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Left Ventricular Remodeling With Carvedilol in Patients With Congestive Heart Failure Due to Ischemic Heart Disease

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Objectives. **The aim of this study, a substudy of the Australia–New Zealand trial of carvedilol in patients with heart failure due to ischemic heart disease, was to determine the effects of this treatment on left ventricular size and function with the use of quantitative two-dimensional (2D) echocardiography.**

Background. **Beta-adrenergic blocking drugs have been shown to improve left ventricular ejection fraction in patients with heart failure due to either ischemic heart disease or idiopathic dilated cardiomyopathy. However, the effects of such treatment on left ventricular size remain uncertain.**

Methods. **One hundred twenty-three patients from 10 centers in New Zealand and Australia participated in the 2D echocardiographic substudy. Echocardiography was performed before randomization and was repeated after 6 and 12 months of treatment. Left ventricular end-diastolic and end-systolic volumes were measured from apical four- and two-chamber views with the use of a modified Simpson's rule method.**

Results. **After 12 months, heart rate was 8 beats/min lower in the carvedilol than in the placebo group, whereas left ventricular end-diastolic and end-systolic volumes were increased in the placebo group but reduced in the carvedilol group. At 12 months, left ventricular end-diastolic volume index was 14 ml/m^2 less in the carvedilol than in the placebo group ($p = 0.0015$); left ventricular end-systolic volume index was 15.3 ml/m^2 less ($p = 0.0001$), and left ventricular ejection fraction was 5.8% greater ($p = 0.0015$).**

Conclusions. **In patients with heart failure due to ischemic heart disease, carvedilol therapy for 12 months reduced left ventricular volumes, increased left ventricular ejection fraction and prevented progressive left ventricular dilation. These changes demonstrate a beneficial effect of carvedilol on left ventricular remodeling in heart failure. The observed changes may explain in part the improved clinical outcomes produced by treatment with carvedilol.**

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Myocardial infarction can lead to ventricular remodeling (1) with compensatory dilation and hypertrophy and subsequent systolic and diastolic dysfunction progressing to the clinical syndrome of congestive heart failure. Activation of neurohormonal systems, including the renin-angiotensin-aldosterone and sympathetic nervous systems, provides initial support for the failing heart. However, the continued neurohormonal activation in chronic heart failure (2) becomes deleterious with excessive vasoconstriction, volume expansion and continued deterioration in cardiac function. Ventricular remodeling can be favorably altered by angiotensin-converting enzyme (ACE) inhibitors (3), agents that have been shown to reduce morbidity and mortality in patients with heart failure (4,5) and asymptomatic left ventricular dysfunction (6).

The beta-adrenergic antagonists may provide further benefit for patients with congestive heart failure through inhibition of sympathetic activation. Several randomized clinical trials (7) have shown that beta-blocker therapy improves left ventricular ejection fraction after 3 to 6 months of treatment, whereas the effects on symptoms and exercise tolerance have been variable. A recent pooled analysis of the results from several trials demonstrated an improvement in left ventricular ejection fraction of ~5% (7). However, little is known about the effects of such therapy on left ventricular size. Although beta-blockade in normal subjects increases left ventricular ejection fraction, the increase is due to an increase in left ventricular volumes as a result of heart rate slowing rather than to any intrinsic improvement in left ventricular function (8). Thus, determination of the effect of beta-blocker therapy on left ventricular size is important to help determine the mechanisms

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ANZ = Australia-New Zealand
CI = confidence interval
NYHA = New York Heart Association
2D = two-dimensional

of the improvement in left ventricular ejection fraction that has been reported. Left ventricular volumes are also powerful predictors of survival after acute myocardial infarction (9,10), more so than left ventricular ejection fraction. Thus, reduction in left ventricular volumes with beta-blocker therapy is consistent with such therapy improving clinical outcomes in patients with congestive heart failure (11).

