Published by Elsevier Inc.

ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2003.07.039

Mechanism(s) of Selective Systolic Blood Pressure Reduction After a Low-Dose Combination of Perindopril/Indapamide in Hypertensive Subjects: Comparison With Atenolol

Gérard M. London, MD,* Roland G. Asmar, MD,† Michaël F. O'Rourke, MD,‡ Michel E. Safar, MD,§ on behalf of the REASON Project Investigators

Fleury-Mèrogis and Paris, France; and Darlinghurst, Australia

OBJECTIVES The goal of this study was to determine if a low-dose combination of the angiotensin-converting enzyme inhibitor perindopril (Per) and the diuretic indapamide (Ind) reduces central (thoracic aorta, carotid artery) as well as brachial systolic blood pressure (SBP) more than the beta-blocker atenolol and to determine the hemodynamic factors influencing independently brachial and central SBP: pulse wave velocity (PWV) and pattern of wave reflections.

BACKGROUND In high cardiovascular risk populations, angiotensin blockade improves survival without affecting brachial SBP and diastolic blood pressure (DBP). Whether central SBP, which is physiologically lower than brachial SBP, is significantly reduced has never been investigated.

METHODS This study was a double-blind randomized trial for one year in patients with essential hypertension.

RESULTS For a similar DBP reduction, Per/Ind decreased SBP significantly more than atenolol, with a more pronounced reduction for central than for brachial SBP. After one year, the difference between brachial and central SBP was maintained by Per/Ind (8.28 ± 1.53 mm Hg) and significantly attenuated by atenolol (0.29 ± 1.61 mm Hg). Under atenolol, the principal factor modulating SBP reduction was mean blood pressure. Under Per/Ind, this parameter played a minor role, and the central SBP reduction implied a major role for disturbed PWV and wave reflections.

CONCLUSIONS Under Per/Ind, but not atenolol, normalization of brachial SBP is achieved with a significantly greater reduction of central SBP. This hemodynamic profile reflects changes of wave reflections issued from distal arterial and arteriolar territory, where Per/Ind, but not atenolol, is known to improve vessel wall structure. (J Am Coll Cardiol 2004;43:92–9)

In several high cardiovascular (CV) risk populations (1–4), it has been suggested that angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II antagonists reduce CV morbidity and mortality without a change in conventional brachial cuff systolic blood pressure (SBP) and diastolic blood pressure (DBP). This assumption may be questioned on several grounds. First, most of the patients were previously treated for hypertension, and baseline brachial SBP and DBP at inclusion were very close to normal. Under these conditions, brachial blood pressure may be difficult to modify by antihypertensive agents, particularly in subjects where only baseline brachial SBP is slightly elevated. Secondly, central SBP is a very complex parameter. Whereas mean blood pressure (MBP) and even DBP remain relatively stable along the arterial tree, SBP is lower in central (thoracic aorta, carotid artery) than in peripheral (brachial) arteries, as a consequence of the summation of incident and reflected pressure waves close to peripheral reflecting sites. Thus, it is relevant to propose that blockade of the renin-angiotensin system might reduce central SBP without major change in brachial SBP, a hemodynamic pattern already observed with other CV vasodilators as nitrates (5). Taken together, these findings focus attention on the hemodynamic mechanisms, such as large artery stiffness and wave reflections, which influence selectively SBP and have the potential to better reduce CV risk in hypertensive populations (6,7).

The association of the ACEI perindopril (Per) with the diuretic compound indapamide (Ind) has been shown to reduce significantly CV morbidity and mortality (8). When compared with atenolol in hypertensive subjects, the Per/Ind combination reduces more SBP than atenolol for the same reduction of DBP. The finding was observed at both the brachial and central (thoracic aorta, carotid artery) levels (9). However, several problems had not yet been clarified. First, it was not verified that normal brachial SBP (<140 mm Hg) under Per/Ind was associated with

From the *Hôpital Manhès, Fleury-Mèrogis, France; †L'Institut Cardiovasculaire, Paris, France; ‡St. Vincent Hospital, Darlinghurst, Australia; and §Hôtel-Dieu, Paris, France. This study was performed with the financial help of INSERM and Laboratoires Servier.

Manuscript received February 4, 2003; revised manuscript received July 28, 2003, accepted July 28, 2003.

Abbreviations and Acronyms

ACEI	= angiotensin-converting enzyme inhibitor
AIa	= augmentation index (aortic)
AIc	= augmentation index (carotid)
CV	= cardiovascular
DBP	= diastolic blood pressure
Ind	= indapamide
ITT	= intention-to-treat
LVET	= left ventricular ejection time
MBP	= mean blood pressure
M0, M6, M12	= month 0, month 6, month 12
Per	= perindopril
PP	= pulse pressure
PWV	= pulse wave velocity
SBP	= systolic blood pressure

lower values of central SBP. Second, it was not determined at which exact period the selective SBP reduction was obtained during the one-year follow-up. Finally, the factors modulating independently brachial and central SBP reduction under Per/Ind or atenolol have not been extensively explored. This report presents new data enabling determination from month 0 (M0) to month 12 (M12) the time-dependent relationships of the main hemodynamic factors influencing the central SBP reduction: wave reflections, arterial stiffness, and/or the cardiac changes generated by atenolol.

