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/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.

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.2 Since then, many studies have confirmed the efficacy of beta-blockers in the management of congestive heart failure3-4. On the other hand, some studies have demonstrated elevated circulating levels of...
various cytokines including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in patients with congestive heart failure. Whether beta-blocker therapy changes the circulating levels of cytokines along with the improvement of congestive heart failure remains uncertain. Ohtsuka et al. 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 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 (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 ± 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.
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 daily. The decrease was already significant when carvedilol had been increased to 10 mg/day. IL-6 = interleukin-6.

Fig. 2 shows the changes in plasma levels of tumor necrosis factor-alpha (TNF-α). The plasma levels of TNF-α 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, and are considered to suppress cardiac function by various mechanisms, such as decreasing left ventricular contractility through nitric oxide production and impairing coupling of beta-adrenergic receptors to adenosine 3′,5′-cyclic monophosphate production. Tsutamoto et al. 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, 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, the ACE inhibitor enalapril, and the angiotensin receptor antagonist candesartan 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. showed that plasma levels of TNF- were progressively elevated with decreasing functional status. Our study failed to show any change of TNF- 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- for unknown reasons. However, our results suggest that IL-6 level reflects the improvement of congestive heart failure better than TNF-.

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 before the initiation of beta-blocker therapy, and their baseline IL-6 levels were lower than those reported in other studies. 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- 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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References


Histamine, thrombin and platelet-activating factor induce a redistribution of P-selectin while interleukine-1 and tumor necrosis factor stimulate synthesis of E-selectin. Firm adhesion is mediated via binding integrin molecules that are located on the leukocyte surface with intercellular adhesion molecule 1 (ICAM-1) located on the endothelial surface. Systemic effects of inflammation include fever, leukocytosis and secretion of C-reactive protein, serum amyloid, globulins, complement, coagulation proteins by liver and behavioral signs such as anorexia, somnolence, and malaise. Local signs include redness, pain, edema and an increased temperature. An increased local temperature and redness result from arterial hyperemia. 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-alpha) 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). TNF-alpha 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. Carvedilol was also later reported to have favorable effects in patients exclusively with idiopathic DCM [35]. In COMET trial, 3,029 patients with CHF were randomized to receive metoprolol tartrate (a second-generation beta blocker) with a target dose of 50 mg twice daily or carvedilol with a target dose of 25 mg twice daily. In pediatric patients with dilated cardiomyopathy, carvedilol at a dose of 0.4 mg/kg/day in addition to standard therapy improves cardiac function and symptoms. Interleukin (IL)-18 is among the pro-inflammatory cytokines involved in cardiovascular changes [53] and serum IL-18/IL-10 ratio is an independent predictor of adverse cardiovascular events in acute coronary syndrome patients [54, 55].