The Australia–New Zealand (ANZ) Heart Failure Research Collaborative Group trial (12) of carvedilol in patients with heart failure due to ischemic heart disease was conducted primarily to determine the effect of such therapy on left ventricular ejection fraction and exercise tolerance. The study demonstrated that carvedilol, in addition to standard heart failure therapy including ACE inhibitors, resulted in sustained improvement in ejection fraction (assessed by radionuclide ventriculography at 6 and 12 months). Exercise performance was maintained despite a marked reduction in rate-pressure product, and symptoms were unchanged at 12 months. Left ventricular end-systolic dimension, assessed by M-mode echocardiography, was significantly lower in the carvedilol group than in the placebo group. However, the reduction in left ventricular end-diastolic dimension was of borderline significance ($p = 0.05$). M-mode echocardiographic assessment of the left ventricle assumes uniform or global abnormalities of size and function (13). However, patients with heart failure due to ischemic heart disease may have multiple regional wall motion abnormalities; consequently, such measurements may not provide the most accurate estimate of left ventricular size. In these circumstances quantitative two-dimensional (2D) echocardiography provides a more accurate assessment of left ventricular size and shape. The present study, a substudy of the ANZ carvedilol trial, was designed to evaluate the effects of beta-blockade on left ventricular size and function by using 2D echocardiography. In this report we examine the effects of carvedilol treatment on left ventricular volumes.

Methods

Study design and subjects. The ANZ carvedilol trial was a randomized, double-blind, placebo-controlled trial of beta-blockade in patients with congestive heart failure. The details of the treatment regimen and outcome assessments for the main study have been described in full elsewhere (12). In brief, the study involved 415 patients with heart failure due to ischemic heart disease and was carried out in 20 hospitals in New Zealand and Australia. Patients were randomized to receive either carvedilol or matched placebo after a 2- to 3-week run-in period of open carvedilol therapy. After randomization, the dosage of carvedilol or placebo was titrated up to 25 mg twice daily, or the highest dose tolerated, during a 5-week period; maintenance treatment was then continued for an average of 20 months. Main end point assessments, including radionuclide left ventricular ejection fraction, treadmill exercise, M-mode echocardiography and symptom assessments, were performed at 6 and 12 months.

The present echocardiographic substudy was conducted at 10 centers (see Appendix) and involved 123 patients. Patients were eligible for the trial if they had 1) chronic stable heart failure due to ischemic heart disease (defined as a documented history of myocardial infarction, an exercise electrocardiogram positive for ischemia or angiographic evidence of coronary artery disease); 2) left ventricular ejection fraction by radionuclide ventriculography <45%; and 3) current New York Heart Association (NYHA) functional class II or III or previous NYHA functional class II to IV. In addition, eligibility for this substudy required adequate echocardiographic images, which included apical four- and two-chamber views suitable for left ventricular volume analysis. These requirements were met by 123 patients (55%) from a total of 225 patients recruited at these 10 centers. Exclusion criteria for the trial have been outlined in detail elsewhere (12).

Echocardiographic methods. Two-dimensional echocardiography was performed at the time of the baseline assessment and at 6 and 12 months. The ultrasound machines used were Acuson 128, Hewlett-Packard and Aloka (Aloka Co., Japan). Echocardiograms were performed by experienced technicians and repeated by the same technician within each center wherever possible, with care to obtain similar serial images. Images were recorded onto videotape at the end of the expiratory phase of normal respiration. A standard protocol was used based on apical four- and two-chamber views according to the recommendations of the American Society of Echocardiography (14).

