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Effects of Carvedilol on Plasma Levels of Interleukin-6 and Tumor Necrosis Factor-Alpha in Nine Patients With Dilated Cardiomyopathy

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Abstract

Objectives. Whether beta-blocker therapy changes the circulating levels of cytokines as congestive heart failure improves remains uncertain.

Methods. Nine patients with idiopathic dilated cardiomyopathy, who had previously received conventional treatment and were classified as New York Heart Association (NYHA) functional class II, received carvedilol by stepwise dose increase up to 20 mg daily, and the plasma interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels were measured.

Results. IL-6 was significantly reduced from 0.80 ± 0.49 pg/m*l* before therapy to 0.21 ± 0.08 pg/m*l* after carvedilol was increased to 20 mg daily ($p < 0.05$). Moreover, IL-6 level had already decreased significantly compared to the baseline when the dose of carvedilol had reached 10 mg daily (0.28 ± 0.12 pg/m*l*, $p < 0.05$). TNF-α levels did not change significantly.

Conclusions. These results demonstrate that IL-6 concentration is significantly decreased by beta-blocker therapy. The efficacy for heart failure may be related to the change of IL-6 concentration.

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Key Words

■**Cytokines** (**interleukin-6, tumor necrosis factor-alpha**)
■**Cardiomyopathies, dilated**
■**Beta-adrenergic receptor blockers** (**carvedilol**)

INTRODUCTION

The potential of beta-blocker therapy for heart failure was first reported by Waagstein *et al*[1]. Since then, many studies have confirmed the efficacy of beta-blockers in the management of congestive heart failure[2–4]. On the other hand, some studies have demonstrated elevated circulating levels of

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various cytokines including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in patients with congestive heart failure[5–10]. Whether beta-blocker therapy changes the circulating levels of cytokines along with the improvement of congestive heart failure remains uncertain. Ohtsuka *et al.*[11] studied 32 patients with idiopathic dilated cardiomyopathy and reported that serum levels of interleukin-10, TNF-α, and soluble tumor necrosis factor receptor-2 were significantly decreased during beta-blocker therapy with metoprolol or bisoprolol. However, no study has investigated whether beta-blockers decrease the circulating level of IL-6.

This study examined whether carvedilol used as beta-blocker therapy for dilated cardiomyopathy decreases the plasma levels of IL-6 and TNF-α.

SUBJECTS AND METHODS

We studied nine patients with idiopathic dilated cardiomyopathy who were admitted to our institute between May 1999 and January 2001. We treated these patients with carvedilol by stepwise dose increase up to 20 mg/day, under monitoring for safety. To confirm the diagnosis, all patients underwent cardiac catheterization to verify absence of significant stenosis of the coronary arteries and left ventricular ejection fraction of less than 30%, and right ventricular biopsy to exclude secondary dilated cardiomyopathy. The patients had no liver dysfunction, renal dysfunction, valvular disease, malignant disease, or collagen disease.

The eight men and one woman were aged 45 to 60 years (mean age 53 years old). The New York Heart Association (NYHA) functional class at admission was II in five patients and III in four patients. Before starting the beta-blocker therapy, all patients were given conventional treatment, and congestive heart failure was controlled at a steady condition. The four patients in NYHA functional class III were receiving no medication (one patient), only diuretics (one patient), or only angiotensin-converting enzyme (ACE) inhibitors (two patients) at admission. These patients improved with the start or addition of conventional therapy. All patients were NYHA functional class II when the beta-blocker therapy was initiated.

Conventional treatments such as digitalis, diuretics, and/or ACE inhibitors given before the initiation of beta-blocker therapy were continued. ACE inhibitors were given to eight patients, angiotensin II receptor blockers to three, nitrates to eight, furosemide to six, spironolactone to six, digitalis to three, and pimobendan to one. During the treatment period, the drug regimens were unchanged unless adverse side effects occurred.

Carvedilol was given at an initial dose of 1.25 mg (two patients) or 2.5 mg (seven patients) daily and gradually increased up to the target dose of 20 mg daily. Exertional dyspnea worsened temporarily with 2.5 mg daily of carvedilol in one patient. She needed more time than usual to increase the dose and took 9 weeks to reach 20 mg daily. However, she did not require decreased dose during the therapy. The other eight patients had no worsening of heart failure and the dose was increased up to 20 mg daily over a period of 4 to 7 weeks.

