Blood Pressure Control Determines Improvement in Diastolic Dysfunction in Early Hypertension

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BACKGROUND

Diastolic dysfunction is common in early hypertension. We hypothesized that improvement in diastolic dysfunction is blood pressure (BP) dependent and may occur early with treatment in newly diagnosed untreated hypertensive patients.

METHODS

Forty untreated hypertensive subjects (age 52 ± 1.4 years, mean ± s.e.m.) with diastolic dysfunction based on Canadian Consensus Guidelines, received either bendroflumethiazide 2.5 mg (1.25 mg for the first month), or candesartan 16 mg (8 mg for the first month). Left ventricular (LV) structure and function, early diastolic velocity (E′) and systolic velocity, and systolic myocardial velocity (Sm) were assessed echocardiographically using M-mode, 2-dimensional, and tissue Doppler imaging (TDI) before and at 1 and 3 months following treatment.

RESULTS

Antihypertensive treatment reduced BP significantly at 3 months (168 ± 2/97 ± 1–143 ± 2/86 ± 1 mm Hg, $P < 0.0001$). Both drugs had similar and significant effects on TDI E′ which increased from 7.8 ± 0.2 to 10 ± 0.3 cm/s ($P < 0.001$). The improvement in TDI E′ was independent of LV mass index (LVMI) regression but was significantly related to the improvement in Sm ($r = 0.73$, $P < 0.0001$) and the fall in systolic BP ($R = 0.51$, $P < 0.001$). Normalization of diastolic function was associated with better control of BP (130 ± 4/81 ± 2 mm Hg vs. 149 ± 2/88 ± 1 mm Hg, $P < 0.05$). In a stepwise regression model, reduction in systolic BP ($P < 0.001$) and TDI Sm ($P < 0.0001$) emerged as independent determinants of improvement in TDI E′ with no contribution from age, gender or change in relative wall thickness (RWT) ($R^2 = 0.68$, $P < 0.0001$).

CONCLUSIONS

Achieving good BP control and enhancement in systolic function determines the improvement in diastolic function in early hypertension.

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A significant proportion of the hypertensive population have diastolic dysfunction.[1,2] Diastolic dysfunction is now considered an important pathophysiological intermediate between hypertension and heart failure. A greater degree of regression and remodeling has been seen with drugs that antagonize the renin–angiotensin–aldosterone system than with other agents in the treatment of systolic heart failure or in hypertensive patients with left ventricular hypertrophy (LVH).[3] Most studies to date that have examined the effect of pharmacotherapy on diastolic function in hypertension have studied people with established LVH. In the Losartan Intervention For Endpoint Reduction in Hypertension Study,[4] antihypertensive therapy with losartan compared with atenolol-based regimen for 1 year was associated with reduced LV mass and significant improvement in diastolic filling parameters and this was independent of BP reduction.[4] In the recent Valsartan in Diastolic Dysfunction study, in patients with diastolic dysfunction treated with β-blockers, diuretics, or calcium channel blockers,[5] the addition of an angiotensin receptor blocker was associated with improvement in diastolic function after 9 months.[5] However, whether these observations apply to untreated patients with early hypertension remains unclear, as does the duration of treatment required to reverse diastolic dysfunction. Therefore, we hypothesized that improvement in diastolic dysfunction may be BP dependent and occur early with treatment in newly diagnosed untreated hypertensive patients.

METHODS

We sequentially studied 40 newly diagnosed untreated hypertensive subjects with evidence of diastolic dysfunction by echocardiography based on Canadian Consensus Guidelines[6] in a single blind parallel group study. Subjects (age 52 ± 1 years, mean ± s.e.m.) were diagnosed with hypertension on the basis of three consecutive separate clinic readings ≥140 and/or ≥90 mm Hg and ambulatory daytime BP ≥135 and/or ≥85 mm Hg. Those with evidence of heart failure (symptoms or

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signs), ischemic heart disease, arrhythmia, diabetes, secondary causes of hypertension, or valvular heart disease or receiving hemodynamically active drug therapy were excluded. Following baseline measurements, patients received either candesartan 8 mg for 1 month, up titrated to 16 mg for a further 2 months, or bendroflumethiazide 1.25 mg for 1 month, up titrated to 2.5 mg for a further 2 months. The study was performed in accordance with the declaration of Helsinki and was approved by the Institutional Ethics Committe, and the patients gave informed consent.

