Relationship Between Treatment-Induced Changes in Left Ventricular Mass and Blood Pressure in Black African Hypertensive Patients

Results of the Baragwanath Trial

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Background—In a single-center study, we compared to what extent changes in conventional and ambulatory blood pressure (BP) predicted regression of left ventricular mass (LVM) index in response to antihypertensive treatment in previously untreated and treated patients with sustained hypertension.

Methods and Results—We enrolled 173 black African patients who, off treatment, had a daytime diastolic BP ranging from 90 to 114 mm Hg. Antihypertensive drugs were titrated and combined to reduce the daytime diastolic BP below 90 mm Hg. Echocardiograms were obtained at baseline and follow-up. Mean systolic/diastolic clinic BP, 24-hour BP, and LVM index were similar in previously untreated (n=64) and previously treated (n=109) patients and averaged 171/102 mm Hg, 151/97 mm Hg, and 118 g/m^2, respectively. At 4 months, these values had decreased ($P<0.001$) by 26/12 mm Hg, 23/14 mm Hg, and 14 g/m^2 in previously untreated patients and by 22/9 mm Hg, 21/13 mm Hg, and 19 g/m^2 in previously treated patients. In the previously untreated patients, the regression in LVM index correlated to a similar degree ($P=0.09$) with the decreases in the conventional ($r=0.34$; $P=0.005$) and the 24-hour ($r=0.26$; $P=0.04$) systolic BP. In the previously treated patients, the corresponding correlations were 0.02 ($P=0.82$) and −0.10 ($P=0.32$), respectively. Compared with the 24-hour systolic BP, automated oscillometric measurements of systolic BP obtained at the clinic yielded similar results.

Conclusions—In previously untreated patients with sustained hypertension followed at a single center, reductions in clinic and ambulatory systolic pressure in response to antihypertensive treatment equally predicted the regression in LVM index. **(*Circulation*. 2002;105:830-836.)**

Key Words: blood pressure ■ hypertrophy ■ hypertension

Left ventricular hypertrophy is a strong and independent predictor of cardiovascular morbidity and mortality[1–3] both in hypertensive patients and in the general population. It is associated with a higher risk of myocardial infarction, stroke, sudden death, and death from any cause. Furthermore, echocardiographically determined left ventricular mass (LVM) confers prognostic information beyond that provided by traditional risk factors, including hypertension.[1] Moreover, recent studies[4,5] and 3 meta-analyses[6–8] on antihypertensive treatment showed that the reduction in LVM correlated with the decrease in blood pressure (BP). However, controversy still exists with regard to what type of BP measurement (conventional, automated, or ambulatory) correlates better with changes in LVM induced by antihypertensive treatment.[4] Most previous studies did not exclude previously treated or white-coat hypertensive patients or were multicentric, which makes clinic measurements of BP more difficult to standardize. In older patients with isolated systolic hypertension, active treatment compared with placebo reduced electrocardiographic voltages only in patients with sustained hypertension and not in those with white-coat hypertension.[5]

The Baragwanath Hypertension Study was a single-center, randomized trial that compared several drug classes to initiate treatment in black African patients with sustained hypertension confirmed by ambulatory BP monitoring.[9] In the present analysis, we compared to what extent changes in conventional and automated BP readings at the clinic and in the ambulatory BP predicted regression of LVM index in response to antihypertensive treatment in previously untreated or treated patients with sustained hypertension.

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Methods

Subjects and Procedures

The Baragwanath Hypertension Study was a single-center, randomized, open-label trial conducted at the Chris Hani-Baragwanath Hospital from 1994 through 1997. The protocol was approved by the Committee for Research on Human Subjects of the University of Witwatersrand. Black men and women could be enrolled if they were 18 to 70 years of age and free of clinically significant cardiovascular or noncardiovascular disorders. Women of reproductive age had to use adequate contraception. All patients gave informed written consent.

