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Effects of Different Degrees of Sympathetic Antagonism on Cytokine Network in Patients With Ischemic Dilated Cardiomyopathy

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ABSTRACT

Background: The proinflammatory cytokines have been implicated in the pathogenesis of heart failure. Recent studies have shown that β-adrenergic blockade can modulate cytokine production. This study investigates the different impact of different degrees of sympathetic antagonism on circulating levels of cytokines in patients with heart failure resulting from ischemic dilated cardiomyopathy (IDC).

Methods and Results: Thirty-five patients with IDC were randomly assigned to receive metoprolol or carvedilol in an open-label study. Echocardiographic measurements and circulating levels of tumor necrosis (TNF)-α and interleukin (IL)-1β and IL-6 were obtained at baseline and after 3 months of treatment. The 2 β-blockers significantly improved the left ventricular ejection fraction and reduced end-diastolic and end-systolic volume. The magnitude of these changes was greater with carvedilol than with metoprolol (respectively $P < .001$, $P < .05$, and $P < .05$). Both treatments induced a significant decrease in the levels of cytokines (for all $P < .01$), but the decrease in TNF-α and IL-1β was more consistent in the carvedilol group ($P < .01$).

Conclusion: Our results support the hypothesis that a more complete block of sympathetic activity by carvedilol induces a greater decrease in the circulating levels of proinflammatory cytokines that could explain, at least in part, the better improvement in the left ventricular remodelling and systolic function in patients with IDC.

Key Words: Heart failure, cytokines, sympathetic antagonism, remodeling.

The role of neurohormonal overactivation, such as the norepinephrine and renin-angiotensin-aldosterone system, in the pathogenesis of heart failure has well been established. Heart failure is characterized by increased plasma norepinephrine levels and increased sympathetic nervous outflow to the heart,[1] and this sympathoexcitation is a major determinant of prognosis in chronic heart failure.[2,3] However, in addition to the classic neurohormones elaborated in failing myocardium, investigators have recently focused their attention on the proinflammatory cytokines. In 1990 Levine et al.[4] demonstrated that circulating levels of tumor necrosis factor (TNF)-α were elevated in patients with end-stage heart failure. Elevated circulating levels of other proinflammatory cytokines, such as interleukin (IL)-1β and IL-6, have also been reported in such patients.[5–8] Thus the immune-mediated mechanism may play an important role in the progression of heart failure. Moreover, a relationship between TNF-α and both New York Heart Association (NYHA) functional class and neurohumoral activation has been detected.[9,10] In a recent study catecholamines stimulation has been shown to modulate rat myocyte cytokine production.[11] During experimental myocardial infarction–induced heart failure, β1-selective adrenergic receptor blockade by metoprolol decreased myocardial expression of TNF-α and IL-1β that was related to unfavorable ventricular remodelling.[12] Likewise, in patients with idiopathic dilated cardiomyopathy, both metoprolol and carvedilol lower the increased levels of TNF-α and the soluble form of its receptor.[13,14] However, because differential effects of the selective and nonselective β-adrenergic receptor blockade on sympathetic activity exist,[15,16] a different impact of different β-adrenergic blocking agents on cytokine production in heart failure may be speculated .

Thus we investigated the effects of metoprolol (β1-selective) versus carvedilol (β-nonselective plus α-adrenergic receptors blockade) on circulating cytokine levels and left

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ventricular remodeling in patients with heart failure resulting from ischemic dilated cardiomyopathy (IDC).

Methods

Study Patients

Thirty-five patients with diagnosis of chronic heart failure secondary to ischemic heart disease were recruited. All patients were symptomatic with a minimum of a 6-month history of NYHA class II, III, or IV and had documented left ventricular (LV) dysfunction with an LV ejection fraction (LVEF) ≤40%. Exclusion criteria included acute coronary syndrome within 3 months or active angina, valvular disease, hypertension, pulmonary disease, kidney failure, diabetes, thyroid disease, chronic infections, malignancy or collagen vascular disease, and history of alcohol. Before the study, patients were treated for at least 2 weeks with constant doses of angiotensin-converting enzyme inhibitors, diuretics, and digoxin. No patients had received anti-inflammatory drugs within the preceding 2 weeks. All patients gave written informed consent, and the study was approved by the Ethic Committee of our Institution. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Study Protocol

After baseline measurements, patients were randomized in an open-label fashion to receive either metoprolol tartrate or carvedilol in addition to the usual treatment. Metoprolol and carvedilol were started at a dose of 6.25 mg and 3.125 mg, respectively, twice daily. The dose was uptritated biweekly with a doubling of the twice-daily dose to a target of 100 mg (50 mg twice daily) of metoprolol and 50 mg (25 mg twice daily) of carvedilol (if tolerated). These doses were selected considering previous large multicenter trials with the 2 drugs[17–19,25] and the body weight of our patients (≤85 kg). During this period patients were reassessed weekly. Maintenance of final doses was continued for an additional 3-month period. At end of this period all measurements were repeated.