All echocardiograms were analyzed at the central research laboratory (University of Auckland) by one observer who had no knowledge of treatment allocation. Cine loops of apical four- and two-chamber views were digitized by using a dedicated off-line computer (ImageVue, NovaMicrosonics) and stored on optical disc. End-diastole was defined as the frame with the largest and end-systole as the frame with the smallest cavity area. Manual planimetry of the endocardial border was performed and papillary muscles and intracavity thrombi (if present) were included in the chamber area. Biplane end-diastolic and end-systolic volumes were calculated by computer software according to a modified Simpson's rule (14) from the areas determined by planimetry. Three cycles (or 10 in the presence of atrial fibrillation) were measured for each assessment, avoiding postectopic beats, and the average volumes obtained. Primary end points were left ventricular end-diastolic and end-systolic volumes. Secondary end points were stroke volume and left ventricular ejection fraction. All volumes were normalized to body surface area (m^2) calculated from the patient's height and weight at each clinic visit. Stroke

volume was calculated as end-diastolic volume − end-systolic volume. Ejection fraction was calculated as stroke volume/end-diastolic volume.

Measurement reproducibility was assessed before analysis of the study recordings by measuring left ventricular volumes in 22 patients with heart failure and adequate echocardiographic images who were screened for the main study but did not meet the inclusion criteria. Each echocardiogram was measured on two occasions >1 week apart. The coefficients of variation for repeated measurements were 5.6% for end-diastolic volume and 6.2% for end-systolic volume. Normal ranges for left ventricular volumes have previously been established in our laboratory (15): left ventricular end-diastolic volume index 56.2 ± 9.9 ml/m^2 (mean ± SD); left ventricular end-systolic volume index 25.7 ± 5.0 ml/m^2; stroke volume index 30.5 ± 5.3 ml/m^2; left ventricular ejection fraction 54.4% ± 3.4%).

Statistical analysis. Data were analyzed by using the statistical software package SAS (version 6.10) (16) according to the original group allocation (i.e., by intention to treat). Differences between the treatment groups at baseline were tested by using the Student *t* test for continuous variables and the chi-square test with continuity equation for categoric variables. A multivariate approach to repeated measures (MANOVA) was performed by using the general linear modeling procedure of SAS, to allow correction for the correlation of repeated observations over time. This procedure protects against departures from type H covariance. The Helmert transformation was used to compare repeated observations of continuous echocardiographic variables. Post-hoc investigations were conducted by using orthogonal contrasts. Results are presented as the F approximation in the Hotelling-Lawley trace. All tests were two-tailed. A sample size of ~60 patients in each treatment group was estimated to provide ≥80% power at the 0.05 level of statistical significance to detect an absolute change in left ventricular end-diastolic volume of 10 ml/m^2 (assuming an SD for left ventricular end-diastolic volume index of 20 ml/m^2). A 5% significance level was used throughout.

Results

Study patients. Of the 123 patients, 63 were randomized to carvedilol treatment and 60 to placebo. The study groups were well matched at baseline (Table 1) and similar to other patients in the main study. Mean baseline values ± SD were 29.5 ± 8.2% for left ventricular ejection fraction, 98 ± 32.9 ml/m^2 for left ventricular end-diastolic volume index; and 71 ± 30 ml/m^2 for left ventricular end-systolic volume index. Seven patients randomized to carvedilol and eight to placebo died before 1 year of follow-up. In addition, 13 patients in the carvedilol group and 14 in the placebo group either had images that were considered inadequate for analysis at 1 year or did not have an echocardiogram performed. Consequently, the analysis of the effect of carvedilol on left ventricular volumes comprised data from 97 patients at 6 months (50 receiving carvedilol, 47 placebo) and 81 at 12 months (43 receiving carvedilol, 38 placebo).

Table 1. Baseline Characteristics of Treatment Groups

	Carvedilol (n = 63)	Placebo (n = 60)
Age (yr)	68.5 ± 5.3	68.3 ± 7.8
Male	86%	87%
NYHA class		
I	17	14
II	40	36
III	6	10
Previous MI	92%	93%
Medications		
ACE inhibitor	86%	90%
Diuretic drug	71%	80%
Digoxin	40%	43%
Heart rate (beats/min)	75.6 ± 11.7	78.1 ± 11.2
Systolic BP (mm Hg)	129.5 ± 16.8	131.6 ± 16.7
Diastolic BP (mm Hg)	77.4 ± 11.8	79.2 ± 11.5
LV EDVI (ml/m^2)	100.2 ± 36	95.7 ± 29
LV ESVI (ml/m^2)	72.9 ± 32	68.2 ± 28
LV EF (%)	30.4 ± 9.1	28.6 ± 7.1
Sinus rhythm	90%	88%

Data are presented as mean value ± SD or number or percent of patients. Between-group comparisons of baseline variables were not significant. ACE = angiotensin-converting enzyme; BP = blood pressure; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; LV = left ventricular; MI = myocardial infarction; NYHA class = New York Heart Association functional class.

