Original Article

Exaggerated Hypertensive Response to Exercise in Patients with Diastolic Heart Failure

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Systolic load elevation during exercise prolongs left ventricular (LV) relaxation, compromises filling, and raises end-diastolic pressure, leading to reduced exercise tolerance. The aim of this study was to test the hypothesis that the hypertensive response to exercise is exaggerated in patients with diastolic heart failure (DHF). Echocardiograms and treadmill testing were performed in patients with DHF (n=20) and age-matched hypertension with LV hypertrophy (HTN; n=20). The Minnesota Living with Heart Failure Questionnaire was used to estimate quality of life (QOL). There were no differences in resting blood pressure or echocardiographic parameters between the groups. The maximum exercise time was significantly shorter in the DHF group than in the HTN group (6.0±3.0 *vs.* 12.5±2.5 min), and the peak systolic blood pressure during exercise was significantly higher in the DHF group (212±18 *vs.* 189±16 mmHg, p<0.05). After 4 weeks of treatment with candesartan, an angiotensin II receptor blocker (8 mg/d), peak systolic blood pressure during exercise decreased to 191±13 mmHg, maximum exercise time increased (10.4±3.0 min; p<0.05), and QOL improved in patients with DHF, while there was no change in patients with HTN, despite the similar resting blood pressure. In patients with DHF, systolic blood pressure markedly increased during exercise, and this was accompanied by impaired exercise tolerance and a decreased QOL, both of which were partly suppressed by blocking angiotensin II. (*Hypertens Res* 2008; 31: 679–684)

***Key Words*: diastolic heart failure, hypertension, exercise, angiotensin II**

Introduction

Recent cross-sectional, population-based echocardiographic studies show that about half of all patients with heart failure have preserved left ventricular (LV) ejection fraction and impaired LV diastolic function (*i.e.*, diastolic heart failure [DHF]) (*1*, *2*). Despite its prevalence, high mortality rates, and economic burden, DHF's pathophysiology remains somewhat controversial, and evidence-based guidelines for management are lacking. Whereas diastolic dysfunction is thought to be a dominant cause of DHF, diastolic abnormalities are also common in hypertensive individuals without heart failure (*3*). Furthermore, hypertensive heart disease is a major cardiovascular disease underlying DHF, and LV hypertrophy (LVH) caused by hypertension is likely related to DHF (*4*). A population-based cohort survey demonstrated that roughly 20% of patients with LVH progress to heart failure (*5*).

In patients with hypertension and diastolic dysfunction, the increase in systolic arterial pressure during exercise is frequently exaggerated, probably due to increased LV and arterial stiffness (*6*, *7*). Systolic-ventricular and arterial stiffening would influence diastole by elevating systolic load, compromising filling, and raising end-diastolic pressure, ultimately leading to decreased exercise tolerance even in the absence of resting symptoms. Thus, a marked increase in systolic blood pressure (BP) during exercise may play a central role in the

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decrease in exercise tolerance in patients with DHF.

The exercise-induced increase in systolic arterial pressure in patients with hypertension and diastolic dysfunction may be partly mediated by angiotensin II, which exhibits an increase in circulating levels during exercise (*8*). Furthermore, angiotensin II directly prolongs LV relaxation, leading to impaired LV filling (*9*). Thus, increases in angiotensin II during exercise may exacerbate diastolic dysfunction by raising BP and by having direct effects on the myocardium. These observations suggest that blocking the action of angiotensin II could improve diastolic function during exercise, thus enhancing exercise tolerance. However, this phenomenon has not been observed in patients with DHF.

Accordingly, the goal of this study was to test the hypothesis that a marked increase in systolic BP during exercise occurs only in patients with DHF and not in patients without heart failure in whom systolic BP and LV mass are similar. Additionally, we also hypothesized that an angiotensin II blocker would improve exercise tolerance and quality of life (QOL) in patients with DHF.