Echocardiographic Measurements

Two-dimensional echocardiography was performed with a phased-array imaging system (ATL HDI system, Bothell, Washington) equipped with a 2.25-MHz transducer. Each patient was studied in the left lateral decubitus position after at least 10 minutes of recumbency. LV end-diastolic (EDV) and end-systolic (ESV) volumes were calculated with the modified Simpson rule and indexed to the body surface area. All measurements were obtained in sinus rhythm as a mean of at least 3 consecutive beats. LVEF was calculated by the formula: LVEF = (EDV − ESV)/EDV × 100. All echocardiographic recordings were made by the same investigator (F.D.) and were evaluated independently by 2 principal investigators (M.L. and L.S.).

Enzyme Immunoassays

Blood was collected from an antecubital vein into pyrogen-free vacuum blood tubes after at least 30 minutes of bed rest. Plasma was immediately separated by centrifugation at 4°C and 1,000 *g* for 15 minutes and the serum samples were stored at −80°C until analysis. Plasma levels of TNF-α, IL-1β, and IL-6 were measured by commercial enzyme amplified sensitivity immunoassay kits according to the manufacturer's specifications (Medgenix Diagnostics, Fleurus, Belgium). Circulating cytokine levels were also measured in 15 age-matched normal subjects (52 ± 9 years), with 10 male and 5 female selected as the control group. The intra- and interassay coefficients of variation were less than 10% for all assays.

Statistical Analysis

Values are expressed as mean ± standard deviation. Because the cytokine levels were not normally distributed, these data are presented as median and 25th to 75th percentiles. Baseline characteristics of the 2 groups of patients were compared by the unpaired *t*-test for continuous variables and the Fischer exact test for categorical variables. Analysis of variance was used for between-group comparison. Within-group comparison was made with the paired *t*-test when data were distributed normally and with the Wilcoxon sign-rank test when tests of normality failed. The NYHA functional class and the absolute (or the percent) change from baseline in LVEF, EDV and ESV were compared between 2 treatment groups with the Mann-Whitney rank-sum test. In the present study a sample size of 35 patients would have 80% power to detect a difference of ± 5.3% in LVEF ($\alpha = 0.05$) using a 2-tailed test. A P value $<.05$ was considered significant.

Results

The baseline clinical characteristics of the 2 treatment groups are shown in Table 1. The 2 groups were homogeneous in age, gender, or clinical signs of chronic heart failure. Three patients withdrew during treatment with metoprolol, 1 because of poor drug compliance and 2 who were hospitalized because of increased breathlessness. In the carvedilol group 2 patients did not complete the study because of worsening symptoms and they were hospitalized. None of the remaining 30 patients were admitted to hospital. In the maintenance phase of treatment the mean daily doses of metoprolol and carvedilol were, respectively, 93 ± 17 and 45 ± 10 mg. Target doses were achieved in 87% of patients in the metoprolol group and 80% of patients in the carvedilol group. The highest dose was 100 and 50 mg and

Table 1. Patients Characteristics

	Metoprolol (n = 15)	Carvedilol (n = 15)	*P* value
Age (y)	57.6 ± 11.9	58.8 ± 11.1	.78
Men/women	9/6	10/5	1.00
NYHA functional class			
II	5	4	1.00
III	7	8	1.00
IV	3	3	1.00
Heart rate (beats/min)	90.6 ± 12.3	89.8 ± 10.2	.85
Systolic blood pressure (mm Hg)	119.6 ± 11.8	121.6 ± 13.9	.67
LV ejection fraction (%)	29.7 ± 7.4	29.9 ± 8.2	.94
Pharmacologic agents			
ACE inhibitors	15 (100%)	15 (100%)	1.00
Diuretics	15 (100%)	15 (100%)	1.00
Digitalis	10 (67%)	11 (73%)	1.00
Nitrates	13 (87%)	14 (93%)	1.00

ACE, angiotensin-converting enzyme; LV, left ventricular; NYHA, New York Heart Association.

the lowest 50 and 25 mg, respectively, for metoprolol and carvedilol.