Among the patients continuing to take study medication at 6 and 12 months, the mean dosages were similar in the two groups: 43 mg daily at both 6 and 12 months in the carvedilol group and the equivalent of 47 and 48 mg daily, respectively, in the placebo group. Among those receiving either captopril (n = 77) or enalapril (n = 24), there were no significant changes in the dosages of these two ACE inhibitors between baseline and 6 or 12 months. Among those receiving furosemide (n = 90) there was a trend to a higher dose requirement in the placebo group and a lower dose requirement in the carvedilol group at 12 months (85 and 94 mg daily at baseline and 12 months, respectively, in the placebo group vs. 87 and 80 mg daily, respectively, in the carvedilol group, p = 0.05 for between-group comparison).

Heart rate and blood pressure. Heart rate was 8 beats/min lower (95% confidence interval [CI], 3.7 to 12.3 beats/min) in the carvedilol group than in the placebo group at 12 months. At 6 months systolic blood pressure was reduced by 5.4 mm Hg (95% CI, −11 to 0.3 mm Hg) between the two groups; although this difference was of borderline significance, its magnitude was similar to that of the highly significant difference observed in the main study with a larger number of patients (5.6 mm Hg, p = 0.001) (12).

Left ventricular volumes. In the carvedilol group, left ventricular end-diastolic volume index was reduced (mean ± SE) by 3.7 ± 1.7 ml/m^2 at 6 months of treatment and by 6 ± 2.8 ml/m^2 at 12 months (Table 2). Conversely, in the placebo

Table 2. Heart Rate, Blood Pressure, Ventricular Volumes and Ejection Fraction at Baseline and 6 and 12 Months

	Baseline (n = 123)	6 Months (n =97)	12 Months (n = 81)	p Value*	
				vs. 6 Months	vs. 12 Months
Rest heart rate (beats/min)					
Carvedilol	75.6 ± 1.5	64.6 ± 1.6	66.5 ± 1.6		
Placebo	78.1 ± 1.5	74.6 ± 1.5	76.5 ± 1.6	0.0002	0.0007
Systolic BP (mm Hg)					
Carvedilol	129.5 ± 2.1	125.7 ± 2.2	126.3 ± 2.1		
Placebo	131.6 ± 2.2	132.5 ± 2.6	132.5 ± 2.5	0.04	0.2
Diastolic BP (mm Hg)					
Carvedilol	77.4 ± 1.5	75 ± 1.3	74.5 ± 1.3		
Placebo	79.2 ± 1.5	78.1 ± 1.8	77.2 ± 1.7	0.5	0.6
LV EDVI (ml/m^2)					
Carvedilol	100.2 ± 4.6	95.9 ± 4.6	95.6 ± 4.9		
Placebo	95.7 ± 3.8	102.2 ± 4.7	106.2 ± 4.9	0.007	0.0015
LV ESVI (ml/m^2)					
Carvedilol	72.9 ± 4.1	65.5 ± 4.2	65 ± 4.5		
Placebo	68.2 ± 3.6	73.8 ± 4.4	76.4 ± 4.5	0.0003	0.0001
SVI (ml/m^2)					
Carvedilol	27.2 ± 0.9	30.4 ± .9	30.7 ± 1.1		
Placebo	27.5 ± 0.9	28.4 ± 1	29.8 ± 1.2	0.2	0.4
LV EF (%)					
Carvedilol	28.6 ± 0.9	33.5 ± 1.2	34.1 ± 1.5		
Placebo	30.4 ± 1.2	29.3 ± 1.2	29.2 ± 1.3	0.0018	0.0015

