Effect of Beta-Blockade on Autonomic Modulation of Heart Rate and Neurohormonal Profile in Decompensated Heart Failure

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Background: One of the putative mechanisms for the salutary effects of beta-blockers in patients with congestive heart failure (CHF) is their ability to improve autonomic dysfunction. However, patients with profound neurohumoral abnormalities derive little survival benefit from beta-blockers. The purpose of the current study was to evaluate the effect of beta-blockers on heart rate variability (HRV) in decompensated CHF.

Methods: Time and frequency domain HRV indices were obtained from 24-hour Holter recordings and compared to assess the role of beta-blockade in 199 patients (mean age 60 ± 14 years) with decompensated CHF. Neurohormonal differences were assessed by measuring norepinephrine, endothelin-1, tumor necrosis factor- α , and interleukin-6 in a subset of 64 patients.

Results: All HRV indices were markedly suppressed but were substantially higher in patients who were on beta-blockers. Time domain measures of parasympathetic cardiac activity, the percentage of R-R intervals with > 50 ms variation (4.9 ± 0.6 vs $7.7 \pm 1.2\%$, $P = 0.006$) and the square root of mean squared differences of successive R-R intervals (22.7 ± 2.0 vs 31.6 ± 4.1 ms, $P = 0.004$), were higher in the beta-blocker group. Spectral analysis revealed that the total power and the ultra-low frequency power were significantly higher in patients on beta-blockers (82% and 59%, respectively). The high frequency power, a spectral index of parasympathetic modulation, was 41% higher in the beta-blocker group (121 ± 25 vs 171 ± 27 ms², $P = 0.02$). Norepinephrine and interleukin-6 levels were substantially lower in patients on beta-blockers (28% and 61%, respectively). However, these differences did not reach statistical significance.

Conclusions: Beta-blockers improve the impaired cardiac autonomic regulation during high sympathetic stress of decompensated CHF. This effect may play an important role in protecting the myocardium and preventing arrhythmias during transient increases in sympathetic activity.

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heart rate variability; heart failure; beta-adrenergic blockers; cytokines

The syndrome of congestive heart failure (CHF) entails a complex autonomic and hormonal response. Profound abnormalities in autonomic control, characterized by sympathetic overactivity and parasympathetic withdrawal,^{1,2} together with activation of endogenous vasoconstrictor systems (norepinephrine, endothelin),³⁻⁵ exert a direct deleterious effect on the heart and contribute to progressive circulatory failure.²

Recently, there has been an increasing appreciation that overexpression of proinflammatory cytokines plays an important role in the pathogenesis of heart failure. In particular, tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) have been repeatedly shown to be increased in patients with CHF,^{6,7} and may contribute to progressive ventricular dysfunction through diverse mechanisms.⁸

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In patients with heart failure, beta-blockade improves myocardial function and prolongs survival.⁹⁻¹¹ One of the putative mechanisms for the salutary effects of beta-blockers in patients with heart failure is their ability to interrupt the sympathetic nervous system.^{2,9-11} However, the effects of beta-blockade in the setting of excessive neurohumoral activation and autonomic dysfunction associated with symptomatic decompensated heart failure are unknown. Indeed, in several studies, patients with profound neurohumoral activation appeared to derive little or no survival benefit from treatment with beta-blockers.^{12,13} The aim of the present study was to determine the effect of beta-blockade on autonomic function and neurohormonal profile in the setting of acutely decompensated heart failure.

METHODS

The study population was enrolled in the Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy (PRECEDENT) study, a randomized, multicenter trial comparing the proarrhythmic and chronotropic effects of nesiritide (human B-type natriuretic peptide) to dobutamine in patients with symptomatic, decompensated heart failure for whom inpatient parenteral vasoactive therapy was considered appropriate. Eligible patients included subjects who were over 18 years of age and had a previous history of New York Heart Association (NYHA) class III or IV heart failure. Exclusion criteria included recent myocardial infarction (< 48 hours), ongoing unstable angina, cardiogenic shock or prolonged hypotension, stroke within the past one month, significant valvular aortic stenosis, obstructive cardiomyopathy, or constrictive pericarditis. The investigational review committees of all participating study sites approved the study protocol and informed consent was obtained in all patients. All heart rate variability (HRV), neurohormonal, and cytokine data presented in the current report were obtained at baseline, *prior* to the administration of the study drugs.

