Blood Pressure. 2006; 15: 268–274

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Effects of long-term lercanidipine or hydrochlorothiazide administration on hypertension-related vascular structural changes

GUIDO GRASSI[1,2,3], FOSCA QUARTI-TREVANO[1], FRANCESCO SCOPELLITI[1], GINO SERAVALLE[1,2,3], CESARE CUSPIDI[1] & GIUSEPPE MANCIA[1,2,3]

Clinica Medica, Dipartimento di Medicina Clinica, Prevenzione e Biotecnologie Sanitarie, Università Milano-Bicocca, Ospedale San Gerardo, Monza (Milan)[1]; Istituto Auxologico Italiano, Milan, Italy[2] and Centro Interuniversitario di Fisiologia Clinica e Ipertensione, Milan, Italy[3]

Abstract

Objectives. Vascular remodelling and hypertrophy represent early therapeutic targets of antihypertensive treatment. The present study was aimed at assessing the effects of 1-year administration of the highly vasoselective calcium-channel blocker lercanidipine (10 mg/day) or the diuretic compound hydrochlorothiazide (25 mg/day) on hypertension-related vascular alterations. The study was also aimed at assessing whether and to what extent: (i) pharmacological regression of vascular hypertrophy is related only to the blood pressure (BP) reduction ''per se'' or also to the specific ancillary properties of a given drug and (ii) treatment provides restoration of vascular function indicative of normal vascular structure. *Design and Methods*. In 26 untreated patients with mild-to-moderate essential hypertension sphygmomanometric and finger BP, heart rate, forearm and calf blood flow (venous occlusion plethysmography) and corresponding vascular resistance (forearm and calf vascular resistance: FVR and CVR) were assessed before and following 6 and 12 months of either lercanidipine or hydrochlorothiazide administration. Vascular resistance was also evaluated following a local ischaemic stimulus (FVR_{min} and CVR_{min}) in order to assess the effects of treatment on arteriolar structural alterations. *Results*. For superimposable BP reductions, lercanidipine caused FVR and CVR to decrease significantly more than hydrochlorothiazide. Similarly, the FVR_{min} and CVR_{min} reductions induced by lercanidipine were markedly and significantly greater than those caused by hydrochlorothiazide (-46.1% and -40.9% vs -22.5% and -19.9%, $p<0.01$ for both). FVR_{min} and CVR_{min}, however, remained higher than those found in 10 age-matched normotensive individuals. *Conclusions.* These data provide evidence that, compared to hydrochlorothiazide, lercanidipine favours a greater regression of the vascular structural changes associated with hypertension, probably through its ''ancillary'' properties. Lercanidipine, however, does not allow restoration of a ''normal'' vascular structure, thereby suggesting that vascular hypertrophy is only in part a reversible phenomenon.

Key Words: *Calcium-channel blockers, diuretics, hydrochlorothiazide, hypertension, lercanidipine, vascular hypertrophy*

Introduction

Several studies have shown that pharmacological reduction of elevated blood pressure (BP) values may often lead to a regression of left ventricular hypertrophy and that this effect depends not only on the improved haemodynamic state, i.e. on the BP reduction, but also on the specific ''ancillary'' properties of a given antihypertensive therapeutic intervention (1–3). Whether the same conclusion holds true also for the effects of antihypertensive treatment on vascular hypertrophy, i.e. one of the earlier and more common hypertension-related cardiovascular structural changes, is still controversial. This is because while in the forearm and in the small artery vascular district antihypertensive drug treatment has been frequently shown to reverse vascular hypertrophy (4–16), no conclusive evidence has been provided in the calf circulation for which conflicting reports with different drugs, or even with

Correspondence: Guido Grassi, Clinica Medica, Ospedale S. Gerardo, Via Pergolesi 33, 20052 Monza (Milano), Italy. Tel: +39 039 233 3357. Fax: +39 039 322 274. E-mail: guido.grassi@unimib.it

(Received 15 August 2006; accepted 17 August 2006)

ISSN 0803-7051 print/ISSN 1651-1999 online © 2006 Taylor & Francis
DOI: 10.1080/08037050600963669

the same drug, have been published so far (4–7,12). Furthermore, it is still uncertain whether and to what extent pharmacological regression of vascular hypertrophy depends on the BP reduction ''per se'' or also on the specific antihypertrophic properties of a given pharmacological intervention (17,18). Finally, almost no data are available as to whether drug-induced regression of hypertension-related vascular hypertrophy can be regarded as a ''true'' normalization of vascular morphology.