Blood pressure measurement. Blood pressure was measured in the right arm in the supine position by an observer blind to therapy using an oscillometric device (Omron, Model HEM 705-CP, Omron Corporation, Tokyo, Japan) in triplicate and the mean was used for further analysis.

Echocardiographic measurements. Assessment was done using a commercially available ultrasound system (Phillips Sonos 5500, Andover, MA) equipped with Doppler tissue echocardiography capabilities. Baseline echocardiography included 2-dimensional and M-mode measurements of left atrial, size, aortic root, left ventricular end diastolic dimension, left ventricular end systolic dimension, interventricular septal dimension, and posterior wall dimension.[7–9] Relative wall thickness (RWT) was measured based on the Canadian society of echocardiography guidelines and >0.42 considered as evidence if concentric remodeling.[8,9] LV mass was calculated from LV linear dimension[8,9] and was indexed to body surface area in m^2. LVH was considered present when the LV mass index (LVMI) exceeded 115 g/m^2 (male) or 95 g/m^2 (female).[8,9] LV diastolic function was defined using the criteria provided by the Canadian Consensus Guidelines[6] using transmitral Doppler with and without the Valsalva maneuver. Transmitral Doppler peak early diastolic E-wave velocity (cm/s), peak late A wave diastolic velocity (cm/s), their ratio E/A, deceleration time (ms) and isovolumic relaxation time (ms) were recorded. The same measurements were repeated during phase II of the Valsalva maneuver. Tissue Doppler diastolic velocities were measured in the two- and four-chamber views. A 5 mm sample volume was placed sequentially at the septal, lateral, inferior, and anterior mitral annuli and averaged. The following measurements were recorded: tissue Doppler imaging (TDI)–derived systolic myocardial velocity (Sm), early diastolic velocity (E′), and late diastolic velocity (A′), and their ratio (E′/A′). The ratio of early diastolic mitral inflow velocity (E) to TDI E′ (E/E′), which correlates with diastolic filling pressure, was calculated. We used the same TDI E′ age-specific cutoff values as used in the Valsartan in Diastolic Dysfunction study.[5]

Statistical analysis. The data were analyzed using JMP software (version 7.0; SAS for Windows, SAS, Cary, NC). Results were expressed as mean ± s.e.m.; $P < 0.05$ was considered significant. Whether the data were normally distributed was tested using the Shapiro–Wilk test. Differences between means were analyzed with Student's *t*-test for continuous data and χ^2-test for categorical data. Univariate analysis was carried out using Pearson's correlation analysis. To test whether improvement in TDI E′ over time was independent of BP reduction and type of antihypertensive used, analysis of variance of repeated measures was performed with age, gender, type of antihypertensive used, and reduction in BP as covariates. To test whether improvement in TDI E′ was related to changes in LV structure, reduction in LVMI was added to the independent variables in the same model mentioned earlier. The determinants of improvement in TDI E′ were analyzed using forward, stepwise, regression analysis with age, gender, and change in systolic BP, RWT, and TDI Sm as covariates.

RESULTS

Clinical characteristics of the patient population are summarized in **Table 1** categorized by the type of antihypertensive drug received, showing no significant difference in age, gender distribution, smoking status, body mass index, BP, heart rate, waist and hip circumference or prevalence of LVH and RWT between the two groups.

There was a significant reduction in both systolic and diastolic BP ($P < 0.0001$) with no significant difference between the two drugs (**Table 2**). Transmitral E/A increased significantly with bendroflumethiazide ($P < 0.05$) but not with candesartan ($P = 0.06$) however, transmitral E/A post Valsalva maneuver, increased ($P < 0.01$) and interventricular relaxation time was reduced significantly ($P < 0.01$) over time with both drugs with no improvement in deceleration time. TDI E′ improved significantly over time; with candesartan, from 6 ± 0.2 to 10 ± 0.5 cm/s, $P < 0.0001$ and with bendroflumethiazide from 8.0 ± 0.2 to 10 ± 0.5 cm/s, $P < 0.0001$ with no significant difference between the two treatments (**Table 2**). In all, 11 patients (6 on candesartan) reverted to normal diastolic function at 3 months

Table 1 | Baseline characteristic of the patient population (*n* = 40, mean ± s.e.m.)

