ADJUNCTIVE SYMPATHOPLIC THERAPY TO ACE INHIBITION IN BLACKS WITH CONGESTIVE HEART FAILURE: A COMPARISON OF ALPHA-1 WITH BETA-1 BLOCKADE ON EXERCISE TOLERANCE AND CARDIAC SYMPATHOVAGAL REFLEX ACTIVITY

OBJECTIVES: Congestive heart failure (CHF) is characterized by an initial compensatory, but subsequently deleterious, activation of both the renin-angiotensin (RAS) and the sympathetic nervous system (SNS). Incomplete suppression of the SNS may contribute to the residual mortality during optimal ACE inhibitor therapy in CHF. Carvedilol, a mixed α and β-blocker with antioxidant properties, and other pure β-adrenoceptor blockers reduce morbidity and mortality in Caucasians with CHF. However, β-blocker monotherapy is of poor efficacy in Blacks with essential hypertension or in the treatment of glaucoma. The efficacy of β-blockers in the treatment of African Americans with congestive heart failure is a controversial issue with conflicting findings. The aims of the present study were to examine and compare the cardiovascular, autonomic, and clinical effects of additional α1- or β1-blockade in ACE-inhibitor treated Black patients with moderate to severe CHF.

METHODS: Twenty-eight Nigerian patients with chronic CHF stabilized on digoxin and diuretics, were randomized to 3 groups of similar demographics according to a single blind, parallel group design. The patients were aged 53 ± 6 years, and comprised 14 men and 14 women, with a mean cardiothoracic ratio of 0.66 ± 0.03, and ejection fraction of 0.38 ± 0.10. 60% hypertensive etiology. Group 1 patients received 5 mg enalapril alone, group 2 received 5 mg enalapril + 1 mg prazosin, and group 3 received 5 mg enalapril + 50 mg atenolol. All medication was taken daily for 4 weeks. Blood pressure, heart rate, pressure rate product, 6-minute walk test, NYHA class, and cardiac autonomic reflexes were measured at baseline and again at 2 and 4 weeks of treatment. Two-way repeated measures ANOVA, and a one-way ANOVA were used in data analysis.

RESULTS: The 3 treatments caused significant (P<.001 ANOVA) and similar improvements for the NYHA class (−1.0 to −1.6), and increased the 6-minute distance covered (+130 m to +205 m). Although no treatment differences were observed, a trend suggesting a greater improvement with enalapril + atenolol became apparent. By the fourth week, the sympathetic treatments, enalapril + atenolol, and enalapril + prazosin, caused significant reductions in the pressure rate product (−3726 ± 1885 mm Hg-beats/min; −3498 ± 396 mm Hg-beats/min, respectively), compared to enalapril alone (−1349 ± 894 mm Hg-beats/min) (P<.001 ANOVA). During the valsalva maneuver, the phase IV bradycardia were significantly greater after treatment with enalapril + atenolol (944 ± 66 msec) or with enalapril + prazosin (825 ± 48 msec), compared to enalapril alone (760 ± 45 msec) (P<.001 ANOVA). The phase II Valsalva tachycardia were similar between treatments. The respiratory sinus arrhythmia ratio increased significantly (P<.005 ANOVA) and equally on all treatments. However, the pressor and chronotropic responses to forearm isometric hand-grip increased significantly on the enalapril + prazosin combination (P<.02), compared to the other treatments.

CONCLUSIONS: Our findings demonstrated not only the safety of providing additional therapy with α1- or β1-receptor blockade concurrent with ACE inhibition in Blacks with CHF, but also the resultant improvement in exercise tolerance and NYHA class. Compared to using ACE inhibition alone, the combined therapies caused a marked reduction in the pressure rate product, an index of myocardial oxygen consumption, and a greater enhancement of cardiac parasympathetic activity. Selective β1-blockade caused a greater enhancement of central baroreceptor vagal activity compared to α1-blockade. Conversely, the pressor and chronotropic abnormalities during forearm isometric handgrip in CHF, were normalized by α1, but not β1, blockade. Thus, the combined reflex cardiac vagal augmentation following selective β1-blockade, and the hemodynamic effects of α1-antagonism with concurrent ACE inhibition, may be of major therapeutic and prognostic benefit in Blacks with non-ischemic (hypertensive) CHF stabilized on digoxin and diuretics. (Ethn. Dis. 2003;13:71–79)