The aim of the present study was to determine the hemodynamic mechanisms explaining the selective SBP reduction obtained with the Per/Ind combination when compared with atenolol, to establish in which conditions such mechanisms varied with time along the one-year follow-up of the study and, finally, to determine whether they differ in the central and peripheral compartments of the arterial tree.

METHODS

The REASON Project (pREterax in regression of Arterial Stiffness in a contrOlled double-bliNd study) is a multicenter, randomized, double-blind, two parallel group study already conducted in 13 countries (9). After a one-month washout placebo period, 471 hypertensive patients, age 18 to 83 years, were selected with a supine SBP $\geq$160 mm Hg and $<$210 mm Hg, and/or a supine DBP $\geq$95 mm Hg and $<$110 mm Hg. Exclusion criteria as well as biochemical changes have been published in detail elsewhere (9). Written informed consent was obtained from each patient, and the protocol was approved by the ethics committees, in accordance with local regulations.

Patients were randomly allocated to receive either Per 2 mg/Ind 0.625 mg or atenolol 50 mg for a 12-month follow-up period. In both groups, the medication was taken orally in the morning as a single dose. For treatment adaptation, the dose was doubled (two capsules once daily) (n = 103 for Per/Ind and n = 92 for atenolol) after three months if SBP remained $>$160 mm Hg and/or DBP $>$90 mm Hg.

Hemodynamic variables were determined 24 h after the last drug intake, just before inclusion (M0), at month 6 (M6), and at the end of the follow-up (M12) using a protocol described in detail elsewhere (9). Brachial SBP and DBP were determined with mercury sphygmomanometer. Pulse wave velocity (PWV) was measured in all subjects, and pulse wave analysis was performed in 181 subjects randomly selected. All measurements were analyzed by two physicians blinded to treatment, clinical data, and physical examination. The PWV was determined using an automatic device, the Complior (Colson, Paris, France). Available data (9) were obtained in 469 of the 471 patients. For pulse wave analysis, measurements were performed in 181 subjects, involving 144 subjects for the carotid artery and 110 for the aorta. Determinations were performed by applanation tonometry using a Sphygmocor device (Alcor, Sydney, Australia) (10) and assuming identical values of MBP and DBP in the totality of the arterial tree (9–12). Calibration and repeatability have been described in detail elsewhere (9,11,12). On the carotid and aortic blood pressure curve, the carotid augmentation index (AIc) and aortic augmentation index (AIa), which evaluate the delay of carotid or aortic wave reflections and their effect on the height of SBP and the left ventricular ejection time (LVET), were determined according to previously validated methods (9–12). Cardiac index, stroke index, and total peripheral resistance were determined at M0 and M12 using standard echocardiography (9). The stroke index on LVET ratio was used as an index of ventricular ejection.

In this study, an intention-to-treat (ITT) analysis was performed, using a SAS software version 8.2 (Cary, North Carolina) for Windows. Means and SDs are given for the description of quantitative variables, and percentage on total categories sample size for qualitative variables. Because the main goal was to investigate the time-dependency of simultaneous determinations of brachial and central parameters, adjustments involved in all comparisons age, gender, body mass index, prior antihypertensive drug therapy, and treatment adaptation if necessary. Other pertinent variables such as heart rate or MBP were potentially added. Treatment group, time of measurements (visits), and interaction group by time were initially tested by a repeated measures analysis. Because of a positive interaction group by time, these two main effects were analyzed separately: time effect test in each group, and group effect at each time. Absolute means analysis variations according to the therapeutic groups and time were analyzed by a general linear model, and baseline values were taken additionally as covariates for 6- and 12-month mean comparisons. Adjusted means were derived from this model.

Central-peripheral SBP amplification was determined as brachial SBP $-$ carotid SBP and expressed in mm Hg. Changes between visits were computed as: 6-month value (M6) $-$ baseline value (M0) $\div$ by baseline value $\times$ 100;

Table 1. Population Descriptions: Main Parameters at Baseline (Mean ± SD) in the Global ITT Population (n = 469, Because in 2 Subjects, PWV Measurements Were Not Available at Baseline) and in the Population of the Ancillary Study With Central Measurements (n = 181)

	ITT Population (n = 469)		Subpopulation With Central Measurements (n = 181)	
	Per/Ind (n = 235)	Atenolol (n = 234)	Per/Ind (n = 88)	Atenolol (n = 93)
Gender (men:women) (%)	66:34	69:31	69:31	76:34
PAT (yes) (%)	73	72	70	74
Trt Adapt (Yes) (%)	44	39	51	42
Age (yrs)	55.0 ± 12.2	54.8 ± 12	55.9 ± 13.4	57.5 ± 14.4
Body mass index (kg/m^2)	26.9 ± 2.9	26.6 ± 2.8	27.0 ± 3.2	26.6 ± 3.0
SBP (mm Hg)	163.1 ± 13.4	161.4 ± 14.8	165.3 ± 13.9	162.5 ± 15.0
DBP (mm Hg)	98.6 ± 6.8	98.6 ± 7.0	97.4 ± 8.2	96.1 ± 8.1
MBP (mm Hg)	120.1 ± 6.4	119.5 ± 7.0	120.0 ± 7.0	118.2 ± 6.9
PP (mm Hg)	64.5 ± 14.9	62.9 ± 16.0	68.0 ± 16.5	66.4 ± 17.9
Heart rate (beats/min)	72.2 ± 9.7	72.4 ± 9.5	70.4 ± 10.4	70.3 ± 8.5
PWV (m/s)	12.20 ± 2.91	12.32 ± 2.87	12.78 ± 3.02	12.59 ± 3.02