Patients diagnosed as being hypertensive after a 2-week placebo run-in period and with a count of returned placebo tablets within 80% to 120% of the expected number qualified for randomization if, in addition, their daytime diastolic BP was 90 to 114 mm Hg. Eligible patients were randomized to nifedipine gastrointestinal therapeutic system (GITS) 30 mg/d, verapamil slow release (SR) 240 mg/d, hydrochlorothiazide 12.5 mg/d, or enalapril 10 mg/d.[9] Patients were followed up at monthly intervals. The target BP was a daytime diastolic pressure of <90 mm Hg. If at the first monthly follow-up visit the target was not reached, the daily dose of the first-line drug was increased, as follows: nifedipine GITS to 60 mg, verapamil SR to 360 mg, hydrochlorothiazide to 25 mg, and enalapril to 20 mg. At 2 months, patients of the nifedipine GITS group who had not achieved the target BP were additionally randomized to 1 of the following 4 treatment strategies: the addition of enalapril (10 mg/d), carvedilol (25 mg/d), or verapamil SR (120 mg/d) or increasing the daily dose of nifedipine GITS to 90 mg. In the uncontrolled patients of the verapamil SR group, the daily dose of the calcium-channel blocker could be increased to 480 mg. Patients not controlled on hydrochlorothiazide 25 mg/d received reserpine 0.125 mg/d, and those not controlled on enalapril 20 mg/d were given hydrochlorothiazide 12.5 mg/d.

All patients randomized in the Baragwanath Trial underwent echocardiography at baseline. However, only patients in whom high-quality echocardiograms could be obtained were eligible for inclusion in the echocardiographic substudy.

BP Measurements

At baseline and at each of 4 follow-up visits, BP was assessed with 3 techniques. First, after the patient had rested in the sitting position for 10 minutes, the study nurse measured the conventional BP 3 times consecutively according to the recommendations of the American Heart Association.[10] The same nurse performed the conventional BP readings in all patients. Subsequently, the sitting BP was recorded 10 times consecutively at 3-minute intervals using calibrated Dinamap 1846 SX oscillometric monitors (Critikon Inc).[11] For analysis, the 3 conventional and 10 Dinamap automated BP measurements were averaged.

Furthermore, oscillometric SpaceLabs 90207 devices[12] (SpaceLabs Inc) were programmed to obtain BP readings every 15 minutes from 6:00 AM to 10:00 PM and every 30 minutes from 10:00 PM to 6:00 AM. The intraindividual BP means were weighted by the time interval between successive BP readings. For analysis, the daytime period was defined as the time interval from 6:00 AM to 6:00 PM and nighttime ranged from 10:00 PM to 4:00 AM. Previous studies in black Africans have shown that this definition excludes the rapid BP changes in the morning and evening.[9]

Echocardiography

At randomization and at 4 months, M-mode, 2-dimensional, pulse and color Doppler echocardiograms were obtained with a Hewlett-Packard Sonos 2500 system using a 2.5-MHz transducer. M-mode echocardiography of the left ventricle was performed in the short-axis view. M-mode variables were analyzed according to the American Society of Echocardiography Convention[13] and included left ventricular end-diastolic and end-systolic diameters and septal and posterior wall thickness. All measurements were recorded on videotape and analyzed by the same experienced echocardiographer who was blinded to the BP and the clinic data of the patients. For statistical analysis, measurements were averaged over 3 heart cycles. Doppler estimation of the stroke volume was assessed as previously described.[14] LVM was adjusted for body size according to an anatomically validated regression method.[15] Replicate measurements of LVM index showed that in the present study population, the interobserver and intraobserver coefficients of variation were 12.4% and 11.4%, respectively.

Statistical Analysis

Database management and statistical analysis were performed with SAS software, version 6.12 (SAS Institute Inc). Previously untreated and treated patients were compared using Student's t test and the χ^2 statistic for continuous measurements and class variables, respectively. Single and stepwise multiple regression analyses were used to analyze the relationship between changes in LVM or LVM index and various explanatory variables, including the treatment-induced BP changes. Multivariate ANOVA was performed to test the null hypothesis of no differences between the parameters of regression equations.[16]

Results

Baseline Demographic Characteristics

Of the 409 patients randomized in the trial, 233 (57%) were eligible for inclusion in the present substudy because echocardiograms of sufficient quality had been obtained. Of the latter patients, 23 (10%) had been withdrawn at 4 months and 37 (16%) did not have all measurements at baseline or at 4 months required for the statistical measurements. Thus, our study includes 173 patients who, compared with the 236 nonparticipants, had similar BP values at entry (Table 1). However, nonparticipants were older, more obese, and included slightly more previously treated patients (46% versus 37%, respectively, $P=0.052$)

The 173 patients (41 men and 132 women) were 51±10 years of age. Their body-mass index averaged 30.3±6.2 kg/m^2. Of the 173 patients, 109 had previously been treated, and 85 patients had been on monotherapy either with diuretics (n=48), angiotensin-converting enzyme inhibitors (n=20), α-methyldopa (n=9), or calcium channel blockers (n=8). Furthermore, 17 patients had been on multiple drugs, including diuretics in 11 patients, and 7 patients could not report which drug treatment they had been taking before the screening visit. Compared with the untreated patients, the previously treated patients included more women and had higher mean body-mass index (Table 1). At entry, clinic, Dinamap and ambulatory BP values (Table 2) as well as all echocardiographic measurements (Table 3) were similar in previously untreated and treated patients ($P>0.04$).