The plasma levels of IL-6 and TNF-α were measured at three points: before the start of the beta-blocker therapy, after carvedilol was increased to 10 mg daily, and at the end of the therapy (9.6 ± 4.5 days after the dose was increased up to 20 mg daily). Blood samples were drawn into a vacutainer containing sodium ethylenediamine tetra-acetic acid (EDTA-2Na) and the plasma was immediately prepared by centrifugation at 3,000 rpm. The samples were stored at −20 ℃ until needed. IL-6 and TNF-α were measured with a commercially available immunoassay kit (QuantiGlo human IL-6 Immunoassay and QuantiGlo Human TNF-α Immunoassay, R&D Systems).

Simultaneously with blood sampling, each patient also underwent echocardiography for measurement of left ventricular dimensions. Left ventricular ejection fraction was calculated by the Teichholz formula from M-mode recordings.

All data are reported as means ± SD. Comparison of variables before and after therapy was performed by Wilcoxon signed-ranks test. All comparisons were two-tailed.

RESULTS

Changes in clinical parameters are shown in **Table 1**. The heart rates decreased significantly after the initiation of carvedilol. The blood pressures were unchanged. All patients were classified as NYHA functional class II before the start of beta-blocker therapy, and five patients were symptomatically improved and classified as class I after therapy. Plasma levels of brain natriuretic peptide decreased significantly, and left ventricular ejection fractions also improved significantly.

Table 1 Changes in clinical parameters of nine patients with dilated cardiomyopathy

	At baseline	Carvedilol		*p* value
		10 mg daily	20 mg daily	20mg vs baseline
Heart rate (beats/min)	76±7	66±6	65±7	<0.05
Systolic blood pressure (mmHg)	104±10	103±9	106±12	NS
Diastolic blood pressure (mmHg)	67±11	64±7	65±9	NS
NYHA class II (patients)	9		4	NS
NYHA class I (patients)	0		5	
BNP (pg/ml)	354±189	171±77*	170±207	<0.05
LVDd (mm)	70±7	68±4**	65±6	<0.05
LVDs (mm)	63±8	60±5**	56±6	<0.05
LVEF (%)	22±8	25±7**	28±7	<0.05

Continuous values are mean±SD. *BNP levels were measured in only five patients at this dose. **Echocardiographic data were obtained in only seven patients at this dose.
NYHA=New York Heart Association; BNP=brain natriuretic peptide; LVDd=left ventricular end-diastolic dimension; LVDs=left ventricular end-systolic dimension; LVEF=left ventricular ejection fraction.

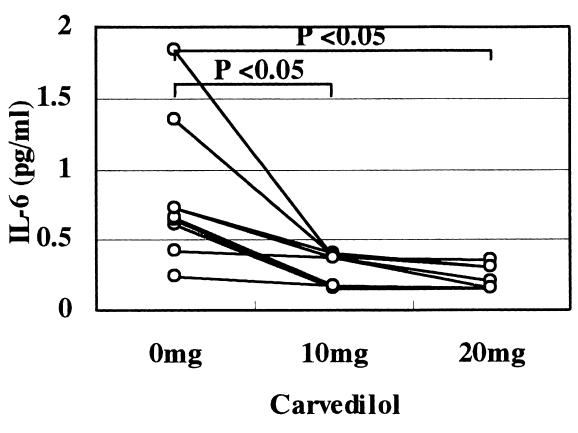

Fig. 1 Changes in plasma levels of interleukin-6
Interleukin-6 was significantly reduced during the therapy. The decrease was already significant when carvedilol had been increased to 10 mg/day.
IL-6 = interleukin-6.

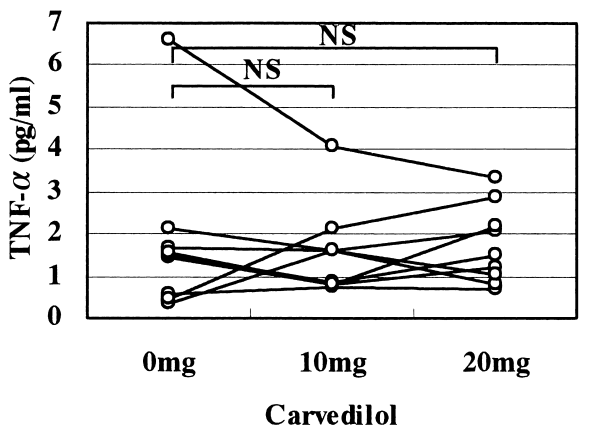

Fig. 2 Changes in plasma levels of tumor necrosis factor-alpha
The plasma levels of tumor necrosis factor-alpha did not change significantly during the therapy.
TNF-α = tumor necrosis factor-alpha.