HRV Analysis

Twenty-four hour Holter monitoring of all patients was conducted before randomization. Three-channel (V1, V5, and aVF) Holter recordings were obtained and analyzed on a commercially available scanner (model 2010, Zymed Medical Instruments,

Camarillo, CA, USA) in the core laboratory at the Beth Israel Deaconess Medical Center, according to published guidelines.¹⁴ After a normal QRS was chosen, computer-assisted rate and arrhythmia analysis were performed with a technician over reading and editing. Excessive noise and artefact were deleted, and ectopy was quantified. Tapes with greater than 15% noise were excluded. Each beat was classified and labeled with respect to site of origin. When atrial or ventricular premature complexes were encountered, the preceding and succeeding R-R intervals were excluded from the sampling. After technician analysis and physician review, the results were downloaded to a computer and analyzed using software developed by JT Bigger and colleagues and Zymed Medical Instruments.¹⁵ The program produced the following time domain variables: (1) average heart rate; (2) average R-R interval; (3) standard deviation of the R-R intervals over a 24 hour period (SDNN); (4) standard deviation of all 5-minute mean R-R intervals (SDANN5); (5) average standard deviation of all 5-minute R-R intervals (ASDNN5); (6) the percentage of R-R intervals with > 50 ms variation (pNN50); and (7) the square root of mean squared differences of successive R-R intervals (RMSSD). In addition, the following frequency domain indexes were obtained using a fast-Fourier transformation over the 24-hour period: (1) total power spectrum (0 to 0.4 Hz); (2) high frequency (HF) power (0.15 to 0.4 Hz); (3) low frequency (LF) power (0.04 to 0.15 Hz); (4) very low frequency (VLF) power (0.003 to 0.04 Hz); and (5) ultra-low frequency (ULF) power ($\leq$ 0.003 Hz).

Neurohormone and Cytokine Measurements

An intravenous catheter was inserted at least 30 minutes before drawing blood. The blood samples were obtained after the patient remained in the supine position for at least 30 minutes. Five milliliters of blood were placed into a prechilled tube containing ethylenediamine tetraacetic acid (EDTA) for measurement of plasma norepinephrine, ET-1, TNF- α , and IL-6. The sample was centrifuged within 1 hour at 4°C at 3000 rpm for 15 minutes. Plasma was then stored at -20°C or colder. Samples were shipped on dry ice to the neurohormone core laboratory at the Mayo Clinic in Rochester, MN.

Neurohormone Assays

Plasma norepinephrine concentration was analyzed by high-performance liquid chromatography.¹⁶ For the endothelin assay, plasma (1 mL) was acidified with 3 mL of 4% acetic acid and immunoreactive endothelin was extracted with a Sep-Pak C₁₈ cartridge (Waters Chromatography Division). The elute was dried by vacuum concentration, reconstituted with 500 μ L of buffer and subjected to a chemiluminescent immunoassay. The assay incorporates a monoclonal capture antibody that recognizes the C-terminal of ET-1 and a monoclonal detection antibody that recognizes the N-terminal of ET-1.¹⁷

Cytokine Assays

Measurements of TNF- α and IL-6 were performed using commercially available enzyme amplified-sensitivity immunoassay (EASIA) kits (Medgenix Diagnostics, Fleurus, Belgium) according to the manufacturer instructions.

Statistical Analysis

Data are expressed as mean $\pm$ SD for clinical characteristics and mean $\pm$ SEM for HRV data. Baseline characteristics of different patient categories were compared by use of the two-sample *t* test for continuous variables and chi-square tests for categorical variables. The distributions of HRV frequency domain variables are skewed and not normally distributed.¹⁸ Therefore, the log transformation of these HRV measures was applied before statistical analyses were performed. The neurohumoral and cytokine data were also not normally distributed and were subjected to logarithmic transformation.⁶ However, to permit comparison with results from other studies, these data are presented as mean $\pm$ SEM.

Comparisons between the two groups were made using nonpaired *t* tests when data were normally distributed, and the Mann-Whitney Rank Sum test was used when the data were not. The Pearson product-moment correlation coefficient was calculated to describe correlations between mean R-R intervals and HRV parameters. Differences were considered significant at the $P < 0.05$ level. All statistical analyses were performed using the SigmaStat statistical software (Jandel Scientific, San Rafael, CA, USA).