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KEY WORDS: Congestive Heart Failure, Blacks, Beta-Blockers, Atenolol, Autonomic Function

INTRODUCTION

Congestive heart failure is a disease of global public health concern, due to its increasing prevalence, high morbidity and mortality, and the pharmaco-economic implications of its optimal management. Angiotensin converting enzyme inhibitors (ACEI) have played a well-documented role in the reduction of morbidity, hospitalization, and mortality rates in CHF.1–3

Raised plasma noradrenaline is a poor predictor of CHF deaths,4 and residual mortality, despite ACE inhibitor therapy of CHF, has been attributed to insufficient blockade of both the activated renin angiotensin system (RAS) and the sympathetic nervous system.5

The original hypothesis was that use of beta-adrenergic blockade would prove...
to be deleterious in CHF, since beta-adrenergic receptors were down-regulated and inotropism was reduced in heart failure. However, a report of the efficacy of beta-adrenergic blockers in dilated cardiomyopathy, and the more recent demonstration of the further reduction in CHF hospitalization rates and mortality by beta-blockers, carvedilol, metoprolol, and bisoprolol in ACE inhibitor treated patients, amounted to a therapeutic paradox, which has resulted in a major paradigmatic shift in the modern neuro-hormonal inhibition therapy of chronic heart failure. In addition, the more recent studies demonstrated a reduction in sudden cardiac death, possibly attributable to a modification of cardiac autonomic sympathetic balance.

The large scale clinical studies demonstrating the benefits of beta-blockade, have focused on Caucasian populations with mainly ischemic heart disease. Studies of the efficacy of beta-blockers in the treatment of congestive heart failure are limited in number and have reported conflicting findings. The COPERNICUS study enrolled 5.2% Black patients (N=121) with advanced heart failure in a double-blind, placebo controlled study of carvedilol. A trend toward a beneficial effect on mortality in African Americans was noted, with a hazard ratio of 0.6 (95% confidence interval of 0.18 to 2.05). By contrast, the BEST study, with bucindolol, demonstrated increased mortality in Black Americans, compared to White subjects, or the placebo arm compared to the active treatment group. It is not clear whether the conflicting outcomes of the studies of beta blockers in CHF treatment in Blacks reflect the different profiles of carvedilol... or bucindolol...

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**Materials and Methods**

The study was that of a single-blind, randomized, prospective parallel group design. Twenty-eight Nigerian patients (14 males and 14 females) with chronic congestive heart failure (NYHA II-IV) who were already on standard daily treatment with either enalapril (5 mg), digoxin (0.125–0.25 mg), or frusemide (40–120 mg) were randomized into 3 groups.

Along with their standard treatments, group 1 (N=10) received a placebo tablet; group 2 (N=8) received additional prazosin (1 mg daily); and group 3 (N=10) received additional atenolol (50 mg daily). Atenolol is a long acting cardio-selective beta-1 receptor antagonist, with a long half life and suitable for single daily dosing. It has no alpha blocking effect and it is the only long acting beta-blocker included in the Nigerian National Essential drug list and formulary. These factors influenced our choice of atenolol. In addition, there are no previous reports of its utility in congestive heart failure. The treatment duration was for 4 weeks each. The inclusion criteria were: being of Nigerian ethnicity, having chronic heart failure (>3 months), and receiving standard therapy. The primary exclusion criterion was a co-morbidity, such as diabetes mellitus, cerebrovascular disease, cor pulmonale, atrial fibrillation, or significant arrhythmias, which may affect cardiac autonomic function tests. The
patients were aged 50–56 years, and had left ventricular ejection fraction of 0.37 ± 0.09.

The etiology of heart failure was hypertension in 60% of the cases. The baseline demographic and clinical characteristics of the 3 groups were well matched as summarized in Table 1. The following were assessed at baseline and again after 2 and 4 weeks of treatment: blood pressure; heart rate; pressure rate product; exercise tolerance assessed using the distance covered in 6 minutes of self-paced walking;27 and clinical and NYHA class. Tests for cardiac autonomic function, the Valsalva maneuver, respiratory sinus arrhythmia, and the pressor and chronotropic responses to forearm isometric exercise were undertaken at the same times, as described earlier.28

The study was reviewed and approved by Obafemi Awolowo University Research and Ethical committee. All subjects provided informed consent prior to inclusion in the study. A group of 30 healthy age- and sex-matched volunteers (aged 51 ± 11 years, 14 men, 16 women) also performed the 6-minute walk test and the autonomic function tests, and served as the normal controls.