Results in Previously Untreated Patients

The number of patients who remained on monotherapy was 27 of 39 in the nifedipine group, 6 of 9 in the verapamil SR group, 2 of 8 in the enalapril group, and 4 of 8 in the hydrochlorothiazide group.

At 4 months, compared with baseline, BP measured at the clinic by the study nurse or by the Dinamap device had significantly ($P<0.001$) decreased (Table 2). In addition, there was a parallel shift ($P<0.001$) of the systolic and diastolic ambulatory BP profiles to lower values (Figure 1 and Table 2). The treatment-induced changes in the BP recorded oscillometrically, either at the clinic or over 24 hours, were significantly correlated with the corresponding

TABLE 1. Clinical Characteristics at Randomization of Participants and Nonparticipants

		Participants		
	Nonparticipants	Previously Untreated	Previously Treated	All Included
No.	236	64	109	173
Age, y	55±10	49±11	52±9	51±10*
Female sex, n (%)	181 (77)	40 (62.5)	92 (84.4)‡	132 (76)
Body mass index, kg/m^2	31.8±7	28.4±6	31.4±6‡	30.3±6.2†
Systolic/Diastolic BP, mm Hg				
Conventional	173±18/103±7	170±17/103±9	172±21/102±9	172±21/102±9
Dinamap	166±18/99±8	162±16/100±7	165±21/100±8	165±21/100±8
24-Hour	150±15/96±7	149±15/96±7	153±15/97±7	153±15/97±7
Daytime	155±14/102±7	153±15/102±7	158±14/103±7	158±14/103±7
Nighttime	139±18/85±10	140±18/86±10	143±20/87±11	143±20/87±11

Values are mean±SD.

*$P<0.001$ and †$P=0.03$, significance of the difference between participants and nonparticipants; ‡$P=0.002$, significance of the difference between previously untreated and previously treated patients.

changes in the conventionally measured office readings (Figure 2).

After 4 months of antihypertensive therapy, LVM and LVM index had decreased ($P<0.001$) by 24 g and 14 g/m^2, respectively (Table 3). This was achieved through a reduction in wall thickness with no significant change in left ventricular end-diastolic diameter. Both before and after standardization for body surface area, there was a positive linear relationship between the decrease in LVM index and the reduction in systolic BP as assessed by conventional or automated measurement at the clinic or by 24-hour ambulatory monitoring (Table 4). The corresponding relationship for diastolic pressure was not statistically significant (Table 4). Considering conventional, Dinamap, and 24-hour BP measurements, there were no significant differences in the regression parameters relating the changes in LVM to those in BP ($P\geq0.09$). These findings remained unaltered when LVM index was used as an outcome variable (Figures 3 and 4). In addition, measurement of the 24-hour or Dinamap BP did not significantly increase the accuracy of the prediction of the changes in LVM ($P>0.40$) or LVM index ($P>0.37$) over and beyond that already provided by conventional systolic pressure.

Results in Previously Treated Patients

The number of patients that remained on monotherapy was 40 of 65 in the nifedipine group, 14 of 17 in the verapamil SR group, 3 of 14 in the enalapril group, and 5 of 13 in the hydrochlorothiazide arm. There were no significant differences in the use of study medications between previously untreated and treated patients ($P>0.42$). Furthermore, at 4 months, the clinic, Dinamap, and ambulatory BP (Table 2 and Figure 1) had fallen to the same extent as in the previously untreated group. After 4 months of antihypertensive therapy with the study medications, LVM and LVM index had decreased by 34 g ($P<0.001$) and 19 g/m^2 ($P<0.001$), respectively (Table 3). This was achieved through a reduction

