Successful treatment of hypertension accounts for improvements in markers of diastolic function – a pilot study comparing hydrochlorothiazide-based and amlodipine-based treatment strategies

Kofo O Ogunyankin MD¹, Andrew G Day MSc²

KO Ogunyankin, AG Day. Successful treatment of hypertension accounts for improvements in markers of diastolic function – a pilot study comparing hydrochlorothiazide-based and amlodipine-based treatment strategies. *Can J Cardiol* 2009;25(12):e406-e412.

BACKGROUND: There is controversy regarding whether blood pressure (BP) medications have relevant therapeutic benefits beyond those due to lowering of BP.

OBJECTIVE: To show that rapid successful treatment of hypertension leads to improvement in cardiac morphology and function regardless of the pharmacological agents used.

METHODS: Hypertension was defined as an average 24 h ambulatory BP of higher than 135/85 mmHg in 38 subjects with a mean ($\pm$ SD) age of 54 ± 7 years. Patients were randomly assigned to treatment with a diuretic-based ($n=20$) or a calcium channel blocker (CCB)-based ($n=18$) medication. All subjects were followed every two weeks, and similar additional medications were added until the BP was lower than 125/80 mmHg, then followed monthly for a total of six months. Echocardiography with tissue Doppler imaging was performed, and was repeated after six months of aggressive pharmacotherapy and lifestyle management.

RESULTS: Baseline ambulatory BP monitoring and echocardiographic measures of diastolic function were similar between both treatment groups. Subjects received 3.5 ± 1 pills and 11 ± 2 follow-up visits. The average 24 h BP was reduced from 145/91 mmHg to 124/75 mmHg ($P < 0.001$) in the CCB group. A greater lowering from 143/91 mmHg to 117/72 mmHg occurred in the diuretic group ($P=0.02$ for the difference between groups) at six months. There was significant improvement in tissue Doppler imaging diastolic function parameters in both groups, with a trend toward greater improvement in the diuretic group. The left ventricular mass/height^{2.7} index decreased from $40 \text{ g/m}^{2.7}$ to $37 \text{ g/m}^{2.7}$ in the diuretic group ($P=0.02$), whereas a nonsignificant change ($41 \text{ g/m}^{2.7}$ to $42 \text{ g/m}^{2.7}$) occurred in the CCB group.

CONCLUSIONS: Aggressive BP lowering is associated with improved left ventricular diastolic function and mass proportional to the extent of BP normalization.

Key Words: Ambulatory blood pressure monitoring; Diastolic function; Left ventricular hypertrophy; Tissue Doppler imaging

Le traitement réussi de l'hypertension suscite des améliorations des marqueurs de la fonction diastolique : Un projet pilote comparant une stratégie thérapeutique à base d'hydrochlorothiazide à une autre à base d'amlodipine

HISTORIQUE : La pertinence des bienfaits des antihypertenseurs pour d'autres applications thérapeutiques que la diminution de la tension artérielle est controversée.

OBJECTIF : Démontrer que le traitement rapide et efficace de l'hypertension suscite une amélioration de la morphologie et de la fonction cardiaques, quels que soient les agents pharmaceutiques utilisés.

MÉTHODOLOGIE : On a défini l'hypertension comme une moyenne de tension artérielle (TA) ambulatoire sur 24 heures de plus de 135/85 mmHg chez 38 sujets d'un âge moyen ($\pm$ ÉT) de 54 ± 7 ans. On a réparti les patients au hasard entre un traitement aux diurétiques ($n=20$) ou aux inhibiteurs calciques ($n=18$). Tous les sujets étaient suivis toutes les deux semaines, et on ajoutait une médication supplémentaire similaire jusqu'à ce que la TA soit inférieure à 125/80 mmHg, puis le suivi se poursuivait tous les mois pendant six mois. On effectuait une échocardiographie par imagerie tissulaire Doppler, qu'on reprenait au bout de six mois de pharmacothérapie agressive et de prise en charge du mode de vie.

RÉSULTATS : Au départ, la surveillance de la TA ambulatoire et les mesures échocardiographiques de la fonction diastolique étaient similaires dans les deux groupes de traitement. Les sujets recevaient $3,5 \pm 1$ comprimés et 11 ± 2 visites de suivi. La TA moyenne sur 24 heures passait de 149/91 mmHg à 124/75 mmHg ($P < 0,001$) dans le groupe prenant des inhibiteurs calciques. On observait une baisse plus importante, de 143/91 mmHg à 117/72 mmHg, dans le groupe prenant des diurétiques ($P=0,02$ pour la différence entre les groupes) au bout de six mois. Les paramètres de la fonction diastolique s'amélioraient de manière significative selon l'imagerie tissulaire Doppler dans les deux groupes, la tendance d'amélioration étant plus élevée dans le groupe prenant des diurétiques. L'indice de masse ventriculaire gauche par rapport à la taille^{2.7} a fléchi de $40 \text{ g/m}^{2.7}$ à $37 \text{ g/m}^{2.7}$ dans le groupe prenant des diurétiques, tandis que le changement n'était pas significatif dans celui prenant des inhibiteurs calciques ($41 \text{ g/m}^{2.7}$ à $42 \text{ g/m}^{2.7}$).