*p values are from repeated measures multivariate analysis of variance (MANOVA) post hoc contrast tests for the difference between carvedilol and placebo in the change from baseline to 6 and 12 months. Data are presented as mean value ± SE. SVI = stroke volume index; other abbreviations as in Table 1.

group this index increased by 4.4 ± 2 ml/m^2 and 8.1 ± 3.1 ml/m^2 at 6 and 12 months, respectively (Table 2). Overall, at 12 months, there was a difference of 14 ml/m^2 (95% CI −22.5 to −5.9 ml/m^2) in left ventricular end-diastolic volume index between the carvedilol and placebo groups (Fig. 1).

Similar changes in left ventricular end-systolic volume index were observed during follow-up (Table 2, Fig. 1). In the carvedilol group left ventricular end-systolic volume index (mean ± SE) was reduced by 6.2 ± 1.6 ml/m^2 and 8.7 ± 2.6 ml/m^2 at 6 and 12 months, respectively. Conversely, in the placebo group this index increased by 4 ± 1.9 ml/m^2 and 6.6 ± 2.7 ml/m^2 at 6 and 12 months, respectively. Overall, at 12 months, left ventricular end-systolic volume index was reduced by 15.3 ml/m^2 (95% CI, −22.7 to −7.9 ml/m^2) between the carvedilol and placebo groups (Fig. 1). Stroke volume index was not significantly different between the two groups at 6 or 12 months (Table 2).

Left ventricular ejection fraction increased by 4.9% (95% CI, 2.4% to 7.3%) in the carvedilol group compared with the placebo group at 6 months, reflecting an increase from 28.6% at baseline to 33.5% among patients assigned to carvedilol (Table 2). These changes were maintained at 12 months (Fig. 2). Left ventricular ejection fraction remained unchanged in the placebo group over the 12 months. A worst case imputed analysis for left ventricular volumes and ejection fraction (average values for the placebo group at 6 and 12 months were imputed for missing data for both treatment groups) revealed statistically significant results similar to those reported above (treatment effects $p = 0.04$, $p = 0.01$ and $p = 0.002$ for left ventricular end-diastolic volume index, end-systolic volume index and ejection fraction, respectively).

Discussion

This study demonstrated that 12 months of treatment with the beta-blocker carvedilol reduced left ventricular volumes in patients with heart failure due to ischemic heart disease. In contrast, there was progressive left ventricular dilation in the placebo-treated group. These changes occurred in patients who were in clinically stable condition on entry to the study and who, in the majority of instances, were already receiving ACE inhibitor therapy. Thus, in addition to reducing left ventricular volumes, carvedilol had a protective effect against the progressive left ventricular remodeling occurring in these patients. Whereas many studies have reported an increase in left ventricular ejection fraction with beta-blocker therapy in

