Comparison of the Effects of Carvedilol and Metoprolol on Exercise Ventilatory Efficiency in Patients With Congestive Heart Failure

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Background The slope of the relationship between ventilation and carbon dioxide production ($\dot{V}_E/\dot{V}_{CO_2}$ slope), obtained during symptom-limited ramp exercise testing, reflects exercise ventilatory efficiency. Importantly, the $\dot{V}_E/\dot{V}_{CO_2}$ slope is related to prognosis in patients with congestive heart failure (CHF). The aim of the present study was to determine the relationship between the institution of β -blockers, carvedilol or metoprolol, and the $\dot{V}_E/\dot{V}_{CO_2}$ slope during exercise in patients with CHF.

Methods and Results Fifty-seven patients with New York Heart Association functional class II or III with a radionuclide left ventricular ejection fraction (LVEF) of less than 40% received carvedilol or metoprolol in a randomized fashion. The $\dot{V}_E/\dot{V}_{CO_2}$ slope, LVEF and plasma brain natriuretic peptide (BNP) concentration were determined before and after 16 weeks of treatment. LVEF improved ($p < 0.01$), but the $\dot{V}_E/\dot{V}_{CO_2}$ slope and BNP did not. A significant improvement in the $\dot{V}_E/\dot{V}_{CO_2}$ slope was observed in patients with LVEF $< 29\%$ or BNP > 63 pg/ml (respective baseline median values) ($p < 0.05$, $p < 0.05$). In patients with BNP > 63 pg/ml, the improvement effect on the $\dot{V}_E/\dot{V}_{CO_2}$ slope with carvedilol was significantly greater than that with metoprolol ($p < 0.05$) and a significant improvement in the $\dot{V}_E/\dot{V}_{CO_2}$ slope was observed only in those who took carvedilol ($p < 0.01$).

Conclusions The $\dot{V}_E/\dot{V}_{CO_2}$ slope was not improved after β -blocker therapy in any of the patients. However, it did improve in patients with a lower LVEF or higher BNP level at baseline, and carvedilol was more effective than metoprolol in improving the $\dot{V}_E/\dot{V}_{CO_2}$ slope in patients with higher BNP levels at baseline. (Circ J 2008; 72: 358–363)

Key Words: Beta-blockers; Exercise; Heart failure; Ventilatory efficiency

The slope of the relationship between ventilation and carbon dioxide production ($\dot{V}_E/\dot{V}_{CO_2}$ slope) is obtained during symptom-limited cardiopulmonary exercise testing, by plotting ventilation ($\dot{V}_E$) vs carbon dioxide production ($\dot{V}_{CO_2}$). The increase in the $\dot{V}_E/\dot{V}_{CO_2}$ slope reflects reduced ventilatory efficiency of gas exchange, which is associated with increased physiological dead space, as well as a decrease in the partial arterial pressure of carbon dioxide (P_aCO_2) regulatory set point.^{1,2} The $\dot{V}_E/\dot{V}_{CO_2}$ slope is probably the best indicator of decreased pulmonary blood flow and is elevated in most patients with congestive heart failure (CHF).^{3,4} Besides the classical risk factors such as left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class IV symptoms and neurohormonal markers, peak oxygen consumption ($\dot{V}O_2$) was found to predict survival in patients with CHF.^{5,6} Recently, the $\dot{V}_E/\dot{V}_{CO_2}$ slope was shown to be a better prognostic indicator than

peak $\dot{V}O_2$,^{7–9} suggesting that improvement in the slope could be used as an indicator of prolonged survival of patients with CHF.

Large clinical trials have established that β -blockers improve left ventricular function and the survival of patients with CHF.^{10–13} Several studies have compared metoprolol with carvedilol for treating patients with mild to moderate CHF,^{14–17} and some have shown that carvedilol is more efficacious than metoprolol in improving LVEF and hemodynamic parameters.^{15,17} The recently published large-scale Carvedilol or Metoprolol European Trial (COMET) demonstrated that carvedilol reduces total mortality to a greater extent than metoprolol.¹⁸ However, the relationship between the institution of β -blocker therapy and the $\dot{V}_E/\dot{V}_{CO_2}$ slope in patients with CHF is still unknown.

