secondary cardiomyopathy. All patients had experienced at least one episode of heart failure requiring short-term hospitalization. Thirty-five patients (28 men and 7 women, with a mean age of 57 ± 15 years) treated for heart failure at Gunma University Hospital or Gunma Prefectural Cardiovascular Center were enrolled in this study betw...e 20 segments. (18) Commercially available QGS software (Cedars-Sinai Medical Center, Los Angeles, CA) with a temporal resolution of 16 frames per RR interval was used to create a 3-dimensional surface cinem...equation: β = 0.83, \( r^2 = 0.83 \), Table II.) However, the plasma CTGF concentration was positively correlated with the plasma TGF-β level (\( r = 0.33 \), Table II). There were no significant correlations between plasma CTGF and either LVEF, LVDd, LVDs, or E/E'.

**Results**

**Clinical characteristics and plasma CTGF levels:** The clinical characteristics of the CHF patients are summarized in Table I. Patients in NYHA class I and class II accounted for 67% of all subjects. The average plasma BNP concentration was 377 ± 394 pg/mL, which was significantly higher than the cut-off level determined for normal subjects. When the plasma levels of CTGF were compared among patients in different NYHA classes, the average plasma CTGF concentration for NYHA classes I, II, III, and IV was 5.54 ± 3.0 ng/mL, 10.45 ± 11.2 ng/mL, 20.33 ± 31.9 ng/mL, and 122.8 ng/mL, respectively. The average plasma BNP concentration was 377 ± 394 pg/mL, which was significantly higher than the cut-off level determined for normal subjects. When the plasma levels of CTGF were compared among patients in different NYHA classes, the average plasma CTGF concentration for NYHA classes I, II, III, and IV was 5.54 ± 3.0 ng/mL, 10.45 ± 11.2 ng/mL, 20.33 ± 31.9 ng/mL, and 122.8 ng/mL, respectively.

**Relation between plasma CTGF and SAS score:** Plasma CTGF levels were also compared among patients with different SAS scores (Figure 1). As the SAS score decreased, the plasma CTGF level was associated with worse exercise capacity.

**Relation between plasma CTGF level and neurohumoral factors:** When simple linear regression analysis was performed to assess the correlation between plasma CTGF and BNP concentrations, CTGF was not correlated with the BNP level (\( r = 0.17, P = 0.33, \) Table II). However, the plasma CTGF concentration was positively correlated with the plasma TGF-β level (\( r = 0.83, P < 0.0001, \) Table II)

**Relation between plasma CTGF level and echocardiography parameters:** The correlation coefficients are listed in Table II. There were no significant correlations between plasma CTGF and either LVEF, LVDd, LVDs, or E/E’.

**Relation between the plasma CTGF level and scintigraphy parameters:** There were no significant correlations between
CTGF and LVEF, LVEDV, LVESV, WR, H/M, or TDS estimated by $^{99m}$Tc-MIBI scintigraphy (Table II). The correlations of CTGF with the total defect score and the H/M ratio obtained from delayed $^{123}$I-MIBG images are shown in Table II. The total defect score was 31.18 ± 16.37, the H/M ratio 1.63 ± 0.35, and the washout rate was 9.14 ± 11.73. Although there were no significant correlations between the plasma CTGF level and total defect score or the H/M ratio, a significant correlation was found between plasma CTGF and the washout rate ($r = 0.45$, $P = 0.008$) (Figure 2).

Figure 3 shows a representative high CTGF patient. $^{123}$I-MIBG uptake was reduced in the whole heart, especially in the inferior to apical wall regions, suggesting that denervation of the heart was widespread. The $^{123}$I-MIBG washout rate was 73% and the delayed H/M ratio was 1.40. In this patient, the plasma CTGF level was 123 ng/mL, the plasma BNP level was 854 pg/mL, LVEF was 21%, and the NYHA class was IV.