In the present study, we addressed the above-mentioned issues by examining the degree of arteriolar thickening in hypertensive patients before and after 1-year effective antihypertensive treatment based on either lercanidipine, i.e. a third-generation calcium-channel blocker with high vascular selectivity (19–21), or a thiazide diuretic. The study also included a group of normotensive individuals, which served as controls in order to assess whether the drug-induced vascular changes were capable of restoring a normal vascular structure.

Methods

Study population

The study population consisted of 26 outpatients of both genders aged from 31 to 56 years with a never-treated mild essential hypertension, characterized by (i) diastolic BP values between 95 and 105 mmHg at repeated sphygmomanometric measurements, (ii) no history and no physical or laboratory evidence of cardiovascular disease or major target organ damage, except for the presence in nine patients of a left ventricular mass index >125 g/m^2 at the echocardiographic examination and (iii) no major concomitant non-cardiovascular disease. A group of 10 age-matched healthy normotensive subjects of both genders served as controls. All patients were in sinus rhythm and none was a cigarette smoker or had a body mass index >27 kg/m^2. The protocol of the study (see below) was approved by the Ethics Committee of our institution. All subjects were informed of the nature and purpose of the investigation and freely agreed to participate.

Measurements

BP was measured by (i) a mercury sphygmomanometer, using the arm contralateral to the one from which blood flow was assessed and taking the first and fifth and Korotkoff sounds to identify systolic and diastolic values and (ii) a finger photoplethysmographic device (Finapres 2300, Ohmeda) capable of providing accurate and reproducible beat-to-beat systolic and diastolic values (22), again using the arm contralateral to the one used for plethysmographic measurements. Heart rate was measured by a tachograph triggered by a standard electrocardiographic lead. In the entire study's population, structural arterioral changes were estimated by the ''minimal vascular resistance'' method proposed by Folkow et al. (23), which provides accurate and reproducible values when repeated in the same subject over different experimental sessions (24). Briefly, blood flow was measured in the dominant forearm and calf by a venous occlusion plethysmograph (EC-4, Hokanson), following exclusion of circulation to the hand or foot by application of a suprasystolic pressure within a cuff encircling the wrist or the ankle, respectively. Measurements were obtained in baseline conditions and at the end of a 12-min local ischaemic stimulus induced by inflating an arm or a tight cuff to suprasystolic BP values and by asking the patients to contract the forearm or the leg muscle rhythmically and exhaustively in the last 2 min of the manoeuvre. The peak blood flow occurring during the hyperaemic period at the end of the ischaemic stimulus was taken as the maximal forearm vasodilation. With the exception of sphygmomanometric BP, all other variables were displayed on a thermic paper of an ink polygraph (Gould 3800, Gould Instrument). The ratio between finger mean arterial pressure (diastolic pressure plus one-third of pulse pressure) and baseline blood flow was used to calculate baseline forearm and calf vascular resistance (FVR and CVR, respectively). The ratio between finger mean arterial pressure and peak blood flow allowed assessment of ''minimal'' vascular resistance values in the two districts (FVR_{min} and CVR_{min}, respectively). Animal data have shown that these values are related to arteriolar wall-to-lumen ratio, validating their use as an index of arterioral structural changes in untreated and treated hypertensive patients (23,25–26). Blood flow was always measured by a single operator, the within-operator coefficient of variation of forearm and calf blood flow measurements amounting to 4.2% and 5.1%, respectively.

Protocol and data analysis

After recruitment, hypertensive patients entered a 1-week placebo run-in period. The study proper consisted of three identical experimental sessions within a randomized single-blind design. In the first session, 13 patients were taken to the laboratory in the morning after a light breakfast. They were placed supine and fitted with the various measuring devices. After 30 min, baseline BP, heart rate, forearm blood