Methods

Patient Population

Patients visiting our hospital were screened for inclusion in the present study. Entry criteria included systolic hypertension, sinus rhythm, LVH (interventricular septal thickness >12 mm, LV posterior wall thickness >12 mm), LV ejection fraction >0.50 by 2-dimensional (2-D) echocardiography, and mitral valve Doppler flow pattern with a peak E wave less than the peak A wave velocity (E/A <1.0). Exclusion criteria included the presence of myocardial ischemia in the treadmill test, abnormal wall motion, valvular heart disease, and other diseases that could limit exercise tolerance. All patients had their ambulatory BP measured, and patients showing white-coat hypertension or white-coat normotension were excluded. Patients taking an angiotensin II receptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, a β-blocker, verapamil, diltiazem, or digoxin were also excluded, while patients taking other medications were included. All subjects had taken a long-acting, non-dihydropyridine calcium-channel blocker as a hypertensive agent. Twenty consecutive patients with DHF were enrolled in the present study (DHF group). DHF was diagnosed if two criteria were met: 1) symptoms and signs of heart failure rigorously defined by Framingham criteria and independently analyzed by two cardiologists, and 2) LV ejection fraction >50% (*4*). All patients with DHF were hospitalized due to pulmonary congestion within the previous 2 years, but not within the previous 3 months. As a control group, 20 consecutive patients with essential hypertension and LVH who met all of the above criteria were enrolled in the study (HTN group).

Table 1. Patient Characteristics

	HTN (n=20)	DHF (n=20)
Age (years)	70±4	70±5
Women (%)	50	60
Clinical history (%)		
Hyperlipidemia	5	5
Diabetes mellitus	5	5
Medications (%)		
Calcium channel blockers	100	100
Diuretics	10	20
Other vasodilators	5	0
Systolic BP at rest (mmHg)	146±12	152±14
Diastolic BP at rest (mmHg)	81±10	81±10
Heart rate at rest (beat/min)	73±14	77±13

HTN, hypertension; DHF, diastolic heart failure; BP, blood pressure.

Protocol

Each subject provided informed, written consent to the protocol that had been approved by our institutional review board. All baseline medications were continued during the study. Baseline plasma angiotensin II and brain natriuretic peptide (BNP) levels, resting 2-D echocardiogram, and Doppler measurements of mitral valve flow velocities were obtained. Clinical symptoms were assessed in the HTN and DHF groups by the Minnesota Living with Heart Failure Questionnaire (*10*). The subjects then underwent a graded symptom–limited maximum treadmill exercise test using the modified Bruce protocol. BP was obtained using a sphygmomanometer at the end of each minute. Immediately after exercise, plasma angiotensin II and BNP levels were measured again. The patients then received 8 mg candesartan every morning for 4 weeks, and the same protocol was repeated.

Echocardiogram

LV mass was calculated using the area length method (*11*). The transmitral flow velocity was measured using pulsed-wave Doppler imaging with the sample volume positioned between the mitral leaflet tips during diastole, as previously described (*12*). The E wave to A wave peak velocities (E/A ratio) and the deceleration time of mitral E-wave velocity were determined.

Statistical Analysis

Data are expressed as means±SD. A nested analysis of variance was used to compare the rest and exercise groups before and after the administration of candesartan. When a significant effect was present, group comparisons were performed using the Student-Newman-Keuls multiple comparison test.

