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ORIGINAL ARTICLE

Adding thiazide to a renin–angiotensin blocker improves left ventricular relaxation and improves heart failure in patients with hypertension

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Hypertension is associated with an increased risk of diastolic dysfunction. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) have failed to show improvement in clinical outcomes for patients with diastolic dysfunction. In this study, we investigated the effect of changing an ACEi or ARB to a combination of losartan and hydrochlorothiazide (HCTZ) on left ventricular (LV) preload and relaxation in patients with hypertension and diastolic dysfunction. We enrolled 371 hypertensive patients with diastolic dysfunction who had not achieved their treatment goals with an ACEi or ARB. We switched the ACEi or ARB to losartan/HCTZ and followed the patients for 24 weeks. The primary end points were changes in septal mitral annular velocity during diastole (*e′*) and in the ratio of mitral inflow velocity to *e′* velocity (*E*/*e′* ratio) from baseline to the end of follow-up. Mean systolic and diastolic blood pressures (BP) decreased by 22 and 11 mm Hg, respectively, after changing from an ACEi or ARB to losartan/HCTZ. The *e′* velocity increased, and the *E*/*e′* ratio and brain natriuretic peptide level decreased significantly. High-sensitivity C-reactive protein also decreased significantly (0.50 *vs.* 0.29 mg dl^{-1}, $P<0.0001$). There were only slight or no changes in glucose levels, homeostasis model assessment insulin resistance (HOMA-R), uric acid and electrolytes after the drug change. Changing from an ACEi or ARB to losartan/HCTZ is associated with a reduction in BP, improvement in LV relaxation, improvement in heart failure state and attenuation of systemic inflammation with few adverse effects in patients with hypertension and diastolic dysfunction.
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INTRODUCTION

Diastolic dysfunction is the most common cause of heart failure (HF) in patients with hypertension.[1] Diastolic HF is associated with considerable morbidity and mortality, and the risk of adverse outcomes increases with the severity of diastolic dysfunction.[2] Patients with diastolic dysfunction have increased activation of the renin–angiotensin–aldosterone system, as do patients with systolic HF, which contributes to the pathogenesis and progression of the condition. However, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) have failed to show a benefit with regard to mortality or morbidity.[3–5] Thiazide is useful for reducing volume load in patients with diastolic dysfunction.[6] However, thiazide monotherapy has not been widely used in patients with diastolic dysfunction. Decreases in blood pressure (BP) are blunted by hypovolemia-induced activation of the renin–angiotensin–aldosterone system. Thiazide monotherapy involves risks of dysglycemia and/or dyslipidemia, and of elevation of C-reactive protein (CRP).[7] To resolve these problems, a small dose of thiazide in combination with an ACEi or ARB is given to allow for the full antihypertensive effect of thiazide and to minimize its adverse effects. However, it remains unknown whether this combination therapy can improve diastolic function or HF state and, if so, which factor has the principal role in the improvement of HF: reduction in left ventricular (LV) pre-load, improvement in its relaxation or both.

To answer these questions, we conducted a prospective, multicenter study to test the hypothesis that changing from an ACEi or ARB to losartan/hydrochlorothiazide (HCTZ) can improve LV diastolic function in patients with hypertension and diastolic dysfunction.

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The aims of this study were (1) to elucidate the impact of changing from an ACEi or ARB to losartan/HCTZ on LV preload, relaxation and severity of HF; (2) to determine the responders and non-responders to combination therapy; and (3) to determine the impact of this drug change on the metabolism of glucose, lipids, uric acid, electrolytes and CRP.

METHODS

Study population

Men and women from 20 to 80 years of age, with a history of stage 1 or 2 essential hypertension (mean BP measurement of >140 mm Hg systolic or >90 mm Hg diastolic), who were receiving treatment with an ACEi or ARB, were screened for inclusion by assessing their systolic and diastolic functions with echocardiography. Mitral annular relaxation velocity of $\leqslant 8\,cm\,s^{-1}$ was used to make a diagnosis of diastolic dysfunction. The exclusion criteria were an LV ejection fraction of $<50\%$, septal mitral annular relaxation velocity $>8\,cm\,s^{-1}$, receiving treatment with diuretics and atrial fibrillation at baseline. The study protocol was approved by individual sites and written informed consent was obtained from all patients before any study procedures.