Data are presented as mean ± SEM. The data were analyzed by either a 2-way repeated measures analysis of variance (RAMOVA), or a one-way analysis of variance, as appropriate, followed by post-hoc Bonferroni t tests when indicated. Treatment effect, time effect, and time-treatment interaction were evaluated. 95% confidence intervals for the difference between treatments have been quoted when indicated. Statistical significance was accepted at P<.05.

RESULTS

General

The 3 groups were well matched in clinical and demographic features, as shown on Table 1. There were no un-toward reactions, such as syncope or mortality, during this preliminary study. All patients had reduced 6-minute exercise tolerance and abnormal cardiac autonomic responses, compared to healthy age- and sex-matched controls.

Exercise Tolerance and NYHA Class

There was a significant increase in the distance covered during the 6-minute walk test for all treatments (P<.001, F=5.36), but no significant differences between treatments were observed (Figure 1a). By the fourth week, the increases were: enalapril alone, 130 ± 47 m; enalapril + prazosin, 175 ± 36 m; and enalapril + atenolol, 204 ± 46 m. The 95% confidence intervals for the differences over time between enalapril + atenolol and enalapril alone averaged −160 to 254 m, and the intervals for the difference between enalapril alone and enalapril + prazosin was −157 to 204 m.

There was a significant (P<.001 ANOVA, F=23.1, df 2) time effect, revealing improvements in the NYHA class for all treatments. There was, however, no significance between treatment effect, or time-treatment interaction. For enalapril alone, the NYHA classes at 2 and 4 weeks were 2.0 ± 0.27 and 1.75 ± 0.25, respectively; for enalapril + prazosin, these classes were 2.1 ± 0.27 and 1.5 ± 0.19, respectively; and for enalapril + atenolol, the classes were 1.63 ± 0.26, and 1.50 ± 0.27 at 2 and 4 weeks, respectively.

Heart Rate and Pressure Rate Product

There were no statistically significant differences in supine heart rates between treatments, being 73 ± 18 beats/min for enalapril; 101 ± 4 beats/min for enalapril + prazosin; and 89 ± 7 beats/minute for enalapril + atenolol. The treatment-induced reduction in supine heart rates were statistically insignificant at −6.4 ± 6.9 beats/min, −19.3 ± 3.3 beats/min, and −8.9 ± 6.6 beats/min, respectively. The measures of systolic blood pressure-heart rate product (mm Hg beats/min) at rest before treatment were 10,516 for enalapril alone; 778 for enalapril + prazosin; 1911 for enalapril + atenolol. With time, all treatments were associated with a significant reduction in the pressure rate product (an index of myocardial oxygen demand) (Figure 1b).

There was a significant time effect and time-treatment interaction (P=.018 ANOVA, F=5.02, df 2). The sympathectolic treatments, enalapril + prazosin and enalapril + atenolol, caused a significantly greater time-related reduction

| Table 1. Baseline clinical and demographic features of the Nigerians with congestive heart failure |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
|                                              | Enalapril Alone | Enalapril + Prazosin | Enalapril + Atenolol |
| N                                            | 10             | 8                  | 10                |
| Age (years)                                  | 49.6 ± 5.1     | 53.9 ± 8.4         | 54.2 ± 4.1        |
| Gender (M/F)                                 | 5/5            | 3/5                | 6/4               |
| CHF etiology                                 |                |                    |                   |
| Hypertension                                 | 3              | 6                  | 8                 |
| Cardiomyopathy                               | 4              | 2                  | 2                 |
| Valvar                                        | 3              | 0                  | 0                 |
| NYHA class                                    | 2.6 ± 0.22     | 3.25 ± 0.25        | 3.0 ± 0.26        |
| Cardiothoracic ratio                         | 0.66 ± 0.02    | 0.67 ± 0.03        | 0.67 ± 0.04       |
| 6 minute distance (m)                        | 305 ± 42       | 180 ± 48           | 201 ± 50          |
| Serum creatinine (μmol/l)                    | 124 ± 30       | 98 ± 8             | 120 ± 13          |
| Serum Na+ (mmol/l)                           | 135 ± 2.6      | 135 ± 2.7          | 132 ± 3.4         |
| Serum K+ (mmol/l)                            | 4.2 ± 0.32     | 3.9 ± 0.37         | 4.2 ± 0.35        |
in the pressure rate product compared to enalapril alone. The 2- and 4-week changes from the baseline values were: enalapril alone, $-1349 \pm 894$ and $-337 \pm 1420$ mm Hg.beats/min, respectively; enalapril + prazosin, $-2829 \pm 535$ and $-3498 \pm 395$ mm Hg.beats/min, respectively; and enalapril + atenolol $-3726 \pm 1885$ and $-3107 \pm 2077$ mm Hg.beats/min, respectively.