RESULTS

The study group consisted of 255 patients enrolled at 46 clinical sites. Information about beta-blocker use was systematically obtained as part of the recruitment and follow up procedure of the PRECEDENT study. Use of a beta-blocker was optional and was left to the discretion of the treating physician.

Technical failure, atrial fibrillation, frequent arrhythmias, and excess artefacts resulted in the exclusion of 56 patients from analysis. Of the remaining 199 patients, 46 were receiving beta-blockers at the time of the study. Carvedilol was the most commonly used drug ($n = 22$), followed by metoprolol ($n = 14$), atenolol ($n = 8$), and labetalol ($n = 2$). Neurohormone (norepinephrine and endothelin-1) and cytokine (TNF- α and IL-6) measurements were available in a subgroup of 64 patients, of whom 20 were receiving beta-blockers.

The clinical characteristics of the two study groups are listed in Table 1. Patients treated with beta-blockers were more likely to have coronary disease as the etiology of their heart failure. No difference in baseline clinical data was observed between the two groups with respect to other clinical variables. The other concomitant treatments were not significantly different between the two groups.

Effect of Beta-Blockade on HRV

The effects of beta-blocker therapy on time and frequency domain parameters of HRV are listed in Table 2. The heart rate was significantly lower in the beta-blocker group (73.4 ± 14.5 vs 86.7 ± 13.9 beats/min, $P < 0.001$). All time and frequency domain indices were markedly suppressed compared to healthy middle-aged subjects,¹⁴ but were substantially higher in patients who were on beta-blockers.

Time and frequency domain indices of long-term variability (SDNN, SDANN5, total power, ULF power) were significantly higher in patients on beta-blockers. The SDNN and SDANN5 were 32% ($P < 0.0001$) and 34% ($P < 0.0001$) higher in the beta-blocker group, respectively. The total power and ULF power were 82% ($P = 0.0008$) and 59% ($P < 0.0001$) higher in the beta-blocker group, respectively.

The two time domain measures of parasympathetic cardiac activity, pNN50 and RMSSD, were 57% ($P = 0.006$) and 39% ($P = 0.004$) higher in the beta-blocker group, respectively. The high frequency power, a spectral index of

Table 1. Baseline Clinical Characteristics

Characteristic	No β -Blocker (n = 153)	β -Blocker (n = 46)
Age (years)	60 $\pm$ 14	61 $\pm$ 13
Gender (Male/Female)	100/54	33/13
Etiology of Heart Failure		
Ischemic	73 (48)	32 (70)*
Idiopathic	43 (28)	6 (13)
Hypertensive	19 (12)	6 (13)
Rheumatic	5 (3)	1 (2)
Other†	13 (9)	1 (2)
New York Heart Association functional class		
Class III	115 (75)	30 (65)
Class IV	38 (25)	16 (35)
Cardiac Medications		
Digoxin	119 (78)	36 (78)
Angiotensin converting enzyme inhibitors	108 (70)	36 (78)
Angiotensin II receptor antagonists	17 (11)	7 (15)
Other vasodilating drugs‡	23 (15)	8 (17)
Antiarrhythmic drugs	18 (12)	6 (13)
Oral anticoagulants	20 (13)	10 (22)

Numbers in parentheses are % of the group; * $P < 0.05$. † Other etiologic groups included alcoholic cardiomyopathy, myocarditis, postpartum cardiomyopathy, and diabetic cardiomyopathy. ‡ Calcium channel blockers, nitrates, hydralazine, or α 1-blockers.

parasympathetic modulation, was 41% ($P = 0.02$) higher in the beta-blocker group, reflecting a higher vagal modulation. The low frequency power was 74% higher in the beta-blocker group, although this difference was not statistically significant.