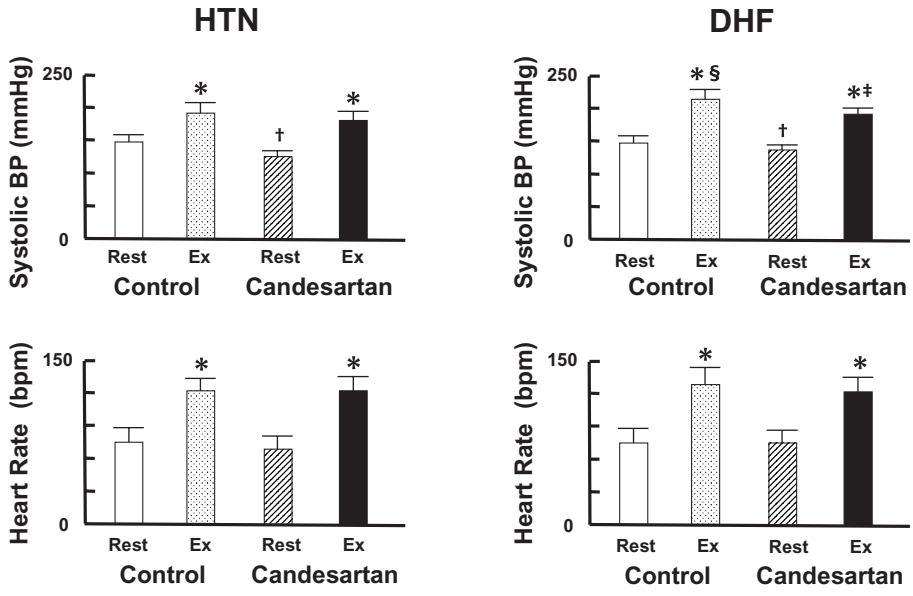

Fig. 1. *Effects of candesartan on systolic blood pressure (BP) and on heart rate at rest (Rest) and during exercise (Ex). *p < 0.05 vs. Rest, †p < 0.05 vs. Control-Rest, ‡p < 0.05 vs. Control-Ex, §p < 0.05 vs. Control-Ex-HTN.*

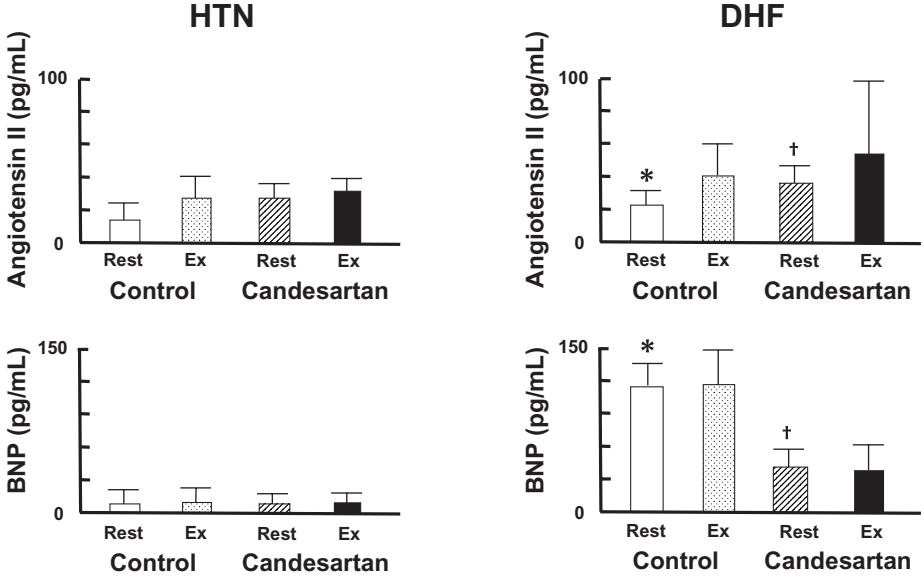

Fig. 2. *Effects of candesartan on plasma angiotensin II and BNP levels at rest (Rest) and during exercise (Ex). *p < 0.05 vs. Control-Rest-HTN, †p < 0.05 vs. Control-Rest.*

The level of significance was taken as $p < 0.05$.