**Relation between plasma CTGF level and hemodynamics:**
There was no significant correlation between CTGF and CI. However, a significant correlation was found between plasma CTGF and PAWP ($r = 0.57$, $P = 0.007$, Table II).

**Discussion**
Evaluation of sympathetic nerve activity and utility of $^{123}$I-MIBG parameter: Cardiac sympathetic nerve activity can be evaluated by $^{123}$I-MIBG imaging to estimate the severity of heart failure, the effect of treatment, and the prognosis of patients with this condition. The H/M ratio and WR determined by $^{123}$I-MIBG imaging have been reported to reflect card-

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**Table I. Baseline Characteristics**

<table>
<thead>
<tr>
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<th>n (%)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 15</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>27 (80)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5 (14)</td>
</tr>
<tr>
<td>II</td>
<td>18 (53)</td>
</tr>
<tr>
<td>III</td>
<td>11 (30)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Plasma BNP (pg/mL)</td>
<td>377 ± 394</td>
</tr>
</tbody>
</table>

**Table II. Relation Between Plasma CTGF Level and Other Parameters**

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>P</th>
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<tbody>
<tr>
<td>LVEF (echo)</td>
<td>-0.12</td>
<td>0.52</td>
</tr>
<tr>
<td>LVDd</td>
<td>0.27</td>
<td>0.12</td>
</tr>
<tr>
<td>LVDs</td>
<td>0.15</td>
<td>0.40</td>
</tr>
<tr>
<td>E/e'</td>
<td>0.12</td>
<td>0.56</td>
</tr>
<tr>
<td>LVEF (QGS)</td>
<td>-0.11</td>
<td>0.60</td>
</tr>
<tr>
<td>LVEDV (QGS)</td>
<td>0.15</td>
<td>0.46</td>
</tr>
<tr>
<td>LVESV (QGS)</td>
<td>0.13</td>
<td>0.52</td>
</tr>
<tr>
<td>MIBI H/M ratio</td>
<td>-0.005</td>
<td>0.98</td>
</tr>
<tr>
<td>MIBI TDS</td>
<td>0.02</td>
<td>0.91</td>
</tr>
<tr>
<td>MIBI WR</td>
<td>0.16</td>
<td>0.46</td>
</tr>
<tr>
<td>MIBG H/M</td>
<td>-0.24</td>
<td>0.17</td>
</tr>
<tr>
<td>MIBG TDS (D)</td>
<td>0.21</td>
<td>0.12</td>
</tr>
<tr>
<td>LVEF (LVG)</td>
<td>-0.21</td>
<td>0.34</td>
</tr>
<tr>
<td>PAWP</td>
<td>0.57</td>
<td>0.007</td>
</tr>
<tr>
<td>CI</td>
<td>0.34</td>
<td>0.15</td>
</tr>
<tr>
<td>BNP</td>
<td>0.17</td>
<td>0.33</td>
</tr>
<tr>
<td>TGF-β</td>
<td>0.83</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; LVEF, left ventricular ejection fraction; LVDd, left ventricular dimension (diastolic); LVDs, left ventricular dimension (systolic); PAWP, pulmonary artery wedge pressure; CI, cardiac index; ACE, angiotensin-converting enzyme; and ARB, angiotensin II receptor blocker.

**Figure 1.** CTGF and SAS. Plasma CTGF levels were also compared among patients with different SAS scores. As the SAS score decreased, the plasma CTGF level was found to increase. ($r = 0.51$, $P = 0.002$). CTGF indicates connective tissue growth factor and SAS, specific activity scale.

