ADJUNCTIVE SYMPATHOPLEGIC 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

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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 α-$_1$ or β-$_1$ 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 sympathoplegic 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 handgrip 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 α-1 or β-1 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 β-1 blockade caused a greater enhancement of central baroreceptor vagal activity compared to α-1 blockade. Conversely, the pressor and chronotropic abnormalities during forearm isometric handgrip in CHF, were normalized by α-1, but not β-1, blockade. Thus, the combined reflex cardiac vagal augmentation following selective β-1 blockade, and the hemodynamic effects of α-1 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)

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

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to be deleterious in CHF, since beta-adrenergic receptors were down-regulated and inotropism was reduced in heart failure.[6] However, a report of the efficacy of β-adrenergic blockers in dilated cardiomyopathy,[7] and the more recent demonstration of the further reduction in CHF hospitalization rates and mortality by β-blockers, carvedilol,[8] metoprolol,[9] and bisoprolol[10] 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,[8–10] possibly attributable to a modification of cardiac autonomic sympathovagal balance.[11,12]

The large scale clinical studies demonstrating the benefits of beta-blockade, have focused on Caucasian populations with mainly ischemic heart disease.[8–10] Studies of the efficacy of beta-blockers in the treatment of congestive heart failure are limited in number and have reported conflicting findings.[13,14] The COPERNICUS study[13] 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,[14] 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 (a non-specific beta blocker with α-1 antagonist and antioxidant properties) or bucindolol (non-specific beta blocker, without alpha-1 blocking effect and with intrinsic sympathomimetic activity). Currently, however, no feasible generalizations on the therapeutic role of beta-adrenergic blockers in congestive heart failure in Blacks exist. We are unaware of any study undertaken in Black patients with CHF that specifically evaluate the impact of either β-adrenergic blockers, or adjunctive sympathoplegic therapy to ACE inhibition. This inquiry is important, both from the theoretical and practical clinical perspectives, since the use of β-blockers has not proven efficacious for either the monotherapy of essential hypertension in Blacks,[15,16] or for ocular hypotensive action, which is associated with a rebound increase in intra-ocular pressure.[17] The poor clinical efficacy of using beta-blockers in Blacks compared to Whites may be accountable by a right-ward shift in the dose response relationships of propranolol reduction in exercise-induced tachycardia,[18] and in inter-ethnic differences in lymphocyte β-receptor population, affinities, and the signal transduction involving AMP.[19,20.]

"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 . . ."

Although sympathetic inhibition with α-1 antagonists in CHF may be associated with tachyphylaxis, or a poor response,[21,22] we have reported not only a reduction in mortality by ACE inhibitors in Black Africans with CHF,[23,24] but also have demonstrated an additional beneficial clinical and exercise tolerance effect of prazosin combined with either captopril[25] or enalapril[26] in Nigerians.

The aim of the present study was to evaluate and compare the clinical efficacy, and cardiovascular, exercise tolerance, and autonomic effects of combining either α-1 adrenergic antagonist prazosin, or the selective β-1 adrenergic blocker atenolol, with the ACE inhibitor enalapril, in the treatment of Black patients with mostly non-ischemic congestive heart failure. Our results provide insight into the mechanistic roles of α-1 or β-1 adrenergic receptor antagonism in the treatment of chronic congestive heart failure.

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 β-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

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)	136 ± 2.6	135 ± 2.7	132 ± 3.4
Serum K+ (mmol/l)	4.2 ± 0.32	3.9 ± 0.37	4.2 ± 0.35

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 Bonneferoni *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 untoward 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 ± 1544 for enalapril alone; 13,236 ± 778 for enalapril + prazosin; and 11,585 ± 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 sympathoplegic treatments, enalapril + prazosin and enalapril + atenolol, caused a significantly greater time-related reduction