Results

Patient Characteristics

Forty patients completed the study, and the baseline patient characteristics are shown in Table 1. The mean age was 70±4 years. All patients had a past history of hypertension, but some had systolic BP below 140 mmHg while on non-dihydropyridine calcium-channel blockers at the time of entry into the study. Resting BP at baseline was 146±12/81±10 mmHg in the HTN group and 152±14/81±10 in the DHF group (Fig. 1). Plasma BNP and angiotensin II levels were higher in the

Table 2. Echo-Doppler Data before and after Treatment with Candesartan

	HTN (n=20)		DHF (n=20)	
	Base	Cande	Base	Cande
LV end-diastolic dimension (mm)	94±21	95±21	103±26	103±25
LV end-systolic dimension (mm)	29±8	28±7	33±13	32±12
LV ejection fraction (%)	70±5	71±5	68±8	70±7
LV mass (g)	88±30	91±28	103±24	103±22
Mitral E-wave velocity (mm/s)	66±10	65±11	63±13	62±14
Mitral A-wave velocity (mm/s)	81±16	80±17	78±10	77±11
Mitral E/A ratio	0.83±0.12	0.83±0.14	0.80±0.13	0.80±0.13
Deceleration time of mitral E-wave velocity (ms)	202±45	209±51	220±28	217±30

HTN, hypertension; DHF, diastolic heart failure; Cande, candesartan; LV, left ventricular.

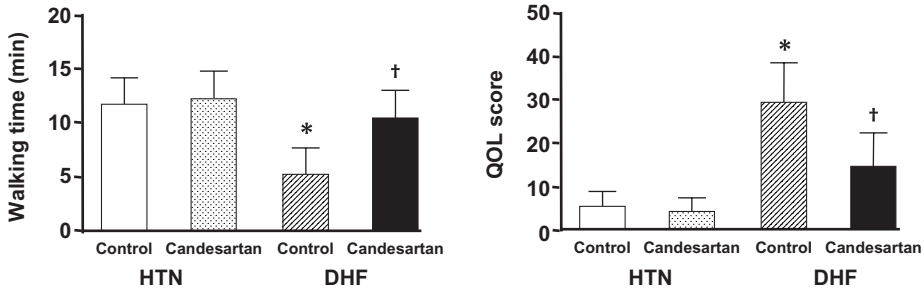

Fig. 3. *Effects of candesartan on walking distance and quality of life (QOL). *$p<0.05$ vs. Control-HTN, †$p<0.05$ vs. Control-DHF.*

DHF group than in the HTN group (BNP: 110±34 *vs*. 13±9 pg/mL) (Fig. 2).

There were no differences between the groups in the resting LV end-diastolic and end-systolic dimensions, or in the LV ejection fraction (Table 2). The resting mitral valve E/A ratio was less than 1.0 in all subjects of both groups (entry criteria). The deceleration time of the mitral E-wave velocity and the LV mass were also similar between the groups.

Effects of Exercise

The maximum exercise time was significantly shorter in the DHF group than in the HTN group; the exercise test was stopped upon the appearance of any symptom necessitating its termination (6.0±3.0 *vs*. 12.5±2.5 min) (Fig. 3). The peak systolic BP during exercise was significantly higher in the DHF group than in the HTN group (212±18 *vs*. 189±16 mmHg, $p<0.05$).

Effects of Candesartan

After the administration of candesartan, resting systolic BP was similarly reduced, to 133±8/73±12 in the HTN group and to 137±11/74±9 mmHg in the DHF group (Fig. 1). Peak systolic BP during exercise was also significantly reduced, to 184±15 mmHg in the HTN group and to 191±13 in the DHF group. Candesartan administration significantly decreased plasma BNP levels in the DHF group (38±23 pg/mL) but not in the HTN group (11±5 pg/mL), while the resting levels of circulating angiotensin II were increased by candesartan administration in both groups (Fig. 2). Candesartan did not affect any baseline echo-Doppler parameters measured in either group (Table 2).

The time spent exercising significantly increased (10.4±3.0 min) and the QOL score improved after candesartan administration in the DHF group, but not in the HTN group (Fig. 3).

