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Effect of Beta-Blockers on Circulating Levels of Inflammatory and Anti-Inflammatory Cytokines in Patients With Dilated Cardiomyopathy

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OBJECTIVES This study was designed to evaluate the beneficial effect of beta-blockers on circulating cytokine levels in patients with dilated cardiomyopathy (DCM).

BACKGROUND Elevated circulating levels of inflammatory cytokines have been reported in patients with DCM. However, alterations of the levels of inflammatory and anti-inflammatory cytokines in association with beta-blocker therapy are unknown.

METHODS We studied 32 patients with idiopathic DCM who had been treated with digitalis, diuretics and angiotensin-converting enzyme inhibitors. In addition to this combination therapy, beta-blockers were started in all patients. Serum levels of interleukin (IL)-10, tumor necrosis factor-alpha (TNF-alpha) and soluble TNF receptors (sTNF-R1 and R2) were measured at baseline and 12 weeks after the initiation of beta-blocker therapy. We also measured plasma levels of neurohumoral factors, as well as left ventricular (LV) size and function. Ten age-matched subjects with no cardiac disease served as the control group.

RESULTS Baseline levels of IL-10, TNF-alpha and sTNF-R2 were significantly higher in patients with DCM than in control subjects ($p < 0.05$). There was a significant positive correlation between IL-10 and TNF-alpha levels ($r = 0.545$, $p = 0.029$). The TNF-alpha/IL-10 ratio correlated well with plasma epinephrine levels ($r = 0.677$, $p = 0.025$), and the level of sTNF-R2 was closely related to LV size. Serum levels of IL-10, TNF-alpha and sTNF-R2 were significantly decreased during beta-blocker therapy ($p < 0.005$).

CONCLUSIONS Our findings indicate that beta-blockers have an important immunoregulatory role in modifying the dysregulated cytokine network in DCM. This effect of beta-blockers may be partly responsible for the efficacy of therapeutic drugs for heart failure. (J Am Coll Cardiol 2001;37:412–7) © 2001 by the American College of Cardiology

Beta-adrenergic blocking agents have been considered to be useful for patients with congestive heart failure (CHF). Large clinical trials have indicated their beneficial effects on morbidity and mortality in such patients (1–4). Very recently, we demonstrated the attenuating effect of beta-blockers on plasma natriuretic peptide levels in patients with idiopathic dilated cardiomyopathy (DCM) who were treated with a combination of diuretics, digitalis and angiotensin-converting enzyme (ACE) inhibitors (5). However, the exact mechanisms of the beneficial effects of beta-blockers have not been elucidated.

Previous studies have shown the increased circulating levels of various inflammatory cytokines in patients with CHF (6–8). It is well known that the overexpression of these inflammatory cytokines can produce left ventricular (LV) dysfunction, pulmonary edema and cardiomyopathy in humans (9). In particular, tumor necrosis factor-alpha (TNF-alpha) and interleukin (IL)-6 are important in association with the progression of CHF. Tumor necrosis factor-alpha is synthesized by activated macrophages, endothelial cells and the myocardium; it also induces cachexia and apoptosis in myocardial cells and produces negative inotropic effects on cardiac tissue (10–12). Two TNF receptors of 55 and 75 kD have been identified on the surface of cell lines and are thought to mediate and regulate most of the effects of TNF-alpha (13,14). Soluble forms of both receptors (sTNF-R1 and R2), the extracellular domain fragments shed from cell surfaces, are supposed to regulate the TNF-alpha bioactivity by inhibiting the binding of TNF trimmers to the membrane receptors (15). Therefore, circulating levels of sTNF receptors are closely related to the activities of TNF-alpha. Moreover, the effects of TNF-alpha are modulated by anti-inflammatory cytokines. Interleukin-10, a cytokine with anti-inflammatory activities, is known to suppress the synthesis of TNF-alpha and to enhance the release of sTNF receptors (16). A recent report has shown that circulating levels of IL-10 are markedly increased in patients with CHF (17). In view of these findings, a dysregulated cytokine network is involved in the development and progression of CHF. In addition, the effects of various cardiovascular treatments on the levels of these cytokines and cytokine receptors are largely unknown.