flow (average of six consecutive rates) and vascular resistance (mean arterial pressure divided by forearm blood flow) were measured during a 20-min period. Forearm ischaemia and exercise was then produced and followed, at the release of the ischaemic stimulus, by BP, heart rate forearm blood flow and vascular resistance measurements over a 2 min. After a further 20-min time interval, all the above-mentioned procedures were repeated replacing forearm with calf blood flow and calf vascular resistance measurements. In the remaining 13 hypertensive patients, the protocol was the same except that calf haemodynamics was studied before the forearm one. The patients were then discharged from the laboratory and randomized in an unblinded fashion to take an oral dose of lercanidipine (10 mg/day, 13 patients) or hydrochlorothiazide (25 mg/day, 13 patients) in the morning and to continue the morning assumption of the drug for 12 months. During the 12-month period, patients were seen at a 4-week interval in the outpatient clinic of our hospital and underwent at the end of the 6th and 12th the second and third experimental session (see above). During this period, no patient reported assumption of cardiovascular drugs other than the ones evaluated in the present study. No lifestyle modifications were advised. Adherence to treatment was verified by pills counting. During the study period, no other drug acting on BP or, more in general on the cardiovascular system, was allowed. In the 10 control normotensive subjects, only one experimental session was performed, following a sequence of interventions identical to the one described for the hypertensive group of patients (first experimental session). Data were calculated by a single investigator unaware of the experimental design. Values from individual subjects were averaged for either groups and expressed as means $\pm$ SEM. The statistical significance of the difference in the means was assessed by two-way analysis of variance. The two-tailed *t*-test for paired or unpaired observations was used to locate the difference either between the no-treatment and treatment condition or between the treatment condition and the control normotensive state. Spearman analysis was used to determine the correlation between different variables. A value of $p < 0.05$ was considered statistically significant.

Results

Baseline values

Baseline characteristics of normotensive and hypertensive subjects are shown in Table I. The two groups were similar for age and body mass index. Hypertensive patients displayed significantly higher sphygmomanometric and finger systolic and diastolic BP, and left ventricular mass index. This was the case also for forearm and calf vascular resistance both when assessed in baseline conditions and following the 12-min hyperaemic stimulus (FVR_{min} and CVR_{min}). Heart rate values were not significantly different between the two groups.

Table I. Baseline characteristics of normotensive and hypertensive subjects.

Variable	Normotensives (n=10)	Hypertensives (n=26)
Sex (male/female)	7/3	18/8
Age (years)	46.0 $\pm$ 1.0	48.3 $\pm$ 0.7
BMI (kg/m^2)	24.2 $\pm$ 0.7	25.1 $\pm$ 0.9
Clinic BP (S/D, mmHg)	131.7 $\pm$ 2.1/ 83.3 $\pm$ 2.5	154.4 $\pm$ 3.1**/ 99.0 $\pm$ 2.3**
Finger BP (S/D, mmHg)	128.1 $\pm$ 1.9/ 80.8 $\pm$ 2.2	151.7 $\pm$ 2.6**/ 97.1 $\pm$ 2.4**
Heart rate (b/min)	71.4 $\pm$ 2.1	73.7 $\pm$ 2.2
LVMI (g/m^2)	97.4 $\pm$ 3.4	126.8 $\pm$ 4.1**
FVR (units)	20.5 $\pm$ 1.9	36.2 $\pm$ 2.5**
CVR (units)	31.6 $\pm$ 2.0	44.8 $\pm$ 2.9**
FVR_{min} (units)	1.25 $\pm$ 0.1	3.44 $\pm$ 0.1**
CVR_{min} (units)	1.94 $\pm$ 0.1	4.56 $\pm$ 0.2**

Data are shown as mean $\pm$ SEM. BMI, body mass index; BP, blood pressure, S, systolic, D, diastolic; LVMI, left ventricular mass index; FVR, forearm vascular resistance; CVR, calf vascular resistance; FVR_{min}, minimal forearm vascular resistance; CVR_{min}, minimal calf vascular resistance. Asterisks (**$p < 0.01$) refer to the statistical significance between groups.

Effects of treatment

As shown in Figure 1, 6-month lercanidipine treatment significantly decreased both sphygmomanometric and finger systo-diastolic BP. This was the case also for FVR and CVR, while heart rate remained almost unaffected by the long-term administration of the calcium-channel blocker. The results obtained at the end of the 1-year treatment were almost superimposable to those seen after 6 months. Figure 1 also shows the effects of diuretic administration on the above-mentioned variables. Following both 6 and 12 months of treatment, hydrochlorothiazide caused a significant reduction in sphygmomanometric and finger systo-diastolic BP, whose magnitude was almost superimposable to that seen in the lercanidipine-treated group. In contrast to lercanidipine, however, hydrochlorothiazide caused only modest reductions in FVR and CVR, both at the 6th and 12th month of treatment. The effects of the two drug treatments on minimal vascular resistance values are shown in Figure 2.

