Selective reduction of cardiac mass and central blood pressure on low-dose combination perindopril/indapamide in hypertensive subjects

Nicola de Luca[a], Roland G. Asmar[b], Gérard M. London[c], Michael F. O'Rourke[d] and Michel E. Safar[e], on behalf of the REASON Project investigators*

Objective In hypertension, blockade of the renin–angiotensin system reduces left ventricular mass (LVM) independently of brachial systolic (S), diastolic (D), and mean (M) blood pressure (BP). From central to peripheral arteries, MBP and DBP are practically unchanged, whereas SBP and pulse pressure (PP) increase significantly. The objective was to determine whether changes in LVM under drug treatment was preferentially associated with changes in central or brachial SBP and PP.

Design A substudy of 146 subjects was selected from 469 hypertensive patients submitted to a double-blind randomized trial comparing the combination of perindopril (2 mg; Per) and indapamide (0.625 mg; Ind) with atenolol (50 mg, one tablet per day).

Main outcome measures Before and after 1 year of treatment: LVM (echocardiography) in 146 subjects and, in 52 of them, central (carotid) BP and timing of wave reflections (tonometry).

Results LVM changes were significantly associated with antihypertensive treatment, with lower LVM with Per/Ind than with atenolol. Changes in SBP and PP, but not in MBP and DBP, were more significantly associated with Per/Ind than with atenolol, with more pronounced effects using central than brachial measurements, and a longer delay in central return of wave reflections under Per/Ind. In the sampling of 52 patients with tonometry, the change in LVM between the two drug regimens was significantly linked to central, but not brachial, PP change.

Conclusions This observational study shows a lower LVM under Per/Ind than under atenolol. The greater change in LVM on Per/Ind was linked to central and not brachial blood pressure. *J Hypertens* 22:1623–1630 © 2004 Lippincott Williams & Wilkins.

Introduction

The time course of the changes in systolic and diastolic blood pressure (SBP, DBP) in response to antihypertensive drug therapy is a key to understanding the reduction in left ventricular mass (LVM). Therapy often provides adequate control of DBP (< 90 mmHg), but is much less successful in controlling SBP (< 140 mmHg) and pulse pressure (PP = SBP – DBP) [1]. This distinction is important in that the major mechanical determinant of cardiac hypertrophy is central (aortic) end-systolic stress. The physiological behaviour of SBP and PP in this regard is highly complex. Whereas mean blood pressure (MBP) and DBP remain practically constant along the totality of the arterial tree, SBP and PP are substantially lower in central (carotid, thoracic aorta) arteries than in peripheral (brachial) arteries. This phenomenon, known as amplification, relates to the forward movement of the pressure wave from larger to smaller arteries and the resulting change in the amplitude and timing of reflected waves returning toward the heart [2]. On this well-established basis, it has been suggested that antihypertensive drugs reduce central SBP and PP, hence LVM, without necessarily effecting major changes in brachial SBP and PP. This haemodynamic scenario has already been observed with nitrate vasodilators [2,3]. Other central haemodynamic parameters also require consideration, such as large artery stiffness and wave reflections, which can selectively influence central SBP and PP, and simultaneously contribute to the reduction of LVM.

*For details, see Appendix.

In controlled trials of hypertensive populations, the very-low-dose combination of perindopril (2 mg) and indapamide (0.625 mg) (Per/Ind) induced significantly greater decreases in SBP and PP than the beta-blocker atenolol, while effecting the same reductions in DBP and MBP. This finding, which predominates much more in the central than in the brachial artery, was confirmed by both intention-to-treat (ITT) and per-protocol statistical analysis [4,5]. Furthermore, while the SBP reduction under atenolol was the simple consequence of MBP reduction, the SBP reduction under Per/Ind involved the additive active role of muscular arteries, with resulting changes in arterial stiffness and wave reflections [6]. However, at least three questions remain outstanding:

1. Is LVM reduced by drug therapy, and if so, is a higher reduction obtained with Per/Ind than with atenolol?
2. Is the change in central SBP and PP on Per/Ind directly associated with the change in LVM?
3. What is the effect on LVM of the haemodynamic factors modulating central SBP and PP under treatment, namely arterial stiffness and wave reflections?

The objective of the present study was to determine whether LVM changes were related to Per/Ind versus atenolol changes, and if so, whether this differential impact was linked more to its effect on central rather than peripheral BP parameters.