Study protocol

The patients were followed at least for 4 weeks to observe that target BP, $<130/80$ mm Hg, was not achieved with an ACEi or ARB. All patients underwent echocardiographic screening for systolic and diastolic functions before the start of treatment with losartan 50 mg/hydrochlorothiazide 12.5 mg. Then, the administration of ACEi or ARB was stopped, and ACEi or ARB was replaced with losartan/HCTZ. No other medications were changed throughout the study period. BP and heart rate were measured in a sitting position at each study visit. The adequacy of anti-hypertensive therapy was determined on the basis of measured BP. The use of concomitant antihypertensive medication was recorded at each study visit. If BP was not adequately controlled, add-on treatment other than diuretics was considered, but such subjects were dropped from this study. Patients were assessed at 4–8-week intervals for at least 24 weeks and underwent echocardiographic assessment at the end of the study. Blood and urine tests were also performed at baseline and at the end of the study.

Echocardiographic data analysis

From the mitral flow velocity pattern, we measured the peak velocities of E and A waves on mitral flow velocity, the ratio of their peak velocities (*E*/*A* ratio), the isovolumic relaxation time (IVRT) and the deceleration time of the E wave. Spectral pulsed-wave Doppler tissue interrogation of longitudinal mitral annular velocity was recorded throughout the cardiac cycle at the septal annulus in the apical four-chamber view. The peaks of apically directed systolic (s' velocity) and early diastolic (e' velocity) myocardial velocities were measured. Additional exploratory analyses included changes in chamber dimensions and the LV ejection fraction. LV mass was measured by using the American Society of Echocardiography-recommended formula and the end-systolic left atrial volume was measured by using the ellipsoid model.[8] Both values were indexed with body surface area in m^2.

The primary endpoints were changes in e' velocity and in the ratio of mitral inflow velocity to e' velocity (E/e' ratio) from baseline to follow-up. The secondary efficacy measures included differences in changes in BP, heart rate, wall thickness, the LV mass index and the left atrial volume index from baseline to follow-up. Blood samples were collected for measurements of brain natriuretic peptide (BNP) and high-sensitivity CRP (hsCRP), along with additional exploratory blood analyses, and urine was collected for measurement of albumin concentrations.

Statistical analysis

All of the results are expressed as the mean ± s.d. or proportions (%). Student's *t*-test was used for parametric data when a normal distribution and equal dispersion were recognized. The Welch's *t*-test was used when the variance was unequal. The paired *t*-test was used for comparing temporal changes in data. Univariate and multivariate analyses were performed to determine the independent factors related to changes in systolic BP, e' velocity and E/e' with changes from ACEi or ARB to losartan/HCTZ. Differences in the categorical data were analyzed by a χ^2 test and Fisher's exact test was used when appropriate. Differences were considered to be statistically significant when *P*-values were <0.05.

RESULTS

After echocardiographic screening, 415 patients with a history of treated or untreated hypertension were enrolled in this study between October 2008 and November 2009. Forty-four patients were excluded from this study, including 32 patients who were lost to follow-up, 7 patients who were excluded for protocol violation, 3 patients who were excluded for poor adherence and 2 patients who were excluded for atrial fibrillation at follow-up. Follow-up study was completed in 371 (89%) of the patients. Baseline characteristics, medication use and echocardiographic parameters before changing to losartan/HCTZ are shown in Table 1. The average interval between baseline and follow-up was approximately 6 months (range, 133–308 days). No patients died,

Table 1 Baseline demographic and clinical characteristics of study patients

Variables	*Population* (n=*371*)
Mean age (s.d.), years	67.5 (9.6)
Women, *n* (%)	135 (36)
Mean SBP (s.d.), mm Hg	155 (15)
Mean DBP (s.d.), mm Hg	87 (11)
Mean pulse (s.d.), b.p.m.	73 (11)
Weight (s.d.), kg	64.8 (11.4)
Body mass index (s.d.), $kg\,m^{-2}$	25.3 (3.4)
NYHA functional class	
Class I, *n* (%)	228 (61.5)
Class II, *n* (%)	138 (37.2)
Class III, *n* (%)	5 (1.3)
Diabetes, *n* (%)	106 (28.6)
Myocardial infarction, *n* (%)	19 (5.1%)
Mean eGFR (s.d.), $ml\,min^{-1}$ per $1.73\,m^2$	68.7(17.7)
Antihypertensive medication, n (%)	
ARB, *n* (%)	324 (87.3)
ACEi, *n* (%)	47 (12.7)
Other hypertensive medications, n (%)	
Calcium channel blocker, *n* (%)	171 (46.9)
Beta-blocker, *n* (%)	89 (24.0)
Alpha-blocker, *n* (%)	12 (3.2)
Echocardiographic parameters	
LVDd (s.d.), mm	47.4 (0.45)
LVDs (s.d.), mm	29.5 (0.45)
Septal wall thickness (s.d.), mm	10.0 (1.6)
LVMI (s.d.), $g\,m^{-2}$	102 (22)
LA dimension, mm	40.9 (8.1)
LA volume index, (s.d.), $ml\,m^{-2}$	25.4 (9.3)
LVEF (s.d.), %	67.2 (9.1)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; bpm, beats per minute; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LA, left atrial; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; SBP, systolic blood pressure; s.d., standard deviation.

