Myocardial Proinflammatory Cytokine Expression and Left Ventricular Remodeling in Patients With Chronic Mitral Regurgitation

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Background—In an animal model, stretch was shown to induce myocardial tumor necrosis factor-α (TNF-α) expression. 

The purposes of this study were to determine whether the left ventricular (LV) volume overload that occurs in patients with chronic mitral regurgitation (MR) can induce myocardial and systemic TNF-α expression and whether there is a relationship between TNF-α expression and LV remodeling.

Methods and Results—Plasma TNF-α and its receptors were measured before mitral valve (MV) repair surgery in 26 MR patients and 23±12 months after MV repair surgery in 9 MR patients. Myocardial mRNA copies of TNF-α were determined in 11 MR and 10 donor hearts using quantitative RT-PCR. Compared with 15 control subjects, pre-MV repair plasma TNF-α (3.59±1.81 versus 2.03±1.02 pg/mL, P<0.005) and its receptor levels were elevated in MR patients. Myocardial TNF-α mRNA copies (corrected for β-actin mRNA expression) in MR patients and donor hearts were 38.96±42.74×10^6 and 0.88±0.75×10^6, respectively (P=0.01). After MV surgery, there was a decrease in the plasma levels of TNF-α (2.79±1.14 versus 3.51±1.34 pg/mL, P=0.02) and its receptors. There was a correlation between myocardial TNF-α expression and preoperative LV end-diastolic and end-systolic volumes. Moreover, there was an inverse correlation between myocardial TNF-α expression and regression in LV end-diastolic (r=−0.76, P=0.007) and end-systolic (r=−0.73, P=0.01) volumes after MV surgery.

Conclusions—TNF-α is expressed in the myocardium and plasma of MR patients. Correction of the LV volume overload with MV surgery results in reversal of TNF-α expression. There is a relationship between TNF-α expression and parameters of LV remodeling, suggesting that TNF-α may play a role in the pathogenesis of the LV remodeling that occurs in MR. (Circulation. 2003;107:831-837.)

Key Words: mitral valve ■ cytokines ■ remodeling ■ hemodynamics ■ surgery

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine that has been consistently found to be elevated in the plasma of patients with congestive heart failure. 1-4 TNF-α is also expressed by the human myocardium in ischemic and nonischemic dilated cardiomyopathy. 5 In addition to its potent negative inotropic effects, TNF-α has been shown to play a key role in the pathogenesis and progression of left ventricular (LV) remodeling. 6-9

Because LV pressure overload and in vitro myocardial stretch are sufficient stimuli to induce TNF-α gene and protein expression in the feline myocardium 10 and in the plasma of patients with aortic stenosis and mitral regurgitation (MR), 11 we sought to determine whether TNF-α plays a role in the pathogenesis of LV remodeling that occurs in patients with chronic MR. Because expression of interleukin 6 (IL-6) may be regulated by TNF-α, plasma levels of IL-6 and its receptor were also examined. 12

Accordingly, the purposes of this investigation were to determine whether myocardial and plasma TNF-α gene and protein expression are increased in MR patients, to determine whether a relationship exists between TNF-α expression and parameters of LV volume overload and remodeling, and to determine whether correction of the LV volume overload with mitral valve (MV) repair surgery leads to a reversal of TNF-α expression and regression of LV remodeling in MR patients.

Methods

Study Subjects

The study group consisted of 26 patients referred for an assessment of the severity of their chronic MR. Patients with coronary artery
assays were performed using commercially available, high-sensitivity, enzyme-linked immunoassays (Quantikine HS, R&D Systems).

**Mitrail Valve Surgery**

All patients were cooled to a systemic temperature of 28°C, and myocardial preservation was achieved by using antegrade and retrograde cardioplegia to maintain a myocardial temperature between 10°C and 15°C. All patients had a successful MV repair. Specimens from the LV were harvested immediately after cardiopulmonary bypass was initiated and were snap-frozen in liquid nitrogen. Samples were stored at −70°C for RNA extraction.