Material and methods
Study design
The REASON (pREterax in regression of Arterial Stiffness in a contrOlled double-bliNd) study is a multicentre randomized investigation in two parallel groups, the main results of which have already been published, including side-effects and patient withdrawals [4,5]. It pre-included 562 patients aged 18 to 84 years with sustained mild to moderate essential hypertension, defined as a supine SBP ≥ 160 mmHg and < 210 mmHg, and/or a supine DBP ≥ 95 mmHg and < 110 mmHg [4,5]. Plasma potassium, creatinine, uric acid, glucose, total cholesterol, and hepatic enzymes were in the normal range at inclusion and did not alter substantially during follow-up. Written informed consent was obtained from each patient and the protocol was approved by the local ethics committees.

Following a wash-out placebo period, 469 patients were randomized to either Per/Ind ($n = 235$) or atenolol 50 mg ($n = 234$) p.o. for a 12-month double-blind active treatment period. The Per/Ind dosage, 2 mg/0.625 mg, was based on dose-finding studies using long-term double-blind titration [4,5]. During the trial, the dosage was adjusted to BP and doubled at 3 months to two

capsules once daily – Per/Ind, $n = 44$; atenolol, $n = 39$ – if SBP and/or DBP continued to exceed 160 mmHg and 90 mmHg, respectively. Seventy-eight percent of patients completed the 12-month treatment [4,5].

Haemodynamic studies were performed within 24 h of the previous drug intake, just before inclusion (M0), and at the end of follow-up (M12). Each patient was investigated in the morning in a controlled environment of $22 \pm 2°C$ (± 1 standard deviation). After a 10-min rest in the supine position, brachial SBP and DBP were determined, together with heart rate, using a mercury sphygmomanometer. Echocardiographic LVM was determined at baseline in 214 patients, 96 of whom also underwent central BP measurement (carotid artery, thoracic aorta) using applanation tonometry (pulse wave analysis).

Echocardiography and applanation tonometry
LVM was determined by two-dimensionally directed M-mode echocardiography performed by a highly experienced sonographer. LV dimensions were evaluated at the end of diastole, as recommended by the American Society of Echocardiography. Centralized readings blinded to treatment, patient and visit were performed by two experienced physicians in five cycles and averaged; the method has been extensively validated [7–11]. The inter-reader correlation for LVM was $r = 0.96$ for two readers. Intra-reader correlation for LVM was $r = 0.93$ [mean difference, 7 g; standard deviation (SD), 10.1 g]. The long-term reproducibility of LVM measures in previous blinded studies [9–11] showed a correlation of $r = 0.98$ (mean difference, 12 g; SD, 11.2 g) between baseline LVM and LVM after 16 weeks of placebo treatment. LVM (g) was calculated using standard formulas and indexed to both body height$^{2.7}$ [12] (LVMI) and body surface area.

Pulse wave analysis treated brachial and radial artery SBP, DBP, and MBP as equivalent, given the practically negligible pressure wave amplification between the two sites [2,11,13]. After double-blind verification of baseline recording stability, wave shape and the abrupt systolic upstroke of the pressure wave (see below), adequate carotid and/or aortic pressure waves were obtained by applanation tonometry in association with a validated non-invasive aortic BP measurement device (Sphygmocor, Atcor Medical, Sydney, Australia) [14]. Calibration was obtained from the radial pressure wave, assuming that MBP (determined by integrating the digitized radial wave) was the same at different sites and that brachial, carotid and aortic DBP were approximately equal [2,11,13]. Carotid and aortic MBP was also obtained after digitizing the area of the central pressure wave in the corresponding heart period and set equal to radial MBP. Carotid and aortic pressure amplitudes were then computed from the DBP and the

position of MBP on the central pressure waves [2,11,13], and were averaged for a series of waves over a 10-s period. The repeatability coefficients for central and peripheral BP measures after intervals of 1 and 3 months have previously been shown to be 6.8 and 7.2 mmHg, which comply with well-established international recommendations [10].

The carotid and aortic augmentation indices (C-AI and A0-AI) were measured on the carotid and aortic BP curve [10,13,15] after identifying the merging point of the incident and reflected wave (inflection point) on the generated carotid or aortic pressure waveform. AI was defined as the peak SBP minus pressure at the inflection point divided by PP, and expressed as a percentage. Larger values of C-AI or A0-AI indicate increased wave reflection from the periphery and/or earlier return of the reflected wave as a result of increased pulse wave velocity or altered reflection coefficients, and vice versa [2]. As C-AI and A0-AI are influenced by heart rate [16], the statistical analysis also adjusted to this parameter. Because C-AI and A0-AI are strongly correlated ($r = 0.85$), only the C-AI changes are presented in this study.

Cardiac output and total peripheral resistance were also measured at M0 and M12 using standard echocardiographic techniques as described previously [4,5].