Correlation between Individual HRV Indices

Table 3 presents correlations between individual time and frequency domain HRV measures. Indices of global variability in the time (SDNN and

Table 2. Effect of β -Blockade on Time and Frequency Domain HRV Parameters

Parameter	No β -Blockers (n = 153)	β -Blockers (n = 46)	P Value
Time Domain			
SDNN (ms)	58.7 $\pm$ 2.4	77.6 $\pm$ 4.9	<0.0001
ASDNN5 (ms)	27.5 $\pm$ 1.5	33.8 $\pm$ 3.4	0.066
SDANN5 (ms)	49.3 $\pm$ 2.0	66.3 $\pm$ 4.1	<0.0001
PNN50 (%)	4.9 $\pm$ 0.6	7.7 $\pm$ 1.2	0.006
RMSSD (ms)	22.7 $\pm$ 2.0	31.6 $\pm$ 4.1	0.004
Frequency Domain			
TP (ms ²)	3926 $\pm$ 407	7114 $\pm$ 1313	0.0008
ULF (ms ²)	2742 $\pm$ 325	4369 $\pm$ 3527	<0.0001
VLF (ms ²)	664 $\pm$ 87	999 $\pm$ 1805	0.31
LF (ms ²)	151 $\pm$ 20	262 $\pm$ 84	0.15
HF (ms ²)	121 $\pm$ 25	171 $\pm$ 27	0.02

Data are expressed as mean $\pm$ SEM. ASDNN5 = average standard deviation of all 5-minute RR intervals; HF = high frequency power; LF = low frequency power; pNN50 = the percentage of RR intervals with >50 ms variation; RMSSD = the square root of mean squared differences of successive RR intervals. TP = total power; SDNN = standard deviation of the RR intervals over a 24 hour period; SDANN5 = standard deviation of all 5-minute mean RR intervals; ULF = ultra low frequency power; VLF = very low frequency power.

Table 3. Pearson's Correlation Coefficients between Individual HRV Indices*

	NN	SDNN	ASDNN5	SDANN5	pNN50	RMSSD	TP	ULF	VLF	LF
SDNN	0.57									
ASDNN5	0.42	0.80								
SDANN5	0.54	0.92	0.57							
pNN50	0.38	0.51	0.67	0.35						
RMSSD	0.44	0.61	0.79	0.41	0.91					
TP	0.47	0.83	0.74	0.78	0.47	0.55				
ULF	0.36	0.67	0.44	0.74	0.25†	0.30	0.88			
VLF	0.28	0.63	0.75	0.51	0.41	0.48	0.8	0.66		
LF	0.37	0.67	0.86	0.49	0.71	0.79	0.74	0.48	0.80	
HF	0.47	0.64	0.83	0.43	0.84	0.92	0.64	0.37	0.59	0.88

* For statistical analyses pNN50, RMSSD, and all frequency domain indices were transformed to their natural logarithms to obtain normality. Statistical significance were all $P < 0.0001$ except for † $P = 0.0003$.

SDANN5) and frequency (total power and ULF power) domain correlated well. Time (pNN50 and RMSSD) and frequency (HF power) domain vagal indices also demonstrated excellent correlations ($r = 0.84$ to 0.92). An excellent correlation was also present between the LF power and HF power ($r = 0.88$).

Relation between Mean R-R Interval and Parasympathetic HRV Parameters

When all the study subjects were considered as a single group, mean 24-hour R-R intervals showed a moderate but significant linear relation with both time and frequency domain HRV indices primarily modulated by parasympathetic activity ($r = 0.38 - 0.47$, $P < 0.0001$). However, the correlation was different between the two study groups, with patients who were receiving beta-blocker displaying a stronger correlation between mean R-R interval and parasympathetic indices (Fig. 1).

Effect of Beta-Blockade on Neurohormonal and Cytokine Profile

In the neurohumoral subgroup, patients with severe HRV depression displayed a more pronounced neurohumoral and cytokine activation. Using the commonly accepted SDNN cutoff values of < 50 ms for highly depressed HRV and $SDNN < 100$ ms for moderately depressed HRV,¹⁴ 25 patients (39%) in the neurohumoral subgroup had a highly depressed HRV and 31 (48%) had a moderately depressed HRV. In patients with highly depressed HRV, plasma norepinephrine (692 ± 87.00 vs 476 ± 49 pg/mL, $P = 0.01$), endothelin-1 (11.8 ± 1.0 vs 8.0 ± 0.7 ng/mL, $P = 0.001$), and interleu-

Figure 1. Scatterplot of the correlation between mean R-R intervals and HRV indices of parasympathetic modulation RMSSD (top panel) and pNN50 (bottom panel). Solid dots indicate patients not receiving beta-blockers and open circles indicate those who were receiving beta-blockers. The lines indicate the trend in groups of patients receiving beta-blockers (solid lines) and those not receiving beta-blockers (dashed lines).

kin-6 (50.9 ± 15.5 vs 13.8 ± 3.4 ng/mL, $P = 0.008$) were higher than in the group with a better-preserved HRV (Fig. 2).