Discussion

Exercise intolerance is the most common symptom in patients with DHF (*4*). A hypertensive response to exercise contributes to LV diastolic dysfunction during exercise, which may cause exercise intolerance (*13*). In the present study, we observed a marked increase in systolic BP during exercise in DHF patients compared to hypertensive patients with similar BP and LV mass. This increase resulted in exercise intolerance. Furthermore, an angiotensin II receptor blocker, candesartan, suppressed the significant increase in systolic BP in response to exercise, and improved exercise tolerance and QOL, although there were no changes in echocardiographic measurements.

Systolic hypertension during exercise occurs in many patients with hypertension (*14–16*). This may be a manifestation of arterial stiffness that often accompanies diastolic LV dysfunction. An increase in arterial systolic pressure increases LV afterload, thus slowing LV relaxation and reducing the extent of ejection. The ventricle may operate at higher volumes, and there is an upward shift of the LV diastolic pressure-volume relation, resulting in an increase in left arterial pressure in response to increased systolic load (*17*). Our results showed that systolic BP increased to >200 mmHg during exercise in DHF patients, which was significantly greater than the increase in systolic BP in hypertensive patients with similar BP and LV mass. The different hypertensive responses between DHF patients and essential hypertensive patients may have been caused by stiff left ventricle and artery, atrial constriction, and/or preload reserve. Furthermore, an exaggerated rise in BP during exercise causes increases in LV afterload and, in turn, further impairment of myocardial relaxation and LV filling. Thus, both myocardial and extramyocardial factors are important to cause abnormalities in diastolic function that lead to the development of DHF.

The addition of the angiotensin II receptor blocker candesartan to the DHF patients' medications improved their ability to walk on a treadmill by approximately 5 min using a modified Bruce protocol. The improvement in treadmill exercise time was also manifest as an increase in QOL as measured by the Minnesota Living with Heart Failure Questionnaire. However, candesartan did not alter any Doppler echocardiographic measurement of resting LV diastolic performance in our study. Warner *et al*. reported that, in patients with diastolic dysfunction and without heart failure, losartan, an angiotensin II receptor blocker, blunts the hypertensive response to exercise and increases exercise tolerance without any changes in echocardiographic parameters (*18*). Candesartan may prevent arterial constriction and increase venous return during exercise, resulting in improved exercise tolerance. It is also possible that a decrease in LV wall stress, suggested by decreased BNP levels after the administration of candesartan, increases exercise tolerance. A longer course of therapy might have produced improvements in diastolic function by inducing regression in patients with LVH (*19*). A recent clinical trial, the CHARM study, shows a trend in favor of candesartan towards fewer detrimental cardiovascular outcomes among patients with preserved LV ejection fraction, although differences in cardiovascular mortality and CHF hospital admissions between the candesartan and the placebo group are of borderline significance (*20*).

Study Limitations

First, we measured exercise tolerance using a modified Bruce protocol of treadmill exercise. The duration of exercise in our study may have been influenced by the patients' motivation and subjective interpretation of their symptoms during exercise. These confounding variables could have affected our ability to observe a benefit from therapy. Alternatively, the lower exercise systolic BP during therapy may have influenced the examiner to push the subject further. However, although both therapies produced similar reductions in BP, exercise tolerance and QOL improved significantly only in patients with DHF.

Second, we did not measure echo-Doppler parameters obtained immediately after peak exercise. Warner *et al*. reported that, in patients with diastolic dysfunction, the angiotensin II receptor blocker losartan did not alter echo-Doppler parameters obtained immediately after peak exercise (*18*). We cannot ignore the possibility that these parameters should be controlled at matched levels of exercise.

Conclusion

In patients with DHF, systolic BP markedly increased during exercise, which impaired exercise tolerance and QOL. The angiotensin II receptor blocker candesartan suppressed this increase in systolic BP and improved exercise tolerance and QOL without affecting echocardiographic measurements. These findings suggest that this severe hypertensive response to exercise may be a potential therapeutic target for treating DHF.