Accordingly, this study was designed to evaluate the beneficial effect of beta-blockers on circulating cytokine levels in patients with DCM and to clarify the alterations of the levels of inflammatory and anti-inflammatory cytokines and cytokine receptors in relation to beta-blocker therapy.

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
ANP	=	atrial natriuretic peptide
BNP	=	brain natriuretic peptide
CHF	=	congestive heart failure
DCM	=	dilated cardiomyopathy
EDD	=	end-diastolic dimension
ESD	=	end-systolic dimension
IL	=	interleukin
LV	=	left ventricular
sTNF-R	=	soluble tumor necrosis factor receptor
TNF-alpha	=	tumor necrosis factor-alpha

METHODS

Subjects. We studied 32 consecutive patients with idiopathic DCM (11 women and 21 men) between June 1996 and May 1999. They were in New York Heart Association functional class II or III and had been treated with digitalis, diuretics and ACE inhibitors for at least six months. They ranged in age from 26 to 74 years (mean 61). Patients who had clinical or laboratory evidence of neoplasms or autoimmune disease or liver or renal dysfunction were excluded from the study. Ten age-matched subjects who had no evidence of organic cardiac disease and no cardiac dysfunction were retrospectively selected as the control group. All subjects participated in this study after giving their informed consent, and the protocol was approved by the Human Investigations Committee of our institution.

Study protocol. In all patients, beta-blockers were administered orally, in addition to the combination therapy after their hospital admission (29 patients received metoprolol and 3 received bisoprolol). The initial dosages of metoprolol and bisoprolol were 2.5 or 5.0 mg and 1.25 or 2.5 mg/day, respectively. The doses were gradually increased up to the maximum levels, which were determined by the end point of either a decrease in systolic blood pressure <90 mm Hg or a decrease in heart rate at rest <50 beats/min during eight weeks. The mean final doses of metoprolol and bisoprolol were 37.3 mg (range 15 to 80) and 8.3 mg (range 5.0 to 12.5), respectively. After determining the final doses, the patients were followed for an additional four weeks.

Blood sampling and immunoassays. After bed rest for at least 30 min, peripheral venous blood samples were collected into chilled tubes and immediately centrifuged at 4°C, and the serum samples were stored at −80°C until assay. Blood samples from patients for the measurement of levels of IL-10, TNF-alpha and sTNF receptors were collected before and 12 weeks after the initiation of beta-blocker therapy. At the same time, plasma levels of epinephrine, norepinephrine, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were also measured in patients, as previously reported (18,19).

Serum levels of IL-10, TNF-alpha and sTNF receptors (sTNF-R1 and R2) were measured by enzyme-linked immunosorbent assays with commercial kits (Immunotech Co., Marseille, France), as previously reported (20,21). The average interassay and intra-assay coefficients of variation were <10% for all assays.

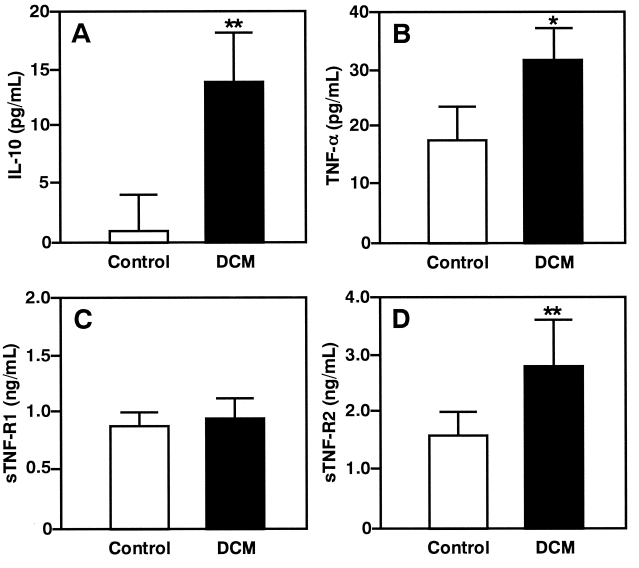

Figure 1. Graphs showing the serum levels of IL-10 **(A),** TNF-alpha **(B),** sTNF-R1 **(C)** and sTNF-R2 **(D)** in 10 age-matched control subjects and in 32 patients with DCM at baseline. *$p < 0.05$. **$p < 0.005$ vs. control subjects.