DBP = diastolic blood pressure; Ind = indapamide; ITT = intention-to-treat; MBP = mean blood pressure; PAT = previous antihypertensive treatment; Per = perindopril; PP = pulse pressure; PWV = pulse wave velocity; SBP = systolic blood pressure; Trt Adapt = treatment adaptation during the study.

12-month value − 6-month value ÷ 6-month value × 100; 12-month value (M12) − baseline value (M0) ÷ baseline value × 100. Stroke change (%) between therapeutic groups at each time were analyzed by a general linear model, and adjusted means were derived from this model. Regression coefficients were obtained by linear regression procedures. Stepwise linear regressions were used to establish the order of trend between the percent change of SBP and the different percent change in the hemodynamic variables influencing SBP: AIc or AIa (%), LVET in ms, PWV in m/s, MBP in mm Hg. Age in years, body mass index in kg/m^2, and three dummy variables (previous antihypertensive treatment, therapeutic adaptation, gender) were again used as covariates.

RESULTS

Population descriptions. The per protocol and ITT analysis of the REASON project have been presented in detail elsewhere (9). Table 1 presents the global ITT population (n = 469) and the population of the ancillary study (n = 181), in which pulse wave analysis was performed.

For the global ITT population (n = 469), the baseline values of blood pressure and the clinical characteristics did not differ between the two drug regimens: Per/Ind and atenolol (Table 1). Figure 1 shows that, whereas brachial DBP decreased with time significantly ($p < 0.001$) and similarly in both treatment groups, brachial SBP decreased more with Per/Ind than with atenolol (9). The difference between the two groups became significant ($p < 0.011$) only at the end of the follow-up (M12).

For the population with pulse wave analysis (n = 181), the baseline characteristics did not differ from those of the global ITT population, whatever the drug regimen may be (Table 1). Because we verified that, under drug treatment, the SBP changes and those of the other hemodynamic variables did not differ between the two populations, whether without (n = 469) or with (n = 181) pulse wave analysis, only the changes of the latter population are now presented in this report.

Study of mean values under drug treatment. Table 2 compares at M0, M6, and M12 the mean values of blood pressure measurements and other hemodynamic variables under Per/Ind and under atenolol. Whereas no significant difference was observed at M0 between Per/Ind and atenolol, significant differences were observed at M12 regarding brachial, carotid, and aortic SBP as well as SBP amplification.

Regarding brachial, carotid, and aortic SBP, the mean values (± SE) at M12 were significantly lower under Per/Ind than under atenolol. In addition, the SBP amplification, that is, the difference between brachial and carotid SBP (adjusted means ± SE) at M0 was 9.40 ± 1.54 for Per/Ind and 9.64 ± 1.50 mm Hg for atenolol (p = NS). At M12, this difference was, respectively, 8.28 ± 1.53 and 0.29 ± 1.61 ($p = 0.0006$), indicating that, under Per/Ind, SBP amplification was maintained, whereas it was reduced under atenolol.

Brachial, carotid, and aortic DBP and MBP did not differ between the two drug regimens, whether at M0, M6, or M12. Heart rate was significantly reduced ($p < 0.0001$), and LVET increased under atenolol and not under Per/Ind. At M12, AIc ($p = 0.0527$) and AIa ($p = 0.0057$) differed between the two drug regimens. These differences disappeared after adjustment for heart rate or LVET variation.

At M0, M6, and M12, PWV did not differ between the two drug regimens. The same findings were observed for MBP, cardiac and stroke index, total peripheral resistance, and mainly the stroke index on LVET ratio (data not shown).

Factors influencing the brachial and central SBP reduction (%) during the follow-up. In the population with pulse wave analysis (n = 181), the percent reduction of

