Effects of *Carvedilol* Upon Intra- and Interventricular Synchrony in Patients With Chronic Heart Failure

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Radionuclide isotopic ventriculography with phase analysis was performed in 30 patients with stable heart failure (HF), determining left ventricular (LV) and interventricular contraction synchrony at baseline and after 6 months of treatment with maximal tolerated doses of carvedilol. Patients with HF had significant ventricular dyssynchrony compared with a normal population. The 50th percentile of patients with the greatest dyssynchrony at baseline showed significant improvement in ventricular synchrony after receiving carvedilol, and this was correlated positively with a reduction in end-diastolic LV volumes.

Different trials have demonstrated that a wide QRS complex is associated with increased mortality in patients with congestive heart failure (HF) and that the correction of synchrony by biventricular pacing is related to a reduction in symptoms and improvements in exercise parameters, neurohumoral profile, and the left ventricular (LV) ejection fraction in patients with HF.[1–8] Carvedilol, an antioxidant and adrenergic antagonist, reduces LV remodeling, morbidity, and mortality in patients with chronic HF.[9,10] As a result of this compelling evidence, β blockers are now considered an important component of standard therapy in HF. In the present study, we investigated the effect of carvedilol on intraventricular (IAV) and interventricular (IEV) synchrony in patients with chronic HF.

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We enrolled 30 patients with chronic HF secondary to coronary artery disease or idiopathic cardiomyopathy. The criteria for inclusion were (1) chronic stable HF of New York Heart Association functional class II or III; (2) ability to complete a symptom-limited treadmill exercise test; (3) evidence of LV dilation and LV ejection fraction $<40\%$, as determined by radionuclide gated pool scan; and (4) stable treatment with diuretics, digitalis, and vasodilators. We excluded patients with (1) coronary artery bypass surgery, angioplasty, or myocardial infarction during the past 6 months; (2) chronic angina; (3) evidence of ischemia in noninvasive tests; (4) uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg); (5) changes in maintenance therapy or the use of β blockers during the past 2 months; (6) implanted pacemakers; or (7) atrial fibrillation and significant valvular disease.

All patients signed an informed consent approved by our institutional review board and ethics committee. All patients received carvedilol. The initial dose was 3.12 mg twice daily, which was increased (if tolerated) at 2-week intervals to 6.25, 12.5, and 25 mg twice daily. All patients were evaluated at baseline and after 6 months of treatment with a 6-minute corridor walk test, a cardiopulmonary exercise test, and radionuclide ventriculography. The radionuclide determinations were compared with 30 healthy subjects without cardiovascular symptoms, with normal physical examination results, and with normal electrocardiographic results.

Red blood cells were labeled in vitro with 740 to 925 MBq of technetium-99m. Electrocardiograms were monitored continuously to ensure R-wave gating of the QRS complex. The elimination of ventricular premature beats was obtained with a window threshold of 20% around the mean RR interval during the acquisition of projections. Extrasystolic and postextrasystolic cycles were excluded. Multigated equilibrium blood pool scintigrams were acquired at rest until 500 heart beats were obtained in the "best septal" left anterior oblique projection to provide optimal right ventricular (RV) and LV blood pool discrimination. The projection was gated with the electrocardiogram to obtain 20 frames spanning 90% of the cardiac cycle. Scintigrams were acquired for each patient in sinus rhythm. The RV and LV regions of interest were acquired at end-diastole and end-systole for the respective ventricles. Regions of

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Table 1
Baseline clinical characteristics of patients with HF (n = 30)

Characteristic	Value
Age (mean ± SE) (yrs)	55 ± 3
Men	21 (70%)
Cause	
Ischemic	10 (33%)
Idiopathic	20 (67%)
Previous myocardial infarction	9 (30%)
Previous coronary bypass surgery	4 (13%)
Previous percutaneous coronary angioplasty	1 (3%)
Diabetes mellitus	5 (17%)
Systemic hypertension	17 (57%)
Total cholesterol >200 mg/dl	7 (23%)
Current smokers	7 (23%)
LV end-diastolic volume (mean ± SE) (cm^3)	226 ± 9
Chronic therapy	
ACE inhibitors	24 (80%)
Losartan	3 (10%)
Isosorbide	7 (23%)
Hidralazine	2 (7%)
Furosemide	24 (80%)
Spironolactone	18 (62%)
Digoxin	16 (53%)

ACE = angiotensin-converting enzyme.