Effects on Clinical Variables

The results are shown in Table 2. There was an overall improvement in NYHA functional class with both metoprolol ($P < .01$) and carvedilol ($P < .01$) treatment. The difference between interventions was not statistically significant. With both β-blockers therapy, heart rate decreased significantly from 90.6 ± 12.3 to 68.4 ± 9.8 beats/min ($P < .001$) after metoprolol and from 89.8 ± 10.2 to 67.8 ± 9.4 beats/min after carvedilol ($P < .001$). There was no between-group difference in the changes. Systolic and diastolic arterial pressure did not change after both treatments.

Effects on LV Remodeling and Systolic Function

After metoprolol LVEF improved from 29.7 ± 7.4% to 31.9 ± 7.6% ($P < .001$), EDV decreased from 121.6 ± 10.5 mL/m^2 to 115.3 ± 13 ml/m^2 ($P < .05$) and ESV decreased from 85.5 ± 13.2 mL/m^2 to 78.4 ± 14.3 mL/m^2 ($P < .01$). After carvedilol LVEF improved from 29.9 ± 8.2 % to 37 ± 10.4% ($P < .001$), EDV decreased from 127 ± 12.5 mL/m^2 to 112.3 ± 12.4 mL/m^2 ($P < .001$) and ESV decreased from 89.4 ± 17.2 mL/m^2 to 70.7 ± 14.9 mL/m^2 ($P < .001$). The magnitude of the changes in LVEF, EDV, and ESV was significantly greater with carvedilol than with metoprolol, respectively, $P < .001$ (+7 ± 4.2% versus +2.2 ± 2.3%), $P < .05$ (−14.6 ± 11.8 mL/m^2 versus −6.3 ± 9.6 mL/m^2) and $P < .001$ (−18.7 ± 7.7 mL/m^2 versus −7.1 ± 8.4 mL/m^2).

Effects on Circulating Cytokines

Serum levels of cytokines were significantly higher in patients with IDC than in normal subjects. In the control group TNF-α was 8 (3-12) pg/mL ($P < .001$), IL-1β 5 (3-8) pg/mL ($P < .001$), and IL-6 4 (2-6) pg/mL ($P < .001$). The treatment with either metoprolol or carvedilol was associated with a significant decrease in TNF-α, IL-1β, and IL-6 (for all $P < .01$). When data were compared between 2 treatment groups, a significant difference was found in mean values of TNF-α and IL-1β ($P < .01$), although there was a similar decrease in the levels of IL-6 (Fig. 1).

Thus EDV and ESV decreased concurrently with the cytokine levels after β-blocker therapy. Nevertheless, a major reduction in EDV and ESV with carvedilol treatment was in line with a greater decrease of TNF-α and IL-1β but not IL-6 (Fig. 2).

Discussion

In this study we have demonstrated in patients with chronic heart failure secondary to coronary artery disease that both metoprolol and carvedilol significantly improved symptoms despite a greater increase in LVEF achieved with carvedilol. In addition, in the carvedilol group we have observed a more substantial benefit on LV remodeling. These observations are consistent with previous studies either the placebo-controlled trials or the trials that directly compared the 2 drugs with each other.[17–19] In contrast, some authors observed no difference between metoprolol and carvedilol treatment in the extent of LVEF changes.[20–22] The reason for the different hemodynamic responses could be related to unlike trial design, etiology distribution (ie, ischemic cardiomyopathy and dilated idiopathic cardiomyopathy) or ethnic derivation. Moreover, in 1 study,[22] patients had already received β-blockers for more than 1 year, so changes in hemodynamic obtained after cross-over may be irrelevant. Even though relevant influence on long-term morbidity and mortality is associated with either metoprolol or carvedilol therapy,[23,24] definitive data on comparison effects of both are now available at the end of the Carvedilol Or Metoprolol European Trial: carvedilol extends survival compared with metoprolol.[25] An increase in the LVEF was the most consistent effect of β-blocker therapy in patients with heart failure. The precise mechanism of this improvement in LV myocardial performance still remains not entirely clear, although the effect of treatment on LVEF, even if small, favorably influences survival.[26] Could the differences observed in our study be related to the minor degree of β_1-receptor blockade with the used dose of metoprolol? The selected doses of metoprolol and carvedilol were comparable to those that have been employed in many large trials

