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ORIGINAL ARTICLE

Effects of losartan titrated to losartan/hydrochlorothiazide and amlodipine on blood pressure and peripheral capillary microcirculation in patients with mild-to-moderate hypertension

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***Objective*: To measure the effects of losartan and amlodipine on peripheral capillary microcirculation in hypertension.**
***Setting*: Medical out-patient clinic, Basel, in a university teaching hospital.**
***Methods*: After a 4-week placebo run-in period 20 patients aged 50 ± 8 (range 36–65) years with mild-to-moderate hypertension were randomly allocated to receive active treatment with losartan 50 mg titrated to losartan 50 mg/hydrochlorothiazide (HCT) 12.5 mg, or amlodipine 5 mg titrated to 10 mg for a 12 week period. Titration was performed if diastolic blood pressure (BP) was ⩾90 mm Hg after 6 weeks of treatment. BP measurements as well as video capillary microscopy of the finger nailfold at the end of the placebo period and after 12 weeks of active treatment were compared. Capillary blood cell velocity was measured at rest and immediately, 1 min and 2 min after local finger cooling.**
***Results*: After 3 months of treatment with amlodipine ($n = 10$) and losartan titrated to losartan-HCT ($n = 10$) sitting BP decreased significantly from 160 ± 7/103 ± 4 mm Hg and 147 ± 7/98 ± 6 mm Hg to 131 ± 10/86 ± 7 mm Hg and 134 ± 17/89 ± 9 mm Hg, respectively ($P < 0.01$). After local finger cooling the area under the curve (AUC) of capillary blood cell velocities was 1.13 ± 0.58 mm (median ± s.d.) at baseline and increased to 1.94 ± 1.15 ($P < 0.05$) in losartan/losartan-HCT treated patients. In amlodipine treated patients the increase in AUC of capillary blood cell velocity did not reach the level of statistical significance (1.59 ± 1.36 to 2.14 ± 1.05 mm).**
***Conclusion*: This small trial shows that the area under the curve of capillary blood cell velocity increases in hypertensive patients treated with both losartan/losartan-HCT and amlodipine compared with baseline values.**

Keywords: losartan; amlodipine; mild-to-moderate hypertension; nailfold capillaroscopy; microcirculation

Introduction

Essential hypertension is characterised by a rise in peripheral vascular resistance and by structural abnormalities of the vasculature and the myocardium.[1,2] Abnormal vasoconstriction and decreased erythrocyte velocity in the finger microcirculation have been found in essential hypertension.[3,4] Moreover, finger microcirculation deteriorates as a function of the severity and duration of chronic heart failure, a common condition observed in end-stage hypertensive heart disease with activated sympathoadrenal tone.[5]

Structural changes and reduced density of capillaries may contribute to the increased peripheral resistance found in essential hypertension.[6] Angiotensin-converting enzyme (ACE)-inhibitors and calcium-antagonists improve structural hypertensive alterations of the small arteries.[7–9] Coronary flow reserve is improved by long-term treatment with enalapril.[10]

In order to achieve sufficient hypertension control, combination drug therapy is often necessary.[11] Both losartan and amlodipine are standard antihypertensive drugs. Likewise, both the combination of ACE-inhibitor, cilazapril with hydrochlorothiazide (HCT)[12] and of the angiotensin-II blocker, losartan with HCT[13] are effective and well tolerated. In hypertensive patients treated with cilazapril and HCT, a trend towards increased capillary blood cell velocity in nailfold microscopy was demonstrated.[14]

The angiotensin-II blocker losartan is expected to improve cardiovascular hypertrophy in hypertension. The calcium antagonist, nifedipine, increases

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finger nailfold capillary blood cell velocity in patients with primary Raynaud Syndrome,[15] but capillary blood cell velocity has not been studied in hypertensive patients treated with any calcium antagonist. Amlodipine causes smooth blood pressure (BP) control and decrease in left ventricular mass without activation of sympathetic nervous system.[16] However, there are no data on amlodipine and nailfold capillaroscopy. Similarly the effects of losartan and losartan/losartan-HCT on peripheral microcirculation measured by finger nailfold capillary microscopy are not known.

In this double-blind trial we compared the effects of losartan/losartan-HCT *vs* amlodipine on BP control and on peripheral microcirculation as assessed by finger nailfold capillary microscopy.