Thus, the purposes of this study were (1) to investigate whether administration of β -blockers can improve the $\dot{V}_E/\dot{V}_{CO_2}$ slope, and (2) to compare the influence of 2 β -blockers, carvedilol and metoprolol, on the $\dot{V}_E/\dot{V}_{CO_2}$ slope in patients with CHF.

Methods

Study Population

A total of 58 patients initially participated, but 1 patient was withdrawn because of sudden death. Therefore, a total of 57 patients with NYHA II–III CHF were examined. The etiology was dilated cardiomyopathy, ischemic, and valvular

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heart diseases. Each patient had an LVEF <40% by radio-nuclide or contrast left ventriculography and were treated with conventional medical treatment including digitalis glycosides, diuretics, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. They had been clinically stable under these medications for more than 3 months. Patients with a heart rate (HR) <50 beats/min, systolic blood pressure (BP) <90 mmHg, significant bradyarrhythmia, atrioventricular block, serum creatinine concentration >3.0 mg/dl, or presence of stenotic valvular heart disease, alcohol abuse, active myocarditis, or hypertrophic obstructive cardiomyopathy were excluded. Because most of this study had been conducted before the release of the Ethical Guidelines of Clinical Research (July 30, 2003), the protocol had not been approved by the ethical committee. However, it conformed to the Ethical Guidelines of Clinical Research of the Ministry of Health, Labor and Welfare of Japan. Informed consent was given by all participants.

Study Protocol

Patients were randomized by lot into 2 groups to take either metoprolol tartrate or carvedilol, which were added to the usual treatment for CHF. Metoprolol and carvedilol were started at 5 mg/day and 2.5 mg/day, respectively, and the doses were gradually increased over 16 weeks until the target dose (80 mg/day and 20 mg/day, respectively) was attained, if tolerated (These are the accepted maximal doses of β -blockers for Japanese patients with CHF^{19,20}). If side-effects developed, the increment in the dose was slowed or the dose was lowered or temporarily discontinued. Before and after 16 weeks of administration of β -blocker, NYHA functional class, HR, and BP were determined, and ultrasound echocardiography and radionuclide ventriculography were performed.

The patients underwent a symptom-limited cardiopulmonary exercise test on an electronically braked computerized bicycle ergometer (Aerobic Exercise Ergometer, Nihon Kohden Corporation, Tokyo, Japan) with respiratory gas exchange measurement at baseline and after 16 weeks of treatment with β -blockers. The protocol consisted of 2 min of pedaling without load, followed by 15 W/min incremental exercise to the point of exhaustion. Dyspnea or fatigue was the required endpoint for termination of exercise. The 12-lead electrocardiogram, HR, and BP were obtained at rest and at each minute during exertion (Q-STRESS, Nihon Kohden Corporation). $\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$ and other exercise variables were computer-calculated. The $\dot{V}E/\dot{V}CO_2$ slope was determined as the linear regression slope of $\dot{V}E$ and $\dot{V}CO_2$ from the start of exercise until the RC point (the time at which ventilation is stimulated by CO_2 output and end-tidal CO_2 tension begins to decrease). Peak $\dot{V}O_2$ was defined as the average oxygen consumption during the final 20 s of maximal exercise. The anaerobic threshold ($\dot{V}O_{2AT}$) was determined using the V-slope method²¹

We divided the study population into 2 groups according to baseline values of the plasma brain natriuretic peptide (BNP) concentration or LVEF as a post-hoc analysis. The median BNP concentration, 63 pg/ml, and median LVEF, 29%, were chosen as cutoff points to divide the study population into 2 groups.

Statistical Analysis

All data are expressed as mean $\pm$ SD unless otherwise indicated. Comparisons of baseline patient characteristics between 2 groups were made by Fisher's exact test or Student's

Table 1 Baseline Characteristics of the Study Population

	Metoprolol (n=29)	Carvedilol (n=28)
Age, years	63 $\pm$ 11	60 $\pm$ 10
Sex, male, n (%)	24 (83)	26 (93)
NYHA class, n, II/III/IV	23/6/0	20/8/0
Ischemic etiology, n (%)	6 (21)	4 (14)
Atrial fibrillation, n (%)	6 (21)	13 (46)
Duration of illness, months	63 $\pm$ 73	41 $\pm$ 42
LVEDD, cm	6.1 $\pm$ 0.7	6.2 $\pm$ 0.8
LVEF, %	28 $\pm$ 8	27 $\pm$ 9
BNP concentration, pg/ml	165 $\pm$ 269	133 $\pm$ 199