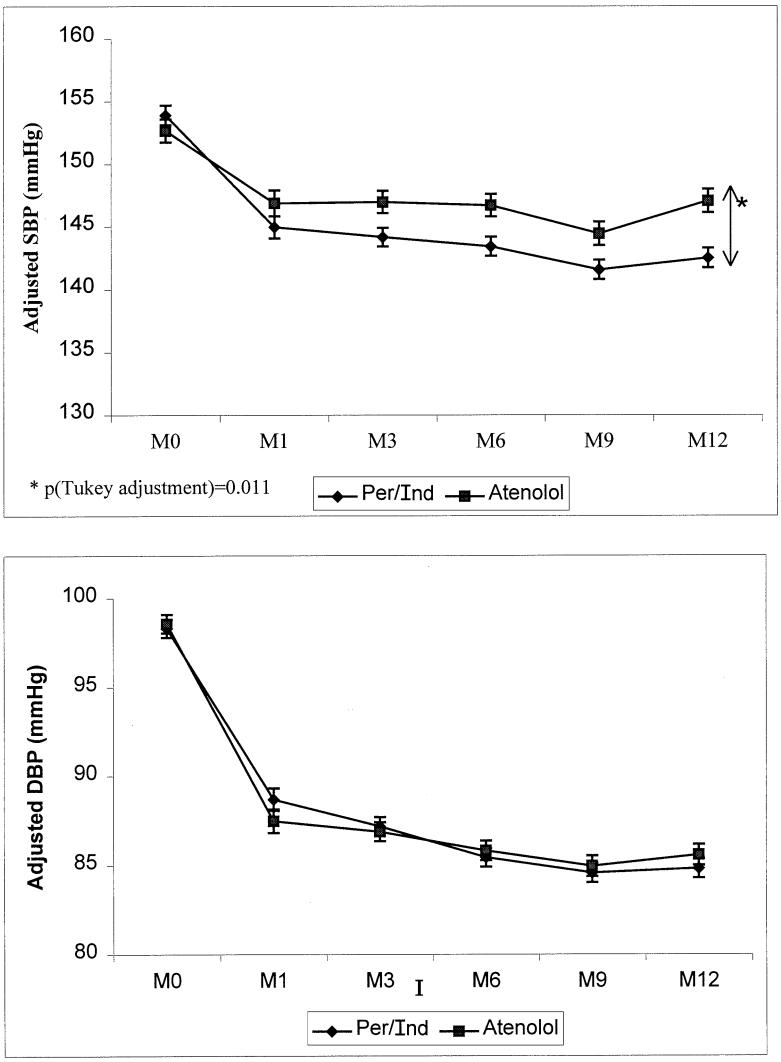

Figure 1. Overall intention-to-treat population: adjusted values (± SD) in brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP), measured each month (M) in perindopril/indapamide (Per/Ind) and atenolol groups. There was no difference between groups for DBP but only for SBP and exclusively at M12.

blood pressure and other hemodynamic variables is studied from M0 to M6, M6 to M12, and, finally, M0 to M12. Table 3 indicates the degree of significance of the time and group effects of the different variables. After six months of treatment, carotid SBP tended to continue to decrease with Per/Ind ($p = 0.06$), but this decrease was significantly attenuated ($p < 0.01$) with atenolol. These findings largely agree with those observed in Table 2.

Figure 2 indicates the mean values of the percent changes of SBP under each of the two drug regimens. Both with brachial and carotid measurements, the SBP reduction was significantly more pronounced with Per/Ind than with atenolol. The difference between the two drug regimens was even more significant for central than for brachial measurements.

Table 4 indicates the hemodynamic factors influencing the brachial and carotid (or aortic) SBP (%) reduction during the different periods of the study: M0 to M6, M6 to M12, and M0 to M12. The table indicates, first, the contribution of MBP (in terms of partial variance) and, second, the possible contribution of the other hemodynamic and clinical variables (for this, see the statistical analysis). When the brachial blood pressure measurements alone are considered (Table 4, upper), whether with Per/Ind or atenolol, MBP change (%) was the principal (and even the unique) factor influencing the SBP change (%). The MBP represented 65% to 86% of partial variance. When the carotid measurements were considered (Table 4, lower), the MBP changes (%) did not contribute or slightly contributed to total variance: 14% for atenolol from M0 to M12, and 12% for Per/Ind from M6 to M12. With Per/Ind, the PWV changes (%) played a significant role in the carotid SBP (%) reduction from M0 to M6 and M0 to M12, whereas AIc played an additional role only between M0 and M6.

Finally, for the mechanism(s) of SBP reduction (%) under atenolol, the systemic MBP reduction had a major role for

Table 2. Population With Central Measurements (n = 181): Main Cardiovascular Parameters: Adjusted Absolute Means ± Standard Error of Means Are Presented at M0, M6, M12