Patients and methods

Twenty patients of the medical out-patient clinic of the University Hospital Basel were included after written informed consent and with permission of the local ethical committee. They had mild-to-moderate hypertension, defined as an average sitting diastolic BP of 95–115 mm Hg at weeks 2 and 4 of the placebo run-in period. Patients with Raynaud's disease and with previous anti-hypertensive treatment were excluded. Conventional and 24-h ambulatory BP measurements and nailfold video capillary microscopy were performed at baseline after the 4 week placebo period. After the placebo period patients were randomly assigned to receive either losartan or amlodipine once daily at 08.00 am for a duration of 3 months. At the end of the active treatment period the baseline examinations were repeated and the results were compared to baseline.

Losartan 50 mg or amlodipine 5 mg was given, titrated to losartan/HCT 50 mg/12.5 mg, or amlodipine 10 mg after 6 weeks of treatment if the BP was not controlled (sitting diastolic BP $\geqslant$ 90 mm Hg).

The nailfold capillaries in the digits of both hands were studied with the help of an incident light microscope coupled to a television monitor. The density of the capillary loops (number of capillary loops per millimetre in the distal row along the edge of the fold) and the diameters of the arterioles and venules in the two limbs were measured. Capillary blood cell velocity was measured at rest and after local cold exposure of the nailfold. Area under the curve of blood cell velocity was calculated. BP was measured by conventional sphygmomanometer after 2 min in a sitting position.

Statistics

For calculation of changes in BP and for calculation of the area under the curve for capillary blood cell velocity, paired *t*-test (two-tailed) was performed using SPSS for Windows version 7.01.

Results

Twenty patients aged 50 ± 8 (range 36–65) years, nine female, 11 male, from our medical out-patient clinic were studied. They had untreated mild-to-moderate essential hypertension.

Baseline characteristics are shown in Table 1. There was no significant difference between the losartan and amlodipine groups concerning age, sex, smoking status, body mass index (BMI), pulse rate, and BP measured by conventional Riva-Rocci method and by ambulatory 24-h registration. Baseline systolic clinical BP was higher in the amlodipine group (160 mm Hg) than in the losartan/losartan-HCT group (147 mm Hg). However, this difference did not reach a level of statistical significance ($P = 0.09$). In nine patients of the losartan/losartan-HCT group and in six patients of the amlodipine group treatment had to be titrated after 6 weeks of active treatment.

Sitting clinical BP decreased in both groups after 3 months of active treatment compared to baseline (Table 2 and Figure 1). Systolic and diastolic BP was reduced from $147 \pm 7/98 \pm 6$ mm Hg to $134 \pm 17/89 \pm 9$ mm Hg and from $160 \pm 7/103 \pm 4$ mm Hg to $131 \pm 10/86 \pm 7$ mm Hg in the losartan and the amlodipine group, respectively ($P < 0.05$). Twelve patients had two complete 24-h BP measurements. Mean ambulatory 24-h systolic and diastolic BP was reduced from 146/98 mm Hg to 128/88 mm Hg in the losartan group ($n = 6$) and from 130/90 mm Hg to 125/85 mm Hg in the amlodipine group ($n = 6$). In both groups 24-h pressure was reduced at virtually every hour over the 24-h period (Figures 1 and 2). Treatment effects on capillary microcirculation are shown in Table 3 and Figures 3 and 4.

Finger nailfold capillary cell velocity was measured at rest and immediately, 1 min and 2 min after local finger cooling at baseline and after 3 months of active treatment. All capillary blood cell velocities as measured at rest and after local cooling increased in the losartan group compared to baseline. In the amlodipine group capillary blood cell velocity increased 2 min after local finger cooling, but remained unchanged at rest and 1 min after local cooling. Baseline capillary blood cell velocity at rest was 0.85 ± 0.73 mm in the losartan group and 1.19 ± 1.09 mm in the amlodipine group. However, this difference was not statistically significant. AUC of blood cell velocities increased from 1.13 ± 0.58 mm to 1.94 ± 1.15 mm (median $\pm$ s.d., $P < 0.05$) in the losartan group, and increased from 1.59 ± 1.36 mm to 2.14 ± 1.05 mm (median $\pm$ s.d., NS) in the amlodipine group. In 20 normotensive controls capillary blood cell velocity at rest was 0.65 ± 0.27.[3] Arteriolar and venular capillary diameter and capillary density did not change in both groups after treatment compared to baseline.

Discussion

Hypertensive alterations of peripheral capillaries[3,4,6] and the response of finger nailfold capillaroscopic findings to anti-hypertensive drug treatment[14] have rarely been investigated.

