

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 III, 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/ml before therapy to 0.21 ± 0.08 pg/ml 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/ml, $p < 0.05$). 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 failure²⁻⁴. 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- α (TNF- α) in patients with congestive heart failure⁵⁻¹⁰). 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 II 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 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 \pm 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 °C 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 \pm SD. Comparison of variables before and after therapy was performed by Wilcoxon signed-ranks test. All comparisons were two-tailed.

RESULTS

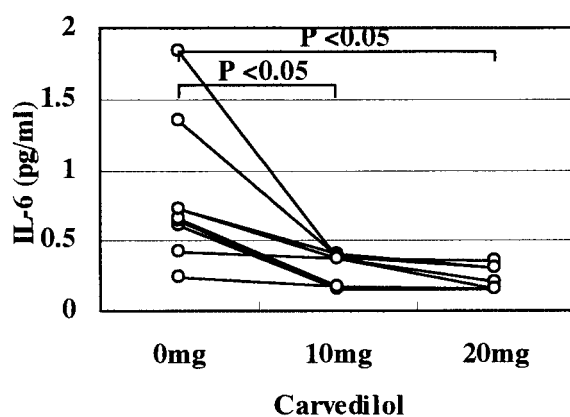
Changes in clinical parameters are shown in **Table 1**. The heart rates decreased significantly after the initiation of carvedilol. The blood pressures were unchanged. All patients were classified as NYHA functional class II before the start of beta-blocker therapy, and five patients were symptomatically 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 20mg vs baseline
		10 mg daily	20 mg daily	
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 (patients)	9		4	NS
NYHA class (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

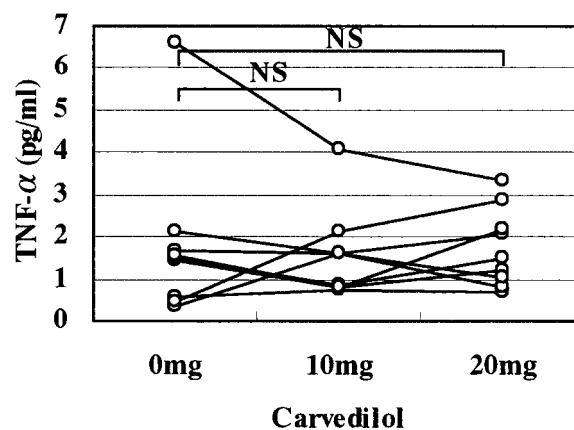
Continuous values are mean ± SD. *BNP levels were measured in only five patients at this dose. **Echocardiographic data were obtained in only seven patients at this dose.

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 10mg/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 20mg/day ($p < 0.05$). Moreover, there was already a significant decrease when carvedilol had been increased to 10mg/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 10mg/day, and 1.74 ± 0.93 pg/ml at 20mg/day.

DISCUSSION

TNF-α, IL-1β, IL-1α, and IL-6 are classified as proinflammatory cytokines¹², and are considered to suppress cardiac function by various mechanisms, such as decreasing left ventricular contractility through nitric oxide production¹³ and impairing coupling of beta-adrenergic receptors to adenosine 3', 5'-cyclic monophosphate production¹⁴. 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 10mg daily. This finding might be informative for deciding the optimal clinical dose of carvedilol for beta-blocker therapy in the future.

The calcium antagonist amlodipine¹⁶, the ACE inhibitor enalapril¹⁷, and the angiotensin receptor antagonist candesartan¹⁸ 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 reasons⁷⁻⁹. However, our results suggest that IL-6 level reflects the improvement of congestive heart failure better than TNF-

, 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 I-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 10mg/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 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20mg/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/mlからカルベジロール20mg/day導入後の 0.21 ± 0.08 pg/mlまで有意に減少した($p < 0.05$)。さらに, カルベジロール10mg/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/ml, $p < 0.05$)。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 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。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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