TABLE 2. Conventional, Dinamap, and Ambulatory BP at Baseline and at 4 Months

BP, mm Hg	Baseline	4 Months	Change
Previously untreated (n=64)			
Conventional	170±17/103±9	144±21/91±11	−26±25/−12±14
Dinamap	162±16/100±7	137±19/88±10	−25±21/−12±11
24-Hour	149±15/96±7	126±14/92±18	−23±15/−14±9
Daytime	153±15/102±7	130±14/87±8	−23±16/−15±9
Nighttime	140±18/86±10	119±17/73±10	−21±16/−13±10
Previously treated (n=109)			
Conventional	172±21/102±9	150±22/93±11	−22±27/−9±14
Dinamap	165±21/100±8	143±20/90±11	−22±26/−10±12
24-Hour	153±15/97±7	132±14/85±9	−21±17/−13±10
Daytime	158±14/103±7	135±15/90±10	−22±17/−13±10
Nighttime	143±20/87±11	124±17/75±10	−19±19/−12±12

All changes in blood pressure were significant ($P<0.001$).

TABLE 3. Echocardiographic Data at Baseline and 4 Months

Characteristic	Baseline	4 Months	Change	*P*
Previously untreated (n=64)				
LVEDD, mm	47.0±4.9	46.4±4.6	−0.6±5.1	0.34
PWT, mm	11.1±0.21	10.3±1.7	−0.7±2.1	0.007
IVS, mm	11.9±2.3	11.0±1.7	−0.9±2.2	0.003
MWT, mm	11.5±2.1	10.7±1.4	−0.8±1.9	0.001
LVM, g	205±55	181±40	−24.2±42.9	<0.001
LVM index, g/m^2	118±33	104±23	−14.3±26.1	<0.001
Stroke volume, mL	73±16	74±18	0.099	0.32
Previously treated (n=109)				
LVEDD, mm	45.7±6.3	43.9±5.8	−1.8±6.4	0.004
PWT, mm	11.5±2.3	10.7±1.8	−0.8±2.3	<0.001
IVS, mm	12.6±2.0	11.6±1.9	−1.0±2.0	<0.001
MWT, mm	12.0±1.9	11.2±1.6	−0.9±1.8	<0.001
LVM, g	212±70	178±55	−33.7±52.6	<0.001
LVM index, g/m^2	118±34	99±26.1	−18.6±29.1	<0.001
Stroke volume, mL	73±17	73±16	−0.00008	0.96

LVEDD indicates left ventricular end-diastolic diameter; PWT, posterior wall end-diastolic thickness; IVS, interventricular septum end-diastolic thickness; and MWT, end-diastolic mean wall thickness.

in wall thickness and left ventricular end-diastolic diameter. Treatment-induced changes in all echocardiographic measurements were similar ($P>0.18$) in previously untreated and treated patients (Table 3). However, in contrast to the previously untreated group, in treated patients, all correlations between the changes in LVM index and any type of BP measurement failed to reach statistical significance (Table 4 and Figure 3). Adjustment for previous treatment with diuretics or other drugs did not alter these findings.

Discussion

The Baragwanath Hypertension Study was a single-center trial that investigated the efficacy of various drug classes to initiate antihypertensive treatment in black African patients.[9] The same trained research nurse obtained all conventional BP readings. Only patients with sustained hypertension were enrolled. The study medications were titrated or combined to reduce the daytime diastolic BP to a level below 90 mm Hg. Four months of antihypertensive treatment significantly lowered clinic, 24-hour, daytime, and nighttime BP, which led to a significant decrease in wall thickness, LVM, and LVM index.

We found significant and positive correlations between the changes in LVM index and all types of systolic BP in response to treatment in previously untreated patients, whereas in previously treated patients these correlations were nonsignificant. Furthermore, in untreated patients, regression of LVM index was not significantly better correlated with the reduction in 24-hour, daytime, or nighttime systolic pressure than with the decrease in the conventional systolic pressure. The latter observations are at variance with 2 previous studies. In the Study on Ambulatory Monitoring of Blood