Patient's follow-up and classification

Pre-trial training sessions were held to define and compare the quality of cardiovascular determinations and recordings [17]. Each investigator received a certificate after blind evaluation by two experts. Baseline recordings were electronically forwarded to the coordination centre and immediately reviewed for validation by a quality control committee. On-line assistance was available to investigators during the trial. At the end of the procedure all measures, including BP, were performed jointly by two physicians blinded to treatment, clinical data and physical examination.

When the REASON study was initiated, non-invasive haemodynamic laboratories were well trained in echocardiography but less so in applanation tonometry, which was therefore performed in fewer centres. Thus, of the 214 patients undergoing baseline LVM measurement, only 96 underwent simultaneous tonometry. During follow-up, 46 patients with LVM data (including 22 with tonometry data) were withdrawn from the global therapeutic protocol for reasons independent of the haemodynamic measures. This proportion (22%) was the same as that of the total ITT population [5]. In addition, 22 patients with LVM data only and 22 other patients with LVM + tonometry data had invalid or missing haemodynamic data at M0 and/or M12. Finally, the present substudy was composed of 146 subjects with LVM measurements at M0 and M12. From them, 52 had simultaneous central BP measurements at M0 and M12.

The two objectives of this report were to determine, first, whether LVM changes were significantly related to treatment with Per/Ind or atenolol, and secondly, whether the changes in LVM were linked to brachial or central BP measures or both. To address these questions, only optimal data were used, i.e. data from patients not withdrawn from the global therapeutic protocol ($n = 469$) and having complete haemodynamic measures at both M0 and M12 ($n = 146$). Because baseline LVM data were available in 146 patients and tonometry data in 52 patients, we subdivided the patients into two populations (Table 1): those with LVM-only data at M0 and M12 ($n = 146$) corresponding to the first question of the study, and those with LVM + tonometry data at M0 and M12 ($n = 52$), corresponding to the second question of the study.

Table 1 Baseline (M0) parameters (mean ± SD) and dose adjustment during the study in the LVM-only and LVM + tonometry populations

	Population			
	LVM-only ($n = 146$)		LVM + tonometry ($n = 52$)	
	Per/Ind ($n = 77$)	Atenolol ($n = 69$)	Per/Ind ($n = 30$)	Atenolol ($n = 22$)
Gender (M/F) (%)	60:40	64:36	67:33	68:32
Previous anti-HT therapy (No:Yes) (%)	29:71	41:59	37:63	41:59
Dose adjustment (No:Yes) (%)	55:45	61:39	60:40	73:27
Age (years)	54.0 ± 11.1	52.8 ± 11.3	51.6 ± 12.5	52.3 ± 13.1
BMI (kg/m^2)	26.7 ± 2.9	26.8 ± 2.8	26.5 ± 3.2	26.8 ± 3.2
Brachial SBP (mmHg)	158.3 ± 14.5	158.3 ± 16.4	159.7 ± 13.7	154.9 ± 13.9
Brachial DBP (mmHg)	96.2 ± 9.8	97.3 ± 9.1	95.8 ± 7.9	96.2 ± 8.3
Brachial MBP (mmHg)	116.9 ± 9.2	117.6 ± 10.1	117.1 ± 6.8	115.8 ± 8.4
Brachial PP (mmHg)	62.2 ± 15.0	61.0 ± 13.8	63.9 ± 16.1	58.7 ± 13.3
Heart rate (b/min)	72.5 ± 10.9	72.5 ± 7.6	71.5 ± 10.2	71.8 ± 5.1

LVM, left ventricular mass; Per/Ind, perindopril and indapamide; M/F, male/female; anti-HT, antihypertensive; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure.

Statistical analysis

The statistical analysis was confined to all data from the randomized treatment group of completers. Because of subgroups not randomly assigned, all conclusions of the analysis must be considered retrospective, i.e. no significant association ($P \leq 0.05$) can be interpreted as causal but only as a hypothesis for future testing. SAS software, version 8.2 (Cary, North Carolina, USA), was used in a Windows environment. Quantitative variables were expressed as means and SD, and qualitative variables as percentages. Calculations comprised change (δ) in percent as the M12 value minus the M0 value, divided by the M0 value, and multiplied by 100.

Mean LVM on Per/Ind versus atenolol

In the LVM-only population (Table 2) the M0, M12 and δ values were tested using a general linear model (GLM) procedure in which means were compared using a single-factor F test (treatment group) adjusted for different covariates. Adjusted means were derived from this model. The GLM model was confirmed valid by residual versus predicted value correlation analysis.