Echocardiographic study. Echocardiographic studies were performed using an SSD-870 echocardiograph with a 3.5-MHz transducer (Aloka Inc., Tokyo, Japan), according to the recommendations of the American Society of Echocardiography (22). In each patient, a standard parasternal long-axis view was recorded at the basal position, and the LV end-diastolic dimension (EDD) and end-systolic dimension (ESD) were determined using M-mode echocardiography. Percent LV fractional shortening was calculated as LV systolic function: ([EDD − ESD]/EDD × 100).

Statistical analysis. All data are expressed as the mean value ± SD. Differences between patients and control subjects were compared by using the Mann-Whitney *U* rank-sum test for unpaired data. Clinical variables and serum levels of cytokines in patients were compared before and during beta-blocker therapy using the Wilcoxon paired sign-rank test. Correlation coefficients for relations between serum levels of cytokines and cytokine receptors and between their levels and clinical variables were tested by using the Spearman rank test. A p value <0.05 was considered statistically significant.

RESULTS

Baseline levels of IL-10, TNF-alpha and sTNF receptors. Figure 1 shows the serum levels of IL-10, TNF-alpha, sTNF-R1 and sTNF-R2 in patients with DCM at baseline and in control subjects. Serum levels of IL-10 and TNF-alpha were significantly higher in patients with DCM than in control subjects (Fig. 1, A and B). Serum sTNF-R2 levels were also higher in patients with DCM than in control

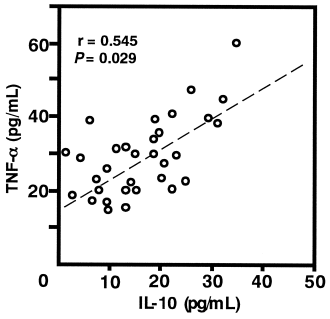

Figure 2. Scatterplots showing a correlation between IL-10 and TNF-alpha in 32 patients with DCM.

subjects (Fig. 1D). However, there was no significant difference in the serum levels of sTNF-R1 between the two groups (Fig. 1C).

Relations among IL-10 and TNF-alpha and sTNF receptors in patients with DCM. In patients with DCM, there was a significant correlation between serum levels of IL-10 and TNF-alpha at baseline ($r = 0.545$, $p = 0.029$) (Fig. 2). However, there were no significant correlations between serum levels of IL-10 and sTNF-R1 and sTNF-R2 levels. In addition, there were no significant correlations between serum levels of TNF-alpha and sTNF-R1 and sTNF-R2 levels.

Relations between IL-10, TNF-alpha or sTNF receptors and clinical variables in patients with DCM. In patients with DCM, there were no significant correlations between serum levels of IL-10 and TNF-alpha and neurohumoral factors, LV size and systolic function at baseline. In addition, both sTNF-R1 and sTNF-R2 levels did not significantly correlate with levels of neurohumoral factors. In contrast, there was a significant correlation between the serum level of sTNF-R2 and EDD ($r = 0.604$, $p = 0.012$) (Fig. 3A), although no correlation was found between sTNF-R1 and EDD. Moreover, the ratio of TNF-alpha/IL-10 significantly correlated with plasma epinephrine levels ($r = 0.677$, $p = 0.025$) (Fig. 3B).

Effects of beta-blockers on clinical variables. Table 1 shows the effects of beta-blockers on hemodynamic variables, LV function and neurohumoral factors in patients with DCM. After treatment with beta-blockers, heart rates were significantly decreased and New York Heart Association functional classes were significantly improved, although systolic blood pressures remained unchanged. In addition, LV size and systolic function were significantly improved, and plasma levels of epinephrine, norepinephrine, ANP and BNP were significantly reduced during beta-blocker therapy.