Valsalva Maneuver and Respiratory Sinus Arrhythmia

**Valsalva Maneuver**

The centrally mediated efferent bradycardia (phase IV bradycardia) was significantly different between treatments ($P=.0036$, $F=6.27$) and time ($P<.0001$, $F=15.02$) by 2-way ANOVA (see Figure 1). Both enalapril combined with prazosin, and enalapril combined with atenolol, caused significantly greater phase IV bradycardia, compared to enalapril alone. At baseline, the phase IV bradycardia (msec) were similar, being $610 \pm 42$ msec for enalapril, $625 \pm 17$ msec for enalapril + prazosin, and $624 \pm 37$ msec for enalapril + atenolol. At 2 and 4 weeks, respectively, the values for enalapril alone were $760 \pm 46$ and $680 \pm 58$ msec; for enalapril + prazosin, $730 \pm 35$ and $825 \pm 48$ msec; and for enalapril + atenolol, $944 \pm 66$ and $888 \pm 64$ msec. The corresponding phase II Valsalva tachycardia at baseline were: enalapril, $546 \pm 38$ msec; enalapril + prazosin, $582 \pm 21$ msec; and enalapril + atenolol, $546 \pm 38$ msec. Neither treatment nor time significantly affected the phase II tachycardic response during the Valsalva maneuver. The Valsalva ratio (ratio of phase IV bradycardia/phase II tachycardia) showed a time dependent increase in all 3 groups ($P<.001$ ANOVA). There was only a trend to increased Valsalva ratio at 4 weeks on enalapril + atenolol ($1.587 \pm 0.29$), compared to either enalapril alone ($1.32 \pm 0.074$), or enalapril + prazosin ($1.266 \pm 0.06$).
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**Respiratory Sinus Arrhythmia**

The respiratory variation of the heart rate with deep breathing was assessed using the sinus arrhythmia ratio (longest R-R heart period/shortest R-R heart period). The respiratory sinus arrhythmia ratio exhibited a significant time effect (P<.0013 ANOVA) increase from the baseline values, but no significant time effect between treatment differences (see Figure 2a). The ratio increased from baseline to 4 weeks as follows: enalapril alone, 1.14 ± 0.32 to 1.38 ± 0.10; enalapril + prazosin, 1.08 ± 0.02 to 1.24 ± 0.04; enalapril + atenolol, 1.13 ± 0.04 to 1.42 ± 0.14.

The Valsalva parameters and respiratory sinus arrhythmia ratio were normalized on the enalapril + atenolol group, while only the respiratory arrhythmia ratio was normalized on enalapril alone (Table 2).

**Forearm Isometric Handgrip**

The pressor and chronotropic responses to isometric handgrip at 30% of pre-determined maximum voluntary contraction were used as indicators of predominantly sympathetic function. There was a significant treatment effect (P=.023 ANOVA) in the chronotropic response to the isometric handgrip. The enalapril + prazosin combination caused a significantly greater rise in heart rate, compared to both the enalapril alone and the enalapril + atenolol combination (P<.05) (Figure 2b). The 95% confidence intervals for the differences were: enalapril + prazosin vs enalapril alone, -1.8 to -25.2 beats/min; enalapril alone vs enalapril + atenolol, -18 to 5.3 beats/min; and enalapril + prazosin vs enalapril + atenolol, -4.1 to 18.6 beats/min.

Similarly, the enalapril + prazosin combination caused an increase in diastolic blood pressure during forearm isometric handgrip from baseline of 8.3 ± 2.1 to 16.5 ± 3.9 mm Hg, which tended to be higher than the change for either enalapril alone (6.25 ± 3.8 to 10.4 ± 3.2 mm Hg), or enalapril + atenolol (17.4 ± 2.7 to 11.1 ± 4.7 mm Hg). Thus the enalapril + prazosin combination normalized the isometric handgrip responses (Table 2).