LVM data at M0 were adjusted for age, body mass index (BMI), gender, and previous antihypertensive treatment, and at M12 for age, BMI, gender, previous antihypertensive treatment, dose adjustment, and M0 value; δ was adjusted for age, BMI, gender, previous antihypertensive treatment, and dose adjustment. When LVM was divided by body height$^{2.7}$ or body surface area, gender and BMI were removed from the list of covariates. The same adjustment rules were applied to the BP analyses, except that changes in MBP (%) were added to the PP model (Table 3).

Intergroup difference in mean LVM change (δ in %) versus changes in brachial or carotid BP (δ in %)

In a previous report [6], we showed that the mechanism(s) of SBP reduction under atenolol and Per/Ind differed substantially, implying mainly, in the former, MBP reduction and, in the latter, active muscular relaxation of conduit arteries with resulting changes in arterial stiffness and wave reflections. Such differences were based mainly on the comparison between central and brachial SBP and PP reduction. These findings imply that, for LVM, the study should be focused mainly on the mean difference in LVM changes (%) between atenolol and Per/Ind. The goal was to test whether the difference in LVM changes was statistically linked to central SBP and/or PP, or to brachial SBP and/or PP, or to both central and brachial measurements. Because the calculations involved both brachial and carotid BP measures, the analysis was performed in the population with LVM + tonometry data at M0 and M12 (Table 1).

To evaluate the effect of the changes (%) in brachial or carotid BP on the difference in the change (%) in LVM between the two therapeutic groups, we used a single-factor GLM model. The variable to study was the mean difference in LVM (g/body weight$^{2.7}$ expressed in %) between the two therapeutic regimens. Adjustments involved age, previous antihypertensive therapy (PAT) and therapeutic adaptation. The two other covariates of the equation were: first, BP changes (%) represented successively by brachial (= carotid) MBP and DBP (%) (data not shown), carotid SBP (%) (Model 1), brachial SBP (%) (Model 2), carotid PP (%) (Model 3), brachial PP (%) (Model 4); secondly, the therapeutic groups (Per/Ind versus atenolol). A P value < 0.05 was

Table 2   LVM and LVMI (adjusted means ± SE) in the LVM-only population ($n = 146$) at M0 and M12 (adjustments include age and previous antihypertensive therapy)

Parameter	Time, δ	Adjustments	Per/Ind ($n = 77$)	Atenolol ($n = 69$)	P
LVM (g)	M0	BMI, gender	241.72 ± 5.00	235.43 ± 5.28	0.3901
	M12	BMI, gender, M0 value, dose	224.47 ± 3.00	235.59 ± 3.17	0.0125*
	δ (%)	BMI, gender, dose	−5.27 ± 2.08	1.49 ± 2.20	0.0281*
LVMI (g/height$^{2.7}$)	M0		58.59 ± 1.41	57.28 ± 1.49	0.5259
	M12	Dose, M0 value	54.55 ± 0.78	57.44 ± 0.82	0.0121*
	δ (%)	Dose	−5.19 ± 2.10	1.41 ± 2.22	0.0330*
LVM (g/m^2)	M0		128.77 ± 2.84	126.04 ± 3.00	0.5113
	M12	Dose, M0 value	120.63 ± 1.65	125.52 ± 1.74	0.0444*
	δ (%)	Dose	−4.77 ± 2.04	0.93 ± 2.16	0.0587

BMI, body mass index; LVM, left ventricular mass; Per/Ind, perindopril and indapamide; δ, change between M0 (baseline) and M12 (end of follow-up) (%); LVMI, left ventricular mass index; *, significant.

Table 3 Haemodynamics (adjusted means ± SE) in LVM + tonometry population at M0 and M12 (adjustments include age, BMI at M0, gender and previous antihypertensive therapy)

Parameter	Time, δ	Adjustments	Per/Ind (n = 30)	Atenolol (n = 22)	P *
Carotid SBP (mmHg)	M0		152.9 ± 3.0	150.2 ± 3.5	0.5656
	M12	M0 value, dose	126.2 ± 2.7	135.2 ± 3.1	0.0355
	δ (%)	Dose	−16.1 ± 2.0	−10.6 ± 2.3	0.0825
Carotid PP (mmHg)	M0	MBP at M0	58.0 ± 2.7	51.0 ± 3.2	0.1018
	M12	M0 value, dose, MBP at M12	41.8 ± 2.0	50.8 ± 2.3	0.0062
	δ (%)	Dose, δ MBP (%)	−20.5 ± 4.4	−1.4 ± 5.2	0.0076
C-AI	M0		33.35 ± 3.18	32.78 ± 3.18	0.8996
	M12	M0 value, dose	26.72 ± 2.48	34.67 ± 2.88	0.0434
	δ (%)	Dose	−5.73 ± 2.45*	2.10 ± 2.84	0.0430