CONCLUSIONS : Une diminution agressive de la TA s'associe à une amélioration de la fonction diastolique ventriculaire gauche et de la masse proportionnelles à l'importance de la normalisation de la TA.

Current hypertension treatment trials attribute relative differences in benefits associated with various treatment regimens to unique pharmacological benefits. These studies typically aim for a treatment systolic blood pressure (BP) goal of lower than 140 mmHg, rather than a deliberate aim to normalize BP (1-3). At study completion, up to 25% of treated subjects in these clinical trials ultimately have BP levels above the treatment goal, and a more substantial proportion of

patients have a BP above the 'optimal' BP of lower than 120/80 mmHg. Epidemiological studies showed that, compared with optimal BP, 'high-normal' BP (130/85 mmHg to 139/89 mmHg) is associated with a higher risk-adjusted hazard ratio for cardiovascular disease (4), and that those with 'high-normal' BP have a RR of 2.3 for the development of cardiovascular disease in 10 years compared with those with 'optimal' BP (5). Hence, to unequivocally address the contributions of

¹Department of Medicine and Feinberg School of Medicine of Northwestern University, Chicago, Illinois, USA; ²Department of Community Health and Epidemiology, Queen's University, Kingston, Ontario

Correspondence: Dr Kofo O Ogunyankin, Division of Cardiology, Northwestern University, 676 North St Clair Street, Suite 600, Chicago, Illinois 60611, USA. Telephone and fax 312-926-2492, e-mail k-ogunyankin@northwestern.edu

Received for publication October 15, 2008. Accepted March 22, 2009

Figure 1) Treatment scheme in randomized subjects. α Alpha; β Beta; ABPM Ambulatory blood pressure monitoring; ACEI Angiotensin-converting enzyme inhibitor; ARB Angiotensin receptor blocker; BP Blood pressure; CCB Calcium channel blocker; HCTZ Hydrochlorothiazide; mo Months; PRN pro re nata (as needed); q Every

persistent hypertension among treated subjects in clinical trials, BP after treatment must be optimal or normal. However, no such trial has been performed to date.

Regression of left ventricular hypertrophy (LVH) is associated with improvement in left ventricular (LV) diastolic function and improved prognosis (6-8). There is also a reduction in stroke with rapid BP lowering compared with gradual lowering, even when the eventual BP attained at the end of two years between treated groups is comparable (9,10). In the present pilot study, we tested the hypothesis that aggressive BP lowering results in similar clinical, morphological and functional benefits regardless of the specific drugs used. We compared changes in diastolic function and cardiac morphology associated with a deliberate effort to normalize BP levels using either a hydrochlorothiazide (HCTZ)-based (diuretic-based) or an amlodipine-based (calcium channel blocker [CCB]-based) treatment strategy.

METHODS

Ethics and trial registration

All studies were approved by the Queen's University research and ethics board. The trial is registered at ClinicalTrials.gov (NCT0029242).

Study overview

Echocardiographic and functional profiles of 38 subjects who completed a six-month protocol of aggressive BP lowering for uncomplicated hypertension were studied. Figure 1 shows the algorithm for the present study. Hypertensive subjects (defined by ambulatory BP monitoring [ABPM] criteria) were seen at two-week intervals after eligibility was determined with additional BP drugs prescribed in a prespecified order, unless office BP was close to normal (approximately lower than 125/75 mmHg). The subjects were subsequently seen at monthly intervals for a total follow-up period of six months. Dietary advice, lifestyle counselling and weight monitoring were provided as required for all subjects at enrollment, and were reinforced throughout the study period. Subjects were randomly assigned to receive (in addition to their usual BP treatments) amlodipine (CCB) or HCTZ, and were not allowed to stop or cross over these medications. Twenty of these subjects received HCTZ and 18 received amlodipine.

Subject recruitment

Subjects (exclusively Caucasian), 20 to 65 years of age, were recruited via direct referrals and newspaper advertisements for the study, and underwent a complete history and physical examination to assess eligibility. The recruitment process is shown in Figure 2. Eligibility was

Figure 2) Recruitment process. ABPM Ambulatory blood pressure monitoring; BP Blood pressure; CCB Calcium channel blocker; Echo Echocardiography; HCTZ Hydrochlorothiazide

defined by a screening office BP of higher than 135/90 mmHg, in spite of taking two or fewer BP medications. Subjects underwent a 10- to 14-day run-in phase, during which they were randomly assigned to amlodipine 5 mg daily or HCTZ 25 mg daily (Figure 1). For participation in the six-month treatment protocol, subjects had to have persistent 'on treatment' hypertension, determined at the end of the run-in period by a 24 h ABPM mean BP higher than 135 mmHg systolic or higher than 85 mmHg diastolic (11). Exclusion criteria were secondary hypertension, clinically apparent heart failure, angina requiring treatment, significant valvular heart disease, atrial fibrillation, pacemaker dependence or comorbidities such as morbid obesity, disabling arthritis that precluded walking, recent protracted hospitalization, and current treatment with both a diuretic and a CCB. Eligible subjects assigned to either treatment regimen who had a pre-ABPM office BP of lower than 125/80 mmHg, or normal mean 24 h ABPM, were excluded.