developed HF or cardiovascular events or were admitted to the hospital in the course of the study.

The effect of change from ACEi or ARB to losartan/HCTZ on BP, echocardiographic parameters and laboratory data

At follow-up, the mean systolic and diastolic BPs and pulse pressure decreased from baseline by 23, 11 and 12 mm Hg, respectively (Table 2). Heart rate decreased by 2 beats min^{-1}. Additional hypertensive medications were given to only 26 patients (7%) and the medications given to most patients were calcium channel blockers (24 patients (6.5%)). The LV wall thickness, LV mass index and left atrial volume were significantly decreased 6 months after changing to losartan/HCTZ. There were no changes in peak E, deceleration time or *E*/*A* ratio. The *e*′ velocity significantly increased (5.5–6.5 cm s^{-1}, $P<0.0001$), implying an improvement in LV relaxation. The *E*/*e*′ ratio significantly decreased, from 12.1 to 10.6 at follow-up ($P<0.0001$), indicating a decrease in LV preload. IVRT also decreased significantly (120–113 ms, $P<0.0001$). Although there was no change in the LV ejection fraction after changing to losartan/HCTZ, *s*′ velocity significantly increased, suggesting improvement in LV long-axis contractile function.

BNP levels decreased after changing from ACEi or ARB to losartan/HCTZ (48.6 *vs.* 36.6 pg dl^{-1}, P=0.0006). Interestingly, hsCRP levels showed a significant reduction after changing to losartan/HCTZ. Urine albumin concentrations also decreased at follow-up. Microalbuminemia ($\geqslant$30 mg per g Cr) was present in 73 patients (19.7%) at baseline, but was present in only 49 patients (13.2%) after 6 months of changing to losartan/HCTZ. There were slight increases in serum creatinine and blood urea nitrogen, and a slight decrease in the estimated glomerular filtration rate at follow-up. In all patients, uric acid did not show a significant change after changing to losartan/HCTZ. In patients with low uric acid levels ($<$7.0 mg dl^{-1}) at baseline

Table 2 Changes in hemodynamic and echocardiographic parameters with changes from ACEi or ARB to losartan/HCTZ