This is the first report on the effects of an angiotensin-II blocker and a calcium channel blocker on peripheral capillary microcirculation in patients with mild-to-moderate hypertension. Losartan

Table 1 Patient characteristics

	Losartan group	*Amlodipine group*
Age (years)	48 ± 8	51 ± 9
Sex (female/male)	5/5	4/6
Smokers	2	0
BMI (kg/m^2, mean ± s.d.)	30 ± 5	30 ± 3
Blood pressure (mm Hg, mean ± s.d.)	147 ± 7/98 ± 6	160 ± 7/103 ± 4
Pulse rate	75/5	77 ± 6

Table 2 Pulse rate, clinical blood pressure (BP, mm Hg, mean ± s.d.) and mean 24-h ambulatory BP (ABPM, mm Hg) at baseline and at weeks 6 and 12 of active treatment

	Baseline	*6 weeks*	*12 weeks*
Clinical BP losartan ($n = 10$)	147 ± 7/98 ± 6	140 ± 9/94 ± 8	134 ± 17*/89 ± 9*
ABPM losartan ($n = 6$)	146/98		128*/88
Pulse rate losartan ($n = 10$)	75 ± 5	72 ± 7	80 ± 7
Clinical BP amlodipine ($n = 10$)	160 ± 7/103 ± 4	137 ± 16/88 ± 8	131 ± 10*/86 ± 7*
ABPM amlodipine ($n = 6$)	130/90		125/85
Pulse rate amlodipine ($n = 10$)	77 ± 6	78 ± 8	75 ± 6

*$P < 0.05$. Indicates a significant different between baseline BP and BP after 12 weeks of treatment.
Difference between baseline BP in the two groups was statistically not significant ($P = 0.09$).

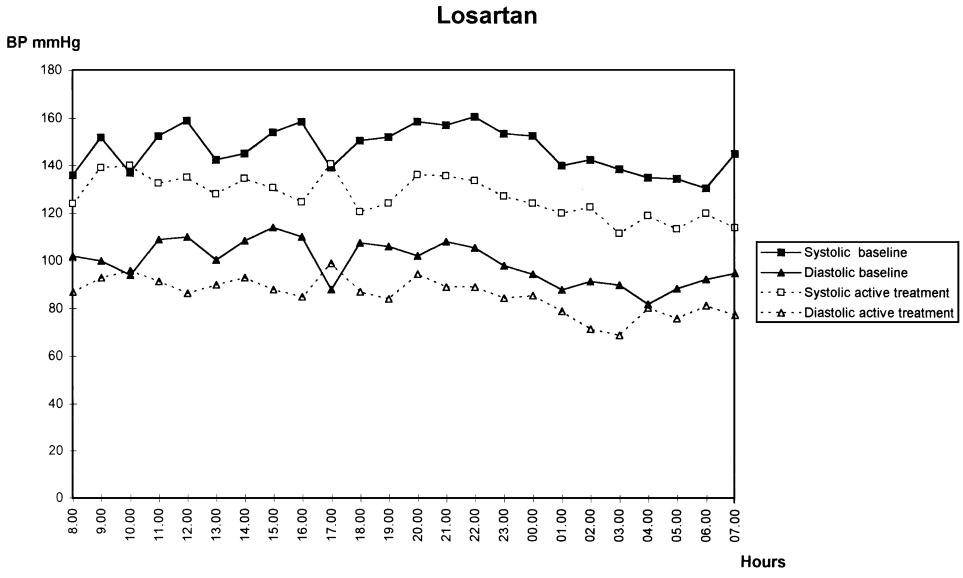

Figure 1 Mean 24-h systolic and diastolic blood pressure (BP, mm Hg) at baseline and after 3 months treatment with 50 mg losartan titrated to losartan/HCT ($n = 6$).

titrated to losartan/HCT improves capillary microcirculation as assessed by finger nailfold capillary microscopy in patients with mild-to-moderate hypertension.

The reproducibility of our capillarscopic method is good. The reproducibility of capillary blood cell velocity after local finger cooling was good whether or not the test was performed after 1 h or after 3 months with $r = 0.72$ and 0.86, respectively, $P < 0.05$.[17] However, baseline variability of capillary blood cell velocity between groups was substantial, although statistically not significant ($P = 0.064$); nevertheless, results have to be interpreted carefully.