Table 2. Effects of β Blockade on Clinical Data

	Metoprolol (n = 15)		Carvedilol (n = 15)		
	Baseline	3 Months	Baseline	3 Months	*P* value
NYHA functional class					
Mean	2.8 ± 0.7	2.2 ± 0.7*	2.9 ± 0.7	1.9 ± 0.6*	.15
I/II/III/IV	0/5/7/3	2/7/6/0	0/4/8/3	4/9/2/0	
Heart rate (beats/min)	90.6 ± 12.3	68.4 ± 9.8†	89.8 ± 10.2	67.8 ± 9.4†	.87
Systolic blood pressure (mm Hg)	119.6 ± 11.8	120.3 ± 11.2	121.6 ± 13.9	118.6 ± 10.4	.67
Diastolic blood pressure (mm Hg)	70.0 ± 8.8	72.3 ± 8.6	72.3 ± 7.7	70.3 ± 6.9	.46

NYHA, New York Heart Association.
P value indicate differences between metoprolol and carvedilol treatment.
*$P < .01$;
†$P < .001$ versus baseline.

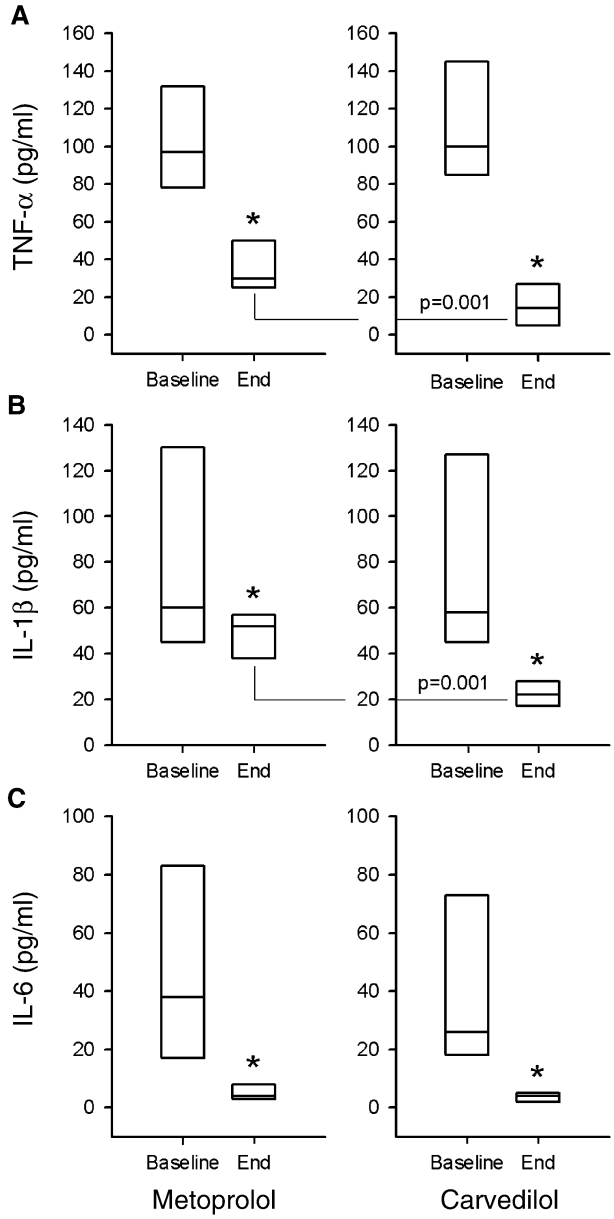

Fig. 1. Different effects of metoprolol and carvedilol on circulating levels of cytokines. Data in box plots are given as median and 25th to 75th percentiles. $^{*}P < .01$ versus baseline.

comparing metoprolol tartrate and carvedilol.[17–19,25] In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure study[24] the mean dose of metoprolol succinate (CR/XL) was 159 mg daily that produced a reduction in heart rate of 14 beats/min. Considering that the extend-release formulation of metoprolol is 30% to 35% less bioavailable than immediate release,[27] the mean dose of metoprolol succinate in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure study is equivalent to 111 to 103 mg of metoprolol tartrate. Moreover, the 2 formulations of metoprolol produce similar hemodynamic effects in patients with heart failure.[28] Finally, our data show a decrease in heart rate of 22 beats/min during treatment with metoprolol tartrate that was comparable to that observed in the carvedilol group. Thus as extensively debated in the Carvedilol Or Metoprolol European Trial study,[25] we believe that at the doses of metoprolol tartrate and carvedilol used in the present study, a comparable degree of β_1 receptor blockade is obtainable and the differences observed between the 2 drugs were probably not related to under dosing of metoprolol.