**Quantitative PCR**

Total RNA was isolated using the Trizol reagent (Life Technologies). Total RNA was reverse transcribed to obtain single-stranded cDNA using AMV Reverse Transcriptase (Boehringer Inc) at 42°C for 60 minutes. Primers for human TNF-α (sense primer 5′-AAGAGTCTCCAGGGACCTCT-3′; antisense primer 5′-TGGGAGTAGATGAGGTACA-3′) and β-actin (sense primer 5′-AGCACGGGTCGTCACCACT-3′; antisense primer 5′-TGCTGGGGGTTGGAAGTGCT-3′) were designed using specific software (DataMinder, NIH). Primers were designed so that they were located on different exons to prevent coamplification of genomic DNA. Copy number standards were generated using the appropriate cDNA clones of human TNF-α and β-actin cDNA (American Type Culture Collection). Real-time quantitative PCR reactions were performed in the LightCycler-32 system (Roche Inc) using the SYBR Green-I method.13 Melting curve analysis was performed to confirm the specific product. PCR reactions that demonstrated amplification were chosen for quantification. Because of the low quantity of the biopsy samples, β-actin mRNA copy numbers were used to normalize the TNF-α mRNA samples. The data are presented as copies of cytokine transcripts per 10^7 copies of β-actin.

**Statistical Analysis**

Data are shown as mean±1 SD. Cytokine levels in the control subjects and MR patients were compared with the Student’s t test. The change in cytokine levels with NYHA class was compared with ANOVA. Paired t tests were used to compare the cytokine levels before and after MV repair surgery. Pearson correlation matrices were constructed to determine the correlations between cytokine expression and hemodynamic parameters and measures of LV size and systolic performance. P<0.05 indicated statistical significance.

**Results**

**Baseline Plasma Cytokine Levels**

Compared with control subjects, MR patients had elevated preoperative plasma TNF-α (3.59±1.81 vs 2.03±1.02 pg/mL, P=0.004), TNFR1 (975±344 vs 738±215 pg/mL, P=0.02), TNFR2 (2156±889 vs 1336±477 pg/mL, P=0.002), and IL-6 (7.80±9.70 vs 2.06±1.43 pg/mL, P=0.03) levels. IL-6 receptor levels were not significantly different between MR patients and control subjects (34.10±8.05 versus 31.00±7.57 ng/mL, P=0.20, Figure 1).

**Plasma Cytokine Levels and NYHA Functional Class**

Plasma TNF-α, TNFR1, TNFR2, and IL-6 levels increased as NYHA functional class deteriorated (P<0.001, ANOVA). Interleukin-6 receptor levels were not significantly different among MR patients in different NYHA functional classes.

**Myocardial TNF-α Gene Expression in MR Patients and Normal Donor Hearts**

Myocardial expression of TNF-α mRNA copies corrected for β-actin mRNA copies was increased in MR patients (38.96±42.74×10^3) compared with otherwise healthy donor
hearts (0.88±0.75×10⁶, P<0.01). There was a trend toward a correlation between the plasma TNF-α levels and myocardial TNF-α gene expression (r=0.47, P=0.15, Figure 2A), but not with its receptors. There was a correlation between the plasma IL-6 levels and myocardial TNF-α mRNA expression (r=0.72, P=0.01, Figure 2B), but not with its receptor.

**Hemodynamic Parameters and Cytokine Expression**

Hemodynamic parameters in MR patients are shown in Table 1. There was a correlation between the plasma TNF-α levels and pulmonary artery systolic (r=0.44 P=0.03), pulmonary artery diastolic (r=0.44 P=0.03), and pulmonary capillary wedge pressures (r=0.43 P=0.04). Both TNF-α receptor 1 and 2 levels had a correlation with the pulmonary capillary wedge pressures (r=0.35 and 0.50, P=0.09 and 0.01, respectively). There was no significant correlation between the plasma levels of IL-6 or its receptor and pulmonary artery pressures. Similarly, there was a trend toward a correlation between myocardial TNF-α gene expression and pulmonary artery systolic (r=0.61, P=0.06), pulmonary artery diastolic (r=0.50, P=0.15), and pulmonary capillary wedge pressures (r=0.59, P=0.07).

**Ejection Fraction and Cytokine Expression**

There was no significant correlation between myocardial TNF-α gene expression and the LV and right ventricular EF.

**LV Volumes and Cytokine Expression**

There was a correlation between the plasma levels of TNF-α and both the LV end-diastolic (r=0.64, P=0.001) and end-systolic volumes (r=0.64, P=0.001, Table 2). Likewise, both TNFR1 and TNFR2 had a correlation with LV end-diastolic and end-systolic volumes. However, there was no significant correlation between the plasma levels of IL-6 and its receptor and LV end-diastolic and end-systolic volumes. There was also a correlation between plasma TNF-α and forward stroke volume (r=0.48, P=0.02) and regurgitant volume (r=0.58, P=0.005). A similar correlation also existed between plasma TNF-α receptor 1 and 2 and the forward stroke and regurgitant volumes (Table 2). These relationships also persisted with TNF-α and its receptors after indexing the volume data to body surface area (Table 2). Moreover, there was a correlation between the myocardial TNF-α gene expression and LV end-diastolic (r=0.67, P=0.006) and end-systolic (r=0.74, P=0.002) volumes before MV surgery.