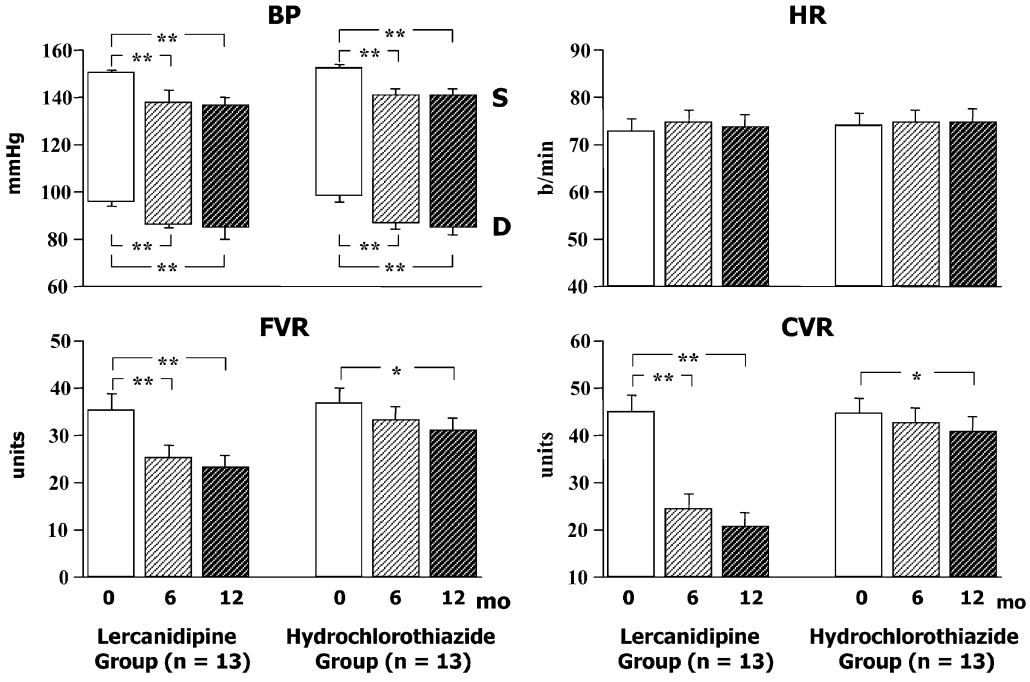

Figure 1. Effects of 6- and 12-month lercanidipine or hydrochlorothiazide administration on systolic (S) and diastolic (D) blood pressure (BP), heart rate (HR), forearm and calf vascular resistance (FVR and CVR) in hypertensive patients. 0: values recorded in the no-drug placebo state, 6 and 12 mo: values recorded following 6 and 12 months of active treatment. Asterisks (*$p<0.05$, **$p<0.01$) refer to the statistical significance of the values recorded before and during lercanidipine or hydrochlorothiazide treatment. Data are shown as means ± SEM.