Office BP measurement: The office BP measurement was performed as recommended (11) using a BpTru monitor (VSM MedTech Ltd, Canada). This machine takes six readings in 1 min or 2 min intervals, and averages the last five readings.

ABPM: The 24 h ABPM was performed using a Spacelabs ABP Monitor model 90207 (Spacelabs Healthcare, USA), calibrated at hook-up and before cuff removal. Subject-specified bedtime and wake-up times were used to determine sleep and awake time periods for data analysis.

Echocardiography: Each echocardiogram was uniquely labelled to facilitate blinded data interpretation. Two-dimensional (2D) echocardiography was performed using a Vivid-5 or Vivid-7 ultrasound scanner (GE Medical Systems, USA). The same sonographer performed all studies. The LV mass was determined from M-mode recordings at the mid-papillary level, and indexed to height (12). The early (E) and late (A) transmitral inflow velocities, as well as the E/A ratio and colour 2D tissue Doppler imaging (TDI) cineloops from the apical four-chamber, two-chamber and long-axis views were recorded. From the TDI cineloops, pulsed-wave TDI velocities of basal segments of the LV

TABLE 1
Clinical and echocardiographic characteristics at baseline by treatment arm

Characteristic	CCB (n=18)	HCTZ (n=20)	P*
Sex, n (%)			
Female	6 (33.3)	5 (25.0)	0.57
Male	12 (66.7)	15 (75.0)	
Age, years	54.2±7.9	54.8±5.5	0.77
Weight, kg	88.1±12.0	87.6±14.6	0.91
Body mass index, kg/m ²	30.5±4.0	29.2±3.4	0.29
24 h ABPM systolic, mmHg	144.6±9.6	143.1±11.5	0.67
24 h ABPM diastolic, mmHg	91.2±8.8	91.1±12.0	0.96
IVSd, mm	1.0±0.1	1.0±0.1	0.61
LVDd, mm	5.3±0.4	5.1±0.5	0.14
LVM, g	171.6±37.8	175.2±60.1	0.83
LVM/height ^{2.7} index, g/m ^{2.7}	41.1±9.1	39.6±10.9	0.66
Mitral E/A ratio	1.1±0.3	1.1±0.4	0.95
Global Sann, cm/s	6.0±1.2	6.3±1.1	0.34
Global E'ann, cm/s	7.0±1.4	6.3±2.0	0.20
Average E'/A'	0.9±0.2	0.8±0.3	0.18
Tei index	0.5±0.2	0.6±0.2	0.69
Office BP systolic, mmHg	145.2±9.9	150.6±15.3	0.21
Office BP diastolic, mmHg	89.6±6.2	93.7±12.8	0.22
6 min walk distance, m	476.5±89.6	491.5±55.6	0.54

Data presented as mean ± SD unless otherwise indicated. The Tei index in the index of isovolumetric contraction. *The t test was used for continuous variables, while the χ^2 test was used for categorical variables. ABPM Ambulatory blood pressure monitoring; IVSd Left ventricular septal thickness in diastole; CCB Calcium channel blocker; E'/A' Ratio of early and late diastolic annular velocities by tissue Doppler imaging; Global E'ann Average of 6 apical early diastolic annular velocities by tissue Doppler imaging; Global Sann Average of 6 apical systolic annular velocities by tissue Doppler imaging; HCTZ Hydrochlorothiazide; LVDd Left ventricular end diastolic dimension; LVM Left ventricular mass; Mitral E/A ratio Ratio of early and late mitral inflow velocity

around the mitral annulus were analyzed, yielding six different annular velocities. The systolic, early (E'ann) and late (A'ann) diastolic annular velocities were measured and averaged to produce a global value. For each parameter, three to five consecutive beats were averaged. All measurements were performed by an experienced echocardiographer. Data were analyzed in batches by a single blinded observer (KO). The intraobserver variability for these measurements in a previous study by the same observer was less than 5% (13).