	Bendroflumethiazide (*N* = 20)	Candesartan (*N* = 20)	*P* value
Age (years)	51 ± 2	54 ± 2	0.8
Sex (male/female)	12/8	13/7	0.7
Smokers (%)	17	19	0.7
Height (cm)	170 ± 2	171 ± 2	0.8
Weight (kg)	79 ± 3	83 ± 3	0.4
Waist (cm)	91 ± 2	93 ± 2	0.8
Hip(cm)	99 ± 2	101 ± 2	0.7
Systolic blood pressure (mm Hg)	167 ± 3	169 ± 2	0.7
Diastolic blood pressure (mm Hg)	98 ± 2	96 ± 1	0.6
Heart rate (bpm)	77 ± 1	76 ± 1	0.7
Patients with LVH (%)	10	15	0.6
Patients with concentric remodeling (%)	30	40	0.5

Table 2 | Left ventricular filling parameters after 1- and 3-month therapy with bendroflumethiazide and candesartan(mean ± s.e.m.)

	Bendroflumethiazide (*N* = 20)				Candesartan (*N* = 20)			
	Baseline	1 month	3 month	*P* value	Baseline	1 month	3 month	*P* value
SBP (mm Hg)	167 ± 3	150 ± 3	146 ± 3	<0.0001	169 ± 2	149 ± 4	141 ± 4	<0.0001
DBP (mm Hg)	98 ± 2	90 ± 2	88 ± 2	<0.0001	96 ± 1	86 ± 2	84 ± 2	<0.0001
Heart rate (bpm)	77 ± 1	77 ± 1	75 ± 1	<0.001	76 ± 1	75 ± 1	71 ± 1	<0.0001
IVRT (m/s)	99 ± 4	98 ± 4	96 ± 4	<0.01	102 ± 5	100 ± 4	96 ± 4	0.02
DT (m/s)	201 ± 8	204 ± 6	197 ± 5	0.32	203 ± 8	207 ± 7	200 ± 6	0.38
TMD E/A ratio	0.9 ± 0.04	1 ± 0.05	1 ± 0.05	<0.05	0.9 ± 0.04	0.95 ± 0.04	1 ± 0.05	0.06
TMD E/A ratio post valsalva	0.7 ± 0.01	0.8 ± 0.04	0.84 ± 0.03	<0.001	0.72 ± 0.01	0.81 ± 0.03	0.87 ± 0.04	0.002
TDI E′ (cm/s)	8 ± 0.2	9 ± 0.4	10 ± 0.5	<0.0001	6 ± 0.2	7 ± 0.4	10 ± 0.5	<0.0001
TDI E′/A′ ratio	0.7 ± 0.01	0.8 ± 0.04	0.9 ± 0.04	<0.0001	0.7 ± 0.06	0.8 ± 0.04	0.9 ± 0.04	<0.0001
TDI Sm	9.6 ± 0.4	10.2 ± 0.3	10.8 ± 0.4	<0.0001	9.45 ± 0.2	10 ± 0.3	11 ± 0.5	<0.0001
E/E′ ratio	7 ± 0.4	7.6 ± 0.3	7 ± 0.2	0.003	8.4 ± 0.4	8.4 ± 0.4	7.3 ± 0.2	0.02

DBP, diastolic blood pressure; DT, deceleration time; IVRT, interventricular relaxation time; SBP, systolic blood pressure; TDI, tissue Doppler imaging; TMD, transmitral Doppler; Sm, systolic myocardial velocity.

Table 3 | Left ventricular structure after 1- and 3-month therapy with bendroflumethiazide and candesartan(mean ± s.e.m.)