	Time	Per/Ind	Atenolol	p*
Brachial SBP (mm Hg)	M0	165.65 ± 1.40	162.18 ± 1.36	0.0786
	M6	**142.39 ± 1.39**	**147.32 ± 1.39**	**0.0144**
	M12	**137.80 ± 1.34**	**142.88 ± 1.41**	**0.0119**
Carotid SBP (mm Hg)	M0	154.46 ± 1.95	152.37 ± 1.90	0.4431
	M6	**133.34 ± 1.62**	**141.23 ± 1.64**	**0.0010**
	M12	**129.50 ± 2.16**	**144.99 ± 2.20**	**<0.0001**
Brachial-carotid SBP (mm Hg) amplification	M0	9.40 ± 1.54	9.64 ± 1.50	0.9125
	M6	**6.37 ± 1.50**	**2.43 ± 1.54**	**0.0709**
	M12	**8.28 ± 1.53**	**0.29 ± 1.61**	**0.0006**
Aortic SBP (mm Hg)	M0	155.63 ± 1.83	151.23 ± 1.80	0.0891
	M6	**135.22 ± 1.78**	**143.40 ± 1.84**	**0.0020**
	M12	**128.32 ± 1.97**	**140.58 ± 2.07**	**<0.0001**
Brachial DBP (mm Hg) (or carotid or aortic)	M0	97.09 ± 0.77	96.33 ± 0.75	0.4822
	M6	85.10 ± 0.79	85.21 ± 0.79	0.9202
	M12	83.93 ± 0.74	83.36 ± 0.78	0.6005
Brachial MBP (mm Hg) (or carotid or aortic)	M0	119.94 ± 0.75	118.28 ± 0.73	0.1137
	M6	104.19 ± 0.87	105.92 ± 0.87	0.1659
	M12	101.83 ± 0.83	103.26 ± 0.87	0.2463
Heart rate (beats/min)	M0	70.12 ± 1.00	70.56 ± 0.97	0.7564
	M6	**69.79 ± 0.79**	**63.01 ± 0.79**	**<0.0001**
	M12	**70.10 ± 0.90**	**62.74 ± 0.95**	**<0.0001**
Carotid LVET (ms)	M0	333.65 ± 2.67	335.88 ± 2.65	0.5555
	M6	**332.05 ± 2.49**	**349.25 ± 2.60**	**<0.0001**
	M12	**329.29 ± 2.52**	**341.76 ± 2.76**	**0.0014**
Carotid augmentation index (%) (AIc)	M0	29.09 ± 2.24	28.77 ± 2.16	0.9175
	M6	25.97 ± 2.13	27.74 ± 2.14	0.5608
	M12	**24.39 ± 1.88**	**29.73 ± 1.93**	**0.0527**
Aortic augmentation index (%) (AIa)	M0	30.06 ± 0.98	30.30 ± 0.97	0.8616
	M6	**27.50 ± 0.91**	**30.97 ± 0.95**	**0.0101**
	M12	**26.28 ± 0.94**	**30.18 ± 1.00**	**0.0057**
PWV (m/s)	M0	12.91 ± 0.26	12.46 ± 0.25	0.2161
	M6	11.90 ± 0.21	12.02 ± 0.21	0.7008
	M12	11.77 ± 0.23	11.90 ± 0.24	0.6945

*p intergroup significant comparisons are presented in **bold** characters.
LVET = left ventricular ejection time; M0, M6, M12 = Month 0, Month 6, Month 12; other abbreviations as in Table 1.

both brachial and central measurements. Under Per/Ind, MBP did not influence markedly the carotid SBP reduction (%). Only PWV played a significant role from M0 to M12, whereas AIc (or AIa) played a role only between M0 and M6.

DISCUSSION

In the REASON study, we identified in the past (9) that, whereas the decrease in brachial and central DBP was similar in both treatment groups, the Per/Ind combination had a more marked effect than atenolol on brachial SBP and mostly on central SBP. In the present report, we observed three additional new results. First, under Per/Ind at M12, even when brachial SBP was below 140 mm Hg, central SBP was substantially lower, whereas with atenolol this physiological amplification was attenuated or even had disappeared. Second, the higher reduction of SBP under Per/Ind than under atenolol became significant only at the end of the one-year follow-up. Third, the mechanism(s) of SBP reduction differed substantially between atenolol and Per/Ind, implying in the latter the active role of muscular large arteries with resulting changes in arterial stiffness and wave reflections and, in the former, the passive consequences of MBP reduction (9–13).

It is well established that any blood pressure curve involves two different components: a steady component, MBP, influenced by cardiac output and vascular resistance, and a pulsatile component, pulse pressure (PP). Using this approach, whereas systemic MBP keeps closely the same level along the totality of the arterial tree, PP (and mostly SBP) is known to be significantly lower in central (carotid) than in peripheral (brachial) arteries, in relation to the well-established mechanism of wave reflections (10). In the present study, we showed that this difference between central and peripheral SBP was maintained under Per/Ind but not under atenolol. In addition, we showed that the specific contribution of MBP to the SBP reduction (%) was of major importance only when brachial, but not carotid or aortic, measurements were considered. Thus, when central measurements are analyzed, it is possible to evaluate, independently of MBP, the role of the specific factors influencing central SBP under Per/Ind or atenolol: pattern of

Table 3. Population With Central Measurements (n = 181): Main Cardiovascular Parameters: Adjusted % Means ± Standard Error of Means Are Presented at M0, M6, M12