Structural changes in capillary diameter or capillary density were not observed. This is in accordance with other findings.[14] Capillary blood cell velocity may increase by anti-hypertensive therapy despite unchanged capillary density or capillary diameter.[18] This could be explained by altered haemorheology in hypertension.[19] Capillary diameter cannot be assessed exactly by capillary microscopy since the erythrocyte but not the plasma column width is measured.[18]

Recently, we reported on similar effects on capillary microcirculation in patients with mild-to-moderate hypertension treated with the ACE-inhibitor cilazapril.[14] ACE-inhibitors reduce the increased media to lumen ratio of small arteries in mild essential hypertension.[7,8] Increased media to lumen ratio

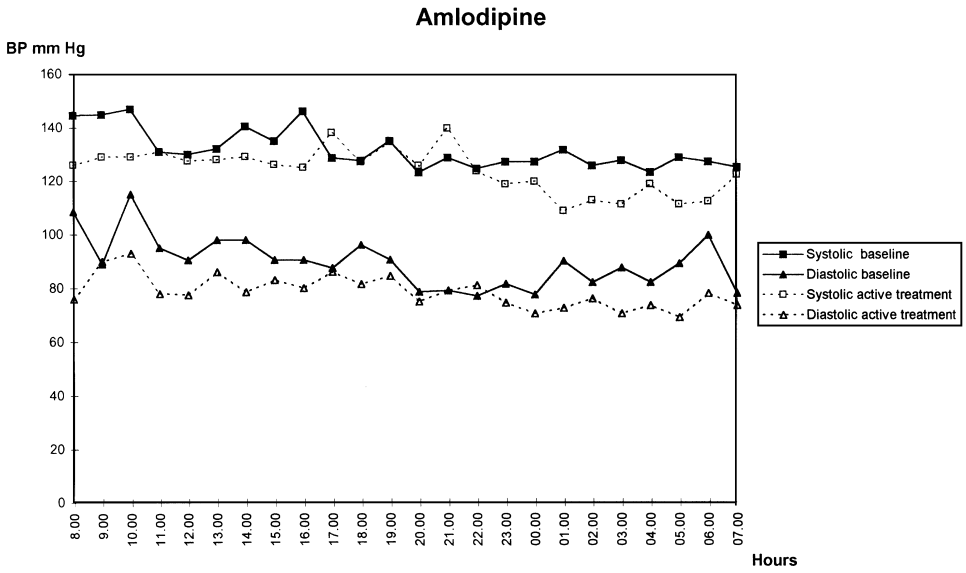

Figure 2 Mean 24-h systolic and diastolic blood pressure (BP, mm Hg) at baseline and after 3 months treatment with 5 mg amlodipine titrated to 10 mg ($n = 6$).

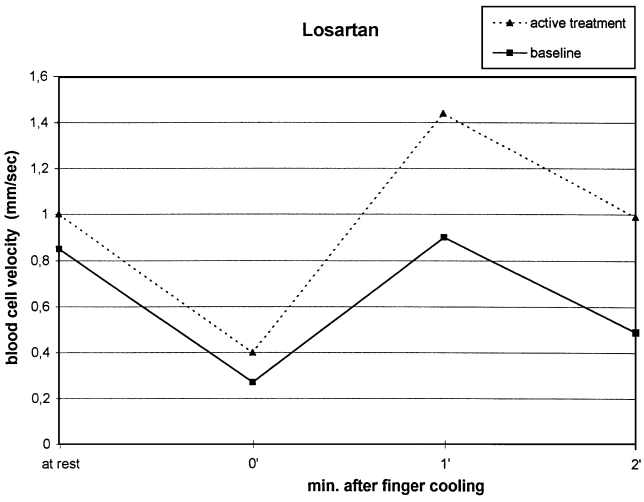

Figure 3 Finger nailfold capillary blood cell velocity (CBV) at rest and after local finger cooling (0, 1 and 2 min) at baseline and after active treatment with 50 mg losartan titrated to losartan/HCT compared to 5 mg amlodipine titrated to 10 mg.