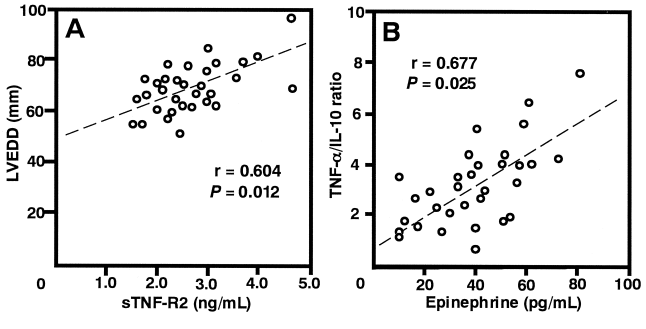

Figure 3. Scatterplots showing correlations **(A)** between sTNF-R2 and left ventricular end-diastolic dimension (LVEDD) and **(B)** between plasma epinephrine levels and the TNF-alpha/IL-10 ratio in 32 patients with DCM.

Effects of beta-blockers on levels of cytokines and cytokine receptors. Figure 4 demonstrates the effects of beta-blockers on serum levels of IL-10, TNF-alpha, sTNF-R1 and sTNF-R2 in patients with DCM. After treatment with beta-blockers, increased levels of both IL-10 and TNF-alpha were significantly reduced (Fig. 4, A and B). Serum levels of sTNF-R2 also decreased significantly, although levels of sTNF-R1 remained unchanged during beta-blocker therapy (Fig. 4, C and D).

DISCUSSION

Increased circulating levels of inflammatory cytokines have been shown in patients with CHF, but most studies have focused on only a few inflammatory cytokines (23,24). Most of the effects of these inflammatory cytokines are regulated by anti-inflammatory cytokines and cytokine receptors. In addition, little is known about the effects of various cardiovascular treatment regimens on the levels of these cytokines and cytokine receptors. In the present study, we demonstrated the major alterations not only in the levels of inflammatory cytokines, but also in the levels of anti-inflammatory cytokines and cytokine receptors in patients with DCM. Our findings clearly indicate that beta-blockers markedly reduce the increased circulating levels of TNF-alpha, and that the reduction of TNF-alpha levels is closely related to the alterations in the levels of IL-10 and sTNF-R2.

Effects of beta-blockers on TNF-alpha levels. Previous studies have indicated the beneficial effects of various cardiovascular treatments on levels of inflammatory cytokines in patients with CHF (24–27). Several reports have shown a significant reduction in circulating IL-6 levels due to ACE inhibitor therapy in CHF (26,27). In particular, Gullestad et al. (27) have indicated that high dose enalapril therapy markedly decreases IL-6 activity in patients with CHF. However, a significant reduction of circulating TNF-alpha levels in patients treated with ACE inhibitors was not observed in these studies. Mohler et al. (25) have shown that the calcium antagonist, amlodipine, lowers plasma IL-6 levels in patients with CHF, but they found no effect of amlodipine on plasma levels of TNF-alpha. These results indicate that treatment with ACE inhibitors and some type of calcium antagonist cannot affect TNF-alpha levels of the circulation in patients with CHF. Therefore, we think that TNF-alpha is an another important therapeutic target in CHF.

In this study, we elucidated, for the first time, to our knowledge, that beta-blockers markedly lower the increased

Table 1. Effects of Beta-Blocker Therapy on Hemodynamic Variables, Left Ventricular Functions and Neurohumoral Factors in Patients With Dilated Cardiomyopathy