Table 2
IAV and IEV synchrony in patients with HF

Synchrony	Healthy (n = 30)	HF Without Left Bundle Branch Block (n = 21)	HF With Left Bundle Branch Block (n = 9)
IAV (ms)	36 ± 2	86 ± 7*	81 ± 10*
IEV (ms)	15 ± 2	38 ± 7*	53 ± 13*†

* p = 0.001 versus healthy group; † p = 0.045 versus HF without left bundle branch block.

Table 3
Changes in IAV and IEV synchrony and LV ejection fraction after 6 months of carvedilol therapy in patients with HF with the worst synchrony (50th percentile)

Variable	Baseline (n = 15)	After 6 Months of Therapy (n = 15)
IAV synchrony (ms)	113 ± 6	94 ± 10*
IEV synchrony (ms)	63 ± 7	39 ± 9*
LV ejection fraction (%)	20 ± 1	24 ± 2†

* p = 0.02, † p = 0.03 versus baseline.

interest were drawn automatically by the computer with adjustments of border definition performed by an observer blinded to the state of conduction. After correction for background counts, RV and LV ejection fractions were computed using a commercially available software (Mirage version 5, Segami Corporation, Columbia, Maryland).

Phase images were generated from the scintigraphic data using phase analysis.[11,12] The identical scintigraphic data used to generate RV and LV ejection fractions were digitally processed to display the "phase" for each pixel overlaying the equilibrium blood pool and gated to the electrocardiographic R wave. The phase program assigns a phase angle to each pixel of the phase image, derived from the first Fourier harmonic of time. The phase angle corresponds to the relative sequence and pattern of ventricular contraction during the cardiac cycle. Color-encoded phase images with corresponding histograms were generated for each patient. Scintigrams were intensity coded for amplitude, the other parameter of Fourier first harmonic study. Phase images were generated for cardiac regions using a continuous color scale, corresponding to phase angles from 0° to 360°. Mean phase angles were computed for RV and LV blood pools as the arithmetic mean phase angle for all pixels in the ventricular region of interest. Mode was the angle with the greatest value on the histogram of phases. IEV dyssynchrony was evaluated with the difference between LV and RV mean phase angles (RV − LV delay) and also with its absolute value (IEV delay), considering that some patients were found to have a negative RV − LV delay. IAV contractile synchrony in each ventricle was measured as the SD of the mean phase angle for the RV and LV blood pools. Results are expressed in milliseconds (mean of the cardiac cycle duration during acquisition × angle/360).

Results are presented as mean ± SE. We used Student's *t* test for paired samples to compare baseline and 6-month determinations. The analysis of variance test with Bonferroni's analysis was used for comparison between patients with HF with and without left bundle branch block and controls. Pearson's analysis was used to correlate synchrony with the LV ejection fraction and end-diastolic volume.

The group consisted of 30 patients with chronic HF (21 men and 9 women) whose mean age was 55 ± 3 years. Eighteen and 12 patients were in New York Heart Association classes II and III, respectively. Ten patients had ischemic dilated cardiomyopathy (5 of whom had undergone previous myocardial revascularization surgery). Nine patients had left bundle branch block, and 9 patients had evidence of previous myocardial infarction by electrocardiographic criteria (Table 1).

All patients were treated with carvedilol, at a mean maintenance dose of 22 mg/day (range 6.25 to 50). After 6 months of therapy, there was an improvement in the LV ejection fraction from 23 ± 1.5% to 31 ± 2% (p = 0.003). There was an increase in 6-minute walk distance, without significant changes in peak oxygen consumption (499 ± 17 to 534 ± 18 m, p = 0.03, and 16.7 ± 1.2 to 15.9 ± 1.1 ml/kg/min, p = 0.8, respectively). From baseline to 6 months, supine heart rate at rest decreased by 18 beats/min (p <0.001). At maximum exercise, heart rate decreased by 19 beats/min (p <0.01). Supine systolic and diastolic blood pressures at rest decreased by 5 and 4 mm Hg (p = 0.1 and 0.3), respectively, and decreased by 20 and 7 mm Hg at maximum exercise (p = 0.01 and 0.04), respectively.