Pharmacological therapies and interval evaluations: Figure 1 shows the predetermined algorithm for incremental escalation of drug therapy including how nonstudy medications were substituted with the same representative drug from each of the five common antihypertensive treatment drugs, such that complementary therapies were standardized. The baseline 2D echocardiogram was performed on the day of the first ABPM in eligible subjects. Echocardiography was also performed after the final ABPM at six months in all subjects. All medications were provided to the subjects at each visit. As shown in Figure 1, CCB and diuretics were disallowed and substituted with a required washout period of seven to 10 days before random assignment. The exclusive angiotensin-converting enzyme inhibitor (ACEI) was perindopril in all, except for ramipril in three subjects. The exclusive angiotensin receptor blocker (ARB) was losartan. All subjects received an ACEI and/or an ARB. For subjects who required additional medications due to failure to meet office BP treatment goals, a beta-blocker (followed, if needed, by an alpha-blocker) was added. The exclusive beta- and alpha-blockers were bisoprolol and doxazosin, respectively. A pill count was performed at each visit, but was only feasible in 80% of the visits. Subjects in whom a pill count could not be performed or

was inconsistent with expected counts on more than four visits were deemed noncompliant.

Statistical analysis

Baseline characteristics were compared between subjects randomly assigned to the diuretic- and CCB-based groups by the χ^2 or independent t test for categorical and continuous variables, respectively. Change from the baseline to final 24 h ABPM systolic BP, diastolic BP, TDI diastolic annular velocities from six apical segments (E'ann and A'ann), and LV mass were compared between the CCB and HCTZ groups using analysis of covariance, adjusting for the baseline values. Pearson's partial correlation coefficient (equivalent to multiple linear regression) was used to measure the association between the change in BP and changes in cardiac morphology and diastolic function parameters after adjusting for treatment assignment, and to assess whether treatment assignment had any effect on the parameters independent of a change in BP. All tests were two-sided without adjustment for multiplicity and were estimated by SAS version 9.1 (SAS Institute Inc, USA).

RESULTS

Subjects

Table 1 compares the baseline characteristics of the diuretic- and CCB-based groups. The subjects randomly assigned to both arms were comparable in age, baseline BP levels and echocardiographic parameters. No subject had overt signs of heart failure or chronic renal disease. One subject had diet-controlled diabetes, three were on antidepressants and 10 were active or recent cigarette smokers. None had diagnosed coronary artery disease or a history of stroke or transient ischemic attack. Ten subjects (26%) had chest pain with a negative exercise stress test. All were in sinus rhythm.

Medication visits and adverse events

At enrollment, subjects in the HCTZ and amlodipine groups took a mean ($\pm$ SD) of 2.0±0.6 and 2.1±0.6 BP drugs, respectively. Although using BP drugs was a prerequisite for enrollment, nine enrolled subjects (five in the HCTZ group and four in the amlodipine group) had stopped taking their prescribed therapies at the time of the run-in phase, and hence, were only on randomly assigned medications at the time of the eligibility ABPM. At six months, subjects required an average of 3.4±1.0 and 3.7±1.0 medications in the HCTZ and amlodipine groups, respectively ($P=0.42$ for difference). The average number of visits after enrollment (scheduled every two to four weeks, or scheduled by the subject) was 11±2 and did not differ by treatment assignment. Although many subjects admitted to lightheadedness, especially during the early stages of the study, lightheadedness triggered a premature follow-up visit in only eight subjects (five in the HCTZ group), and led to a temporary reduction in the dosage of doxazosin in three. There were no hospitalizations or emergency room visits because of hypotension or syncope, angina or heart failure. There was no withdrawal because of medicine intolerance. Pretibial edema developed in seven subjects, five of whom were in the CCB group, but medication discontinuation was not necessary. Five subjects (three assigned to CCB therapy) were deemed not fully compliant with prescribed drug therapies. The total number of medications used increased similarly in both groups.

Changes in 24 h ABPM and office BP

A significant reduction in BP was apparent in all subjects at six months (Figure 3), but there was a greater reduction in 24 h ABPM systolic pressures in the diuretic-based group compared with the CCB-based group (mean decrease 26.5±1.9 mmHg and 19.6±2.0 mmHg, respectively, $P=0.02$) (Table 2). Similarly, the diuretic-based group attained a superior lowering of nighttime ABPM systolic BP (decrease of 20.2±1.9 mmHg versus 11.3±2.1 mmHg, respectively, $P=0.0036$). The average nighttime diastolic BP lowering was also greater in the diuretic-based group (Table 2). Using the mean 24 h ABPM criteria of the American Heart Association (11), 12 (60%) and 16 (80%) of those in the diuretic group met the goals of optimal BP and normal BP,

respectively, compared with eight (44%) and 13 (72%), respectively, for the CCB group. Alternatively, using The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) office BP criteria (14) to grade treatment efficacy, 13 (65%) and six (30%) of those in the diuretic group achieved normal and prehypertension levels, respectively, and one (5%) had stage 1 hypertension. Of those in the CCB group, only five (28%) met the JNC-7 normal BP goal, 11 (61%) had prehypertension and two subjects (11%) had stage 1 hypertension.