LVM, left ventricular mass; BMI, body mass index; Per/Ind, perindopril and indapamide; SBP, systolic blood pressure; PP, pulse pressure; C-AI, carotid augmentation index; M0, baseline; M12, end of follow-up; *, intergroup comparison using a general linear model procedure (variance–covariance analysis).

considered as significant, thus indicating that the %LVM difference [expressed as mean ± 95% confidence interval (CI)] was statistically linked, or not, with brachial SBP or brachial PP, or carotid SBP or carotid PP, or both (brachial and carotid) type of parameters.

Results
Change in LVM in the LVM-only substudy (Table 2)
Baseline LVM and LVMI did not differ between the Per/Ind and atenolol groups. At M12, however, LVM was significantly lower on Per/Ind. The intergroup difference was significant, whether expressed in g ($P = 0.0125$) or as LVMI ($P = 0.0121$). The changes (%) in LVMI between M0 to M12 differed significantly ($P = 0.0330$) between Per/Ind and atenolol. Similar results were observed with LVM expressed in g/m^2. Differences in LVM were due mainly to a difference in reduction of end-diastolic diameter ($P < 0.02$) and posterior wall thickness ($P < 0.03$) (data not shown).

Change in brachial and carotid BP in the LVM + tonometry sample
Earlier studies [4,6] showed that, despite similar and significant reductions in brachial or carotid DBP and MBP at M12 in both treatment groups, the reductions in brachial and, especially, carotid PP and SBP were significantly greater in the Per/Ind than in the atenolol group. The present study of the LVM + tonometry sample confirmed these results.

Regarding brachial BP measurements, baseline values (M0) are indicated in Table 1 and do not differ between the two therapeutic groups. At M12, brachial DBP was, for Per/Ind, 84.48 ± 1.11 and, for atenolol, 83.02 ± 1.37 mmHg (NS). However, in each therapeutic group, brachial SBP was 136.55 ± 1.98 (Per/Ind) and 141.23 ± 1.65 mmHg (atenolol), and brachial PP was 53.48 ± 1.57 (Per/Ind) and 58.05 ± 1.95 (atenolol) ($P < 0.05$).

Regarding carotid BP measurements, whereas DBP was identical in the carotid and the brachial arteries and did not differ between the Per/Ind and atenolol groups at M0, mean carotid SBP, PP and C-AI were significantly lower at M12 with Per/Ind than with atenolol, with a greater percentage change of Per/Ind versus atenolol (Table 3). Adjustment for heart rate somewhat attenuated the differences in C-AI (at M12, the P values before and after adjustment were respectively 0.0434 and 0.0522).

Cardiac output, total peripheral resistance and the changes (%) in these parameters between M0 and M12 did not differ between the treatment groups (data not shown).

Statistical link of brachial or carotid BP (% change) with the mean intergroup difference in LVMI (% change)
As shown in Table 4, when carotid PP (% change) was added to the other covariates, it was a significant factor ($P = 0.0197$) (Model 3) influencing the mean intergroup difference in LVMI (% change). In addition, the difference between the two therapeutic groups was statistically significant ($P = 0.0288$). The same statistical procedure was not significant when either DBP or MBP (data not shown) or brachial SBP or brachial PP or carotid SBP were used as covariate (Models 1, 2, 4).

Table 5 summarizes the overall results of this study. The adjusted mean difference in LVM (% change)

Table 4 Antihypertensive therapy (effect of Per/Ind versus atenolol): LVM change (%) versus BP change (%) using either central or brachial BP

Covariates	*P* values			
	Model 1 (carotid SBP)	Model 2 (brachial SBP)	Model 3 (carotid PP)	Model 4 (brachial PP)
Age (years)	0.9517	0.6021	0.9751	0.9761
PAT (0/1)	0.3000	0.4149	0.3222	0.4198
Therapeutic adaptation (0/1)	0.5166	0.4650	0.3008	0.3896
Blood pressure change (%)	0.0825	0.6021	**0.0197**	0.4665
Therapeutic groups (means comparison Per/Ind versus atenolol)	0.0747	0.1537	**0.0288**	0.1322

The general linear model (GLM) procedure used (see statistical evaluation) was:
LVM (Per/Ind) change (%) − LVM (atenolol) change (%) = age + PAT + Therapeutic adaptation + Blood pressure change (%) + Therapeutic group (Per/Ind versus atenolol).
LVM, left ventricular mass; Per/Ind, perindopril and indapamide; PAT, previous antihypertensive therapy. Blood pressure change (%) is represented by carotid systolic blood pressure (SBP) in model 1, brachial SBP in model 2, carotid pulse pressure (PP) in model 3 and brachial PP in model 4. In each model the *P* value of each tested parameter (age, PAT, therapeutic adaptation, blood pressure change) is represented. The last row tests the difference between the two therapeutic groups.