Variables	*ACEi or ARB*	*6 months of losartan/HCTZ*	P-*value*
SBP, mm Hg	155 (15)	132 (12)	<0.0001
DBP, mm Hg	87 (11)	76 (10)	<0.0001
Pulse pressure, mm Hg	68 (16)	56 (12)	<0.0001
Pulse, b.p.m.	73 (11)	71 (11)	0.0006
Echo parameters			
e′ velocity, cm s^{-1}	5.4 (1.4)	6.5 (1.8)	<0.0001
s′ velocity, cm s^{-1}	7.7 (2.6)	8.2 (2.6)	<0.0001
E/*e*′ ratio	12.1 (3.8)	10.6 (3.7)	<0.0001
IVRT, ms	120.3 (31.1)	112.7 (27.2)	<0.0001
DT, ms	238.3 (54.6)	233.7 (47.8)	0.1214
E velocity, m s^{-1}	64.0 (15.8)	63.9 (14.7)	0.9118
A velocity, m s^{-1}	82.3 (17.7)	79.3 (17.0)	<0.0001
E/*A* ratio	0.80 (0.21)	0.83 (0.22)	0.0013
Septal thickness, mm	10.0 (1.6)	9.7 (1.5)	<0.0001
LVEF, %	67.2 (9.1)	67.0 (10.6)	0.6504
LVMI g m^{-2}	102 (22)	96 (22)	<0.0001
LA volume index, ml m^{-2}	25.4 (9.3)	23.6 (8.7)	<0.0001
Laboratory data			
BNP, pg dl^{-1}	48.6 (73.2)	36.6 (55.7)	0.0006
HsCRP, mg dl^{-1}	0.50 (0.62)	0.29 (0.73)	<0.0001
Urine albumin, mg per g Cr	71.8 (219.6)	47.0 (228.3)	0.0010
BUN, mg dl^{-1}	17.0 (4.5)	18.2 (5.3)	<0.0001
Serum creatinine, mg dl^{-1}	0.83 (0.24)	0.86 (0.25)	0.0001
eGFR, ml min^{-1}	68.7(17.7)	66.6 (18.3)	0.0001
Uric acid, mg dl^{-1} (all)	5.9 (1.4)	6.0 (1.5)	0.7318
Uric acid (<7.0), mg dl^{-1}	5.3 (1.0)	5.6 (1.4)	<0.0001
Uric acid ($\geqslant$7.0), mg dl^{-1}	7.7 (0.7)	6.9 (1.2)	<0.0001
Na, mEq dl^{-1}	141.7 (1.9)	141.3 (2.4)	0.0032
K, mEq dl^{-1}	4.3 (0.4)	4.1 (0.4)	<0.0001
Cl, mEq dl^{-1}	104.0 (2.4)	103.0 (3.1)	<0.0001
Fasting BS, mg dl^{-1}	111.1 (26.8)	110.9 (28.2)	0.8732
HbA1c, %	6.19 (0.74)	6.14 (0.75)	0.2368
HOMA-R	3.73 (5.01)	3.53 (4.61)	0.5218
Total cholesterol, mg dl^{-1}	202 (31)	195 (31)	<0.0001
HDL cholesterol, mg dl^{-1}	55 (14)	54 (14)	0.0011
Triglyceride, mg dl^{-1}	157 (108)	141 (66)	0.0004

Abbreviations: BNP, brain natriuretic peptide; BS, blood sugar; BUN, blood urea nitrogen; Cr, creatinine; DBP,diastolic blood pressure; DT, deceleration time; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; hsCRP, high sensitivity C-reactive protein; IVRT, isovolumetric relaxation time; LA, left atrial; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; SBP, systolic blood pressure
All values are expressed as the mean (s.d.).
HOMA-R: (IRI*FBS/405).

it increased slightly, and it decreased in patients with a high uric acid level ($\geqslant 7.0\,mg\,dl^{-1}$) at baseline. There were no changes in fasting glucose levels, hemoglobin A1c, fasting insulin levels or homeostasis model assessment insulin resistance (HOMA-R) after changing to losartan/HCTZ.

Factors related to changes in *e′* velocity and *E/e′* ratio

We studied the impact of the magnitude of reduction in systolic BP with drug changes on *e′* velocity and the *E/e′* ratio. A greater reduction in systolic BP was associated with a greater increase in *e′* velocity and a greater reduction in the *E/e′* ratio (Figure 1). There was a close relationship between changes in *s′* velocity and changes in *e′* velocity (Figure 2).

We analyzed baseline factors related to the magnitude of changes in systolic BP, *e′* velocity and the *E/e′* ratio with a change from ACEi or ARB to losartan/HCTZ (Table 3). The factors included age, sex, diabetes, body mass index, New York Hypertension Association (NYHA) class, systolic BP, pulse pressure, heart rate, hsCRP, HOMA-R, BNP, estimated glomerular filtration rate, LV mass index, left atrial volume index and microalbuminemia. Multivariate analysis showed that baseline systolic BP and NYHA class were independent factors ($P<0.05$) related to the magnitude of reduction in systolic BP after changing to losartan/HCTZ. Multivariate analysis also showed that age, body mass index, NYHA class, systolic BP and hsCRP were independent factors related to changes in *e′* velocity after changing to losartan/HCTZ. NYHA class, systolic BP and hsCRP were independent factors related to the magnitude of changes in the *E/e′* ratio after changing to losartan/HCTZ.