References

1. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss C, Levy D: Congestive heart failure in subjects with normal *versus* reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999; **33**: 1948–1955.
2. Masoudi FA, Havranek EP, Smith G, *et al*: Gender, age, and heart failure with preserved left ventricular systolic function. *J Am Coll Cardiol* 2003; **41**: 217–223.
3. Little WC, Ohno M, Kitzman DW, Thomas JD, Cheng CP: Determination of left ventricular chamber stiffness from the time for deceleration of early left ventricular filling. *Circulation* 1995; **92**: 1933–1939.
4. Zile MR, Brutsaert DL: New concept in diastolic dysfunction and diastolic heart failure: part 1. Diagnosis, prognosis, and measurements of diastolic function. *Circulation* 2002; **105**: 1387–1393.
5. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D: Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2001; **37**: 1042–1048.
6. Fleg JL, O'Connor F, Gerstenblith G, *et al*: Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. *J Appl Physiol* 1995; **78**: 890–900.
7. Fagard R, Staessen J, Thijs L, Amery A: Prognostic significance of exercise *versus* resting blood pressure in hypertensive men. *Hypertension* 1991; **17**: 574–578.
8. Aldigier JC, Huang H, Dalmay F, *et al*: Angiotensin-con-

verting enzyme inhibition does not suppress plasma angiotensin II increase during exercise in humans. *J Cardiovasc Pharmacol* 1993; **21**: 289–295.
9. Cheng CP, Suzuki M, Ohte N, Ohno M, Wang ZM, Little WC: Altered ventricular and myocyte response to angiotensin II in pacing-induced heart failure. *Circ Res* 1996; **78**: 880–892.
10. Rector TS, Tschumperlin LK, Kubo SH, *et al*: Use of the living with heart failure questionnaire to ascertain patients' perspectives on improvement in quality of life *versus* risk of drug-induced death. *J Card Fail* 1995; **1**: 201–206.
11. Schiller NB, Shah PM, Crawford M, *et al*: Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr* 1989; **2**: 358–367.
12. Oh JK, Appleton CP, Hatle LK, *et al*: The noninvasive assessment of left ventricular diastolic function with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 1997; **10**: 246–270.
13. Zampaglione B, Pascale C, Marchisio M, Cavallo-Perin P: Hypertensive urgencies and emergencies: prevalence and clinical presentation. *Hypertension* 1996; **27**: 144–147.
14. Stratton JR, Levy WC, Cerqueira MD, Schwartz RS, Abrass IB: Cardiovascular responses to exercise: effects of aging and exercise training in healthy men. *Circulation* 1994; **89**: 1648–1655.
15. Arita M, Hashizume T, Wanaka Y, *et al*: Effects of antihypertensive agents on blood pressure during exercise. *Hypertens Res* 2001; **24**: 671–678.
16. Takamura T, Onishi K, Sugimoto T, *et al*: Patients with a hypertensive response to exercise have impaired left ventricular diastolic function. *Hypertens Res* 2008; **31**: 257–263.
17. Little WC, Braunwald E: Assessment of cardiac function, in Braunwald E (ed): Heart Disease, 5th ed. Philadelphia, W.B. Saunders, 1997, pp 421–444.
18. Warner JG Jr, Metzger DC, Kitzman DW, Wesley DJ, Little WC: Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. *J Am Coll Cardiol* 1999; **33**: 1567–1572.
19. Hawkins NM, Wang D, McMurray JJ, *et al*, CHARM Investigators and Committees: Prevalence and prognostic implications of electrocardiographic left ventricular hypertrophy in heart failure: evidence from the CHARM program. *Heart* 2007; **93**: 59–64.
20. Yusuf S, Pfeffer MA, Swedberg K, *et al*, CHARM Investigators and Committees: Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003; **362**: 777–781.