Changes in diastolic function and LV mass

The baseline TDI indexes of diastolic function, such as the average E'ann from all six corners of the annulus, as well as the traditional, load-dependent marker of diastolic function (mitral E/A ratio) are shown in Table 3, along with changes in these and other echocardiographic markers of LV function and mass with six months of therapy. There were improvements in common measures of diastolic function with therapy, with most parameters improving in all subjects regardless of treatment assignment. However, the magnitude of the improvement in the measures of diastolic function appeared to be greater in the diuretic group than in the CCB group. The LV mass/height^{2.7} index (LVMHI) showed regression in subjects in the diuretic group who manifested a reduction in LV end-diastolic diameter, but LVMHI increased slightly in the CCB group.

There was a moderate, statistically significant correlation between the six-month change in 24 h ABPM systolic BP and the change in the average E'ann from all six corners of the annulus, the average apical A'ann from all six corners of the annulus and the mitral E/A ratio ($r = -0.51$, $P = 0.001$; $r = 0.35$, $P = 0.03$; and $r = -0.35$, $P = 0.03$, respectively). There was an even greater correlation of the same parameters with change in diastolic BP ($r = -0.59$, $P < 0.001$; $r = 0.47$, $P = 0.003$; and $r = -0.52$, $P = 0.001$, respectively). After adjusting for treatment assignment, the partial correlations remained virtually unchanged for both systolic BP change ($r_p = -0.48$, $P = 0.003$; $r_p = 0.35$, $P = 0.03$; and $r_p = -0.52$, $P = 0.001$, respectively) and diastolic BP change ($r_p = -0.58$, $P < 0.001$; $r_p = 0.47$, $P = 0.003$; and $r_p = -0.35$, $P = 0.03$, respectively). Notably, there were no statistically significant differences in the six-month changes in these parameters between drug groups after regression analysis, adjusting for changes in systolic or diastolic BP.

Although statistically insignificant, the difference in the change of LV mass index associated with diuretic treatment persisted after adjustment for the change in systolic or diastolic BP ($P = 0.12$ and $P = 0.18$, respectively). LV mass index was not significantly correlated with systolic or diastolic BP after adjusting for BP treatment ($r_p = -0.23$, $P = 0.16$; and $r_p = -0.17$, $P = 0.32$, respectively).

DISCUSSION

The main goal of the present study was to determine whether rapid normalization of BP (defined by mean 24 h ABPM levels [11] within six months of aggressive management) in asymptomatic hypertensive subjects results in similar improvement in echocardiographic indexes of diastolic function and cardiac morphology, regardless of treatment strategy.

An important observation of the present study is that in the majority of subjects, the baseline LVMHI was within the normal reference limits of 18 g/m^{2.7} to 44 g/m^{2.7} (12). Baseline traditional diastolic function parameters were also within the limits accepted as normal by epidemiological data (15), as were the colour 2D TDI parameters for subjects of similar ages in previous publications (16,17). However, following aggressive BP lowering, there were detectable changes in these parameters in the direction of improvement, which appear related in magnitude to the magnitude of BP lowering. The magnitude of improvement was greater if BP became completely normal, and because more attained this status in the diuretic group, there were additional significant differences in favour of the diuretic group. The increase in global E' is likely related to improved LV relaxation, and appears to be primarily related to the magnitude of BP lowering. A

Figure 3 Blood pressure changes in individual subjects, presented in mmHg. The only patient who failed to improve from baseline to six months in the hydrochlorothiazide (HCTZ) group was noncompliant because of a job change to the night shift and a variable sleep schedule. ABPM Ambulatory blood pressure monitoring; CCB Calcium channel blocker

similar trend has been demonstrated in patients with heart failure with normal systolic function (most of whom have hypertension) when treated with various BP lowering medications (18). Our finding of a reduction in global A' and mitral A diastolic flow velocities suggests that improvement in LV relaxation leads to enhanced early diastolic filling with less reliance on later atrial systole. The finding of a greater reduction in the A' in the CCB group is less easily explained, but may relate to the interplay between atrial volume and atrial relaxation. An intriguing notion suggested by these findings is that widely accepted population cut-off limits for normal diastolic function parameters and LV mass index are so broad that they may conceal the presence of reversible pathology related to hypertension.

In the present study, virtually all of the subjects who needed three or more BP medications were prescribed an ACEI and/or an ARB. Hence, any potential BP-independent benefits attributable to the angiotensin mechanism (19-22) uniformly applied to both the CCB and HCTZ groups. The relative effects of specific antihypertensive medications used on the cardiac parameters measured require a larger sample of subjects.