**Post-Treatment Normalization of Cardiac Autonomic Function**

All autonomic function tests exhibited statistically significant (P<.01 ANOVA) differences in healthy volunteers (N=30), compared to the starting values in CHF patients (N=28). Treatment for 4 weeks with enalapril + atenolol abolished some of these differences, resulting in no statistically significant differences in the respiratory sinus arrhythmia ratio. The 95% confidence intervals for the RSA ratio difference between healthy volunteers and treated CHF were -0.204 to 0.22, P=.95. For Phase IV bradycardia, the intervals were -220 to 201, P=.932; and for the Valsalva ratio, -0.57 to 0.33, P=.59. The enalapril + prazosin treatment abolished the difference in the heart rate response to isometric hand grip (95% CI -21 to 13, P=.66), and the diastolic pressor response (95% CI -15.6 to 9.4, P=.62) (Table 2).

**DISCUSSION**

Our study contrasts the clinical, cardiovascular, and reflex sympathovagal effects of adjunctive α-1 adrenoceptor an-
Table 2. Comparison of treated heart failure patients (4th week) with matched healthy volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Controls (N=30)</th>
<th>95% Confidence Intervals for Healthy Controls</th>
<th>Enalapril + Atenolol (N=8)</th>
<th>Enalapril + Prazosin (N=10)</th>
<th>Enalapril Alone (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 minutes distance walked (m)</td>
<td>540 ± 50</td>
<td>522–568</td>
<td>405 ± 41</td>
<td>355 ± 49</td>
<td>435 ± 52</td>
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<tr>
<td>Respiratory sinus arrhythmia</td>
<td></td>
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<tr>
<td>RSA ratio</td>
<td>1.39 ± 0.19</td>
<td>1.32–1.45</td>
<td>1.38 ± 0.1*</td>
<td>1.24 ± 0.04</td>
<td>1.42 ± 0.14*</td>
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<tr>
<td>Valsalva maneuver</td>
<td></td>
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<tr>
<td>Phase II tachycardia [ms]</td>
<td>649 ± 85</td>
<td>619–679</td>
<td>593 ± 56</td>
<td>634 ± 57</td>
<td>548 ± 50</td>
</tr>
<tr>
<td>Phase IV bradycardia [ms]</td>
<td>935 ± 101</td>
<td>899–971</td>
<td>944 ± 66*</td>
<td>825 ± 48</td>
<td>680 ± 58</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>1.47 ± 0.2</td>
<td>1.39–1.54</td>
<td>1.59 ± 0.29*</td>
<td>1.27 ± 0.06</td>
<td>1.32 ± 0.07</td>
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<tr>
<td>Isometric handgrip</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Δ Diastolic BP (mm HG)</td>
<td>13.4 ± 6.0</td>
<td>11.3–15.5</td>
<td>11.1 ± 4.7</td>
<td>16.5 ± 3.9*</td>
<td>10.4 ± 3.2</td>
</tr>
<tr>
<td>Δ Heart rate (beats/min)</td>
<td>12.0 ± 8.4</td>
<td>10.5–13.5</td>
<td>11.1 ± 3.4*</td>
<td>16.6 ± 2.4*</td>
<td>7.6 ± 2.8</td>
</tr>
</tbody>
</table>

All the parameters showed significant improvements from the baseline value in the heart failure patients. * Indicates the parameters among the treated congestive heart failure patients which improved to within the 95% confidence intervals for age- and sex-matched healthy volunteers, hence can be regarded as being normalized by the therapeutic combinations.
"Thus, ACE inhibition with adjunctive cardioselective β-1 and/or a selective α-1 adrenergic antagonist, singly or in combination may be preferable in treating Blacks with CHF who are critically dependent on residual cardiac adrenergic drive."

Our findings demonstrate a significant (P<.001 ANOVA) time-related improvement in exercise tolerance (distance covered in 6 minutes) and NYHA class, but no significant between-treatment differences. However, we did observe a trend suggesting that sympathoplegic therapy, in particular, the enalapril + atenolol combination, caused the greatest benefit. We have previously reported that the addition of prazosin to enalapril in treating chronic heart failure, or to captopril in treating acute pulmonary edema in Nigerians, resulted in additional significant increases in exercise tolerance and clinical status and NYHA class.