There was also a strong correlation between preoperative LV regurgitant volume and end-diastolic volume (r=0.79, P=0.0001). The intercept of this relationship at zero regurgitant volume occurred at an LV end-diastolic volume of 132 mL. This suggests that the degree of LV dilatation in these patients with chronic MR was directly proportionate to the extent of MV regurgitation.

**Transmyocardial Cytokine Expression**

The levels of TNF-α and IL-6 and their receptors were not significantly different between the simultaneously drawn arterial and coronary sinus plasma samples.

**Reversal of Cytokine Expression After MV Surgery**

At 23±12 months (range, 10 to 39 months) after MV repair, there was a decrease in the plasma levels of TNF-α (2.79±1.14 versus 3.51±1.34 pg/mL, P=0.02, Figure 3), TNFR1 (774±177 versus 931±187 pg/mL, P=0.007, Figure 4A), and TNFR2 (1450±254 versus 1989±381 pg/mL, P<0.006).
Postoperative plasma levels of IL-6 (2.90 ± 1.78 versus 6.07 ± 6.58 pg/mL, \( P = 0.13 \)) and its receptor (31.3 ± 8.1 versus 36.0 ± 5.2 ng/mL, \( P = 0.16 \)) were not significantly different compared with the preoperative levels.

Reverse LV Remodeling After MV Surgery

Parallel to the postoperative decrease in cytokine expression in MR patients after MV repair, there was a decrease in LV end-diastolic diameter (\( P = 0.001 \)) and LV end-diastolic volume (\( P = 0.01 \), Table 3). There was also a trend toward a decrease in LV end-systolic volume (\( P = 0.07 \)) and NYHA functional class (\( P = 0.05 \)) after MV surgery (Table 3). However, there was no significant change in LV end-systolic diameter and fractional shortening or LVEF.

Relationship Between TNF-\( \alpha \) Expression and LV Reverse Remodeling After MV Surgery

There was an inverse correlation between myocardial TNF-\( \alpha \) gene expression and the change in radionuclide LV end-diastolic (\( r = -0.76, P = 0.007 \)) and end-systolic (\( r = -0.73, P = 0.01 \)) volume after MV repair (Figures 5 and 6). The extent of reduction in LV volumes was larger in patients with increased levels of preoperative myocardial TNF-\( \alpha \) mRNA expression.

Preoperative plasma TNFR1, IL-6, and IL-6R levels did not show a significant correlation with the extent of postoperative change in LV volumes, there was an inverse correlation between the preoperative plasma TNFR2 and change in LV end-diastolic (\( r = 0.61, P = 0.03 \)) and end-systolic (\( r = 0.51, P = 0.09 \)) volumes.

### Table 1. Hemodynamic Parameters in Patients With MR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>68 ± 14</td>
<td>42–99</td>
</tr>
<tr>
<td>RA, mm Hg</td>
<td>5.2 ± 2.9</td>
<td>0–11</td>
</tr>
<tr>
<td>PA systolic, mm Hg</td>
<td>31.5 ± 14.5</td>
<td>14–67</td>
</tr>
<tr>
<td>PA diastolic, mm Hg</td>
<td>13.8 ± 7.6</td>
<td>4–32</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>13.5 ± 7.0</td>
<td>0–29</td>
</tr>
<tr>
<td>LV EDP, mm Hg</td>
<td>13.5 ± 5.7</td>
<td>0–24</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>5.5 ± 1.5</td>
<td>3.5–9.7</td>
</tr>
<tr>
<td>CI, L/min per m²</td>
<td>2.9 ± 0.6</td>
<td>2.1–4.5</td>
</tr>
<tr>
<td>SVR, dyne/s per cm²</td>
<td>1197 ± 339</td>
<td>544–1909</td>
</tr>
<tr>
<td>PVR, dyne/s per cm²</td>
<td>102 ± 67</td>
<td>25–283</td>
</tr>
<tr>
<td>LV EDV, mL</td>
<td>270 ± 191</td>
<td>85–1011</td>
</tr>
<tr>
<td>LV ESV, mL</td>
<td>104 ± 84</td>
<td>25–432</td>
</tr>
<tr>
<td>LV EF</td>
<td>0.59 ± 0.15</td>
<td>0.26–0.82</td>
</tr>
<tr>
<td>LV RI</td>
<td>2.8 ± 2.1</td>
<td>1.3–11.1</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD. HR indicates heart rate; RA, right atrial; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; EDP, end-diastolic pressure; CO, cardiac output; CI, cardiac index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; and RI, regurgitant index.