Table 5 Summary of results

Adjustment (Adj) with	Left ventricular mass change (%)		
	Adj mean (Per/Ind) (95% CI)	Adj mean (atenolol) (95% CI)	Adj mean (Per/Ind − atenolol) (95% CI for difference)
Carotid SBP (Model 1)	−6.6 (−10.2 to −3.0)	−1.4 (−5.7 to +2.8)	−5.17 (−10.88 to +0.53)
Brachial SBP (Model 2)	−6.2 (−9.9 to −2.5)	−2.0 (−6.4 to +2.4)	−4.19 (−10.00 to +1.62)
Carotid PP (Model 3)	−7.2 (−10.8 to −3.6)	−0.7 (−4.9 to +3.6)	**−6.50 (−12.31 to −0.71)**
Brachial PP (Model 4)	−6.3 (−10.0 to −2.6)	−1.8 (−6.2 to +2.6)	−4.53 % (−10.48 to +1.42)

Adjusted (Adj) means [95% confidence interval (CI)] (derived from the general linear model of Table 4) for: left ventricular mass (LVM) change (%) in the Per/Ind (perindopril and indapamide) group; LVM change (%) in the atenolol group; and LVM change (%) in the (Per/Ind − atenolol) groups. Only model 3 (carotid PP) reaches statistical significance. SBP, systolic blood pressure; PP, pulse pressure.

between Per/Ind and atenolol was statistically linked to central (carotid), and not brachial, PP measurements (% change). When carotid PP (Model 3) was used, the per cent difference in LVM was: −6.50% (−12.31 to −0.71%).

Discussion

The REASON project is a randomized controlled trial comparing the antihypertensive effect of two regimens, Per/Ind and atenolol, after treatment for 1 year. Although both regimens effected a similar reduction in brachial DBP and MBP, the reduction in SBP and PP was significantly greater with Per/Ind [4,5]. The difference in central rather than brachial BP was more significant still. The two new findings of this study are that LVM lowering was more significantly associated with Per/Ind than with atenolol, and that the intergroup difference in LVM under treatment was statistically linked to central, not brachial, PP.

Reports by others that angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II antagonists induce greater reductions in LVM than atenolol [18–20] have been confirmed by meta-analysis [21]. In those studies, as in the present report, the degree of brachial MBP and DBP reduction did not differ significantly between the two regimens. In addition, in the present study, the intergroup difference in LVM was unchanged whether brachial DBP or even brachial SBP and PP were used as covariates. This suggests that peripheral mechanical factors, such as brachial BP, have little effect on the intergroup difference in LVM. Because central, not brachial, BP is known to act physiologically on cardiac structure and function [2], this finding should be interpreted with caution. It has been reported in the past that central SBP and PP (but not DBP and MBP) are physiologically lower than peripheral (brachial) SBP and PP, and that this physiological difference is significantly modified by several factors such as age, heart rate and even drug treatment [3]. Thus, the working

hypothesis of the present study was that the change of cardiac hypertrophy on antihypertensive drug therapy might be statistically linked more to central than to brachial SBP and PP, SBP and PP being expressed in percentage change under treatment.

Any study corresponding to our working hypothesis involves the measurement of LVM and BP both before and after long-term treatment, in the present case at M0 and M12. The requirement for both LVM and tonometry data meant that relatively few of the REASON patients were statistically evaluable. However, the possible loss of statistical power was offset by the use of a double-blind evaluation of data, both for LVM and brachial and carotid BP. In addition, this was, to our knowledge, the first observational substudy to explore central BP under valid conditions before and after 1-year antihypertensive therapy.