There were no significant differences between the study groups in the baseline characteristics. Data are expressed as mean $\pm$ SD or number (%) of patients. NYHA, New York Heart Association; LVEDD, left ventricular end-diastolic dimension; LVEF, left Ventricular ejection fraction; BNP, brain natriuretic peptide.

unpaired t-test. Comparison of each parameter before and after the introduction of β -blockers was performed using Student's paired t-test. Comparison of changes in each parameter between the 2 groups was made by a repeated measure analysis of variance. Statistical significance was defined as a p-value <0.05.

Results

Patients' Characteristics

There were 29 patients who received metoprolol and 28 who received carvedilol. Table 1 summarizes the baseline characteristics of the study groups. There were no differences in age, sex, NYHA functional class, etiology of heart failure, duration of illness, left ventricular end-diastolic dimension (LVEDD) on echocardiography, LVEF, or plasma BNP concentration. There was no difference between the 2 groups in usage of concomitant medication.

Cardiac Function and Cardiopulmonary Exercise Testing

LVEDD significantly decreased in the metoprolol group only, but LVEF significantly increased in both groups 16 weeks after the start of therapy (Fig 1). The plasma BNP concentration did not significantly change after treatment in either group.

The HR at rest decreased significantly after treatment in both the metoprolol and carvedilol groups (Table 2). During exercise, HR decreased with both β -blockers after 16 weeks from the start of therapy. There was no change in maximal workload, peak $\dot{V}O_2$, or the ratio of the change in oxygen uptake to work rate from baseline to 16 weeks after the start of therapy in either group.

Changes in Exercise Ventilatory Efficiency Based on Baseline Cardiac Function

In the overall patient group, the $\dot{V}E/\dot{V}CO_2$ slope had not significantly changed after 16 weeks of therapy (32.3 $\pm$ 0.7 at baseline vs 32.2 $\pm$ 0.7 at 16 weeks).

Next we investigated the changes in the $\dot{V}E/\dot{V}CO_2$ slope based on the baseline plasma BNP concentration or LVEF. In patients with a baseline BNP concentration >63 pg/ml, the $\dot{V}E/\dot{V}CO_2$ slope had significantly improved 16 weeks after the start of therapy (Fig 2). In contrast, in patients with a baseline BNP concentration <63 pg/ml, the slope had significantly deteriorated from the start of therapy. Furthermore, in patients with a baseline LVEF <29%, the $\dot{V}E/\dot{V}CO_2$ slope had

Fig 1. Left ventricular end-diastolic dimension (LVEDD), left ventricular ejection fraction (LVEF), and plasma brain natriuretic peptide (BNP) concentration at baseline (0W) and 16 weeks (16W) in patients treated with metoprolol (solid bars) or carvedilol (open bars). Data are mean $\pm$ SD. * $p < 0.05$ vs baseline.