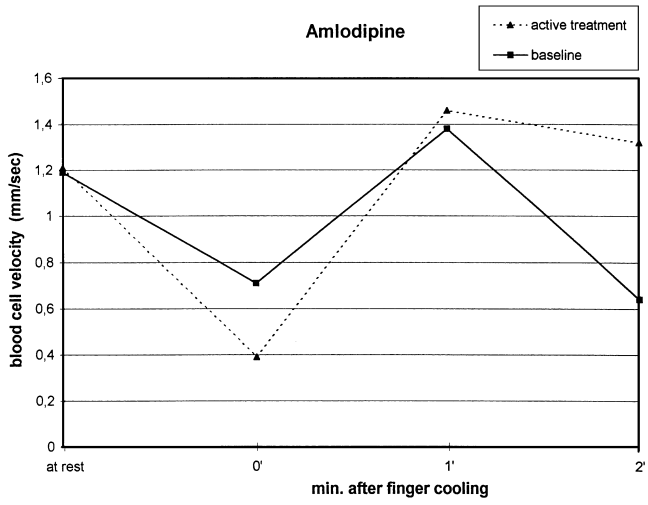

Figure 4 Finger nailfold capillary blood cell velocity (CBV) at rest and after local finger cooling (0, 1 and 2 min) at baseline and after active treatment with amlodipine.

Table 3 Finger nailfold capillary blood cell velocity (mm/sec, median ± s.d.) at baseline and after 3 months of treatment with losartan titrated to losartan/hydrochlorothiazide or amlodipine

		Blood cell velocity				
		At rest	*After local finger cooling*			*Area under the curve*
			immediately	*1 min*	*2 min*	
Losartan	baseline	0.85 ± 0.73	0.27 ± 0.21	0.90 ± 0.80	0.49 ± 0.30	1.13 ± 0.58
	active treatment	1.00 ± 0.75	0.4 ± 0.37	1.44 ± 0.86	0.99 ± 0.72	1.94 ± 1.15
Amlodipine	baseline	1.19 ± 1.09	0.71 ± 0.78	1.38 ± 1.00	0.64 ± 0.30	1.59 ± 1.36
	active treatment	1.21 ± 0.84	0.39 ± 0.22	1.46 ± 0.80	1.32 ± 0.83	2.14 ± 1.05

of subcutaneous gluteal small arteries corresponds closely to increased forearm minimal vascular resistance in humans.[20] For the study of hypertensive small vessel alterations invasive methods (biopsies, arterial puncture) are required.[21] In contrast, capillary microscopy is a non-invasive method suitable for the investigation of the peripheral capillary vasculature. Non-invasive methods for routine clinical

assessment of hypertensive vascular damage should be evaluated.

The exact mode of action by which anti-hypertensive drugs may improve the peripheral capillary microcirculation is not yet clear. However, both moxonidine and losartan decrease plasma catecholamines.[22,23] Catecholamines may modulate peripheral capillary microcirculation.[24] Some other findings underline the correlation between vasomotion and sympathetic activity. In spontaneously hypertensive rats noradrenaline hyperresponsiveness may favour arterial closure[25] and local ACE activity in arterioles of skeletal muscle microcirculation is higher than in normotensive control rats causing significant vasoconstriction.[26] Capillary blood flow decreases promptly following adrenaline infusion.[27] Plasma catecholamine decrease correlated significantly with left ventricular mass index decrease in hypertensive patients with calcium antagonist therapy.[28] Sympathetic activity may be stimulated by nicotine.[29] All but two patients in our study were non-smokers. We did not measure plasma catecholamines in our patients.

BP measured by conventional sphygmomanometer decreased significantly in both the amlodipine and the losartan/losartan-HCT group. The BP-lowering effects of losartan are similar to those observed in the literature.[13] Our results show a smooth 24-h BP decrease in losartan and amlodipine-treated patients over 24 h.

An important limitation of our study is the substantial variability in capillary blood cell velocity in the losartan and the amlodipine group. However, baseline differences between groups were not statistically significant ($P = 0.064$).

Another limitation is the small number of patients studied. We found that the change in capillary blood cell velocity in the losartan/losartan-HCT group is statistically different but does not reach the level of clinical significance we assumed in planning the study. Therefore, the results have to be interpreted with caution. The sample size compares well with that of other capillaroscopic studies in this field.

In conclusion, in a limited number of patients we assessed peripheral microcirculation by finger nailfold capillary microscopy measuring capillary blood cell velocities at rest and after local cooling. Area under the curve of capillary blood cell velocities increased in patients with mild-to-moderate hypertension treated with the angiotensin-II blocker losartan titrated to losartan-HCT. This increase was statistically though not clinically significant. It needs to be further elucidated how changes in peripheral capillary microcirculation compare with other hypertensive cardiovascular target organ damage and with clinical end-points.

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