### Table 2. Correlation Between LV Volumes and Plasma Cytokine Levels

<table>
<thead>
<tr>
<th></th>
<th>EDV</th>
<th>EDVI</th>
<th>ESV</th>
<th>ESVI</th>
<th>SVₙ</th>
<th>SVₙI</th>
<th>RV</th>
<th>RVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-( \alpha )</td>
<td>R</td>
<td>0.64</td>
<td>0.65</td>
<td>0.64</td>
<td>0.65</td>
<td>0.48</td>
<td>0.48</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>( P )</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.02</td>
<td>0.02</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TNFR1</td>
<td>R</td>
<td>0.55</td>
<td>0.55</td>
<td>0.55</td>
<td>0.55</td>
<td>0.53</td>
<td>0.52</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>( P )</td>
<td>0.008</td>
<td>0.008</td>
<td>0.009</td>
<td>0.008</td>
<td>0.01</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>TNFR2</td>
<td>R</td>
<td>0.69</td>
<td>0.69</td>
<td>0.70</td>
<td>0.71</td>
<td>0.51</td>
<td>0.51</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>( P )</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IL-6</td>
<td>R</td>
<td>0.08</td>
<td>0.07</td>
<td>0.03</td>
<td>0.01</td>
<td>0.05</td>
<td>0.05</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>( P )</td>
<td>0.70</td>
<td>0.70</td>
<td>0.90</td>
<td>0.97</td>
<td>0.83</td>
<td>0.96</td>
<td>0.56</td>
</tr>
<tr>
<td>IL-6R</td>
<td>R</td>
<td>0.27</td>
<td>0.25</td>
<td>0.26</td>
<td>0.24</td>
<td>0.27</td>
<td>0.24</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>( P )</td>
<td>0.23</td>
<td>0.25</td>
<td>0.25</td>
<td>0.28</td>
<td>0.23</td>
<td>0.28</td>
<td>0.32</td>
</tr>
</tbody>
</table>

SVₙ indicates forward stroke volume; RV, regurgitant volume; and I, index by body surface area.
Main Findings

The main findings in this study are the following: (1) TNF-α expression is increased both in the myocardium and plasma of patients with chronic MR; (2) there is a relationship between the extent of LV dilatation and TNF-α expression; (3) correction of the LV volume overload state with MV repair leads to reversal of TNF-α expression; and (4) the extent of regression in the LV remodeling, ie, reverse LV volume overload and the resultant stretch stimulus may have led to TNF-α expression. These findings suggest that TNF-α may play a key role in the LV remodeling that occurs in patients with chronic MR.

TNF-α Expression in Patients With Chronic MR

Both myocardial TNF-α mRNA expression and plasma levels of TNF-α were elevated in MR patients. Similar to observations from an animal model of hemodynamic overload, LV volume overload and the resultant stretch stimulus may have led to TNF-α expression. Although the findings of this study do not unequivocally prove that TNF-α was first produced in the heart, there is myocardial production of TNF-α in MR patients, whether it be primary or secondary. However, all of these patients had primary MR without evidence of systemic disease that could be responsible for systemic TNF-α expression. Therefore, it is very likely that TNF-α was first expressed in the heart with subsequent activation of systemic TNF-α expression. There was no detectable spillover of TNF-α across the heart in this study. It is possible that once there is robust TNF-α expression, the tests used may not be sensitive enough to detect very small gradients across the myocardium. Moreover, the rate of TNF-α biosynthesis may have been small in the steady state.

TNF-α mRNA expression was assayed in the extracts from myocardial biopsy specimens. Therefore, it is not possible to identify the cellular source of myocardial TNF-α expression based on the findings of this study. However, prior studies from animals and humans have shown that cardiac myocytes themselves are capable of TNF-α gene and protein expression. It is also possible that cellular components of the interstitium, including mast cells and others, may have contributed to cytokine expression.

TNF-α and Its Receptors in Patients With Chronic MR

Similar to TNF-α, plasma levels of TNF-α receptors 1 and 2 were elevated in MR patients. Receptor shedding frequently occurs during states of TNF-α expression. Increased levels of plasma TNF-α receptors observed in this study confirm that there is a heightened state of TNF-α expression in MR patients. Receptor shedding may be a mechanism of autoprotection by downregulating the number of TNF-α receptors available on the cell surface.