As baseline hsCRP is an independent factor related to changes in *e′* velocity and the *E/e′* ratio, we compared temporal changes in these parameters in patients with high hsCRP ($\geqslant 2.0\,mg\,dl^{-1}$) and those with low hsCRP ($<0.2\,mg\,dl^{-1}$) (Figure 3). Reductions in the *E/e′* ratio and increases in *e′* velocity were greater in patients with high hsCRP at baseline. We studied the impact of NYHA class on changes in *e′* velocity and the *E/e′* ratio after changing to losartan/HCTZ. Our data showed that increases in *e′* velocity and decreases in the *E/e′* ratio were greater in patients with NYHA class 2 or 3 than in patients with NYHA class 1.

Adverse events. Adverse events were observed in 22 patients. The adverse events included photosensitivity or skin eruption (11 patients), dizziness (5 patients), general fatigue (4 patients), an increase in BP (1 patient) and worsening of renal function (1 patient). Losartan/HCTZ was withdrawn in 14 patients and they were dropped from the study.

DISCUSSION

We showed that changes from ACEi or ARB to losartan/HCTZ further lowered BP, improved LV relaxation (an increase in *e′* velocity), reduced LV preload (a decrease in the *E/e′* ratio), and improved HF state (a decrease in BNP) in patients with hypertension and diastolic dysfunction. The drug change was also associated with reductions in hsCRP. We first documented that the change from ACEi or ARB to losartan/HCTZ could improve LV relaxation and HF in patients with diastolic dysfunction, and that these improvements were associated with attenuation of systemic inflammation.

The optimization of hemodynamics is achieved primarily by reducing cardiac preload and afterload in patients with diastolic dysfunction. An ACEi or ARB may affect myocardial relaxation and compliance by reducing BP and arterial stiffness and by reducing interstitial collagen deposition, but it cannot reduce LV preload. Diuretics are effective for reducing LV preload. Our results showed

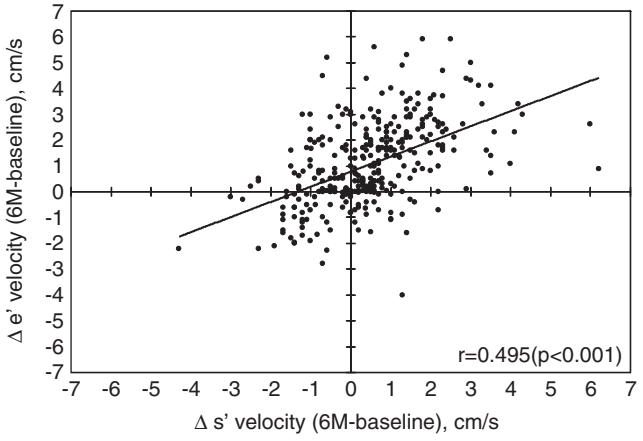

Figure 2 Relationship between changes in *e′* velocity and changes in *s′* velocity. There was a close relationship between changes in *s′* velocity and changes in *e′* velocity.

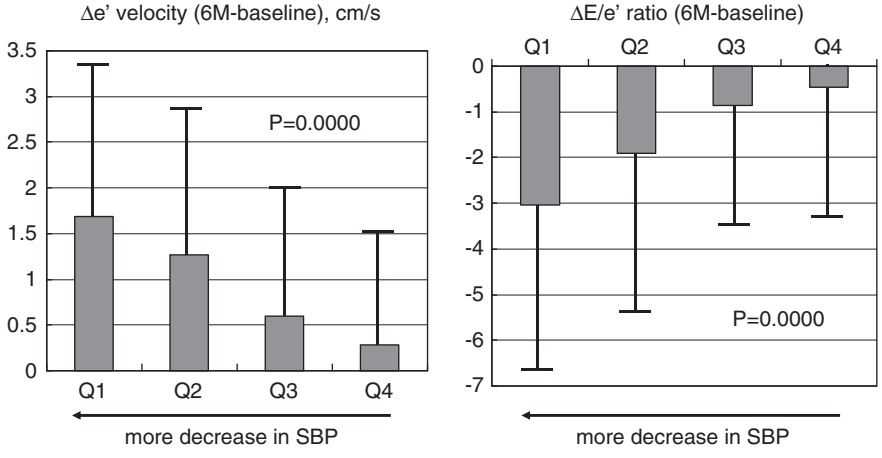

Figure 1 Changes in *e′* velocity and *E/e′* ratio for each quartile of systolic BP decrease after change to losartan/HCTZ. A greater reduction in systolic BP was associated with a greater increase in *e′* velocity and a greater reduction in *E/e′*. The range of decrease in systolic BP was 72–35 mm Hg in Q1, 34–22 mm Hg in Q2, 21–13 mm Hg in Q3 and 12–27 mm Hg in Q4. Data are expressed as mean ± s.d.