	Time	Per/Ind	Atenolol	p*
Brachial SBP (mm Hg)	**M0–M6**	**−13.27 ± 0.85†§**	**−9.78 ± 0.85†§**	**0.0044**
	M6–M12	−0.70 ± 0.90	1.23 ± 0.94	0.1433
	M0–M12	**−15.05 ± 0.85†§**	**−10.95 ± 0.90†§**	**0.0013**
Carotid SBP (mm Hg)	**M0–M6**	**−12.15 ± 1.13†§**	**−6.53 ± 1.14†§**	**0.0007**
	M6–M12	**−2.60 ± 1.36‖**	**4.56 ± 1.46‡**	**0.0006**
	M0–M12	**−14.46 ± 1.52†§**	**−4.31 ± 1.55‡**	**<0.0001**
Aortic SBP (mm Hg)	**M0–M6**	**−12.01 ± 1.18†§**	**−6.04 ± 1.22†§**	**0.0007**
	M6–M12	**−2.20 ± 1.20**	**1.67 ± 1.30**	**0.0323**
	M0–M12	**−15.29 ± 1.34†§**	**−6.50 ± 1.40†§**	**<0.0001**
Brachial DBP (mm Hg) (or carotid or aortic)	M0–M6	−11.81 ± 0.85†§	−11.53 ± 0.85†§	0.8171
	M6–M12	0.60 ± 0.99	0.11 ± 1.04	0.7371
	M0–M12	−12.89 ± 0.81†§	−13.17 ± 0.85†§	0.8170
Brachial MBP (mm Hg) (or carotid or aortic)	M0–M6	−12.56 ± 0.74†§	−10.81 ± 0.74†§	0.0972
	M6–M12	−0.05 ± 0.84	0.53 ± 0.89	0.6426
	M0–M12	−13.97 ± 0.70†§	−12.29 ± 0.74†§	0.1059
Heart rate (beat/min)	**M0–M6**	**0.49 ± 1.35**	**−10.15 ± 1.35†§**	**<0.0001**
	M6–M12	0.69 ± 1.54	0.26 ± 1.62	0.8506
	M0–M12	**0.34 ± 1.41**	**−10.89 ± 1.48†§**	**<0.0001**
Carotid LVET (ms)	**M0–M6**	**−0.48 ± 0.84**	**4.40 ± 0.87†§**	**0.0001**
	M6–M12	−0.65 ± 0.81	−0.83 ± 0.92	0.8834
	M0–M12	**−1.22 ± 0.85**	**2.61 ± 0.93‡**	**0.0035**
Carotid augmentation index (%) (AIc)	M0–M6	−1.32 ± 2.13	0.45 ± 2.14	0.5608
	M6–M12	**−2.78 ± 1.91§**	**2.18 ± 2.03**	**0.0441**
	M0–M12	**−4.11 ± 1.88§**	**1.23 ± 1.93**	**0.0527**
Aortic augmentation index (%) (AIa)	**M0–M6**	**−2.13 ± 0.91§**	**1.34 ± 0.95**	**0.0101**
	M6–M12	**−1.33 ± 0.92**	**1.41 ± 1.02**	**0.0512**
	M0–M12	**−3.66 ± 0.94†**	**0.25 ± 1.00**	**0.0057**
PWV (m/s)	M0–M6	−6.05 ± 1.00†	−4.05 ± 1.64§	0.3924
	M6–M12	1.02 ± 1.59	0.21 ± 1.65	0.7261
	M0–M12	−6.47 ± 1.94‡	−4.35 ± 2.02§	0.4572

*p intergroup significant comparisons are presented in **bold** characters; †p (time effect) <0.001; ‡p (time effect) <0.01; §p (time effect) <0.05; ‖p = 0.06.
Abbreviations as per Tables 1 and 2.

ventricular ejection, change of aortic PWV and/or AIc (or AIa), and, finally, modifications in vascular reflectance (change in the site and/or intensity of wave reflections) (10).

Because, during the follow-up, we showed that changes in ventricular ejection and PWV did not differ between the two drug regimens, none of these factors alone could explain the selective SBP reduction under Per/Ind. Only heart rate and LVET should have to be taken into consideration for a possible contribution of cardiac factors to the central SBP reduction (%). The reduction of heart rate and the longer LVET produced by the beta-blocking agent atenolol may have delayed the peak of the forward wave, which induces an increase of AIc (or the AIa) and, therefore, modified more the AIc (or AIa) changes with atenolol than with Per/Ind (10). However, we and others (9,14,15) have previously shown that the differential role of this factor disappears after adjustment to LVET or heart rate and, thus, played a minor role in this study. Finally, the weight of evidence suggests that the central SBP reduction (%) cannot be influenced by a single hemodynamic parameter but rather by the modulation of the overall hemodynamic alterations, which varied substantially with time during the follow-up for each drug regimen (9,14,15). In this context, we showed that, under Per/Ind, PWV influenced SBP reduction from M0 to M12, whereas AIc (or AIa) influenced SBP reduction only from M0 to M6 (Table 4). In addition, the significant difference in SBP reduction between Per/Ind and atenolol was mostly observed at M12 (Fig. 1). Thus, the overall results suggest that, at the end of the follow-up, the Per/Ind-induced changes of arterial stiffness were associated with structural, rather than functional, alterations of the vessel walls, thereby altering the transit time from the peripheral reflection sites toward central arteries and changing the timing of incident and reflected waves.