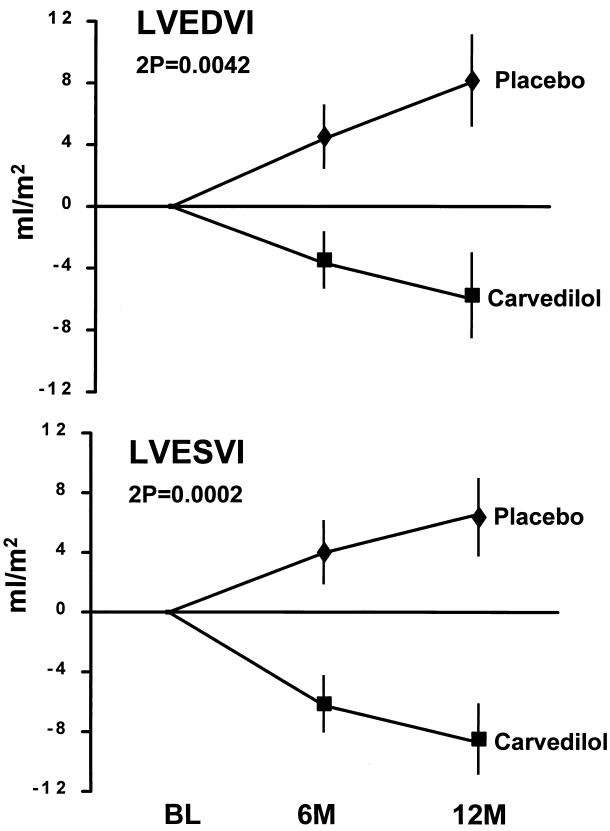

Figure 1. Changes in left ventricular end-diastolic (LVEDVI) and end-systolic (LVESVI) volume index from baseline (BL) to 6 months (6M) and 12 months (12M). Data are presented as mean value ± SE. p values comparing carvedilol and placebo are for repeated measures multivariate analysis of variance (MANOVA) over 12 months of treatment.

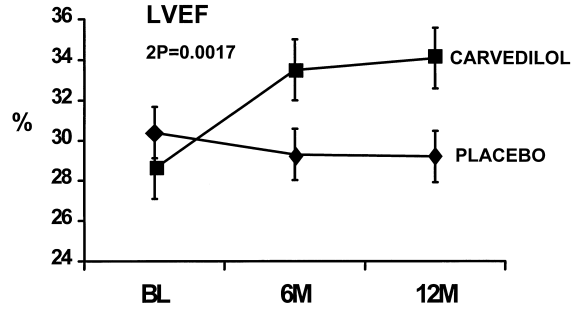

Figure 2. Absolute change in left ventricular ejection fraction (LVEF) from baseline to 6 and 12 months. Data are presented as mean value ± SE. p values comparing carvedilol and placebo are for repeated measures multivariate analysis of variance (MANOVA) over 12 months of treatment. Abbreviations as in Figure 1.

patients with heart failure, the associated changes in left ventricular size have not been reliably determined. One study (17) demonstrated a significant reduction in end-diastolic dimensions with the beta-blocker bucindolol compared with placebo. However, in the subset of patients with ischemic heart disease in that trial, ejection fraction did not increase despite this apparent decrease in left ventricular size.

Clinical importance of reduction in left ventricular volumes. Heart failure is a progressive disease, and the marked neurohormonal activation that occurs in patients with heart failure contributes to this progression (18). Progressive left ventricular dilation may continue with no detectable changes in left ventricular ejection fraction (19), an occurrence well illustrated by the changes in left ventricular volumes in the placebo group in the present study. Thus, when considering the effect of an intervention on left ventricular ejection fraction as a marker of left ventricular function, it is important to consider the associated changes in left ventricular volumes.

Left ventricular volumes have been shown (9,10) to be the most important predictors of survival after myocardial infarction. In the study by White et al. (10), end-systolic volume was the most powerful predictor of survival and the addition of end-diastolic volume or ejection fraction in a multivariate model added no further prognostic power. Aside from the prognostic value of left ventricular volumes, agents that can reduce left ventricular size may also improve clinical outcomes. The ACE inhibitor captopril attenuates left ventricular enlargement after myocardial infarction (15) and improves survival in patients with left ventricular dysfunction after infarction (20). The main ANZ carvedilol trial (12) demonstrated a 26% reduction in a combined end point of death or hospital admission after 20 months of treatment. In addition, clinical studies from the United States (11) recently reported a large reduction in mortality with carvedilol therapy in patients with heart failure, although the number of events in these studies was relatively small (53 deaths among 1,094 patients). The beneficial effect of carvedilol on left ventricular remodeling reported in the current study would be consistent with favorable effects of this agent on mortality.