Mechanisms of findings

Diastolic function is impaired early in the pathogenesis of hypertension. Likewise, improvement in diastolic function may represent one of the earliest markers (23-26) of end-organ damage reversal, and can occur even in the absence of LVH (27). The assumption that the observed changes in cardiac morphology and function seen in the present study relate predominantly to improvement in BP is reasonable because weight, which was the only index of lifestyle modification measured in the study, did not change significantly during the six-month observation period. However, other unmeasured consequences of this aggressive management, including exercise and dietary management, may have contributed to observed benefits. The tendency toward improvement in diastolic function parameters, even when measured LV mass change was minimal, likely reflects the influence of afterload reduction and pharmacological reduction of LV wall stress, which, over the short term (six months), may precede morphological changes. Schulman et al (27) treated BP from a mean of 165±22/98±9 mmHg to a final BP of 128±12/80±5 mmHg over a period of eight to 12 months in subjects without electrocardiographic

TABLE 2

Baseline values and changes in 24 h ambulatory blood pressure monitoring (ABPM) measurements and office blood pressure (BP)

Variable	CCB (n=18)		HCTZ (n=20)		Δ CCB – Δ HCTZ	
	6 month – baseline,		6 month – baseline,		Mean (95% CI)	P
	Baseline	mean $\pm$ SE	Baseline	mean $\pm$ SE		
Average 24 h ABPM systolic BP, mmHg	144.6	-19.6 $\pm$ 2.0	143.1	-26.5 $\pm$ 1.9	6.8 (1.2 to 12.5)	0.02
Average 24 h ABPM diastolic BP, mmHg	91.2	-16.3 $\pm$ 1.7	91.1	-18.9 $\pm$ 1.6	2.6 (-2.3 to 7.4)	0.28
Average heart rate, beats/min	81.8	-10.7 $\pm$ 2.1	77.4	-11.0 $\pm$ 2.0	0.4 (-5.6 to 6.3)	0.90
Office BP systolic, mmHg	145.2	-23.9 $\pm$ 2.1	150.6	-30.1 $\pm$ 2.0	6.2 (0.2 to 12.2)	0.04
Office BP diastolic, mmHg	89.6	-15.6 $\pm$ 1.6	93.7	-18.4 $\pm$ 1.5	2.8 (-1.8 to 7.4)	0.23
Average daytime ABPM systolic BP, mmHg	150.4	-22.3 $\pm$ 2.2	147.7	-27.9 $\pm$ 2.1	5.6 (-0.5 to 11.7)	0.07
Average daytime ABPM diastolic BP, mmHg	96.3	-18.7 $\pm$ 1.9	95	-20.1 $\pm$ 1.8	1.5 (-3.8 to 6.7)	0.58
Average nighttime ABPM systolic BP, mmHg	127.9	-11.3 $\pm$ 2.1	129.6	-20.2 $\pm$ 1.9	8.8 (3.1 to 14.6)	0.004
Average nighttime ABPM diastolic BP, mmHg	76.8	-8.5 $\pm$ 1.5	80.1	-14.5 $\pm$ 1.4	5.9 (1.8 to 10.1)	0.006

All changes within both groups are statistically significant at $P < 0.001$. Δ CCB – Δ HCTZ = Difference between changes in the amlodipine (calcium channel blocker [CCB]) and hydrochlorothiazide (HCTZ) groups. SE Standard error

TABLE 3

Baseline values and changes in echocardiographic and clinical measures after six months of therapy

Selected parameters	CCB (n=18)		HCTZ (n=20)		Δ CCB – Δ HCTZ	
	6 month – baseline,		6 month – baseline,		Mean (95% CI)	P
	Baseline	mean $\pm$ SE	Baseline	mean $\pm$ SE		
LV septal thickness, cm	0.95	0.02 $\pm$ 0.03	0.97	-0.03 $\pm$ 0.03	0.06 (-0.02 to 0.13)	0.14
LV diastolic diameter, cm	5.27	-0.09 $\pm$ 0.06	5.05	-0.17 $\pm$ 0.06*	0.08 (-0.09 to 0.26)	0.34
LV posterior wall thickness, cm	0.94	-0.03 $\pm$ 0.03	0.96	-0.03 $\pm$ 0.03	0.00 (-0.08 to 0.08)	0.94
Mitral E, m/s	0.77	0.06 $\pm$ 0.03	0.74	-0.01 $\pm$ 0.03	0.07 (-0.02 to 0.15)	0.12
Mitral A, m/s	0.72	-0.08 $\pm$ 0.03*	0.69	-0.11 $\pm$ 0.03†	0.02 (-0.07 to 0.11)	0.61
Mitral E/A ratio	1.12	0.23 $\pm$ 0.09*	1.12	0.25 $\pm$ 0.08†	-0.02 (-0.26 to 0.22)	0.86
Average 'global' E'ann, cm/s	7.00	0.81 $\pm$ 0.28†	6.26	1.23 $\pm$ 0.26†	-0.43 (-1.21 to 0.36)	0.28
Average 'global' A'ann, cm/s	7.93	-0.92 $\pm$ 0.17†	8.13	-0.37 $\pm$ 0.16†	-0.55 (-1.01 to -0.08)	0.02
LV mass/height ^{2.7} index, g/m ^{2.7}	41.10	1.16 $\pm$ 1.51	39.61	-3.35 $\pm$ 1.43†	4.51 (0.29 to 8.73)	0.04
6 min walk distance, m	476.50	49.6 $\pm$ 13.3†	491.50	47.3 $\pm$ 12.6†	2.4 (-35.0 to 39.7)	0.90
Number of BP medications	2.06	1.61 $\pm$ 0.19†	1.95	1.45 $\pm$ 0.18†	0.16 (-0.38 to 0.70)	0.55