Cardiac load is traditionally described as having resistive, capacitive and, to a lesser extent, inertial components [2]. In the previously published REASON study [5], as in the present report, the changes in MBP and total peripheral resistance were similar on Per/Ind and atenolol, suggesting that the resistive component of cardiac load had little impact on the difference in LVM. It seems likely that the capacitive, and possibly inertial, components played a greater role, since, in addition to MBP, the major factors influencing the difference in LVM on Per/Ind versus atenolol were the percentage changes in C-AI and carotid SBP and PP. These results clearly indicate not only that the differential change in LVM on drug treatment is largely uninfluenced by systemic MBP, but that it should be evaluated with respect mainly to central, not brachial, BP. In this regard, the major finding of the present investigation was that the intergroup difference in LVM (%) was significant using as covariate carotid PP (%), a major central artery mechanical factor predictive of cardiovascular risk [22–24]. Of course, this finding cannot establish a cause-to-effect relationship between LVM and PP changes, but indicates the presence of a statistical link between LVM changes and central, and not brachial, mechanical factors.

Central SBP and PP are haemodynamically influenced by three parameters: ventricular ejection, arterial stiffness, and the amplitude and timing of wave reflections. Since the REASON study has already reported no significant difference between Per/Ind and atenolol in the first two factors [4,5], our findings suggest that differences in wave reflections might be the major explanation for the lower central SBP and PP on Per/Ind. The lower C-AI on Per/Ind supports this hypothesis. Unlike beta-blockers, ACEIs delay the timing of wave reflections, so that the BP wave returns in the central arteries during end-systole or diastole, causing a

selective reduction in SBP and PP. This is never observed on atenolol and therefore helps to explain why the reduction in LVM should be greater on Per/Ind [2]. An alternative hypothesis could be that the reduction of heart rate due to atenolol might contribute to increase C-AI and enhance the differences in C-AI between the two drug regimens. This possibility may be suggested by the slight attenuation in the C-AI difference between the two drug regimens observed after adjustment to heart rate [4,5]. However, a major role of this mechanism does not seem likely since C-AI under atenolol is poorly modified (2%) between M0 and M12. Furthermore, we showed previously that, along the 1-year REASON trial, the role of wave reflections in the mechanism of SBP and PP reduction tended to decrease, while, on the other hand, the role of arterial stiffness tended to increase [6].

Traditional therapeutic studies of LVM regression have suggested that antihypertensive therapy, mainly with ACEIs or angiotensin II antagonists, reduces LVM independently of (or 'beyond') the brachial BP level [18–20]. The present findings strongly suggest that demonstration of LVM reduction 'beyond' the effects of BP requires the measurement not only of brachial but also central BP. It is noteworthy that central BP is a stronger predictor of cardiovascular risk than brachial BP in high-risk hypertensive populations [22–24]. However, the role of central mechanical factors on cardiac mass does not exclude some additional pressure-independent myocardial effect by renin–angiotensin system blockade, as suggested by many animal experiments in the past [2,8,18–20].

In conclusion, the present substudy in a group of patients with essential hypertension has shown that the very-low-dose combination of Per/Ind effects a significantly greater change in LVM than the standard comparator atenolol, despite inducing a similar change in MBP. The consistent differential effect is associated with an improvement in large artery function involving central wave reflections, which helps to bring about a selective change in central SBP and PP. However, the present finding remains purely observational. Long-term follow-up is required to demonstrate the predominant role of central BP measurements on the mechanism(s) of LVM reduction.

Acknowledgements

References

1   Black HR. The paradigm has shifted, to systolic blood pressure. *Hypertension* 1999; **34**:386–387.

2   Nichols WW, O'Rourke M. In: Nichols WW (editor): *McDonald's blood flow in arteries: theoretical, experimental and clinical principles*. London: Oxford University Press; 1998, pp. 54–113, 201–222, 284–292, 347–401.

3   O'Rourke MF, Nichols WW. Effect of ramipril on cardiovascular events in high-risk patients. *N Engl J Med* 2000; **343**:64–66.

4   Asmar RG, London GM, O'Rourke MF, Mallion JM, Romero R, Rahn KH, *et al*. Amelioration of arterial properties with a perindopril/indapamide very-low-dose combination. *J Hypertens* 2001; **19(suppl 4)**:S15–S20.

5   Asmar RG, London GM, O'Rourke ME, Safar ME, and 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**:922–926.

6   London GM, Asmar RG, O'Rourke MF, Safar ME, on behalf of the REASON Project Investigators. Mechanism(s) of selective systolic blood pressure reduction after a low-dose combination of perindopril/indapamide in hypertensive subjects: comparison with atenolol. *J Am Coll Cardiol* 2004; **43**:92–99.

7   Trimarco B, Ricciardelli B, De Luca N, De Simone A, Cuocolo A, Galva MD, *et al*. Participation of endogenous catecholamines in the regulation of left ventricular mass in progeny of hypertensive parents. *Circulation* 1985; **72**:38–46.