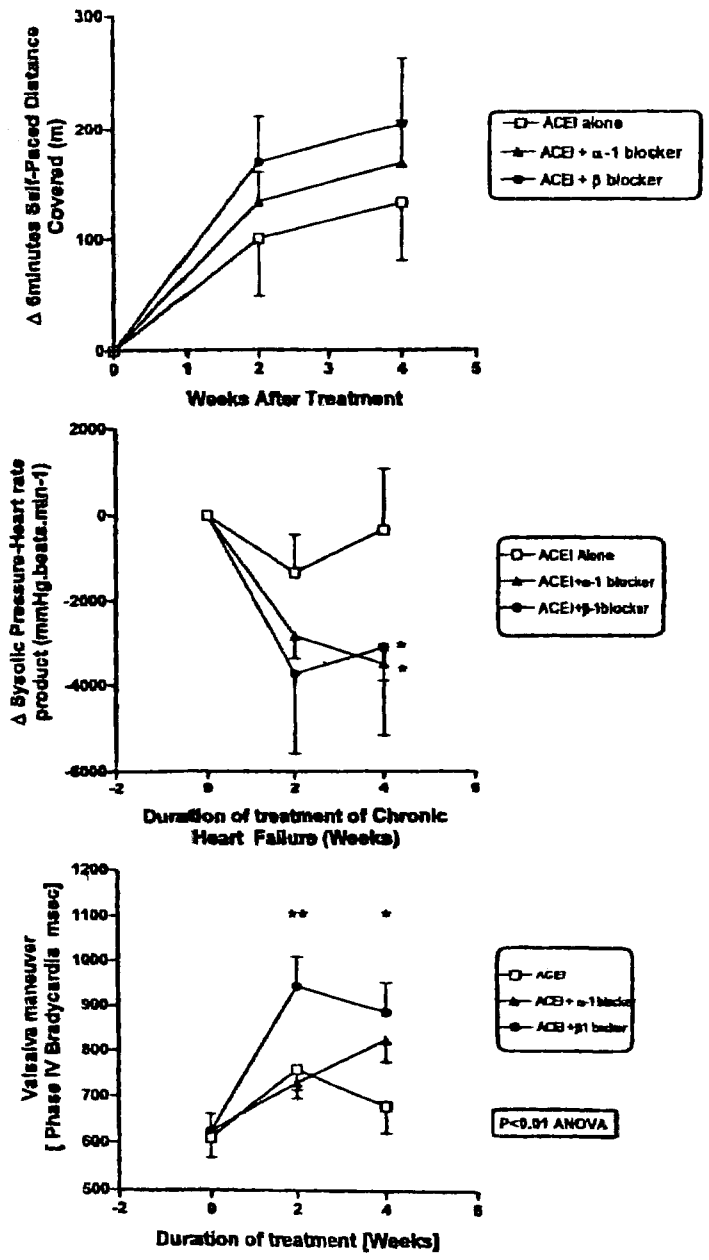

Fig 1. The time course of the effects of enalapril (ACEI) alone, enalapril + prazosin (α-1 blocker) and enalapril + atenolol (β-1 adrenergic blocker) on exercise tolerance (upper panel), change in pressure rate product (middle panel), and efferent baroreceptor mediated reflex vagal activity (lower panel) in patients with non-ischemic CHF. Enalapril (*N*=10), enalapril + prazosin (*N*=8), enalapril + atenolol (*N*=10).

****P*<.05 by post hoc Boneferonni *t* test between treatments, after treatment effect is demonstrated by ANOVA (*P*<.01 ANOVA) for pressure rate product and phase IV bradycardia.**

in the pressure rate product compared to enalapril alone. The 2- and 4-week changes from the baseline values were: enalapril alone, −1349 ± 894 and −337 ± 1420 mm Hg.beats/min, respectively; enalapril + prazosin, −2829 ± 535 and −3498 ± 395 mm Hg.beats/min, respectively; and enalapril + atenolol −3726 ± 1885 and −3107 ± 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 (msecs) were similar, being 610 ± 42 msec for enalapril, 625 ± 17 msec for enalapril + prazosin, and 624 ± 37 msec for enalapril + atenolol. At 2 and 4 weeks, respectively, the values for enalapril alone were 760 ± 46 and 680 ± 58 msec; for enalapril + prazosin, 730 ± 35 and 825 ± 48 msec; and for enalapril + atenolol, 944 ± 66 and 888 ± 64 msec. The corresponding phase II Valsalva tachycardia at baseline were: enalapril, 546 ± 38 msec; enalapril + prazosin, 582 ± 21 msec; and enalapril + atenolol, 546 ± 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 ± 0.29), compared to either enalapril alone (1.32 ± 0.074), or enalapril + prazosin (1.266 ± 0.06).