Table 3 Predictors of changes in SBP, *e′* velocity and *E*/*e′* ratio after changing from ACEi or ARB to losartan/HCTZ

	Changes in SBP		*Changes in e′ velocity*		*Changes in E/e′ ratio*	
	Univariate analysis P-*value*	*Multivariate analysis* P-*value*	*Univariate analysis* P-*value*	*Multivariate analysis* P-*value*	*Univariate analysis* P-*value*	*Multivariate analysis* P-*value*
Age	0.9693		0.0009	0.0001	0.0923	
BMI	0.0994		0.0281	0.0065	0.0341	0.2024
NYHA 1 *vs.* 2 or 3	0.0000	0.0030	0.0000	0.0000	0.0000	0.0010
SBP	0.0000	0.0000	0.0000	0.0043	0.0000	0.0189
HsCRP	0.0000	0.9939	0.0000	0.0001	0.0000	0.0000

Abbreviations: BMI, body mass index; HCTZ, hydrochlorothiazide; hsCRP, high sensitivity C-reactive protein; NYHA, New York hypertension association; SBP, systolic blood pressure

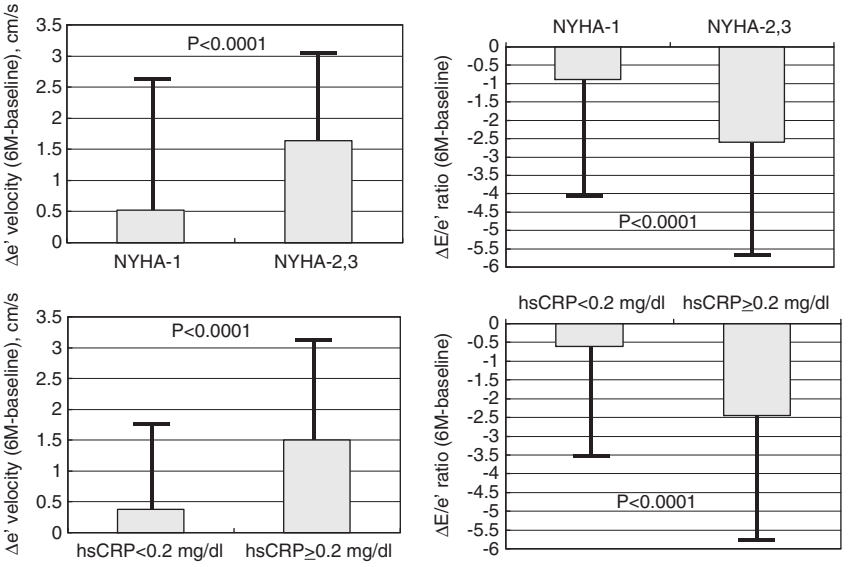

Figure 3 Comparisons of temporal changes in *e′* velocity and *E*/*e′* ratio between NYHA class, high and low hsCRP, and high and low HOMA-R. The magnitude of changes in *e′* velocity and the *E*/*e′* ratio was higher in patients with NYHA-2 or 3 than those with NYHA-1. The magnitude of changes in *e′* velocity and the *E*/*e′* ratio was greater in high hsCRP patients than in low hsCRP patients. The magnitude of changes in *e′* velocity was greater in patients with high HOMA-R than in those with low HOMA-R. However, there was no difference in the *E*/*e′* ratio between the two groups. A full color version of this figure is available at the *Hypertension Research* journal online.

that changing an ACEi or ARB to losartan/HCTZ is associated with a reduction of the *E*/*e′* ratio and an increase in *e′* velocity. A decrease in IVRT after the drug change also suggests an improvement in LV relaxation. IVRT is sensitive to LV preload and relaxation. In the case of reduced preload, IVRT decreases only when LV relaxation improves, as shown in this study. The combination of improvement in LV relaxation and a decrease in preload can be attributed to a reduced left atrial volume index and BNP level at follow-up.