Variables	Baseline	Week 12	p Value
Heart rate (beats/min)	71.7 ± 12.4	65.5 ± 8.20	0.0098
Systolic blood pressure (mm Hg)	116.8 ± 13.0	114.3 ± 14.4	0.1831
New York Heart Association functional class	2.15 ± 0.65	1.85 ± 0.61	0.0285
Echocardiographic values			
LVEDD (mm)	69.6 ± 11.6	64.0 ± 7.51	0.0014
LVESD (mm)	59.2 ± 12.7	50.4 ± 9.79	0.0010
Fractional shortening (%)	15.5 ± 5.91	21.8 ± 7.02	0.0026
Neurohumoral factors			
Epinephrine (pg/ml)	310.2 ± 52.6	141.5 ± 22.4	0.0033
Norepinephrine (pg/ml)	341.1 ± 33.9	218.4 ± 34.0	0.0021
ANP (pg/ml)	83.4 ± 27.4	60.2 ± 26.5	0.0031
BNP (pg/ml)	253.5 ± 112.2	184.8 ± 114.0	0.0008

Data are presented as the mean value ± SD.
ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension.

circulating level of TNF-alpha in patients with DCM. This finding suggests that the beneficial effect of beta-blockers in CHF may be partly due to a suppression of TNF-alpha activities in the circulation. Very recently, Prabhu et al. (28) reported that the beta-blocker, metoprolol, selectively decreased myocardial expression of TNF-alpha and IL-1-beta, but not IL-6, in rats with LV dysfunction after myocardial infarction. In addition, it was reported that treatment with beta-blockers in patients with CHF did not change the plasma IL-6 levels (24). In view of these reported data and our results, there seems to be at least two major cytokine networks related to the condition of CHF. One is a network mainly associated with IL-6, which is influenced by ACE inhibitors and some type of calcium antagonist. The other is a network mainly regulated by TNF-alpha, which is influenced by beta-blockers. Very recently, we reported that beta-blocker therapy could reduce the plasma levels of ANP and BNP and improve the LV remodeling in patients with heart failure treated with ACE inhibitors (5). This finding indicates that the mechanism for the beneficial effect of beta-blockers is different from that of ACE inhibitors. Therefore, combination therapy with beta-blockers and ACE inhibitors in patients with DCM may perfectly modify the dysregulated networks associated with two major inflammatory cytokines.

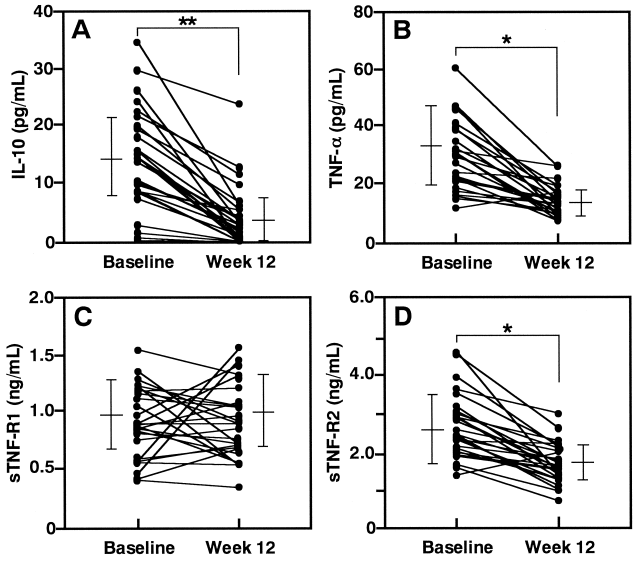

Figure 4. Comparisons of serum levels of IL-10 **(A),** TNF-alpha **(B),** sTNF-R1 **(C)** and sTNF-R2 **(D)** at baseline and 12 weeks after the initiation of beta-blocker therapy in 32 patients with DCM. *$p < 0.005$. **$p < 0.001$ vs. control subjects.