In untreated hypertensive subjects, it is well established that the wall on lumen ratio of musculo-elastic proximal arteries, of muscular distal arteries, and of arterioles is significantly increased (16,17). After one year of treatment by ACEI with or without diuretics (16,17), the wall/lumen ratio of muscular distal arteries and of arterioles (but not of proximal musculo-elastic arteries) is significantly reduced (17,18), in conjunction with changes in endothelial function and smooth muscle tone (16,17). In parallel, and under the same durations of treatment, it has been shown that the pattern of wave reflections is significantly modified by ACEI, involving a reduction in reflection coefficients of distal muscular arteries and arterioles and a decrease in the amplitude of the backward pressure wave (14,19). All these

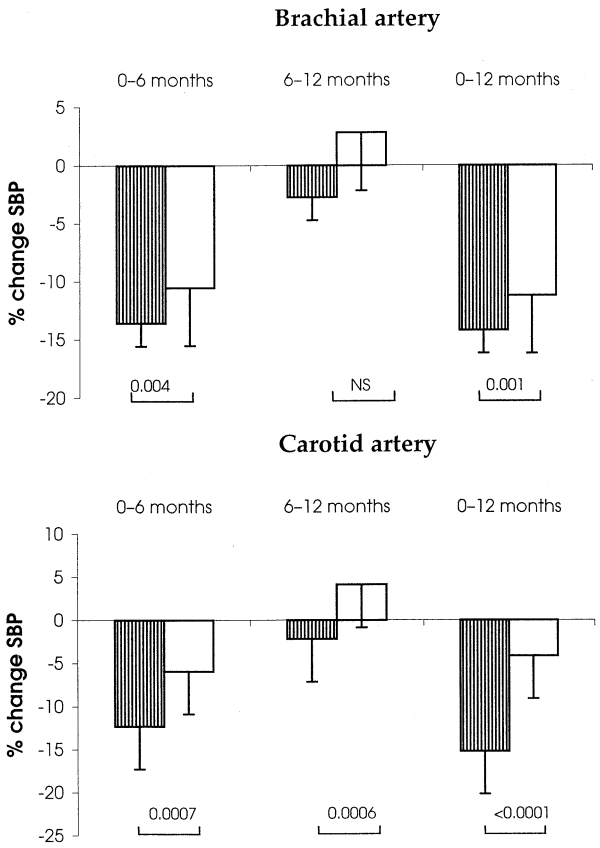

Figure 2. Population with central measurements: adjusted changes (± SD) in systolic blood pressure (SBP) (%). With perindopril/indapamide (Per/Ind) **(lined bars)**, SBP reduction (%) was more pronounced than for atenolol **(open bars)** at both the carotid and the brachial artery sites between 0 to 6 months and 0 to 12 months. Between 6 to 12 months, the SBP reduction continued under Per/Ind and tended to decline under atenolol. The p values are represented as Per/Ind versus atenolol.

changes are observed under ACEI (with or without diuretics) but not under atenolol (14,17,19). Thus, it seems relevant to propose that, under Per/Ind, the peripheral modifications of vascular structure and function have modified the reflectance of peripheral arterial and arteriolar vascular beds, thereby altering reflection coefficients and the amplitude of wave reflections and contributing to reduce central SBP. In this context, it is noteworthy that changes in sodium balance (8,9,14,17) and in the renin-angiotensin system (14,16,17) may substantially influence the geometry, the physical properties, the tone, and the effective number of smaller arteries and arterioles, particularly at their branching points (10).

As mentioned in the introduction, the results of several therapeutic trials in high CV risk populations (1–4) have suggested that ACEI or angiotensin II antagonists might reduce CV risk "beyond blood pressure control." However, other therapeutic trials, also performed in populations with high CV risk (20) have suggested that the pharmacologic treatment of hypertension improves more substantially CV mortality when two different hemodynamic alterations are independently achieved: 1) the MBP reduction should be associated with a PWV attenuation and a selective reduction of SBP and pulse pressure; and 2) an ACEI should be given among the various antihypertensive agents displayed during the follow-up. All these results taken together suggest that ACEI cannot be considered as acting on CV risk without a substantial effect on SBP and DBP. In order to demonstrate the point, the principal condition is that central blood pressure measurements, and not only brachial blood pressure measurements, should be measured. This proposition agrees with the recent evidence that prediction of CV risk is

Table 4. Factors Modulating Brachial and Carotid Adjusted-SBP Changes (%) Under Drug Treatment: Stepwise Linear Regressions for Brachial (Upper Panel) and Central (Lower Panel) Measurements

			Brachial Artery SBP Measurements			
	Period	MBP	1° Var	CR (SE)	R^2	p
Per/Ind	M0–M6	78%	PWV	0.07 (0.03)	2%	0.0204
Atenolol		73%	—	—	—	—
Per/Ind	M6–M12	77%	—	—	—	—
Atenolol		80%	—	—	—	—
Per/Ind	M0–M12	86%	—	—	—	—
Atenolol		65%	—	—	—	—

			Carotid Artery SBP Measurements							
	Period	MBP	1° Var	CR (SE)	R^2	p	2° Var	CR (SE)	R^2	p
Per/Ind	M0–M6	No	PWV	0.24 (0.08)	14%	0.003	AIc	0.14 (0.05)	8%	0.0158
Atenolol		No	Trt Adapt	6.42 (2.389)	13%	0.008	PAT	6.56 (2.69)	9%	0.0182
Per/Ind	M6–M12	12%								
Atenolol		No								
Per/Ind	M0–M12	No	PWV	0.21 (0.08)	11%	0.014				
Atenolol		14%								

Only the significant variables of the regression are presented in the table. (Y axis = SBP [brachial or carotid] change; X axis = [LVET, AIc, PWV and MBP changes]).