There are several mechanisms by which *e′* velocity can increase with changes from ACEi or ARB to losartan/HCTZ. Reductions in systolic BP themselves can be associated with increases in *e′* velocity.[9–11] The CALVLOC (Clinical Impact of Azelnidipine on Left VentricuLar Diastolic Function and OutComes in Patients with Hypertension) trial documented that a reduction in systolic BP with a calcium channel blocker, azelnidipine, was associated with an increase in *e′* velocity.[10] This study showed that a greater increase in *s′* velocity after changing to losartan/HCTZ was associated with a greater increase in *e′* velocity. Many patients with diastolic dysfunction may have subtle abnormalities of systolic contractile function. The LV longitudinal contractile function is a primary contributor to LV pumping and is particularly sensitive to the effects of afterload.[12] It is speculated that further reduction in afterload with losartan/HCTZ can improve LV longitudinal contractile function (an increase in *s′* velocity), resulting in improvement of LV relaxation. Reduction of the LV mass index can also contribute to improvement in LV relaxation.[13]

In this study, hsCRP significantly decreased with changes from ACEi or ARB to losartan/HCTZ. CRP level is a marker of systemic inflammation. Higher levels of CRP are associated with higher BP.[14] CRP levels are also elevated in patients with diastolic dysfunction, and they correlate with disease severity, as well as LV preload.[15] The mechanism of CRP elevation in patients with diastolic dysfunction has not been elucidated. Organ congestion and hypoperfusion might influence the secretion of interleukin-6 by hepatic, renal, endothelial, mononuclear and even cardiac myocytes.[16] Elevated inflammatory markers have been associated with an increased risk of developing symptomatic HF.[17] CRP may be an active participant in the development of diastolic dysfunction. CRP can inhibit nitric oxide production, impede endothelial function and activate the complement cascade.[18] Interleukin-6, which affects CRP, has been shown to promote myocyte hypertrophy.[19] Reductions in BP and LV preload with changes to losartan/HCTZ may contribute to a reduction in CRP. Therefore, the attenuation of the systemic inflammatory response with changes to losartan/HCTZ may contribute to the improvement of LV diastolic function.

Previous studies have suggested that BNP,[20] the left atrial volume index,[21] the LV mass index[22] and hsCRP are useful for risk stratification in patients with HF. A lower BNP, left atrial volume index or LV mass index is associated with better clinical outcomes, and lower rates of morbidity and mortality. These parameters are now regarded as excellent surrogate end points for assessing the utility of therapeutic interventions. Our results showed that BNP, the left atrial volume index and the LV mass index significantly decreased with changes from ACEi or ARB to losartan/HCTZ. Therefore, the combination of an ARB and a small dose of thiazide might be a good therapeutic choice for reducing hospitalization due to HF, and mortality in patients with hypertension and diastolic dysfunction.

Much of the criticism against thiazides has been directed toward their adverse-effect profile. Thiazides can reduce the excretion of uric acid and thereby increase its plasma level. Our results, however, showed that there was no change in uric acid levels with changes from ACEi or ARB to losartan/HCTZ. This finding was because of the potential of losartan to augment the excretion of uric acid.[23] Some patients with diastolic dysfunction are sensitive to preload reduction and may develop severe pre-renal azotemia. In this study, blood urea nitrogen and creatinine levels showed only slight increases with changes to losartan/HCTZ. New-onset diabetes has been reported in patients receiving thiazides.[24] Maintaining potassium homeostasis is essential because epidemiologic evidence implicates hypokalemia in the pathogenesis of thiazide-induced dysglycemia.[25] In this study, there were no changes in potassium levels or levels of blood glucose, HbA1c, serum insulin and HOMA-R after changing to losartan/HCTZ.

Limitations

Some limitations should be noted. This study was a single-arm trial. The main objective of this study was not to monitor clinical outcomes, but to detect changes in objective parameters to assess the change made upon LV diastolic function after changing from ACEi or ARB to losartan/HCTZ. We did not simply add a small dose of HCTZ to each ACEi or ARB, but changed them to losartan/HCTZ to improve patient adherence. Only three patients dropped out because of poor adherence. Most of the patients were mildly to moderately hypertensive and without clinical HF. The findings in this study may not be applicable to patients with severe diastolic dysfunction. In this study, however, the magnitude of increase in e' velocity was greater and the magnitude of decrease in the E/e' ratio was also greater in patients with symptomatic HF. It is not clear whether an increase in e' velocity by $1.0\,\mathrm{cm\,s^{-1}}$ or decrease in the E/e' ratio by 1.5 is clinically meaningful or whether it would be associated over time with improvement in outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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