8   Trimarco B, De Luca N, Rosiello G, Ricciardelli B, Marchegiano R, Condorelli M, *et al*. Effects of long term antihypertensive treatment with tertatolol on diastolic function in hypertensive patients with and without left ventricular hypertrophy. *Am J Hypertens* 1989; **2**:278S–283S.

9   London GM, Marchais SJ, Guerin AP, Metivier F, Safar ME, Fabiani F, *et al*. Salt and water retention and calcium blockade in uremia. *Circulation* 1990; **82**:105–113.

10 London GM, Pannier B, Guerin AP, Marchais SJ, Safar ME, Cuche JL. Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease. Comparative effects of ACE inhibition and calcium channel blockade. *Circulation* 1994; **90**: 2786–2796.

11 London GM, Guerin AP, Marchais SJ, Pannier B, Safar ME, Day M, *et al*. Cardiac and arterial interactions in end-stage renal disease. *Kidney Int* 1996; **50**:600–608.

12 De Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitis O, *et al*. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 1992; **20**:1251–1260.

13 Topouchian J, Asmar R, Sayegh F, Rudnicki A, Benetos A, Bacri AM, *et al*. Changes in arterial structure and function under trandolapril–verapamil combination in hypertension. *Stroke* 1999; **30**:1056–1064.

14 Smulyan H, Siddiqui DS, Carlson RJ, London GM, Safar ME. Clinical utility of aortic pulses and pressures calculated from applanated radial-artery pulses. *Hypertension* 2003; **42**:150–155.

15 Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, *et al*. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J Hypertens* 1998; **16**:2079–2084.

16 Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol* 2000; **525**:263–270.

17 Asmar R, Topouchian J, Pannier B, Benetos A, Safar M. Pulse wave velocity as end-point in large-scale intervention trial. The Complior study. Scientific, Quality Control, Coordination and Investigation Committees of the Complior Study. *J Hypertens* 2001; **19**:813–818.

18 Lievre M, Gueret P, Gayet C, Roudaut R, Haugh MC, Delair S, *et al*. Ramipril-induced regression of left ventricular hypertrophy in treated hypertensive individuals. Hycar Study Group. *Hypertension* 1995; **25**:92–97.

19 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; **342**:145–153.

20 Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, Faire U, *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.

21 Jennings G, Wong J. Regression of left ventricular hypertrophy in hypertension: changing patterns with successive meta-analyses. *J Hypertens Suppl* 1998; **16**:S29–S34.

22 Nakayama Y, Tsumura K, Yamashita N, Yoshimaru K, Hayashi T. Pulsatility of ascending aortic pressure waveform is a powerful predictor of rest-enosis after percutaneous transluminal coronary angioplasty. *Circulation* 2000; **101**:470–472.

23 Nishijima T, Nakayama Y, Tsumura K, Yamashita N, Yoshimaru K, Ueda H, *et al*. Pulsatility of ascending aortic blood pressure waveform is associated with an increased risk of coronary heart disease. *Am J Hypertens* 2001; **14**:469–473.

24 Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM, *et al*. Central pulse pressure and mortality in end-stage renal disease. *Hypertension* 2002; **39**:735–738.

Appendix

REASON project chairman

M.E. Safar (Hôpital Broussais, Paris, France).

REASON project echocardiography co-ordinator

N. de Luca (Università degli Studi, Naples, Italy).

REASON project contributors

R.G. Asmar (L'Institut Cardiovasculaire, Paris, France); G.M. London (Hôpital Manhès, Fleury-Mérogis, France); M.F. O'Rourke (St Vincent's Hospital, Darlinghurst, Australia); J.M. Mallion (Hôpital Universitaire, Grenoble, France); R. Romero (Hospital Germans Trias y Pujol, Badalona, Spain); K.H. Rahn (University of Münster, Germany); B. Trimarco (Università degli Studi, Naples, Italy); D. Fitzgerald (Royal College of Surgeons in Ireland, Dublin, Ireland); T. Hedner (Sahlgrenska Hospital, Gothenburg, Sweden); D. Duprez (Universitair Ziekenhuis, Gent, Belgium); P.W. De-Leeuw (Academisch Ziekenhuis, Maastricht, The Netherlands); P. Sever (St. Mary's Hospital Medical School, London, UK); E. Battegay (Medizinische Universitäts Poliklinik, Basel, Switzerland); G. Hitzenberger (Institut fur Hypertoniker, Vienna, Austria); P. Polónia (Faculdade de Medicina, Porto, Portugal); A. Bénétos (Unité INSERM 337, Paris, France); C. Chastang (Hôpital Saint-Louis, Paris, France); J.P. Ollivier (Hôpital Val de Grâce, Paris, France).