Table 2 Cardiopulmonary Exercise Testing

	Metoprolol (n=29)		Carvedilol (n=28)	
	Baseline	16 weeks	Baseline	16 weeks
BW, kg	65 $\pm$ 11	66 $\pm$ 12	66 $\pm$ 12	66 $\pm$ 11
HR rest, beats/min	86 $\pm$ 20	65 $\pm$ 13 [†]	87 $\pm$ 19	69 $\pm$ 13 [†]
HR exercise, beats/min	149 $\pm$ 25	121 $\pm$ 21 [†]	161 $\pm$ 37	136 $\pm$ 34 [†]
SBP rest, mmHg	126 $\pm$ 25	125 $\pm$ 24	130 $\pm$ 22	122 $\pm$ 20
SBP exercise, mmHg	184 $\pm$ 31	181 $\pm$ 30	192 $\pm$ 23	179 $\pm$ 29*
Work load AT, W	58 $\pm$ 14	61 $\pm$ 14	64 $\pm$ 11	63 $\pm$ 12
Maximal work load, W	109 $\pm$ 25	112 $\pm$ 28	118 $\pm$ 24	121 $\pm$ 24
$\dot{V}O_2$ rest, ml $\cdot$ kg ⁻¹ $\cdot$ min ⁻¹	3.4 $\pm$ 0.9	3.3 $\pm$ 0.8	3.3 $\pm$ 0.8	3.0 $\pm$ 0.7
$\dot{V}O_2$ AT, ml $\cdot$ kg ⁻¹ $\cdot$ min ⁻¹	10.8 $\pm$ 2.5	11.2 $\pm$ 2.4	11.5 $\pm$ 2.2	10.8 $\pm$ 2.6
Peak $\dot{V}O_2$, ml $\cdot$ kg ⁻¹ $\cdot$ min ⁻¹	19.2 $\pm$ 3.8	19.8 $\pm$ 5.2	20.3 $\pm$ 4.2	20.3 $\pm$ 3.7
$\Delta\dot{V}O_2/\Delta WR$	8.2 $\pm$ 1.4	8.7 $\pm$ 1.7	8.5 $\pm$ 2.7	8.5 $\pm$ 1.1
$\dot{V}E/\dot{V}CO_2$ slope	32.6 $\pm$ 5.0	33.1 $\pm$ 5.3	31.9 $\pm$ 4.9	31.3 $\pm$ 4.6

These measurements were done during symptom-limited cardiopulmonary exercise testing with measurement of respiratory gas exchange at baseline and at 16 weeks after the start of treatment with β -blockers.

Data are mean $\pm$ SD. * $p < 0.05$, [†] $p < 0.01$ vs baseline.

HR, heart rate; SBP, systolic blood pressure; $\dot{V}O_2$, oxygen consumption; $\dot{V}O_2$ AT, anaerobic threshold; $\Delta\dot{V}O_2/\Delta WR$, ratio of change in oxygen uptake to work rate; $\dot{V}E/\dot{V}CO_2$ slope, ratio of ventilation to carbon dioxide production.

Fig 2. Changes in the ratio of ventilation to carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ slope) based on baseline (0W) plasma brain natriuretic peptide (BNP) concentration. The $\dot{V}E/\dot{V}CO_2$ slope significantly increased in patients with BNP concentration < 63 pg/ml (solid circles), and significantly decreased in patients with BNP concentration > 63 pg/ml (open circles). Data are mean $\pm$ SD. 16W, 16 weeks.

Fig 3. Changes in the ratio of ventilation to carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ slope) based on baseline (0W) left ventricular ejection fraction (LVEF). The $\dot{V}E/\dot{V}CO_2$ slope significantly decreased in patients with LVEF $< 29\%$ (solid triangles), and significantly increased in patients with LVEF $> 29\%$ (open triangles). Data are mean $\pm$ SD. 16W, 16 weeks.

Fig 4. Changes in the ratio of ventilation to carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ slope) with β -blocker therapy. In the overall patient group, the $\dot{V}E/\dot{V}CO_2$ slope did not significantly change in patients treated with metoprolol (solid squares) or in those with carvedilol (open squares). In patients with a baseline (0W) plasma brain natriuretic peptide (BNP) concentration >63 pg/ml (BNP-high), the changes in the $\dot{V}E/\dot{V}CO_2$ slope with carvedilol were significantly greater than those with metoprolol and a significant improvement in the $\dot{V}E/\dot{V}CO_2$ slope was observed only in those who took carvedilol. Data are mean $\pm$ SD. 16W, 16 weeks.

significantly improved at 16 weeks after the start of therapy (Fig 3), but in patients with a baseline LVEF $>29\%$, the slope had significantly deteriorated from the start of therapy.