Plasma norepinephrine and interleukin-6 levels were substantially lower in patients on beta-blockers (28% and 61%, respectively). However, these differences did not reach statistical significance (Fig. 3).

DISCUSSION

The neurohumoral axis is thought to represent one of the principle determinants of the clinical status and ultimately the survival of patients with heart failure.¹⁻³ Impaired sympathovagal balance, characterized by sympathetic overactivity and parasympathetic withdrawal, is thought to be an important part of neuroendocrine activation in heart failure.^{1,2,19,20} As patients progress from early asymptomatic or mildly symptomatic left ventricular dysfunction to overtly decompensated heart failure, additional progressive neuroendocrine activation^{21,22} and autonomic dysfunction¹⁹ occur.

Previous studies have shown a beneficial modulating effect of beta-adrenergic blockade on HRV indices in a small number of patients with stable heart failure.^{23,24} However, in the presence of profound neurohumoral activation, such as in the setting of decompensated heart failure, the efficacy of beta-blockade may be less apparent. It has been suggested that beta-blocker may enhance HRV in

Figure 2. Bar graph of plasma neurohormone and cytokine levels in patients with highly depressed HRV (open bars) and those with a better preserved HRV (filled bars). * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.005$. SDNN = standard deviation of the R-R intervals over a 24 hour period; ET-1 = endothelin-1; IL-6 = interleukin-6; NE = norepinephrine; TNF = tumor necrosis factor- α .

Figure 3. Bar graph of plasma neurohormone and cytokine levels in patients receiving (open bars) and not receiving (filled bars) beta-blockers. ET-1 = endothelin-1; IL-6 = interleukin-6; NE = norepinephrine; TNF = tumor necrosis factor- α .

stable patients with a low degree of neurohumoral activation who are subject to normal daily stress, but cannot prevent or significantly attenuate adrenergic effects during surges of sympathetic activity.²⁵ For example, experimental studies have shown that beta-blockade may maintain normal autonomic balance during mental performance but cannot prevent or significantly attenuate adrenergic effects during exercise.²⁵ In the Survival and Ventricular Enlargement (SAVE) neurohumoral sub-study, patients with elevated plasma norepinephrine levels appeared to derive little or no benefit from treatment with beta-blockers. The benefit of beta-blockers was limited to those without activation of plasma norepinephrine.¹³ Similarly, in the Australia-New Zealand Heart Failure study, plasma norepinephrine was a negative predictor of benefit when beta-blocker (carvedilol) therapy was added.¹² These findings are in sharp contrast to previous studies showing the greatest survival benefit from treatment with angiotensin converting-enzyme inhibitors in patients with chronic heart failure who had the most marked neurohumoral activation.^{22,26}

Effect of Beta-Blockade on HRV

The results of the present study demonstrate in a large group of patients that beta-adrenergic blockade helps to maintain the balance of autonomic regulation even in the setting of decompensated heart failure. HRV parameters that are modulated

predominantly by low-frequency cyclical changes such as the SDNN, SDANN5, total power, and the ULF power were substantially and significantly higher in patients on beta-blockers. These HRV parameters have been repeatedly shown to be strong consistent predictors of mortality in patients with heart failure.^{19,27-30} Furthermore, all three HRV parameters that are primarily modulated by vagal tone, the pNN50, RMSSD, and HF power,¹⁴ were significantly higher in patients who were on beta-blockers.

In normal subjects, the resting heart rate is primarily determined by vagal tone, while in patients with heart failure the correlation between resting heart rate and parasympathetic measures decreases as sympathetic activation and parasympathetic withdrawal progress.^{28,29} In accord with previous reports on patients with heart failure,²⁷⁻²⁹ we found a moderate correlation between the mean R-R intervals and HRV measures indicative of parasympathetic activity. However, although part of the effect of beta-blockade on parasympathetic measures may be ascribed to differences in heart rate, patients in the beta-blocker group exhibited a stronger correlation between indices of parasympathetic modulation and heart rate (Fig. 1), despite a smaller number of patients in this group. This suggests that the higher vagal HRV indices in these patients reflect a higher parasympathetic modulation of the sinus node rather than simply being related to the higher mean R-R interval in this group.