Alteration of sTNF receptor levels. Most of the effects of TNF-alpha are mediated through two TNF receptors and anti-inflammatory cytokines. The two soluble TNF receptors circulate in normal serum, and high levels of these receptors are present in patients with CHF (8). In particular, it is known that the levels of sTNF-R2 are strongly correlated with clinical variables, such as ejection fraction and cardiac output, and are closely related to a poor prognosis in patients with CHF (29). In our study, we also demonstrated increased circulating levels of sTNF-R2 in patients with DCM, although no elevation of sTNF-R1 was found. The levels of sTNF-R2 were markedly decreased, in accordance with the reduction of TNF-alpha levels, due to beta-blocker therapy. These findings suggest that sTNF-R2 is a very important factor in modulating TNF-alpha activities in patients with DCM. In addition, a recent study has shown that etanercept, a sTNF-R2 fusion protein that binds to TNF-alpha, leads to improvement in the functional status of patients with advanced CHF (30). Our findings show that the increased levels of sTNF-R2 were closely related to LV size in DCM. In contrast, the increase of circulating sTNF-R2 was not associated with activation of neurohumoral factors. Therefore, the LV functional status of patients with DCM may be partly determined by levels of sTNF-R2.

Relations between TNF-alpha and IL-10 in DCM. In addition to an increased circulating level of sTNF-R2, our patients also had alterations in IL-10 levels. Interleukin-10 downregulates the production of inflammatory cytokines in a variety of cell types and enhances the release of sTNF receptors; thus, it is known that IL-10 has potential

beneficial effects in terms of its cardioprotective properties in CHF (31,32). However, to date, the mechanism involved in a high level of IL-10 production in CHF remains undefined. Our findings demonstrate that circulating levels of IL-10 increased in relation to elevated TNF-alpha levels in patients with DCM, and may support the concept that the increase of IL-10 levels enhances the release of sTNF-R2. Moreover, increased levels of IL-10 were markedly decreased, in accordance with the reduction of TNF-alpha levels, due to beta-blocker therapy. Therefore, IL-10 may be a potential therapeutic agent, as an immunoregulatory factor, in CHF.

One of the major findings in our study is that the TNF-alpha/IL-10 ratio was strongly correlated with plasma epinephrine levels in patients with DCM. Indeed, several reports have clarified the relation between cytokine activities and sympathetic activation. Yamaoka et al. (17) have reported that the levels of catecholamines are associated with IL-10 production in patients with CHF. In particular, epinephrine is related to IL-10 production in lipopolysaccharide stimulation through an increase in intracellular cyclic adenosine monophosphate levels (33). In addition, a very recent report has shown that activation of the adrenergic nervous system contributes to increased myocardial expression of TNF-alpha in rats with heart failure (28). Thus, we suggest that beta-blockade may regulate the balance between TNF-alpha and IL-10 levels in patients with DCM. Accordingly, beta-blockers may have an important immunoregulatory role in establishing the optimal level of IL-10 for suppressing TNF-alpha production in DCM.

Study limitations. One limitation of our study is that the cellular source of circulating IL-10, TNF-alpha or sTNF receptors is not known yet. To determine whether these cytokines and sTNF receptors are released from the heart, we must compare their levels in the coronary sinus with those levels in other organs. We excluded from this study patients who had clinical or laboratory evidence of malignancy or inflammatory disease or liver or renal dysfunction. In addition, circulating levels of IL-10, TNF-alpha and sTNF-R2 were markedly decreased, in accordance with the improvement of LV size and function during beta-blocker therapy. Therefore, it is likely that their source is associated with secretion from the heart. To confirm this, however, further studies must be performed. Another limitation of this study is the lack of a placebo group. Although circulating TNF-alpha levels were found to reduce by beta-blocker therapy, we cannot exclude the alterations of TNF-alpha activities that might exist without beta-blockade. However, the patients in our study showed increased circulating levels of TNF-alpha, despite combination therapy with digitalis, diuretics and ACE inhibitors. Thus, we think that cardiovascular agents, except for beta-blockers, can not affect TNF-alpha activities in the circulation of patients with CHF.

Conclusions. We have clarified that beta-blockers can lower the circulating level of TNF-alpha in patients with DCM, and that the reduction of TNF-alpha levels was closely related to the alterations of circulating levels of IL-10 and sTNF-R2. In view of these findings, the beneficial effect of beta-blockade may involve the attenuation of TNF-alpha activities and the enhancement of the release of sTNF-R2 by increasing the levels of anti-inflammatory cytokines in CHF. Therefore, beta-blockers may have an important immunoregulatory effect to modify the dysregulated cytokine network in DCM.

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