Changes in Exercise Ventilatory Efficiency With β -Blockers

In the overall patient group, the $\dot{V}E/\dot{V}CO_2$ slope did not significantly change after treatment with either metoprolol or carvedilol, and the improvement effect on the $\dot{V}E/\dot{V}CO_2$ slope did not differ significantly between the metoprolol and carvedilol groups (Fig 4). In patients with a baseline BNP concentration >63 pg/ml, the $\dot{V}E/\dot{V}CO_2$ slope significantly improved in the carvedilol group ($p<0.01$), but not in the metoprolol group. Furthermore, in patients with a baseline BNP concentration >63 pg/ml, the improvement effect on the $\dot{V}E/\dot{V}CO_2$ slope with carvedilol was significantly greater than that with metoprolol ($p<0.05$). There were no significant differences between the 2 groups in their baseline characteristics (BNP >63 pg/ml metoprolol group vs BNP >63 pg/ml carvedilol group) (Table 3). In patients with a baseline BNP <63 pg/ml, the $\dot{V}E/\dot{V}CO_2$ slope did not change in either treatment group (Table 4). According to the baseline LVEF, in patients with a baseline LVEF $>29\%$, the $\dot{V}E/\dot{V}CO_2$ slope significantly deteriorated in the metoprolol group ($p<0.05$). In patients with a baseline LVEF $<29\%$, although the $\dot{V}E/\dot{V}CO_2$ slope did not significantly change after either treatment, the changes in the slope of the carvedilol group tended to be greater than those in the metoprolol group. There were no significant differences between the 2

Table 3 Baseline Characteristics of Patients With BNP >63 pg/ml at Baseline

	Metoprolol (n=14)	Carvedilol (n=14)
Age, years	65 $\pm$ 12	62 $\pm$ 10
Sex, male, n (%)	12 (86)	13 (93)
NYHA class, n, II/III/IV	10/4/0	7/7/0
Ischemic etiology, n (%)	4 (29)	2 (14)
Atrial fibrillation, n (%)	4 (29)	9 (64)
Duration of illness, months	53 $\pm$ 50	34 $\pm$ 38
LVEDD, cm	6.3 $\pm$ 0.9	6.6 $\pm$ 0.9
LVEF, %	28 $\pm$ 9	22 $\pm$ 7
BNP concentration, pg/ml	316 $\pm$ 341	224 $\pm$ 253

There were no significant differences in the baseline characteristics of the 2 treatment groups of patients with BNP >63 pg/ml at baseline. Data are expressed as mean $\pm$ SD or number (%) of patients. See Table 1 for abbreviations.

groups in the baseline characteristics (LVEF $<29\%$ metoprolol group vs LVEF $<29\%$ carvedilol group).

Discussion

The present study demonstrated that (1) the $\dot{V}E/\dot{V}CO_2$ slope had not significantly changed in 57 patients with NYHA class II or III heart failure after 16 weeks of treatment with either metoprolol or carvedilol, (2) the $\dot{V}E/\dot{V}CO_2$

Table 4 Cardiopulmonary Exercise Testing According to Baseline Plasma BNP Concentration or LVEF Level

	Metoprolol		Carvedilol	
	Baseline	16 weeks	Baseline	16 weeks
BNP >63 pg/ml	n=14		n=14	
Peak $\dot{V}O_2$, ml $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$	18.5 $\pm$ 3.3	18.6 $\pm$ 3.8	18.5 $\pm$ 2.0	18.9 $\pm$ 2.8
$\dot{V}E/\dot{V}CO_2$ slope	34.3 $\pm$ 5.4	34.2 $\pm$ 5.8	33.9 $\pm$ 4.3	30.9 $\pm$ 4.2 [†]
BNP <63 pg/ml	n=15		n=14	
Peak $\dot{V}O_2$, ml $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$	20.0 $\pm$ 4.3	20.4 $\pm$ 5.9	22.1 $\pm$ 4.8	21.8 $\pm$ 4.1
$\dot{V}E/\dot{V}CO_2$ slope	31.0 $\pm$ 4.3	32.1 $\pm$ 4.9	30.0 $\pm$ 4.9	31.6 $\pm$ 5.1
LVEF $>29\%$	n=16		n=13	
Peak $\dot{V}O_2$, ml $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$	18.7 $\pm$ 3.2	18.8 $\pm$ 5.2	20.7 $\pm$ 4.0	20.8 $\pm$ 3.4
$\dot{V}E/\dot{V}CO_2$ slope	32.4 $\pm$ 5.1	34.3 $\pm$ 6.4*	31.2 $\pm$ 4.8	31.8 $\pm$ 5.5
LVEF $<29\%$	n=13		n=15	
Peak $\dot{V}O_2$, ml $\cdot$ kg $^{-1}$ $\cdot$ min $^{-1}$	19.9 $\pm$ 4.6	20.4 $\pm$ 4.9	19.9 $\pm$ 4.3	19.9 $\pm$ 4.0
$\dot{V}E/\dot{V}CO_2$ slope	32.8 $\pm$ 5.1	31.8 $\pm$ 3.3	32.6 $\pm$ 5.1	30.8 $\pm$ 3.9