Patients with HF had IAV and IEV dyssynchrony (Table 2). IAV dyssynchrony was independent of the presence of left bundle branch block. However, patients with left bundle

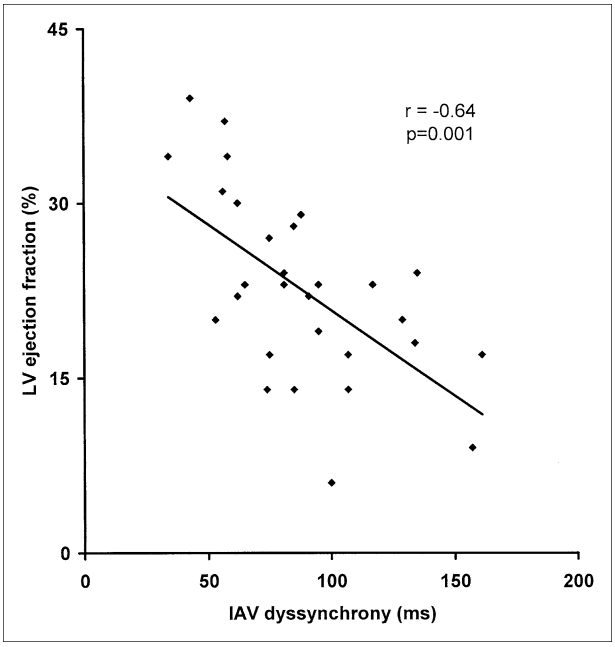

Figure 1. Correlation between IAV synchrony and the LV ejection fraction in patients with HF.

branch block had more severe IEV dyssynchrony. There was a significant correlation between IAV dyssynchrony and the LV ejection fraction (Figure 1) and between IAV dyssynchrony and LV end-diastolic volume ($r = -0.64$, $p = 0.01$, and $r = 0.45$, $p = 0.01$, respectively). After 6 months of therapy, there were no significant changes in dyssynchrony parameters (IAV: 86 vs 77 ms, $p = 0.39$; IEV: 37 vs 34 ms, $p = 0.65$). However, the patients with greater dyssynchrony (50th percentile) had improved IAV and IEV synchrony after carvedilol treatment (Table 3). This improvement was significant in nonischemic patients (nonischemic: IAV synchrony 104 to 78 ms, $p = 0.04$, IEV synchrony 60 to 35 ms, $p = 0.02$; ischemic: IAV synchrony 126 to 115 ms, $p = 0.3$, IEV synchrony 52 to 47 ms, $p = 0.6$) and independent of the presence of left bundle branch block. There was a significant positive correlation between the changes in IAV synchrony and LV end-diastolic volumes ($r = 0.53$, $p = 0.004$). No significant correlation was found between synchrony indexes and LV ejection fraction improvement or reduction in heart rate.

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Medical treatment with carvedilol was associated with a significant improvement in IAV and IEV synchrony indexes in patients with HF and greater degrees of dyssynchrony. In a subgroup analysis, this effect was limited to patients with nonischemic etiology; the lack of significant benefit in patients with ischemic HF might be explained by the small number of patients evaluated or by the absence of myocardial viability in this population.

The present study showed a positive correlation between LV end-diastolic volumes and IAV dyssynchrony. Moreover, the improvement in synchrony was related to a decrease in LV volume. Although the mechanism involved in the restoration of synchrony with carvedilol was not elucidated, favorable effects in LV remodeling could explain the action of this β blocker.

The main limitations of the present study are the small number of patients studied and the absence of a control group. Moreover, patients with the greater dyssynchrony were arbitrarily defined, and the small group of patients precluded a subgroup analysis. Further large studies are needed to validate our findings.

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