TNF-α and IL-6

Because expression of IL-6 may be regulated by TNF-α, plasma levels of IL-6 were also measured in this study. There

**Discussion**

**Main Findings**

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**TABLE 3. Postoperative Changes in Patients With Mitral Regurgitation**

<table>
<thead>
<tr>
<th></th>
<th>Before Surgery</th>
<th>After Surgery</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>9</td>
<td>...</td>
</tr>
<tr>
<td>Age</td>
<td>56 ± 13</td>
<td>58 ± 13</td>
<td>...</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>23/3</td>
<td>9/0</td>
<td>...</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1.96 ± 0.82 (1–3)</td>
<td>1.33 ± 0.50 (1–2)</td>
<td>0.05</td>
</tr>
<tr>
<td>LV EDD, mm</td>
<td>57.2 ± 8.6 (45–73)</td>
<td>47.2 ± 4.7 (40–54)</td>
<td>0.001</td>
</tr>
<tr>
<td>LV ESD, mm</td>
<td>38.4 ± 6.0 (27–51)</td>
<td>34.4 ± 5.1 (29–46)</td>
<td>0.18</td>
</tr>
<tr>
<td>LV FS</td>
<td>0.37 ± 0.11</td>
<td>0.31 ± 0.07</td>
<td>0.14</td>
</tr>
<tr>
<td>LV EDV, cm³</td>
<td>258 ± 132 (142–501)</td>
<td>154 ± 96 (76–329)</td>
<td>0.047</td>
</tr>
<tr>
<td>LV ESV, cm³</td>
<td>105 ± 52 (25–185)</td>
<td>67 ± 47 (21–172)</td>
<td>0.069</td>
</tr>
<tr>
<td>LV EF</td>
<td>0.58 ± 0.08 (0.50–0.75)</td>
<td>0.58 ± 0.10 (0.41–0.74)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD. Range is shown in parentheses.

EDD indicates end-diastolic diameter; ESD, end-systolic diameter; and FS, fractional shorting.
was a relationship between myocardial TNF-α gene expression and plasma levels of IL-6. This observation suggests that myocardial expression of TNF-α may be the primary source of TNF-α in response to LV stretch with subsequent activation of IL-6 biosynthesis.

**TNF-α and LV Remodeling and Reverse Remodeling in Patients With Chronic MR**

An important finding of this study is that there was a relationship between TNF-α expression and LV remodeling in MR patients. Although it seems that TNF-α expression occurs secondary to LV dilatation, the role of TNF-α may have been more than just passive, as a result of ongoing LV stretch. Rather, TNF-α may play a role in LV remodeling and, therefore, perpetuate the LV remodeling process that occurs in MR patients. In a recent animal study, infusion of TNF-α was associated with LV remodeling, and, when the infusion was discontinued, there was at least partial reversal of LV remodeling.9 In another study of human subjects with congestive heart failure, administration of soluble TNF-α receptors was associated with an improvement in LV remodeling.18

Recently, activation of matrix metalloproteinases (MMPs) was implicated in the pathogenesis of LV remodeling in congestive heart failure.19,20 Moreover, TNF-α was shown to activate MMPs in the heart with subsequent LV remodeling, and treatment with TNF-α–binding proteins resulted in reversal of LV remodeling.21,22 It seems that the balance between tissue inhibitors of MMPs and MMPs in the normal heart20 may be altered with a disproportionate increase in MMP levels compared with tissue inhibitors of MMP levels in response to TNF-α, resulting in LV remodeling.21

There was also a significant inverse relationship between the quantity of myocardial TNF-α expressed before MV surgery and the extent of regression in LV end-diastolic and end-systolic volumes, i.e., reverse LV remodeling, after correction of the LV volume overload state with MV repair. Therefore, it is apparent that as the stimulus for expression of MMPs responsible for LV remodeling is removed, there is regression in LV dilatation. TNF-α may be the key link between LV stretch and activation of MMPs, which results in LV remodeling.

**Conclusions**

This is the first study to report that both myocardial and plasma levels of TNF-α and its receptors are elevated in patients with chronic MR, a state of LV volume overload that results in a stretch stimulus to myocytes. Because there is a relationship between myocardial TNF-α expression and LV remodeling, an inverse relationship exists between the extent of reverse LV remodeling and myocardial TNF-α expression, and reversal of TNF-α expression occurs after elimination of LV stretch with MV surgery. TNF-α seems to be the biochemical mediator between LV stretch and LV remodeling in MR patients.

**Acknowledgments**

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**References**


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