Values of LF oscillations, which reflect both sympathetic and vagal modulation,¹⁴ were also considerably higher with beta-blockade, although not reaching statistical significance. A possible explanation is that the decrease in the sympathetic component was blunted by the increase in the parasympathetic component.²⁴

The mechanisms by which beta-blockade exerts beneficial effects on parasympathetic activity in stable heart failure are likely to be different from those in decompensated heart failure. In patients with stable heart failure, the autonomic effects of beta-blockers may result, in part, from the hemodynamic improvements known to occur during long-term therapy with these agents.¹¹ In the setting of acute sympathetic stress during decompensated heart failure, beta-blockers may interfere with sympathetic afferent input to central vagal outflow,³¹ or diminish cardiac afferent sympathetic restraint of parasympathetic activity.^{32,33}

Effect of Beta-Blockade on Neurohormone and Cytokine Levels

Although beta-blockers had no statistically significant effect on plasma neurohormone and cytokine levels, this finding may be related to the small number of patients in the neurohormonal sub-study. Plasma norepinephrine and interleukin-6 were considerably lower in patients on beta-blockers (Fig. 3). The later finding is interesting considering recent experimental data suggesting that adrenergic activation serves as a stimulus for cytokine expression in heart failure.^{7,34} Several lines of evidence suggest that increased sympathetic outflow to the peripheral tissues and norepinephrine released from sympathetic terminals may function as a mediator and/or modulator to facilitate the synthesis and release of IL-6 in the sympathetic nerve-innervated organs.³⁵ For example, catecholamines increase IL-6 production by cardiac myocytes,³⁶ and isoproterenol infusion increases interleukin-6 mRNA and protein expression in the rat heart.³⁴

Clinical Implications

Whether the improved HRV profile in patients who were on beta-blockers during heart failure decompensation translates directly into cardiac protection is not known. Maintaining the balance of autonomic regulation in the setting of decompensated heart failure may provide protection from the deleterious effect of sympathetic activity surges on the myocardium.² Furthermore, increased vagal modulation during heart failure decompensation in patients on beta-blockers may counteract the proarrhythmic effects of sympathetic nervous system activity on the electrophysiologic properties of the ventricular myocardium.^{37,38}

It should be emphasized, however, that HRV indices were markedly decreased and plasma neurohormones and cytokines were elevated both with and without beta-blockade. This raises the possibility that beta-blocker doses used in our patients may have been inadequate to block the deleterious effects of neurohumoral activation,¹³ especially in the setting of decompensated heart failure.

Study Limitations

Our study is subject to several important limitations. Some patients who were not on beta-blocker therapy may have been tried on this therapy and

subsequently withdrawn due to aggravation of heart failure. Such patients may be different in terms of their autonomic and neurohumoral status from those who could tolerate beta-blockers. Notwithstanding, most patients (85%–90%) in clinical trials are able to tolerate short- and long-term treatment with these agents.¹¹

Results of human trials and animal experiments suggest that the central effects of beta-blockade are more marked with lipophilic drugs,³⁹ although data from several clinical studies indicates equal effects of lipophilic metoprolol and hydrophilic atenolol with regard to cardiac vagal-sympathetic balance, as reflected by HRV analysis.^{25,40} Our study included only 10 patients on hydrophilic drugs (atenolol and labetalol), thus precluding a separate statistical analysis due to lack of power.

The modulating effects of angiotensin converting-enzyme inhibitors⁴¹ and digoxin⁴² on HRV have been demonstrated in patients with heart failure. The clinical status of our patients would not allow changes or withdrawal of drug therapy. However, both groups were matched with respect to the use of angiotensin converting-enzyme inhibitors and digoxin.

CONCLUSION

Beta-blockade helps to maintain the balance of autonomic regulation during high sympathetic stress of decompensated heart failure. This effect of beta-blockers may play an important role in protecting the myocardium and preventing ventricular arrhythmias during transient increases in sympathetic activity.

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