Other results of this study showed that both metoprolol and carvedilol treatment decreased circulating levels of cytokines including TNF-α, IL-1β, and IL-6 that could in part explain the clinical benefit of 2 β-blockers. Our observation could apparently be in contrast with the results of the recent Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial.[29] This study strongly showed the lack of beneficial effects of TNF-α antagonist infliximab in patients with heart failure, generating the hypothesis that TNF-α did not act as a deleterious factor. Infliximab is a recombinant monoclonal antibody that specifically neutralizes the TNF-α but not the other circulating cytokine that might maintain their toxic effects. However, in the ATTACH trial, at 14 weeks, when IL-6 levels were suppressed, LVEF significantly increased in patients treated with infliximab versus the placebo group, but not at 28 weeks when IL-6 levels increased toward baseline. So, the data of this trial cannot exclude with certainty that other cytokine, and maybe TNF-α, may play a role in the pathogenesis of heart failure by the direct toxic effects on the myocardium as extensively documented in the literature. In fact, clinical and basic research studies support the hypothesis that the progression of heart failure is associated with production of proinflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-10.[4–7,9,10] These cytokines are capable of modulating cardiovascular structure and function by several mechanisms that mimic the phenotypic changes of heart failure including myocyte apoptosis,[30] extracellular matrix alterations,[31] and chamber remodelling.[32] So, some analogy exists between the biologic effects of cytokines and sympathetic overdrive in the failing heart. A time-dependent elevation of IL-1β and IL-6 after norepinephrine infusion has also been observed. This was prevented when combined α- and β-receptor antagonist carvedilol was infused with norepinephrine.[33] The increase in circulating levels of IL-6 is mainly associated with the activation of the sympathetic nervous system in patients with congestive heart failure, even though it is a prognostic predictor independent of plasma norepinephrine and LVEF.[7] Nevertheless, in a recent study achieved on a rabbit model of myocardial infarction-induced heart failure, Prabhu et al[12] have suggested that prolonged β-adrenergic activation is a stimulus for myocardial TNF-α and IL-1β expression but not for IL-6 and that β-blockade with metoprolol decreased myocardial cytokine expression with a positive effect on LV remodeling. Similar effects of metoprolol on circulating levels of TNF-α and anti-inflammatory cytokines were also reported in patients with idiopathic dilated cardiomyopathy.[8,13,14]