Data are mean $\pm$ SD. * $p<0.05$, [†] $p<0.01$ vs baseline. See Tables 1, 2 for abbreviations.

slope significantly improved in patients with a higher baseline BNP concentration or a lower baseline LVEF, and (3) the changes in $\dot{V}E/\dot{V}CO_2$ slope with carvedilol were significantly greater than those with metoprolol in patients with a higher baseline BNP concentration.

Measurement of the $\dot{V}E/\dot{V}CO_2$ slope plays an important role in the treatment of patients with CHF, because it has been shown that an abnormally high slope predicts an increased risk of death among these patients, to an even greater degree than peak $\dot{V}O_2$.⁷⁻⁹ Earlier studies have demonstrated that patients with a $\dot{V}E/\dot{V}CO_2$ slope of more than 34 have significantly higher 1-year cardiac-related mortality than other patients²² and that patients with a $\dot{V}E/\dot{V}CO_2$ slope of more than 35 have a similarly high mortality as those with a peak $\dot{V}O_2 < 10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.²³ A combination of $\dot{V}O_2AT < 11 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and $\dot{V}E/\dot{V}CO_2$ slope > 34 better identifies patients at high risk for early death from CHF and is considered a better parameter for prioritizing patients for heart transplantation.²⁴ These findings suggest that an improvement in the $\dot{V}E/\dot{V}CO_2$ slope reflects prolongation of survival of patients with CHF.

There are a few studies that have documented the changes in $\dot{V}E/\dot{V}CO_2$ slope after β -blocker therapy in patients with CHF. Recently, Agostoni et al demonstrated that the $\dot{V}E/\dot{V}CO_2$ slope in heart failure patients decreases after chronic administration of carvedilol.²⁵ In our study, the $\dot{V}E/\dot{V}CO_2$ slope did not significantly decrease after administration of either carvedilol or metoprolol. Importantly, however, our results demonstrated that an improvement in the $\dot{V}E/\dot{V}CO_2$ slope occurred after administration of β -blockers in patients with a higher baseline BNP concentration or a lower baseline LVEF. A higher plasma BNP concentration or a lower LVEF reflects poorer cardiac function, because plasma BNP is constitutively secreted by the ventricular myocardium and therefore reflects ventricular overloading.²⁶ Thus our results imply that the $\dot{V}E/\dot{V}CO_2$ slope improved only in patients with poorer baseline cardiac function. The patient population in the study done by Agostoni et al had a higher percentage classified as NYHA functional class III (9 patients: 60% vs 6 patients (40%) in class II)²⁵ whereas in the present study more patients were classified as NYHA functional class II (43 patients: 75% vs III [14 patients]: 25%). The fact that Agostoni et al's study included patients with poorer cardiac function than ours may have contributed to them finding a correlation between $\dot{V}E/\dot{V}CO_2$ slope decrease and carvedilol administration. Considering that the $\dot{V}E/\dot{V}CO_2$ slope is a strong prognostic indicator, our results are consistent with those in a previous report from the Australia-New Zealand Heart Failure Group, which stated that in patients with CHF carvedilol prolonged life expectancy to a greater extent in patients with a higher baseline BNP concentration than in those with a lower baseline BNP concentration.²⁷