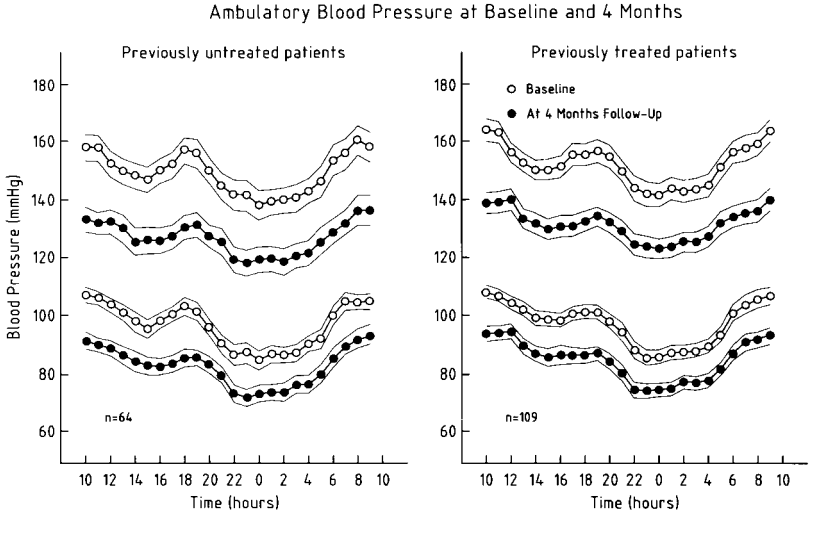

Figure 1. Systolic and diastolic BP profiles at baseline (open symbols) and at 4 months (closed symbols). Values are hourly BP means with 95% CIs. Results are given separately for previously untreated and treated patients.

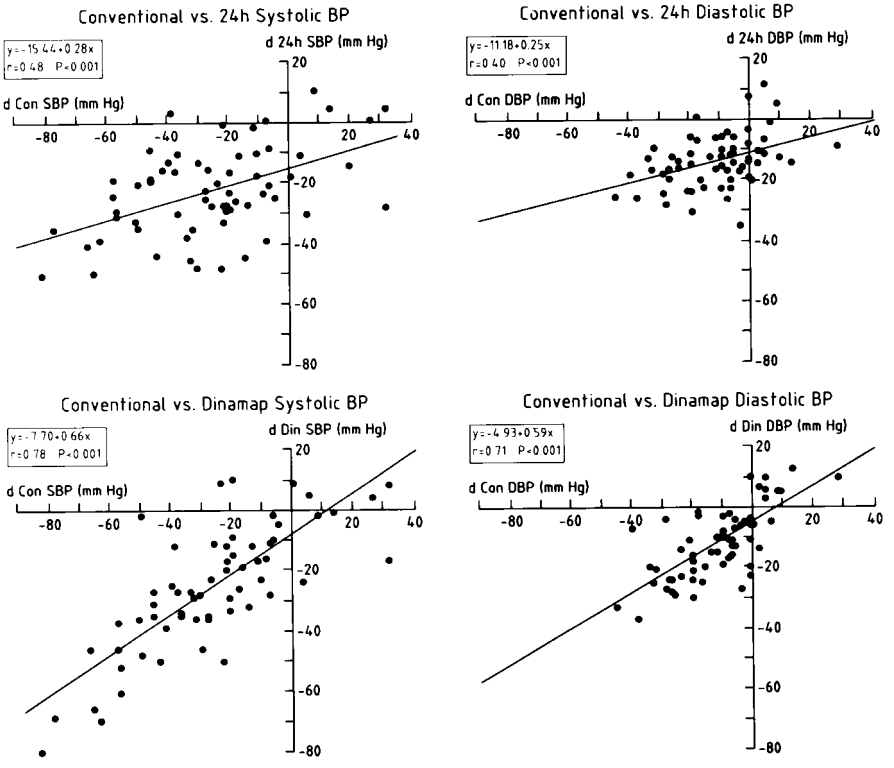

Figure 2. Relationships in 64 previously untreated patients between changes in 24-hour (d 24h) or Dinamap (d Din) measurements of systolic BP (SBP) and diastolic BP (DBP) and the corresponding changes in the conventionally measured BPs (d Con).