Mechanism of improvement in left ventricular function. Although the reduction in left ventricular volumes demonstrated in the current study confirms that carvedilol has beneficial effects on left ventricular function, the mechanism of this improvement cannot be determined exactly because left ventricular function was not assessed under standard loading conditions. Carvedilol has both beta-blocking and alpha$_1$-blocking (vasodilating) effects (21). Although alpha$_1$-antagonists alone can potentially reduce left ventricular volumes immediately by reducing preload and afterload, there is evidence (22) of rapid development of tolerance to the effects of such agents and some data (23) suggest that similar tolerance to the vasodilating effects of carvedilol may occur with long-term administration.

When administered to normal subjects, beta-blockers increase left ventricular ejection fraction but with accompanying increases in both end-diastolic and end-systolic volumes (8). Similarly, short-term beta-blockade in subjects with impaired left ventricular function increases left ventricular volumes (24), an action consistent with an acute negative inotropic effect. However, the mechanisms of the reduction in left ventricular volumes reported here with long-term beta-blocker use may be

quite different. Long-term slowing of heart rate alone, particularly where sympathetic activation and resultant tachycardia have been prominent, may contribute to an eventual improvement in intrinsic left ventricular function. Heart rate slowing without such improvement would be expected to increase rather than decrease left ventricular volumes. The improvement in left ventricular ejection fraction with metoprolol treatment in heart failure has been related (25) to the change in heart rate with treatment but not to the baseline heart rate. This suggests that patients with a wide range of baseline heart rates at rest, not just those with very marked sympathetic activation, may benefit from beta-blocker therapy. Although the reduction in heart rate in the current study is undoubtedly part of the mechanism of improvement in left ventricular function, it is likely that other mechanisms are also contributory. Previous studies (26) using load-independent indexes have suggested that long-term beta-blockade in heart failure improves left ventricular contractility and mechanical work without increasing myocardial oxygen consumption. Other mechanisms may include beneficial effects on diastolic function (26), direct protective effects against catecholamine excess on myocytes (27), and improved regional wall motion. Hibernating myocardium may play an important role in the mechanism of heart failure in patients with underlying ischemic heart disease (28). In this situation improved left ventricular function through favorable alterations in myocardial oxygen supply and demand imbalance with beta-blockade may be relevant. Carvedilol has several unique properties that include potent antioxidant and anti-inflammatory effects (21). These properties are not shared by other beta-blockers and may contribute to the beneficial effects of this drug on left ventricular remodeling in patients with heart failure.

Conclusions. Carvedilol therapy for 1 year in patients with chronic heart failure due to ischemic heart disease reduces left ventricular volumes, increases left ventricular ejection fraction and protects against progressive left ventricular dilation. These beneficial effects on left ventricular remodeling provide further evidence of the benefit of beta-blockade in addition to standard treatment for heart failure, including ACE inhibitors. The reduced volumes may mediate the beneficial effects of such treatment on hospital admissions and survival at least in part and provide a reliable surrogate for long-term outcomes in patients with heart failure.

Appendix

Australia–New Zealand Heart Failure Research Collaborative Group

Echocardiography substudy participating centers

Australia: Austin Hospital, Melbourne (H. Krum, Y. Murray, A. Tonkin,* A. Trotter); Fremantle Hospital (R. Burton, J. Garrett, G. Lane,* J. Watts); Princess Alexandra Hospital, Brisbane (C. Geddes, C. Hall, J. Stephensen, S. Woodhouse*); Prince Henry Hospital, Sydney (T. Davidson, C. Hall, J. Turner, W. Walsh*); Repatriation Hospital, Melbourne (J. Bradbury, A. Hamer,* L. Hopkins, D. Jackson); Royal Brisbane Hospital, Brisbane (D. Cross,* F. Moreland, C. Hall, B. Hawtin); Royal Hobart Hospital, Hobart (V. Kimber, M. Saunders, A. Thomson*); Wesley Hospital, Brisbane (D. Colquhoun,* J. Goldsmith, B. Hicks).

New Zealand: Auckland Hospital, Auckland (C. Bond, R.N. Doughty,* S. Flett, J. Murphy, N. Sharpe,* G. Whalley); Tauranga Hospital, Tauranga (J. Bruning, T. Jellyman, L. Nairn*).

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