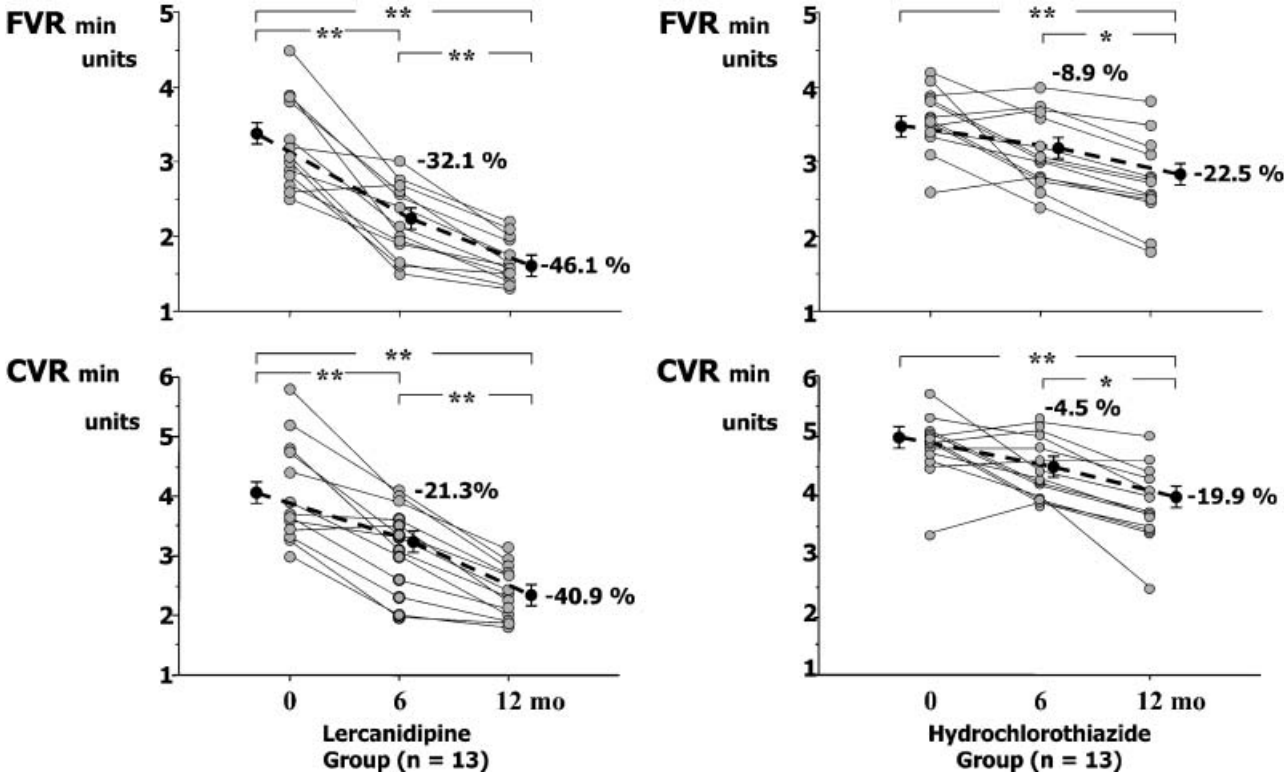

Figure 2. Effects of lercanidipine or hydrochlorothiazide administration on minimal forearm and calf vascular resistance (FVR_{min} and CVR_{min}, respectively) in patients of Figure 1. Individual (open symbols, continuous lines) and mean ± SEM (closed symbols, dashed lines) values are shown. Other symbols as in Figure 1.

Following a 6-month lercanidipine administration, both FVR_{min} and CVR_{min} were significantly reduced, a further reduction being detectable at the end of the 12th month of treatment. In contrast, in the hydrochlorothiazide-treated group, 6-month treatment did not significantly affect both FVR_{min} and CVR_{min}, which showed a modest but significant reduction only at the end of the year of treatment. The FVR_{min} and CVR_{min} values recorded at the 1-year treatment, although lowered by lercanidipine administration, were still higher than those found in normotensive healthy subjects (1.57 ± 0.1 vs 1.25 ± 0.1 units and 2.68 ± 0.1 vs 1.94 ± 0.1 units respectively, $p < 0.05$ for both). The reduction in vascular resistance induced by lercanidipine treatment was significantly related to the mean arterial pressure fall induced by treatment in the forearm but not in the calf circulation (Figure 3). In contrast, no relationship was found in the hydrochlorothiazide-treated group between the BP and the vascular resistance changes induced by diuretic treatment ($r = 0.28$ and $r = 0.17$ respectively, p=NS).

Discussion

The present study provides three new sets of data. First, it shows that for similar BP lowering effects, lercanidipine is superior to hydrochlorothiazide in inducing a reduction in FVR_{min} and thus in favouring a regression of vascular hypertrophy. It also shows that the favourable vasoprotective effects of this calcium-channel blocker are not confined to a specific vascular district but it involves resistance arteries, which are exposed to haemodynamic forces (forearm circulation) or to both hydrostatic and haemodynamic forces (calf circulation). It finally shows that pharmacological regression of vascular hypertrophy (i) depends not only on "mechanical" or haemodynamic mechanisms but also on extra-haemodynamic factors through which calcium-channels blockers exert arterial vasoprotection and (ii) does not allow to fully restore a "normal" vascular structure, thereby suggesting that vascular hypertrophy is only in part a reversible phenomenon.

Previous studies have shown that angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, α-adrenoreceptor blockers and some beta-adrenoreceptor blocking agents with sympathomimetic activity may reduce FVR_{min} and thus decrease arteriolar hypertrophy and wall-to-lumen ratio (5,6,10,12,15,16). They have also shown that this effect more likely occurs in hypertensive patients in whom FVR_{min} values before treatment are markedly increased, whereas less clear effects are detectable in those patients displaying less pronounced structural vascular alterations (4,27,28). The results of the present study add to this information the evidence that calcium-channel blockers of the third generation, such as lercanidipine, may exert favourable effects on hypertension-related vascular remodelling, thereby documenting that, along with the above-mentioned classes of antihypertensive drugs, highly vasoselective compounds interfering with the cellular calcium influx display favourable effects on hypertension-related structural vascular abnormalities. Our data do not allow the clarification of the mechanisms through which lercanidipine may induce a regression of vascular hypertrophy. Although the BP lowering effects of the drug certainly play a role, mechanisms other than the haemodynamic ones are likely to be involved. This conclusion is supported by the evidence that in our patients, diuretic treatment, although reducing BP values to an extent almost superimposable to the one achieved by lercanidipine administration, displayed only a modest effect on FVR_{min} and thus on vascular hypertrophy. It is also supported by the limited correlation found in the lercanidipine-treated group of patients between the