Pressure and Lisinopril Evaluation (SAMPLE),[17] after 12 months of follow-up of 184 patients, the decreases in systolic/diastolic pressure were 26/18 mm Hg for the clinic pressure and 18/12 mm Hg for the 24-hour pressure. LVM index decreased from 158 to 133 g/m^2. The reduction in LVM index was not correlated with the changes in the clinic BP ($r=0.11/0.11$), but it was significantly ($P<0.01$) correlated with the changes in the 24-hour BP ($r=0.42/0.38$). In the study by Fagard et al,[4] during 6 months of follow-up of 54 patients, the reductions in systolic/diastolic BP were 22/16 mm Hg for the conventional pressure, 19/12 mm Hg for Dinamap measurements performed at the clinic, and 17/11 mm Hg for the 24-hour BP. LVM decreased from 237 to 212 g. Changes in LVM were significantly related to changes in systolic BP. The correlation coefficients, adjusted for sex and body size, amounted to 0.39 and 0.40 for the conventional and automated measurements of clinic systolic pressures, respectively, and to 0.55 for the 24-hour systolic pressure. The 24-hour systolic pressure added 7.4% ($P<0.05$) and 6.2% ($P=0.06$) to the variance of the changes in LVM explained in

TABLE 4. Regression Coefficients Between Changes in LVM Index and in BP Over 4 Months

	Systolic Pressure		Diastolic Pressure	
	Regression Coefficient (95% CI)	*P*	Regression Coefficient (95% CI)	*P*
Previously untreated (n=64)				
Conventional	0.37 (0.14 to 0.61)	0.004	0.14 (−0.32 to 0.60)	0.56
Dinamap	0.34 (0.05 to 0.63)	0.03	0.42 (−0.12 to 0.97)	0.13
24-Hour	0.46 (0.03 to 0.89)	0.04	0.60 (−0.013 to 1.34)	0.11
Daytime	0.34 (−0.05 to 0.73)	0.10	0.42 (−0.27 to 1.10)	0.24
Nighttime	0.40 (−0.01 to 0.81)	0.06	0.55 (−0.06 to 1.17)	0.08
Previously treated (n=109)				
Conventional	0.02 (−0.18 to 0.23)	0.82	−0.05 (−0.45 to 0.34)	0.80
Dinamap	−0.06 (−0.28 to 0.15)	0.57	−0.21 (−0.66 to 1.24)	0.37
24-Hour	−0.17 (−0.48 to 0.14)	0.32	−0.17 (−0.73 to 0.39)	0.56
Daytime	−0.19 (−0.50 to 0.12)	0.23	−0.22 (−0.75 to 0.30)	0.41
Nighttime	−0.09 (−0.38 to 0.20)	0.54	−0.53 (−0.39 to 0.48)	0.98

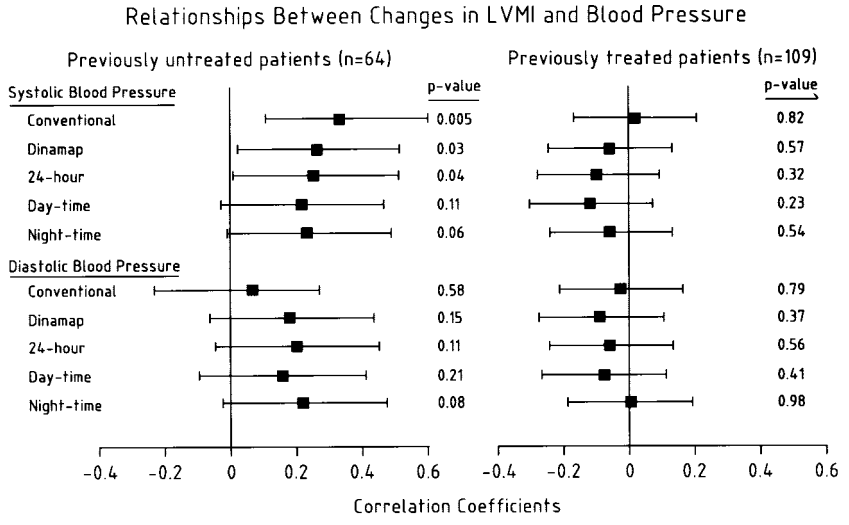

Figure 3. Partial correlation coefficients with 95% CIs between changes in LVM index and changes in BP after 4 months of treatment with the study medications in 64 previously untreated and 109 previously treated patients.

terms of the conventional and automated measurements of clinic systolic pressures, respectively.