Fig. 1 shows the changes in plasma levels of IL-6. Plasma IL-6 was significantly reduced from 0.80 ± 0.49 pg/ml before therapy to 0.21 ± 0.08 pg/ml after carvedilol was increased up to 20 mg/day ($p < 0.05$). Moreover, there was already a significant decrease when carvedilol had been increased to 10 mg/day (0.28 ± 0.12 pg/ml, $p < 0.05$), with all patients showing decreased levels of IL-6 at this dose.

Fig. 2 shows the changes in plasma levels of TNF-α. The TNF-α levels did not change significantly during therapy: 1.80 ± 1.89 pg/ml before therapy, 1.58 ± 1.05 pg/ml at carvedilol 10 mg/day, and 1.74 ± 0.93 pg/ml at 20 mg/day.

DISCUSSION

TNF-α, IL-1-α, IL-1-β, and IL-6 are classified as proinflammatory cytokines[12], and are considered to suppress cardiac function by various mechanisms, such as decreasing left ventricular contractility through nitric oxide production[13] and impairing coupling of beta-adrenergic receptors to adenosine 3',5'-cyclic monophosphate production[14]. Tsutamoto *et al.*[15] reported high plasma level of IL-6 as a prognostic predictor in patients with congestive heart failure. Suppression of these proinflammatory cytokines may provide a new therapeutic strategy for congestive heart failure.

The study demonstrated that IL-6 concentration was significantly reduced by beta-blocker therapy, accompanied by improvement of congestive heart failure. Some studies have reported that IL-6 concentration is related to disease severity in patients with congestive heart failure[6,10], consistent with our findings. In addition, all our patients had decreased level of IL-6 when the dose of carvedilol was increased to 10 mg daily. This finding might be informative for deciding the optimal clinical dose of carvedilol for beta-blocker therapy in the future.

The calcium antagonist amlodipine[16], the ACE inhibitor enalapril[17], and the angiotensin II receptor antagonist candesartan[18] also lower plasma IL-6 levels in patients with congestive heart failure. It remains to be determined whether the underlying mechanisms are common or not.

Torre-Amione *et al.*[10] showed that plasma levels of TNF-α were progressively elevated with decreasing functional status. Our study failed to show any change of TNF-α level during the therapy. This result may be related to the small sample size, and should be interpreted cautiously. However, this result may also be related to the fact that not all patients with heart failure elaborate TNF-α, for unknown reasons[7–9]. However, our results suggest that IL-6 level reflects the improvement of congestive heart failure better than TNF-α, at least in the short term.

The major limitation of our study is the small sample size. Additional studies with larger numbers of subjects are needed. In addition, we did not include patients with severe congestive heart failure. All our patients were classified as NYHA functional class II before the initiation of beta-blocker therapy, and their baseline IL-6 levels were lower than those reported in other studies[6,10,15]. Furthermore, we do not yet have data on whether the decreased IL-6 levels are maintained in the long term.

CONCLUSIONS

In conclusion, carvedilol as beta-blocker therapy for dilated cardiomyopathy decreased the plasma levels of IL-6 during therapy, but had no effect on TNF-α levels. All patients showed decreased levels of IL-6 when the carvedilol dose was increased to 10 mg/day. The efficacy of beta-blocker therapy for heart failure may be associated with decreased IL-6 level, and IL-6 suppression may provide a new therapeutic strategy for congestive heart failure.

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要　　約

カルベジロールがインターロイキン6および腫瘍壊死因子アルファの血漿中濃度に及ぼす影響: 拡張型心筋症9例の検討

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目　的: 心不全例に対するβ遮断薬療法のサイトカイン濃度に及ぼす影響はいまだ明らかでない.

方　法: 我々は一般的治療を受けNYHA心機能分類II度にある特発性拡張型心筋症9例にカルベジロールを20 mg/dayまで導入し，インターロイキン6および腫瘍壊死因子αの血漿中濃度を測定した.

結　果: インターロイキン6は治療前の0.80±0.49 pg/m*l*からカルベジロール20 mg/day導入後の0.21±0.08 pg/m*l*まで有意に減少した($p<0.05$)．さらに，カルベジロール10 mg/dayまで増量した時点ですでに治療前に比べ有意な減少があった(0.28±0.12 pg/m*l*, $p<0.05$)．腫瘍壊死因子αについては有意な変化はなかった.