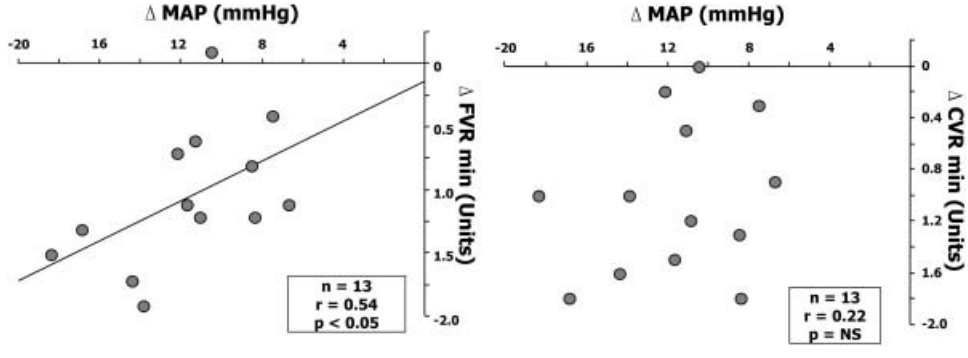

Figure 3. Correlations between changes in mean arterial pressure (ΔMAP) induced by lercanidipine administration and the corresponding changes in minimal forearm and calf vascular resistance, FVR_{min} (ΔFVR_{min} left panel) and CVR_{min} (ΔCVR_{min}, right panel).

magnitude of the BP reduction and the degree of FVR_{min} decrease induced by the drug. The mechanisms more likely responsible for the vasoprotective properties of lercanidipine are multifold and include the drug-related improvement in endothelial function, the direct vasodilatory properties of the compound, the reduction in metalloproteinase-9 activity and the antioxidant effects (29–31). Since endothelial dysfunction, metalloproteinase-9 activation and oxidative stress are involved in the pathogenesis of the atherosclerotic process (32,33), it is likely that the vasoprotective effects of the drug are mediated by the antiatherogenic properties of lercanidipine (34). Other mechanisms, however, should not be disregarded, such as the neutral profile of the drug on neuroadrenergic function, on the renin–angiotensin system, on the metabolic axis and on insulin sensitivity (19,35), i.e. on variables known to participate at the development and progression of vascular structural changes (36) and to be adversely affected by diuretic treatment (37).

The present study also shows that the reduction in FVR_{min} induced by lercanidipine is paralleled by a reduction in CVR_{min}, i.e. that the regression of arteriolar hypertrophy associated with calcium antagonist treatment involves more than one vascular district. The two phenomena, however, showed important differences because (i) in both treatment groups, the effects of the therapeutic intervention on vascular structure occurred at an earlier time period in the forearm than in the calf circulation and (ii) at variance from the forearm circulation, in the calf circulation no relationship was found between the antihypertensive effects of lecarnidipine and its vascular effects. Despite these differences, however, the finding that both forearm and calf circulation are favourably affected by calcium-channel blocking treatment (and only in part by diuretic treatment) suggests that regression of arteriolar hypertrophy by antihypertensive drugs is likely to be a widespread but not necessarily a homogeneous phenomenon. Indeed, our data suggest that in some vascular districts, the responses appear to be of earlier occurrence and/or of greater magnitude than those detectable in others.

Three other points deserve to be mentioned. Firstly, in our hypertensive patients, 1-year antihypertensive treatment with lercanidipine has allowed the achievement of a regression but not a normalization of vascular structure. This suggests that antihypertensive treatment with lercanidipine (and presumably with other vasoprotective agents such as ACE inhibitors and angiotensin II receptor blockers) is not capable of fully restoring a normal vascular structure in treated hypertensive patients. It may also suggest, however, that the temporal window of 12 months of antihypertensive treatment is too short to allow a full normalization of vascular structure to be obtained. Secondly, because the vessels we examined were largely muscular in nature, the question remains as to whether and to what extent calcium-channel blocking treatment triggers a regression of the vascular alterations to vital organs and/or splanchnic areas. A recent study, however, showing that the angiotensin II receptor blocker losartan is capable of lowering FVR_{min} and concomitantly decreasing intima-media thickness at the level of the carotid arteries (15), suggests this may be indeed the case. Finally, our data refer to a highly vasoselective third-generation calcium-channel blocker, i.e. to lercanidipine. It is likely, however, that the same effects characterize other calcium-channel blockers, since a previous study based on nitrendipine administration has also documented a regression of hypertension-related vascular changes (38).