	Bendroflumethiazide (*N* = 20)				Candesartan (*N* = 20)			
	Baseline	1 month	3 month	*P* value	Baseline	1 month	3 month	*P* value
LA (cm)	3.7 ± 0.09	3.6 ± 0.08	3.5 ± 0.06	0.03	3.8 ± 0.08	3.7 ± 0.07	3.6 ± 0.07	0.001
AR (cm)	3.19 ± 0.08	3.10 ± 0.07	3.05 ± 0.07	0.02	3.14 ± 0.07	3.05 ± 0.06	3.01 ± 0.06	0.004
IVSD (cm)	0.99 ± 0.02	0.94 ± 0.02	0.89 ± 0.02	<0.0001	1.02 ± 0.02	0.95 ± 0.02	0.91 ± 0.02	<0.0001
PWD (cm)	0.95 ± 0.01	0.89 ± 0.02	0.85 ± 0.02	<0.0001	0.99 ± 0.02	0.93 ± 0.02	0.89 ± 0.02	<0.0001
RWT	0.39 ± 0.01	0.36 ± 0.01	0.34 ± 0.01	<0.0001	0.41 ± 0.01	0.38 ± 0.01	0.34 ± 0.01	<0.0001
RWT >0.42%	25%	15%	15%	NA	40%	20%	10%	NA
LVDD	4.89 ± 0.07	4.9 ± 0.06	4.9 ± 0.04	0.39	5 ± 0.08	5 ± 0.06	5 ± 0.05	0.14
EF%	62 ± 1	65 ± 0.9	67 ± 1.1	<0.0001	61 ± 0.7	64 ± 0.8	65 ± 0.8	<0.0001
LVMI (g/m^2)	91 ± 4	85 ± 4	79 ± 4	<0.0001	87 ± 3	81 ± 3	78 ± 3	<0.0001

AR, aortic root; EF, ejection fraction; IVSD, interventricular septal diameter; LA, left atrium; LVDD, Left ventricular diastolic diameter; LVMI, left ventricular mass index; PWD, posterior wall diameter; RWT, relative wall thickness.

and BP in these subjects was significantly lower (130 ± 4/81 ± 2 mm Hg) than in those with ongoing diastolic dysfunction (149 ± 2/88 ± 1 mm Hg, $P < 0.05$). TDI Sm increased significantly with over time with no significant difference between the two drugs (Table 2).

Overall LVMI and RWT decreased over time ($P < 0.0001$) with no difference between the two drugs (Table 3). The prevalence of LVH decreased from 10% to 5% with bendroflumethiazide and from 15% to 10% with candesartan. However, the prevalence of concentric remodeling decreased a baseline value from 40% to 10% with candesartan and from 30% to 15% with bendroflumethiazide at the end of 3 months. There was no correlation between reduction in LVMI with reduction in systolic ($r = 0.02$, $P = 0.82$) or diastolic ($r = 0.08$, $P = 0.60$) BP or improvement in E′ ($r = 0.03$, $P = 0.89$). However, there was a significant correlation between reduction in RWT and fall in systolic ($r = 0.48$, $P < 0.001$) and diastolic ($r = 0.22$, $P < 0.001$) BP and improvement in TDI E′($r = 0.31$, $P < 0.05$) with no significant relationship with improvement in TDI Sm or reduction in LVMI. The left atrial and LV dimensions were reduced and the ejection fraction increased significantly over time with both treatments (Table 3).

To further explore the effect of BP control on improvement in diastolic dysfunction, we divided patients into responders to treatment (BP achieved at 3 months <140/90 mm Hg) and nonresponders (BP achieved at 3 months >140/90 mm Hg) in each drug group and evaluated the changes in LV structure and function. In the bendroflumethiazide group, there were 7 (35%) responders compared with the candesartan group where 11 (55%) patients were responders. There was a significant interaction between responder status and improvement in TDI E′ ($P < 0.05$) and RWT ($P < 0.001$) over time, but none of them was seen between responder status and type of antihypertensive drug used. There was no interaction between reduction in LVMI over time and BP response. In a stepwise regression model, TDI Sm ($P < 0.0001$) and reduction in