As Wasserman et al stated, an increase in the $\dot{V}E/\dot{V}CO_2$ slope reflects reduced ventilatory efficiency of gas exchange, which is associated with an increased ratio of physiological dead space volume to tidal volume (V_D/V_T), as well as with a decrease in the $PaCO_2$ regulatory set point.^{1,2,28} First, let us consider the possibility that amelioration of the $\dot{V}E/\dot{V}CO_2$ slope is attributable to decreased V_D/V_T . The increment in cardiac output because of improved cardiac function with β -blockers increases pulmonary flow, resulting in improved ventilation/perfusion mismatch and decreased V_D/V_T , and therefore, a decrease in the $\dot{V}E/\dot{V}CO_2$ slope. Thus, the poorer the original cardiac function, the greater the improve-

ment in cardiac function and resulting V_D/V_T and ventilation/perfusion mismatch, which explains why patients with poorer cardiac function show greater improvement in the $\dot{V}E/\dot{V}CO_2$ slope. However, in the present study, there were no significant differences between the effect on amelioration of LVEF by carvedilol and that by metoprolol in patients with baseline poorer cardiac function, although the $\dot{V}E/\dot{V}CO_2$ slope improved only in those patients who were treated with carvedilol. These findings raise the possibility that there is another factor affecting the $\dot{V}E/\dot{V}CO_2$ slope, other than improvement of V_D/V_T and ventilation/perfusion mismatch because of increment of LVEF.

Although carvedilol has been shown to improve the $\dot{V}E/\dot{V}CO_2$ slope in heart failure patients,²⁵ there has not been a study comparing the effects between carvedilol and metoprolol on the $\dot{V}E/\dot{V}CO_2$ slope. The present study demonstrated that in patients with a higher baseline BNP concentration the $\dot{V}E/\dot{V}CO_2$ slope significantly improved in those treated by carvedilol, but not in those treated by metoprolol, and the changes in the $\dot{V}E/\dot{V}CO_2$ slope with carvedilol were significantly greater than those with metoprolol. These findings suggest that carvedilol is more effective than metoprolol in improving the $\dot{V}E/\dot{V}CO_2$ slope in patients with advanced CHF. There are some differences in the pharmacologic properties of metoprolol and carvedilol. Metoprolol is a second-generation 1-selective blocking agent, and carvedilol is a third-generation 1-, 2-, and 1-blocker.²⁹ Carvedilol decreases the coronary sinus norepinephrine concentration and tends to suppress the number of myocardial α -receptors, whereas metoprolol tends to increase the coronary sinus norepinephrine concentration.^{4,30} Because of these actions, the chronotropic response to exercise, which is an accurate measure of the cardiac response to sympathetic stimulation,^{31,32} has been shown to be attenuated more effectively by carvedilol than by metoprolol.¹⁷ The greater improvement in clinical outcome in patients treated with carvedilol, which was reported recently by the COMET Study Group,^{18,33} may be related to its ability to provide more comprehensive protection against the deleterious actions of the sympathetic nervous system on the heart during stress. Carvedilol decreased cardiac norepinephrine spillover, but such changes were not apparent in CHF patients treated with metoprolol.³⁴ On the other hand, the $\dot{V}E/\dot{V}CO_2$ slope is significantly increased by the actions of the sympathetic nervous system,³⁵ because the sympathetic nervous system controls CO_2 sensitivity, a factor determining the $\dot{V}E/\dot{V}CO_2$ slope, other than V_D/V_T , and the ventilatory response to exercise.^{36,37} These findings suggest that carvedilol may contribute to improvement of the $\dot{V}E/\dot{V}CO_2$ slope in patients with CHF not only through amelioration of ventilation-perfusion mismatching, but also through regulation of CO_2 sensitivity caused by inhibition of sympathetic nervous system activity. Furthermore, intrinsic sympathetic activity is high in patients with advanced CHF with a high baseline plasma BNP concentration,³⁸ suggesting that sympathetic activity influences the $\dot{V}E/\dot{V}CO_2$ slope more in patients with a higher baseline BNP concentration than in other patients. Taken together, these findings may explain why in the present study carvedilol was more effective than metoprolol in improving the $\dot{V}E/\dot{V}CO_2$ slope in patients with a higher baseline BNP concentration.

Study Limitations

The main finding (ie, the significant improvement in the $\dot{V}E/\dot{V}CO_2$ slope with carvedilol in selected patients) was

obtained only by a post-hoc, retrospective analysis. The present patients were followed up for only 16 weeks, and thus the long-term effects of β -blocker therapy on the $\dot{V}E/\dot{V}CO_2$ slope are unknown. The severity of heart failure in the present patients was mild, as indicated by the high prevalence of NYHA II (75%) patients and a median BNP level of 63 pg/ml. A study of patients with more severe heart failure at baseline may be needed in the future.

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