References

1. Klingbeil AU, Schneider M, Martus P, Messerli FH, Scmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med. 2003;115:41–46.
2. Mancia G. Role of outcome trials in providing information on antihypertensive treatment. Importance and limitations. Am J Hypertens. 2006;19:1–7.
3. Otterstad JE, Smiseth O, Kjeldsen SE. Hypertensive left ventricular hypertrophy: Pathophysiology, assessment and treatment. Blood Press. 1996;5:5–15.
4. Sivertsson R, Hansson L. Effects of blood pressure reduction on the structural vascular abnormality in skin and muscle vascular beds in human essential hypertension. Clin Sci Mol Med. 1976;3:77s–79s.
5. Sivertsson R, Andersson O, Hansson L. Blood pressure reduction and vascular adaptation. A study on long-term effects of treatment with mefruside or atenolol. Acta Med Scand. 1979;205:477–482.
6. Svensson A, Gudbrandsson T, Sivertsson R, Hanson L. Haemodynamic effects of metoprolol and pindolol: A comparison in hypertensive patients. Br J Clin Pharmacol. 1982;13 Suppl 2:259S–267S.
7. Giannattasio C, Cléroux J, Cuspidi C, Sampieri L, Stella ML, Seravalle G, et al. Cardiac and vascular hypertrophy in essential hypertension. High Blood Press. 1993;2:299–306.
8. Schiffrin EL, Deng LY, Larochelle P. Effects of a beta-blocker or a converting enzyme inhibitor on resistance arteries in essential hypertension. Hypertension. 1994;23:83–91.
9. Thybo NK, Stephens N, Cooper A, Aalkjaer C, Heagerty AM, Mulvany MJ. Effect of antihypertensive treatment on small arteries of patients with previously untreated essential hypertension. Hypertension. 1995;25:474–481.
10. Kiowski W, Linder L, Nuesch R, Martina B. Effects of cilazapril on vascular structure and function in essential hypertension. Hypertension. 1996;27:371–376.
11. Rizzoni D, Muiesan ML, Porteri E, Castellano M, Zulli R, Bettoni G, et al. Effects of long-term antihypertensive