* $P < 0.05$ by paired t test for within-group change; † $P < 0.01$ by paired t test for within-group change. Δ CCB – Δ HCTZ = Difference between changes in the amlodipine (calcium channel blocker [CCB]) and hydrochlorothiazide (HCTZ) groups. A Late diastolic transmitral inflow velocity; BP Blood pressure; E Early diastolic transmitral inflow velocity; Global A'ann Average of 6 apical late diastolic annular velocities by tissue Doppler imaging; Global E'ann Average of 6 apical early diastolic annular velocities by tissue Doppler imaging; LV Left ventricular; SE Standard error

signs of LVH and concluded that diastolic function improved without a significant change in LV mass. In the current study, a more rigorous lowering of BP over a shorter interval of time similarly showed improvements in diastolic function and a slight reduction in LV mass in the diuretic group where BP lowering was more effective.

Comparison with previous studies

A closer look at the echocardiographic substudy of the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study (6,8), which showed that LV mass regression may be independent of BP, and that diastolic function did not improve without LV mass regression, puts the findings of the present study into perspective. The LIFE study enrolled older subjects (55 to 80 years of age) with a mean LVMHI of 56.2 g/m^{2.7} and an office BP of 174/95 mmHg at baseline, and treated them to a final BP of 151/84 mmHg at 12 months (a 13% reduction in systolic BP). In contrast, subjects in the current study were younger (47 to 61 years) with a mean LVMHI of 45 g/m^{2.7} and a baseline office BP of 148/92 mmHg, which became 121/75 mmHg within six months. In the LIFE study subjects, LV mass decreased by 12% and E/A ratio increased by 9%. Likewise, in the diuretic arm of the current study, systolic BP decreased by 20%, which was associated with an 8% reduction in LV mass index, a 22% increase in the E/A ratio and a 20% increase in mitral E'ann.

Compared with the majority of previous published hypertension treatment protocols (6-9), the frequency and intensity of follow-up in

the present study were high, and the abnormal BP was lowered rapidly.

Limitations

Although the findings of the present study truly demonstrate the salutary effects of aggressive treatment of hypertension, the study was inadequately powered to detect modest associations or group differences. A much larger study is needed to confirm these observations. Also, the unique characteristics that predispose some subjects to incomplete normalization of BP when subjected to treatment regimens effective in others cannot be determined from the present study. Nevertheless, these findings raise the possibility that small treatment differences attributed to certain therapies in clinical trials may be due to differences in the number of partial responders in compared groups, rather than specific mechanisms.

The assumption that observed changes in cardiac function seen in the present study are due to BP reduction may be questioned because the study was not powered to disprove other potential explanations. Furthermore, the present study did not account for differences caused by previous exposure to pharmacological therapies, or the possibility that a small portion of the observed changes may be due to regression toward the mean, although this is unlikely to explain the overall trend. On the other hand, given that BP control was suboptimal in the eligible subjects despite treatment at enrollment, the findings of the present study emphasize that treatment of hypertension to normal BP

values results in detectable morphological and functional changes regardless of previous treatments. One of the unique objectives of the present study was to determine whether there are benefits associated with attempts to normalize high BP. The ability to detect changes in echocardiographic measurements within a very brief treatment period (six months) during which BP was rapidly lowered, makes the relationship between the echocardiographically determined diastolic function and hypertension treatment plausible.

The change in LV mass with treatment shown in the present study was modest. It is well recognized that echocardiography is insensitive to interval changes in LV mass due to its inherent margins of error in reproducibility (28). Nevertheless, the trend toward improvement in the HCTZ group is consistent with our hypothesis. We used colour 2D TDI, which allows multiple simultaneous assessment of the mitral annulus. This method has been shown by others to have prognostic data in patients with diastolic dysfunction that are similar to data reported for the more commonly used spectral TDI (17,29). The consistent improvements seen in the diastolic function parameters reinforce the key finding that cardiac function improves within a short period of successful BP lowering.

The randomization method used here does not allow for intention-to-treat analysis because only those who took medications, and still remained hypertensive after a run-in period of 10 to 14 days, were included. However, the baseline characteristics remained well balanced between arms after postrandomization exclusions, and the analysis adjusted for potential baseline differences. The protocol used in the present study could serve as a template for an adequately

powered study in which the goal is normalization of BP with aggressive therapy and lifestyle management. Only with such studies can the long-term clinical implications and cost-effectiveness of BP normalization be determined.

Significance and implications

The present hypothesis-generating pilot study showed that it is possible to lower BP significantly within six months in hypertensive subjects by adopting more frequent monitoring, patient motivation and rapid escalation of therapies than is currently practiced. Focusing on the normalization of BP rather than the combination of medication used may represent a more effective strategy for minimizing the end-organ damage caused by hypertension. If the benefits of aggressive treatment to normal BP suggested by the present study are validated, health care providers may be encouraged to strive harder toward achieving hypertension treatment goals and overcome the 'therapeutic inertia' (30).