Table 4 | Data for all of the covariates and their coefficients, 95%, CI in stepwise regression analysis

	r^2 Change	s.e.	β	95% CI	P
Change in TDI E velocity, adjusted $r^2 = 0.68$, $P < 0.0001$					
Change in TDI Sm (units)	54	0.17	1.3	0.69–1.5	<0.0001
Change in systolic BP (mm Hg)	14	0.01	0.06	0.04-0.08	<0.001

BP, blood pressure; TDI, tissue Doppler imaging; Sm, systolic myocardial velocity. Age, gender, and change in relative wall thickness did not enter the model.

systolic BP ($P < 0.001$) emerged as independent determinants of improvement in E′ with no contribution from age, gender, or change in RWT ($R^2 = 0.68$, $P < 0.0001$) (Table 4).

DISCUSSION

This study demonstrates improvement in diastolic function in treatment naive hypertensive patients as early as 1 month after commencing antihypertensive therapy. The improvement in diastolic function was independent of age, changes in LV size, and geometry and type of antihypertensive agent used, but significantly related to improvement in LV systolic function and BP fall.

Our finding that improvement in left ventricular diastolic function depended significantly on BP reduction was also observed in the Valsartan in Diastolic Dysfunction study in chronic hypertension using multiple agents.[5] In our study, those achieving normalization of diastolic dysfunction had significantly lower BP. Previous studies have suggested a greater improvement in diastolic function in patients treated with maximum blockade of the renin–angiotensin–aldosterone system.[10] In our study, we found that the improvement in systolic function (TDI Sm) and the reduction in systolic BP were the only significant determinants of improvement in diastolic function, with no contribution from age, gender, change in heart rate, type of antihypertensive drug, or LV mass regression.

Terpstra *et al.*[11] found that 2 years of treatment with either amlodipine or lisinopril decreased LVMI and increased the E/A ratio in elderly previously untreated hypertensive subjects. Interestingly, we have shown that the improvement in diastolic function can be seen as early as at 1 month. In the Swedish Irbesartan Left Ventricular Hypertrophy Investigation vs. Atenolol study[12] in a large number of subjects with established hypertension and LVH there was some evidence of improved diastolic dysfunction by the first assessment at 12 weeks with further improvement at 24 and 48 weeks. We observed significant changes at 4 weeks which were more marked at 12 weeks following an escalation of dosage and associated with a greater reduction in BP. Although we observed significant improvements in our primary end point, TDI E′, it should be noted that there was no significant improvement in deceleration or isovolumic relaxation time. Thus, at the end of the study period, ~73% of subjects still had some diastolic dysfunction.

We did not observe any significant relationship between the type of antihypertensive drug used and improvement in diastolic dysfunction. There was suggestion of greater BP lowering in the candesartan group so we divided patients into responders and nonresponders to treatment. Responders to treatment achieved greater improvement in diastolic dysfunction and reduction in concentric remodeling compared with nonresponders irrespective of type of antihypertensive treatment.

Although the improvement in diastolic dysfunction and reduction in concentric remodeling was related to fall in BP, regression in LVMI was not. This may reflect the nature of the study patients which consist of early hypertension characterized by diastolic dysfunction and concentric remodeling with LVH not a prominent feature which may be seen in more long-standing hypertension. This finding reiterates the importance of detecting and treating early echocardiographic abnormalities in hypertension before irreversible changes occur.

The short duration of follow-up and the small sample size are limitations of the present study and long-term echocardiographic studies are needed to see if sustained reversal of structural and functional cardiac abnormalities are related to type of antihypertensive agent used which was not observed in the present study.

In a population with ever increasing levels of obesity and diabetes, which also predispose to diastolic heart failure, the issue of identifying and improving diastolic dysfunction assumes greater importance. In this study, reduction of BP, rather than agent, appears to be of fundamental importance. The extent of reduction required remains to be quantified but in hypertensive patients with diastolic dysfunction, achievement of BP <140/90 mm Hg may not be associated with restoration of normal diastolic function at 3 months and may indeed suggest a need to investigate the impact of greater BP lowering in hypertensive patients with diastolic dysfunction in a large randomized clinical trial with a longer follow-up.

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