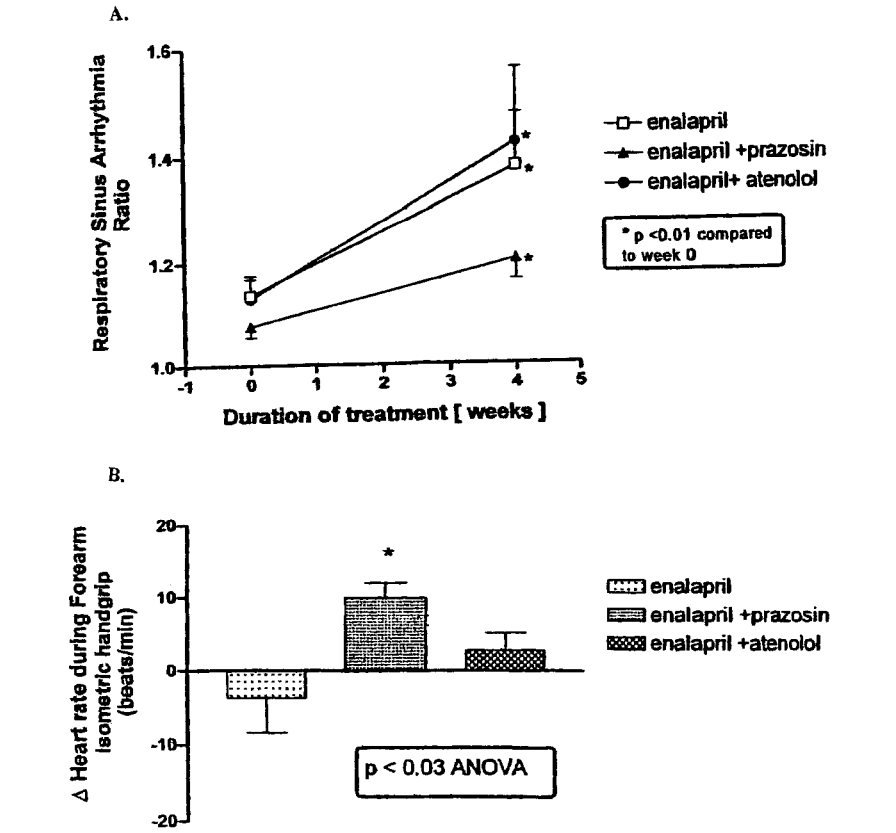

Fig 2. (a) Increase in respiratory variation with deep breathing on the treatments. There was a significant time effect (*$P<.01$) but no treatment differences. (b) Significant treatment effect on the chronotropic response to forearm isometric handgrip ($P=.022$ ANOVA).

***$P<.05$ by post hoc Boneferroni *t* test on enalapril + prazosin ($N=8$).**

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 hand grip 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

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

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.

tagonism with prazosin with those of β-1 adrenergic blockade in congestive heart failure patients receiving concurrent ACE inhibitor therapy. Evidence is emerging for ethnic differences in the natural history of congestive heart failure. According to the study of left ventricular dysfunction,[29] Black patients with heart failure may have a worse prognosis for the progression of left ventricular systolic dysfunction and a higher mortality rate, as compared to Caucasians, even after adjusting for socioeconomic differences. This underscores the urgent need to determine the most efficacious neuro-hormonal inhibitor therapy in the Black population. The available information on the efficacy and survival benefit of beta-adrenergic antagonists in CHF in African Americans is conflicting and, prior to this study, was non-existent for Black Africans. To our knowledge, this is the first controlled study examining the effects of adding the beta-adrenergic blocker atenolol to ACE inhibitors in Black patients with non-ischemic congestive heart failure.

Many studies have reported the poor efficacy of β-adrenergic blockers in Blacks and Africans,[15–19] which might have contributed to the skeptical approach researchers take toward investigating the blockers' utility in congestive heart failure. However, during congestive heart failure, there is neuro-endocrine activation involving elevated catecholamine concentration, which correlates with poor prognosis in heart failure,[30] but which is amenable to manipulation by sympathoplegic therapy. The plasma renin activity (which is under β-1 adrenergic control) is also elevated, and can be reduced via beta blockade.[8] Further, there are reports of salutary effects of beta-blockers on reflex cardiac activity and heart rate in heart failure,[11,12] which have been proposed to contribute to the reduction in mortality and sudden death in beta-blocker treated patients with CHF, as reported in large scale clinical trials.[8–10] Whereas the landmark COPERNICUS study[13] demonstrated sustained survival benefit in carvedilol treated patients with advanced heart failure (including a trend to reduced mortality in Blacks), the BEST study[14] using bucindolol found a conflicting result of no survival benefit, or an even worse outcome, in Black patients with CHF. Our results may provide insights into this discrepancy. Carvedilol is a non-selective beta-blocker with both alpha-adrenergic antagonist and antioxidant properties. It is also the beta-blocker which has shown a beneficial trend on mortality in Blacks with CHF.[13]

Bucindolol is a non-selective beta-adrenoceptor antagonist, but lacks an alpha-1 blocking action. In addition, bucindolol, but not carvedilol caused a down regulation of β-adrenergic receptor density in cardiac myocytes in chicks.[31] In use with humans, bucindolol has a more prominent β-2 adrenoceptor blocking effect, compared to carvedilol.[32] The BEST study reported that bucindolol reduced systemic noradrenaline levels, and that this effect was especially pronounced in Blacks, who showed no therapeutic or survival benefit from bucindolol.[32,33] Carvedilol, due to its α-1 antagonist properties, allows a baroreceptor reflex-mediated increase in norepinephrine release, which mitigates the excessive non-selective beta-adrenergic blockade.[13] It appears that a residual level of cardiac adrenergic stimulation is necessary for the optimal effects of beta-blockers in Blacks.[13,32,33] 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

"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."[13,14,32–34]

dependent on residual cardiac adrenergic drive.[13,14,32–34]

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[26] in treating chronic heart failure, or to captopril in treating acute pulmonary edema in Nigerians,[25] 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.[35] 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.[36,37] Angiotensin II, which is grossly elevated in CHF, causes peripheral pre-synaptic and central inhibition of reflex cardiac vagal tone.[38,39] ACE inhibitor therapy has been shown to increase cardiac parasympathetic tone in Caucasians with ischemic heart failure,[40,41] as well as in Black patients with non-ischemic CHF.[42] This action has been proposed to contribute to the reduction in malignant ventricular arrhythmias and mortality following the use of the drugs in CHF.[8–12] 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.[43] 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,[11] 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-

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,[44] 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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