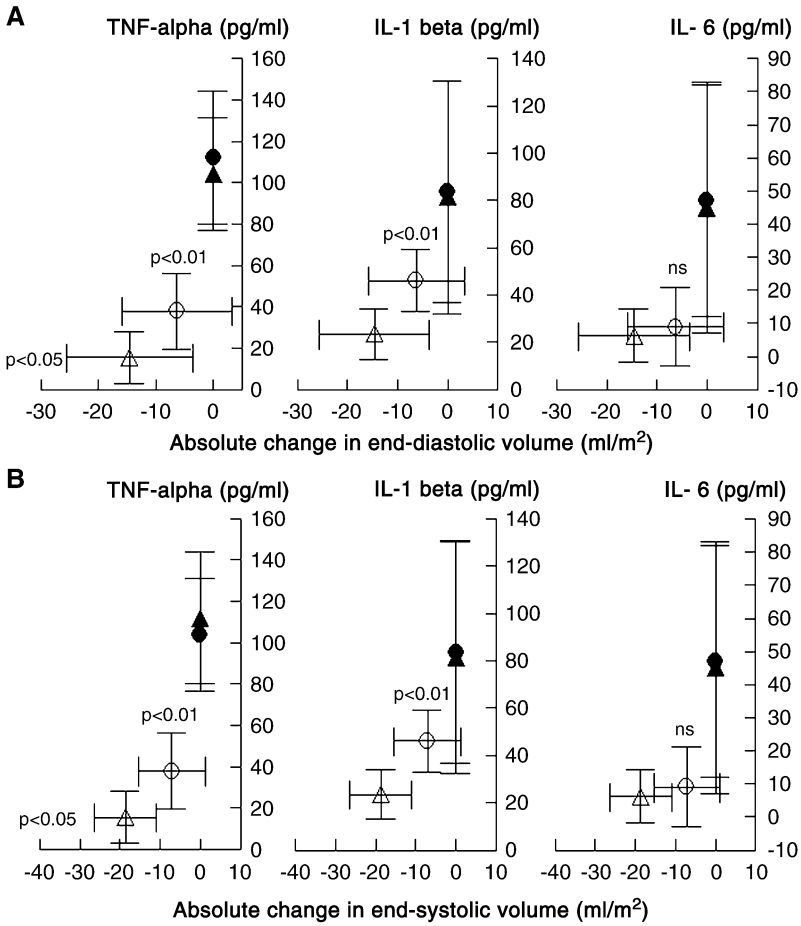

Fig. 2. Relationship between left ventricular remodeling and circulating levels of cytokines in the metoprolol (circle) and carvedilol (triangle) groups at baseline (solid symbols) and at the end of the treatment period (open symbols).

But the most interesting finding of our study is the greater reduction in TNF-α and IL-1β, but not IL-6, after carvedilol treatment at the same time as the greater reduction in EDV and ESV. These data suggested that the different degrees of sympathetic antagonism were associated with the distinct response on both the circulating levels of cytokines and remodeling. Carvedilol differs from metoprolol as it is a nonselective β_2 and α_1 receptor antagonist. There is evidence that doxazosin treatment, in addition to metoprolol, produced identical effects as those seen in patients receiving metoprolol alone,[34] suggesting that during treatment with carvedilol, the peripheral α_1 antagonism does not appear to be functionally important.[35] These observations suggested the lack of influence of α_1-blockade properties of carvedilol to determine differences with metoprolol in heart failure. Recently, it has been demonstrated that carvedilol induced a significant reduction in cardiac and systemic norepinephrine spillover, the indirect measure of norepinephrine release, but not in patients treated with metoprolol as resulted from a postganglionic effect that is regulated, at least in part, by prejunctional β_2-adrenergic receptors.[16]

In view of our data, we speculate that a more complete sympathetic activity inhibition by carvedilol can produce a greater block of cytokine production that could most likely account for different effects on myocardial remodeling and on clinical outcome. Nevertheless, we cannot exclude that the different impact of the 2 β-receptors blockade on left ventricular remodeling might be related to the antioxidant property of carvedilol.[36] Oxidative stress is elevated in failing myocardium,[37,38] and administration of carvedilol causes a reduction in the oxidative level together with improvement in cardiac function.[38] An important stimulus for increased oxidative stress is the local production of TNF-α.[37] Thus it is possible to speculate that at least part of the antioxidative effect of carvedilol could depend on its interaction with cytokine. But, further studies are needed to identify the precise relationship between sympathetic overdrive, cytokine, oxidative stress, and remodeling.

Although part of the source of the increase in IL-6 is the peripheral vascular tissue[39] in response to various vasoconstrictors such as angiotensin II and endothelin-1, the main origin is leukocytes, including macrophages and

lymphocytes. The similar decrease in levels of IL-6 produced by either metoprolol or carvedilol in our study population, suggests that the failing myocardium-induced increase in IL-6 could be dependent on prevalent β_1-adrenergic receptors stimulation of target cells.

Limitations of the Study

Some limitations of our research must be pointed out. A major limitation of this study is the relatively small number of patients. We recognize that a wider sample size could have improved the power of our results. The severe patient inclusion criteria have prevented the enrollment of a large study population in a reasonable period. Nevertheless, the study sample size did not preclude obtaining statistically significant differences between the 2 treatment arms because of the accuracy of the statistical analysis performed. Although our results are not conclusive, we believe that they generate an interesting hypothesis needing to be confirmed in further large trials. Second, this study was not randomized to treatment but open label. This could be relevant for subjective parameters as NYHA class, even if we have not considered symptoms as a primary objective. Furthermore, echocardiographic determinations and enzyme immunoassay analysis were performed in a blinded manner with regard to the treatment.

Conclusion

The data of the present study suggest that the inhibition of sympathetic overactivation in patients with dilated cardiomyopathy secondary to ischemia through both β-blockers reduces the elevated levels of TNF-α, IL-1β, and IL-6. However, more marked inhibition of systemic and cardiac sympathetic activity with carvedilol produces a greater decrease in the circulating levels of proinflammatory cytokines concurrently with a better effect on the LV remodeling and systolic function. The differential effects of the nonselective versus the selective β-adrenergic antagonist on cytokine network will be helpful in explaining, at least in part, the clinical and hemodynamic outcome of comparative large trials. However, further studies are needed to verify this interesting hypothesis.

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