ACKNOWLEDGEMENTS: We are grateful to Colleen C Campbell RN RDCS, who performed the echocardiograms on these subjects, Xuran Jiang MD MSc, who performed some of the statistical analyses, and the late Luis Gabriel Melo, who provided critical reviews of the draft of this manuscript.

FUNDING: This study was supported in part by an investigator grant from Pfizer Inc.

REFERENCES

1. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97.
2. Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): A multicentre randomised controlled trial. *Lancet* 2005;366:895-906.
3. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;359:2417-28.
4. Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345:1291-7.
5. Kshirsagar AV, Carpenter M, Bang H, Wyatt SB, Colindres RE. Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. *Am J Med* 2006;119:133-41.
6. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet* 2002;359:995-1003.
7. Okin PM, Devereux RB, Jern S, et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004;292:2343-9.
8. Wachtell K, Bella JN, Rokkedal J, et al. Change in diastolic left ventricular filling after one year of antihypertensive treatment: The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study. *Circulation* 2002;105:1071-6.
9. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. *Lancet* 2004;363:2022-31.
10. Weber MA, Julius S, Kjeldsen SE, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE trial. *Lancet* 2004;363:2049-51.
11. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals – Part 1: Blood pressure measurement in humans – a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005;45:142-61.
12. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group. *J Am Soc Echocardiogr* 2005;18:1440-63.
13. Ogunyankin KO, Burggraf GW, Abiose AK, Malik PG. Validity of revised Doppler echocardiographic algorithms and composite clinical and angiographic data in diagnosis of diastolic dysfunction. *Echocardiography* 2006;23:817-28.
14. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 2003;289:2560-72.
15. Paulus WJ, Brutsaert DL, Gillebert TC, et al. How to diagnose diastolic heart failure. *Eur Heart J* 1998;19:990-1003.
16. Nikitin NP, Witte KKA, Thackray SDR, et al. Longitudinal ventricular function: Normal values of atrioventricular annular and myocardial velocities measured with quantitative two-dimensional color Doppler tissue imaging. *J Am Soc Echocardiogr* 2003;16:906-21.
17. Wang M, Yip GWK, Wang AYM, et al. Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. *J Am Coll Cardiol* 2003;41:820-6.
17. Yip GWK, Wang M, Wang T, et al. The Hong Kong Diastolic Heart Failure Study: A randomised controlled trial of diuretics, irbesartan and ramipril on quality of life, exercise capacity, left ventricular global and regional function in heart failure with a normal ejection fraction. *Heart* 2008;94:573-80.
19. Gosse P. Left ventricular hypertrophy as a predictor of cardiovascular risk. *J Hypertens* 2005;23:S27-S33.
20. Mathew J, Sleight P, Lonn E, et al. Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril. *Circulation* 2001;104:1615-21.
21. Schmieder RE, Messerli FH. Is the decrease in arterial-pressure the sole factor for reduction of left-ventricular hypertrophy. *Am J Med* 1992;92:S28-S34.

22. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension – a meta-analysis of randomized double-blind studies. *JAMA* 1996;275:1507-13.
 23. Fagard R, Pardaens K. Left ventricular diastolic function predicts outcome in uncomplicated hypertension. *Am J Hypertens* 2001;14:504-8.
 24. Fouadtarazi FM. Left-ventricular diastolic dysfunction in hypertension. *Curr Opin Cardiol* 1994;9:551-60.
 25. Franz IW, Tonnesmann U, Muller FM. Time course of complete normalization of left ventricular hypertrophy during long-term antihypertensive therapy with angiotensin converting enzyme inhibitors. *Am J Hypertens* 1998;11:631-9.
 26. Laufer E, Reid C, Qi XL, Jennings GL. Absence of detectable regression of human hypertensive left ventricular hypertrophy following drug treatment for 1 year. *Clin Exp Pharmacol Physiol* 1998;25:208-15.
 27. Schulman DS, Flores AR, Tugoen J, Dianzumba S, Reichel N. Antihypertensive treatment in hypertensive patients with normal left ventricular mass is associated with left ventricular remodeling and improved diastolic function. *Am J Cardiol* 1996;78:56-60.
 28. Masaaki T, Tomoko N, Victor M, et al. Measurement of left ventricular mass by real-time three-dimensional echocardiography: Validation against magnetic resonance and comparison with two-dimensional and M-mode measurements. *J Am Soc Echocardiogr* 2008;21:1001-5.
 29. Ogunyankin KO, Day AG, Lonn E. Cardiac function stratification based on echocardiographic or clinical markers of left ventricular filling pressures predicts death and hospitalization better than stratification by ventricular systolic function alone. *Echocardiography* 2008;25:169-81.
 30. Okonofua EC, Simpson KN, Jesri A, et al. Therapeutic inertia is an impediment to achieving the healthy people 2010 blood pressure control goals. *Hypertension* 2006;47:345-51.
-