AIc = augmentation index (carotid); CR (SE) = regression coefficient and standard error; MBP (%) = partial variance of mean blood pressure explained if a significant link with SBP ($p < 0.05$) is observed; No = no significant link with SBP; P = significance of link with SBP; R^2 = % partial variance explained; 1° Var = first variable in the final equation; 2° Var = second variable in the final equation; other abbreviations as in Tables 1 and 2.

more adequately evaluated from central rather than from brachial blood pressure measurements (21).

In conclusion, the present investigation has shown that, in subjects with essential hypertension, the Per/Ind combination reduces SBP more than the standard comparator atenolol for the same decrease of DBP. This highly significant differential effect, which is not obtained with ACEI alone (14), is more pronounced in central than in peripheral arteries. The decrease in central SBP reflects a significant improvement of large artery function and a changing pattern in both peripheral reflection coefficients and structural arteriolar network, two modifications commonly observed under ACEI treatment within the distal compartment of the hypertensive arterial tree. Finally, the selective SBP reduction under Per/Ind requires the simultaneous alterations of both macrocirculation and microcirculation.

Acknowledgment

The authors would like to thank Mrs. Rudnicki for statistical evaluations.

Reprint requests and correspondence: Dr. Michel E. Safar, Centre de Diagnostic, Hôtel-Dieu, 1 Place du Paris Notre Dame, Paris, 75004. E-mail: michel.safar@brs.ap-hop-paris.fr.

REFERENCES

1. Yusuf S, Sleight P, Pogue J, Davies R, Dagenais G. Effects of angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: the Heart Outcome Prevention Evaluation Study Investigators. N Engl J Med 2000;342:145–53.
2. Lewis EJ, Hunsicker LG, Clarke WR, et al., and Collaborative Study Group. Renoprospective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–60.
3. Brenner BM, Cooper ME, De Zeeuw D, et al., and RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–9.
4. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention End point reduction in hypertension study (LIFE): a randomized trial against atenolol. Lancet 2002;359:995–1003.
5. O'Rourke MF, Nichols WW. Effect of ramipril on cardiovascular events in high-risk patients. N Engl J Med 2000;343:64–6.
6. Sagie A, Larson MG, Levy D. The natural history of borderline isolated systolic hypertension. N Engl J Med 1993;329:1912–7.
7. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997;157:2413–46.
8. PROGRESS Collaborative Group. Randomized trial of a perindopril-based blood pressure-lowering regimen among 6,105 individuals with previous stroke of transient ischemic attack. Lancet 2001;358:1033–41.
9. Asmar RG, London GM, O'Rourke ME, Safar ME, and for the REASON Project Coordinators and Investigators. Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patients: a comparison with atenolol. Hypertension 2001;38:922–6.
10. Nichols WW, O'Rourke M. McDonald's Blood Flow in Arteries. Theoretical, Experimental and Clinical Principles, 4th edition. London, Sydney, Auckland: Arnold E, 1998:54–401.
11. Nichols WW, Singh BM. Augmentation index as a measure of peripheral vascular disease state. Curr Opin Cardiol 2002;17:543–51.
12. Pannier BM, Guerin AP, Marchais SJ, London GM. Different aortic reflection wave responses following long-term angiotensin-converting enzyme inhibition and beta-blocker in essential hypertension. Clin Exp Pharmacol Physiol 2001;28:1074–7.
13. Nichols WW, Edwards DG. Arterial elastance and wave reflection augmentation of systolic blood pressure: deleterious effects and implications for therapy. J Cardiovasc Pharmacol Ther 2001;6:5–21.
14. Chen CH, Ting CT, Lin SJ, et al. Different effects of fosinopril and atenolol on wave reflections in hypertensive. Hypertension 1995;25:1034–41.
15. O'Rourke MF. Effects on ACE inhibitor therapy on derived central arterial waveforms in hypertension (letter). Am J Hypertens 2002;15:476.
16. Safar M, Van Bortel L, Struijker-Boudier H. Resistance and conduit arteries following converting enzyme inhibition in hypertension. J Vasc Res 1997;81:34–67.
17. Intengan HD, Thibault G, Li JS, Schiffrin EL. Resistance artery mechanics, structure, and extracellular components in spontaneously hypertensive rats: effects of angiotensin receptor antagonism and converting enzyme inhibition. Circulation 1999;100:2267–75.
18. Girerd X, Giannattasio C, Moulin C, Safar M, Mancia G, Laurent S. Regression of radial artery wall hypertrophy and improvement of carotid artery compliance after long term antihypertensive treatment in elderly patients. J Am Coll Cardiol 1998;31:1064–73.
19. Ting CT, Chen C-H, Chang M-S, Yin FCP. Short- and long-term effects of antihypertensive drugs on arterial reflections compliance and impedance. Hypertension 1995;26:524–30.
20. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation 2001;103:987–92.
21. Safar ME, Blacher J, Pannier B, et al. Central pulse pressure and mortality in end-stage renal disease. Hypertension 2002;39:735–8.