**Figure 2.** CTGF and WR. Significant correlation was found between plasma CTGF and the washout rate ($r = 0.45$, $P = 0.008$). CTGF indicates connective tissue growth factor and WR, washout rate.
**cardiac sympathetic function.** Patients with severe heart failure have a higher norepinephrine concentration and lower cardiac \(^{123}\)I-MIBG uptake (H/M) than those with moderate heart failure. Compared with controls, moderate heart failure patients showed decreased cardiac \(^{123}\)I-MIBG uptake despite no difference in the circulating norepinephrine concentration, so \(^{123}\)I-MIBG is a more sensitive marker than norepinephrine for detecting moderate heart failure. The WR is increased and the H/M ratio is decreased in patients with severe heart failure, and \(^{123}\)I-MIBG myocardial imaging is useful for predicting the response to \(\beta\)-blocker therapy in heart failure patients with idiopathic dilated cardiomyopathy.

Recently Koitabashi, et al studied 52 Japanese patients with chronic heart failure. Their study included patients with idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, and ischemic cardiomyopathy, most of whom were in NYHA classes I and II. Among several plasma and urine parameters of heart failure, plasma BNP and TGF-\(\beta\) were independent predictors of plasma CTGF levels. They also examined the relations between plasma CTGF and echocardiographic parameters, and found that the CTGF level was associated with NYHA class, a history of congestive failure, the plasma BNP level, and E/E’ demonstrated by echocardiography.

In the present study, plasma CTGF was not significantly correlated with plasma BNP or E/E’ because our population was limited to DCM patients with severe heart failure. However, the CTGF level and the progression of cardiac symptoms and hemodynamics in heart failure are related because the NYHA class and PAWP increase as CTGF becomes higher. Moreover, CTGF increases as the SAS score decreases, which means that exercise capacity is inversely related to the CTGF level. Thus, CTGF seems to be a useful marker for heart failure.

**Relation between CTGF and TGF-\(\beta\):** TGF-\(\beta\) has been demonstrated to cause cardiac fibrosis, as well as fibrosis in other organs. It has been shown that the profibrotic effects of TGF-\(\beta\) are partly mediated through ctgf induction in various organs.

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Sanderson, et al have shown that the plasma TGF-\(\beta\) level is elevated in patients with dilated cardiomyopathy, but analysis of the association between the circulating TGF-\(\beta\) level and the NYHA class or other humoral factors has not been performed. In this study, we compared plasma CTGF and TGF-\(\beta\) levels to determine which factor was better correlated with other parameters of heart failure. Although plasma CTGF was significantly correlated with the NYHA class and the WR, plasma TGF-\(\beta\) was not correlated with either of these parameters.

**Relation among CTGF, fibrosis and sympathetic nerve activity:** In our study, there was no relation between the CTGF level and the extent of myocardial damage estimated by myocardial perfusion \(^{99m}\)Tc-MIBI imaging, which reflects myocardial fibrosis. CTGF promotes fibrosis, but it is not a marker that reflects the severity of myocardial fibrosis. That is, it is not produced by cells in an area of fibrosis, and it is more likely to be produced by cells that can cause additional fibrosis in the future.

In the failing heart, the RAAS is activated and angiotensin II induces expression of CTGF. In addition, the RAAS activates cardiac sympathetic nerve activity and exacerbates congestive heart failure. On the other hand, CTGF induced by angiotensin II causes the hypertrophy of cardiac myocytes, the development of myocardial fibrosis, and cardiac remodeling. In this situation, the plasma CTGF level can be strongly related with the condition of the failing heart, in other words, cardiac sympathetic nerve activity.

**Limitations:** This study has several limitations. We only evaluated patients with DCM and the CTGF level was only correlated with the WR on \(^{123}\)I-MIBG imaging, and with SAS score, but not with the TDS or H/M ratio on \(^{123}\)I-MIBG imaging, or with E/E’ (an echocardiographic indicator of diastolic function). These results were probably affected by the small number of patients and the severity of their heart failure. Moreover, on the correlations between the CTGF and the WR or SAS score, some values may have contributed to the significant correlations. Further study in multicenter trials with a
larger number of institutions is needed.

Conclusions: The plasma CTGF level can be strongly related with cardiac sympathetic nerve activity in heart failure in DCM patients.

References