The discordance between our findings and the 2 previous studies may depend on various factors, such as the characteristics of the study participants, duration of follow-up under treatment with study medications, precision and standardization of the conventional BP readings, and recruitment of previously treated patients. Our earlier studies demonstrated that under antihypertensive treatment, LVM decreased to a similar extent in white patients and black African patients.[18,19] Furthermore, previous studies showed that 3 months of antihypertensive treatment is sufficient to maximally reduce LVM.[20,21] However, a recent analysis of the Losartan Intervention For Endpoint Reduction (LIFE) study[22] suggested that maximum effect on left ventricular hypertrophy of antihypertensive treatment may not be achieved for at least 2 years. The results of the Prospective Randomized Enalapril Study Evaluating Regression of Left Ventricular Enlargement (PRESERVE) trial[23] will undoubtedly shed more light on this issue. In the SAMPLE study, the 12-month change in LVM index correlated equally with the change in the 24-hour systolic pressure in previously untreated ($r=0.49$) and previously treated ($r=0.39$) patients, whereas such relationships were not observed for the changes in the clinic BP. However, the clinic BP in the SAMPLE study was the average of only 2 conventional readings, which were obtained by different observers across 11 centers. Conventional BP readings are more difficult to standardize in multicenter studies. In our study, only one study nurse measured the clinic BP at baseline and follow-up in all patients. The strength of the reported associations of LVM index with conventional BP readings has varied greatly, with correlation coefficients ranging from close to zero[24] to approximately 0.5.[25] Fagard et al[26] produced convincing evidence suggesting that differences among studies may be partly attributable to the variable degrees of standardization and the divergent number of conventional BP readings.

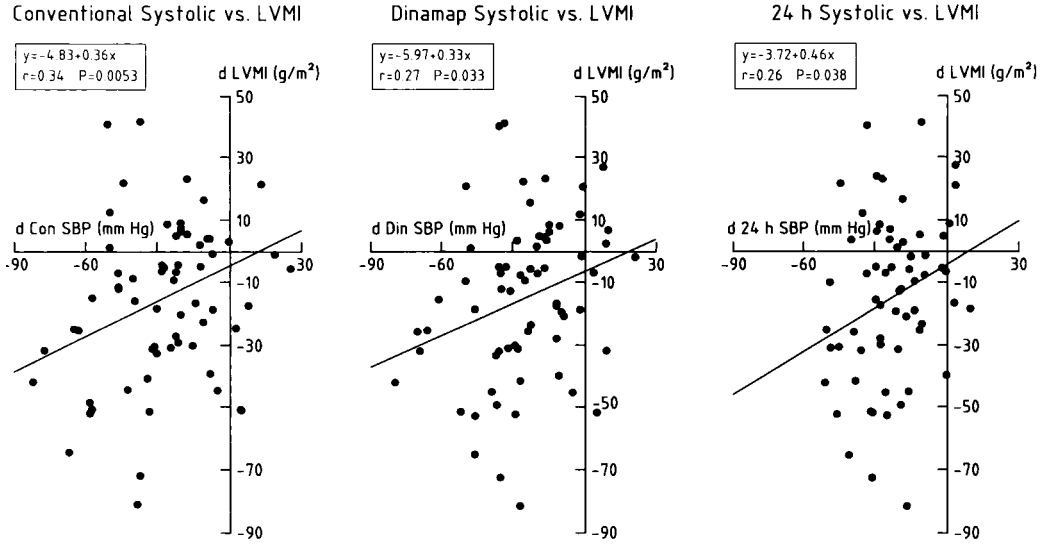

Figure 4. Relationships between the changes in LVM index (LVMI) and in systolic BP (SBP) as assessed by 3 techniques of BP measurement in 64 previously untreated patients. d Con indicates conventional measurement; d Din, Dinamap; and d 24 h, 24-hour.

In the Baragwanath Trial, all patients had a daytime diastolic BP ranging from 90 to 114 mm Hg. Patients with white-coat hypertension were therefore excluded. In the 2 previous studies,[4,17] patients were exclusively selected on the basis of conventional BP readings at the clinic. Furthermore, depending on the number of clinic visits, the number of conventional BP readings averaged to diagnose hypertension, and the level of the conventional BP, the prevalence of white-coat hypertension among patients with elevated clinic pressure on conventional measurement may range from 5%[27] to >70%.[28] In white-coat hypertensive patients, the clinic BP does not reflect the usual BP load and therefore may be expected to be only weakly correlated or not correlated with LVM. We hypothesize that the high degree of standardization of the conventional BP measurements in the clinic and the exclusion of white-coat hypertensive patients explain why in our previously untreated patients, in contrast to earlier studies, the correlations between the changes in LVM and in systolic BP were of similar magnitude for all types of BP measurement.

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