結　論: 我々の知る限り本稿はβ遮断薬療法がインターロイキン6の濃度を有意に減少させたことを示す初の報告である．β遮断薬療法の心不全に対する効果は，インターロイキン6の濃度低下

と関連している可能性がある.

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References

1) Waagstein F, Hjalmarson A, Varnauskas E, Wallentin I: Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. Br Heart J 1975; **37**: 1022−1036
2) Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH, for the U.S. Carvedilol Heart Failure Study Group: The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996; **334**: 1349−1355
3) CIBIS-Ⅱ Investigators and Committees: The Cardiac Insufficiency Bisoprolol Study Ⅱ (CIBIS-Ⅱ): A randomised trial. Lancet 1999; **353**: 9−13
4) MERIT-HF Study Group: Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; **353**: 2001−2007
5) Aukrust P, Ueland T, Lien E, Bendtzen K, Müller F, Andreassen AK, Nordoy I, Aass H, Espevik T, Simonsen S, Froland SS, Gullestad L: Cytokine network in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1999; **83**: 376−382
6) Munger MA, Johnson B, Amber IJ, Callahan KS, Gilbert EM: Circulating concentrations of proinflammatory cytokines in mild or moderate heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1996; **77**: 723−727
7) Matsumori A, Yamada T, Suzuki H, Matoba Y, Sasayama S: Increased circulating cytokines in patients with myocarditis and cardiomyopathy. Br Heart J 1994; **72**: 561−566
8) Levine B, Kalman J, Mayer L, Fillit HM, Packer M: Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990; **323**: 236−241
9) Wiedermann CJ, Beimpold H, Herold M, Knapp E, Braunsteiner H: Increased levels of serum neopterin and decreased production of neutrophil superoxide anions in chronic heart failure with elevated levels of tumor necrosis factor-alpha. J Am Coll Cardiol 1993; **22**: 1897−1901
10) Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL: Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: A report from the Studies Of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol 1996; **27**: 1201−1206
11) Ohtsuka T, Hamada M, Hiasa G, Sasaki O, Suzuki M, Hara Y, Shigematsu Y, Hiwada K: Effect of beta-blockers on circulating levels of inflammatory and anti-inflammatory cytokines in patients with dilated cardiomyopathy. J Am Coll Cardiol 2001; **37**: 412−417
12) Mann DL, Young JB: Basic mechanisms in congestive heart failure: Recognizing the role of proinflammatory cytokines. Chest 1994; **105**: 897−904
13) Finkel MS, Oddis CV, Jacob TD, Watkins SC, Hattler BG, Simmons RL: Negative inotropic effects of cytokines on the heart mediated by nitric oxide. Science 1992; **257**: 387−389
14) Gulick T, Chung MK, Pieper SJ, Lange LG, Schreiner GF: Interleukin 1 and tumor necrosis factor inhibit cardiac myocyte beta-adrenergic responsiveness. Proc Natl Acad Sci 1989; **86**: 6753−6757
15) Tsutamoto T, Hisanaga T, Wada A, Maeda K, Ohnishi M, Fukai D, Mabuchi N, Sawaki M, Kinoshita M: Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. J Am Coll Cardiol 1998; **31**: 391−398
16) Mohler ERⅢ, Sorensen LC, Ghali JK, Schocken DD, Willis PW, Bowers JA, Cropp AB, Pressler ML: Role of cytokines in the mechanism of action of amlodipine: The PRAISE Heart Failure Trial: Prospective Randomized Amlodipine Survival Evaluation. J Am Coll Cardiol 1997; **30**: 35−41
17) Gullestad L, Aukrust P, Ueland T, Espevik T, Yee G, Vagelos R, Froland SS, Fowler M: Effect of high-versus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure. J Am Coll Cardiol 1999; **34**: 2061−2067
18) Tsutamoto T, Wada A, Maeda K, Mabuchi N, Hayashi M, Tsutsui T, Ohnishi M, Sawaki M, Fujii M, Matsumoto T, Kinoshita M: Angiotensin Ⅱ type 1 receptor antagonist decreases plasma levels of tumor necrosis factor alpha, interleukin-6 and soluble adhesion molecules in patients with chronic heart failure. J Am Coll Cardiol 2000; **35**: 714−721