treatment with lisinopril on resistance arteries in hypertensive patients with left ventricular hypertrophy. J Hypertens. 1997;15:197–204.
12. Marceau M, Kouame N, Lacourciere Y, Cleroux J. Vascular structure in the forearm and calf after 6 months of angiotensin converting enzyme inhibition in elderly hypertensive subjects with left ventricular hypertrophy. J Hypertens. 1998;16: 673–679.
13. Schiffrin EL, Park JB, Intengan HD, Toyuz RM. Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonist losartan. Circulation. 2000;101:1653–1659.
14. Rizzoni D, Porteri E, De Ciuceis C, Sleiman I, Rodella L, Rezzani R, et al. Effect of treatment with candesartan or enalapril on subcutaneous small artery structure in hypertensive patients with noninsulin-dependent diabetes mellitus. Hypertension. 2005;45:659–665.
15. Olsen MH, Wachtell K, Neland K, Bella JN, Rokkedal J, Dige-Petersen H, et al. Losartan but not atenolol reduce carotid artery hypertrophy in essential hypertension. A LIFE substudy. Blood Press. 2005;14:177–183.
16. Dell'Omo G, Penno G, Pucci L, Pellegrini G, Scotti A, Del Prato S, et al. The vascular effects of doxazosin in hypertension complicated by metabolic syndrome. Coron Artery Dis. 2005;16:67–73.
17. Agabiti-Rosei E, Muiesan ML, Rizzoni D. Cardiovascular structural alterations in hypertension: Effect of treatment. Clin Exp Hypertens. 1996;18:513–522.
18. Izzard AS, Rizzoni D, Agabiti-Rosei E, Heagerty AM. Small artery structure and hypertension: Adaptive changes and target organ damage. J Hypertens. 2005;23:247–250.
19. Bang LM, Chapman TM, Goa KL. Lercanidipine: A review of its efficacy in the management of hypertension. Drugs. 2003;63:2449–2472.
20. Wirtz S, Herzig S. Molecular mechanisms of vasoselectivity of the 1,4-dihydropyridine lercanidipine. Br J Pharmacol. 2004;142:275–84.
21. Brixius K, Gross T, Tossios P, Geissler HJ, Mehlhorn U, Schwinger RH, et al. Increased vascular selectivity and prolonged pharmacological efficacy of the L-type Ca^{2+} channel antagonist lercanidipine in human cardiovascular tissue. Clin Exp Pharmacol Physiol. 2005;32:708–713.
22. Parati G, Casadei R, Groppelli A, Di Rienzo M, Mancia G. Comparison of finger and intra-arterial blood pressure monitoring at rest and during laboratory testing. Hypertension. 1989;13:647–655.
23. Folkow B, Gribby G, Thulesius O. Adaptative structural changes of the vascular walls in hypertension and their relation to the control of the peripheral resistance. Acta Physiol Scand. 1958;44:255–272.
24. Thijssen DHJ, Bleeker MWP, Smits P, Hopman MT. Reproducibility of blood flow and post-occlusive reactive hyperaemia as measured by venous occlusion plethysmography. Clin Sci. 2005;108:151–156.
25. Folkow B, Hansson L, Sivertsson R. Structural factors in the pathogenesis of hypertension. In: Robertson JIS, editor. Handbook of hypertension. Amsterdam: Elsevier, 1983. p 133–150.
26. Mulvany M, Hansen PK, Aalkjaer C. Direct evidence that the greater contractility of resistance vessels in spontaneously hypertensive rats is associated with a narrowed lumen, a thickened media and an increased number of smooth muscle cell layers. Circ Res. 1978;43:854–864.
27. Jern S. Reversibility of vascular hypertrophy in pharmacologically treated patients. J Cardiovasc Pharmacol. 1987;10: s112–s115.
28. Gretzer I, Duner H, Lagerback B. Haemodynamic effects of pindolol in essential hypertension with special reference to resistance vessels in the forearm during maximal vasodilatation. J Hypertens. 1985;3:s215–s217.
29. Taddei S, Virdis A, Ghiadoni L, Versari D, Salvetti G, Magagna A, et al. Calcium antagonist treatment by lercanidipine prevents hyperpolarization in essential hypertension. Hypertension. 2003;41:950–955.
30. Tomlinson B, Benzie IF. Antioxidant effect of lercanidipine. Hypertension. 2003;42:e10–e11.
31. Martinez ML, Lopes LF, Coelho EB, Nobre F, Rocha JB, Gerlach RF, et al. Lercanidipine reduces matrix metalloproteinase-9 activity in patients with hypertension. J Cardiovasc Pharmacol. 2006;47:117–122.
32. Brunner H, Cockcroft JR, Deanfield J, Donald A, Ferrannini E, Halcox J, et al. Endothelial function and dysfunction. Part II: Association with cardiovascular risk factors and diseases. J Hypertens. 2005;23:233–246.
33. Schulze PC, Lee RT. Oxidative stress and atherosclerosis. Curr Atheroscler Rep. 2005;7:242–248.
34. Canavesi M, Baldini N, Leonardi A, Sironi G, Bellosta S, Bernini F. In vitro inhibitory effect of lercanidipine on cholesterol accumulation and matrix metalloproteinases secretion by macrophages. J Cardiovasc Pharmacol. 2004;44: 416–22.
35. Grassi G, Seravalle G, Turri C, Bolla G, Mancia G. Short- versus long-term effects of different dihydropyridines on sympathetic and baroreflex function in hypertension. Hypertension. 2003;41:558–562.
36. Grassi G. Role of the sympathetic nervous system in human hypertension. J Hypertens. 1998;16:1979–1987.
37. Grassi G, Seravalle G, Dell'Oro R, Trevano FQ, Bombelli M, Scopelliti F, et al. Comparative effects of candesartan and hydrochlorothiazide on blood pressure, insulin sensitivity, and sympathetic drive in obese hypertensive individuals: Results of the CROSS study. J Hypertens. 2003;21: 1761–1769.
38. Agabiti-Rosei E, Muiesan ML, Rizzoni D, Romanelli G, Beschi M, Castellano M. Regression of cardiovascular structural changes after long-term antihypertensive treatment with the calcium antagonist nitrendipine. J Cardiovasc Pharmacol. 1991;18 Suppl 5:s5–s9.