Compared to treatment with enalapril alone, the sympathoplegic treatments exerted a statistically significant reduction on the pressure rate product, an index of myocardial oxygen demand, which is also a predictive factor for mortality in CHF. By the 4th week of treatment, the pressure rate product diminished significantly (P<.05) by -3107 ± 2077 mm Hg-beats/min. for enalapril + atenolol, and by -3498 ± 395 mm Hg-beats/min for enalapril + prazosin (see Figure 1). Thus, the additional survival benefits associated with β-adrenergic blockade in CHF may be attributable, at least in part, to a reduction in heart rate and myocardial oxygen requirement.

A major goal of this study was to evaluate and compare the impact of α-1 or β-1 blockade on cardiac reflex sympathovagal balance in non-ischemic CHF. We have previously reported the enhancement of cardiac parasympathetic tone by using ACE inhibitors, in general, with healthy volunteers. Angiotensin II, which is grossly elevated in CHF, causes peripheral pre-synaptic and central inhibition of reflex cardiac vagal tone. ACE inhibitor therapy has been shown to increase cardiac parasympathetic tone in Caucasians with ischemic heart failure, as well as in Black patients with non-ischemic CHF. This action has been proposed to contribute to the reduction in malignant ventricular arrhythmias and mortality following the use of the drugs in CHF. Our results show that additional β-1 blockade, with atenolol, α-1 antagonism with prazosin, independently significantly (P=.0036 ANOVA) enhanced the centrally mediated reflex vagal bradycardia (phase IV Valsalva bradycardia), compared to enalapril alone (Figure 1). The sympathetically mediated phase II tachycardia did not differ between treatments. The values of the phase IV bradycardia and the Valsalva ratio attained on enalapril + atenolol were well within the normal range for healthy age- and sex-matched controls. Similarly, the respiratory sinus arrhythmia ratio (a measure of tonic vagal heart rate variability), which was depressed at baseline, was increased to the normal range in the enalapril + atenolol treated CHF patients.

These results concur with our earlier findings of the cardiac vagotonic effects of enalapril in CHF in Blacks. Thus, the addition of prazosin, or, in particular, atenolol, to enalapril caused a significantly greater augmentation of reflex cardiac vagal activity compared to using enalapril alone in Black patients with non-ischemic systolic CHF. This finding confirms earlier results with other beta-blockers, especially carvedilol, which increased the R-R or heart rate variability during 24-hour Holter monitoring, and with metoprolol in patients with ischemic heart failure. It is noteworthy that the normalization of reflex cardiac vagal reactivity by beta-1 blockade even precedes the maximal effect on exercise tolerance (Table 2).

Addition of prazosin, but not atenolol, to enalapril normalized the pressor and chronotropic responses during forearm isometric handgrip such that these responses were comparable to those of healthy volunteers (see Figure 2 and Table 2). This finding indicates a contrast in the autonomic effects of α-1 or β-1 adrenoceptor antagonism in CHF patients stabilized on ACE inhibitors. The reflex peripheral vasodilator responses are normalized earlier by the blockade of alpha-adrenergically mediated vasoconstriction than by beta-blockade. The selective post-junctional α-1 adrenoceptor blockade with prazosin permits the pre-junctional α-2 receptors to regulate catecholamine release, which may stimulate chronotropic cardiac β-1 receptors or vasodilatory β-2 vascular receptors during forearm exercise. Beta-1 blockade attenuates the chronotropic response to handgrip.

This study demonstrates the safety of treatment with a combination of beta-blockade and ACE inhibition in Blacks with non-ischemic heart failure, and provides preliminary evidence that such treatment may even result in modest improvements in exercise tolerance and clinical status. Adjunctive beta-1 receptor blockade also caused a significant reduction in the pressure rate product, suggesting improvement in myocardial oxygen utilization, and exerted a highly significant augmentation of reflex cardiac vagal activity in heart failure in Blacks. Thus, despite the reported poor efficacy of beta-blocker monotherapy in Blacks, using adjunctive beta-1 blockade with low dose atenolol resulted in beneficial clinical, autonomic, and cardiovascular effects in CHF, which could further improve prognosis and symp-

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toms in this population characterized by a less favorable prognosis for systolic heart failure. The efficacy of beta-blockade with carvedilol, deduced from meta-analysis in reducing mortality in Blacks, as recently reported by Yancy et al, is consistent with the findings of this study. Combined beta-1 blockade and ACE inhibition is likely to result in considerable therapeutic benefits in Blacks with congestive heart failure, both in Africa, where hypertension is the predominant etiology, and in America, where ischemic cardiomyopathy is a leading contributor to heart failure.

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