Oedema formation with the vasodilators nifedipine and diazoxide: direct local effect or sodium retention?

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Objective To determine whether the common side effect of ankle oedema with arteriolar vasodilators such as the calcium entry blocker (CEB) nifedipine and the potassium channel opener (PCO) diazoxide is the direct result of peripheral vasodilation or merely a consequence of renal sodium retention.

Design In 12 healthy sitting volunteers we studied for 3 h the effects of 20 mg nifedipine, 150 mg diazoxide intravenously, 25 mg captopril and placebo on oedema formation and sodium excretion.

Conclusions Foot swelling was determined with a new accurate device (coefficient of variation 0.30%), which uses Archimedes principle to measure water displacement induced by immersion of the foot. Blood pressures were recorded with a Hawksley random-zero sphygmomanometer.

Results All of the active drugs decreased diastolic blood pressure (captopril by 9 ± 2%, nifedipine by 4 ± 3% and diazoxide by 2 ± 2%, compared with an increase of 5 ± 2% with placebo). Foot volume increased acutely after administration of nifedipine (by 2.6 ± 0.4%), whereas it remained stable with placebo and the other drugs. Administration of captopril and nifedipine induced increases of fractional sodium excretion (by 20 ± 9% and 40 ± 20%, respectively) in contrast to the decreases with placebo and diazoxide (by 13 ± 11% and 24 ± 10%, respectively). Only administration of nifedipine induced significant, albeit small, increases in haemoglobin and serum albumin levels.

Conclusions Administration of nifedipine increased foot volume and natriuresis simultaneously, thereby supporting the hypothesis that development of ankle oedema with CEB is a local phenomenon at the site of vasodilation. The absence of a similar increase in foot volume with diazoxide administration should be interpreted with caution because of the rather minor effect of this dose of diazoxide on blood pressure. However, it could be indicative of a different mechanism of oedema formation with PCO.

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Keywords: foot volume, new method, natriuresis, healthy volunteers, calcium entry blockers, potassium channel openers, captopril

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Introduction

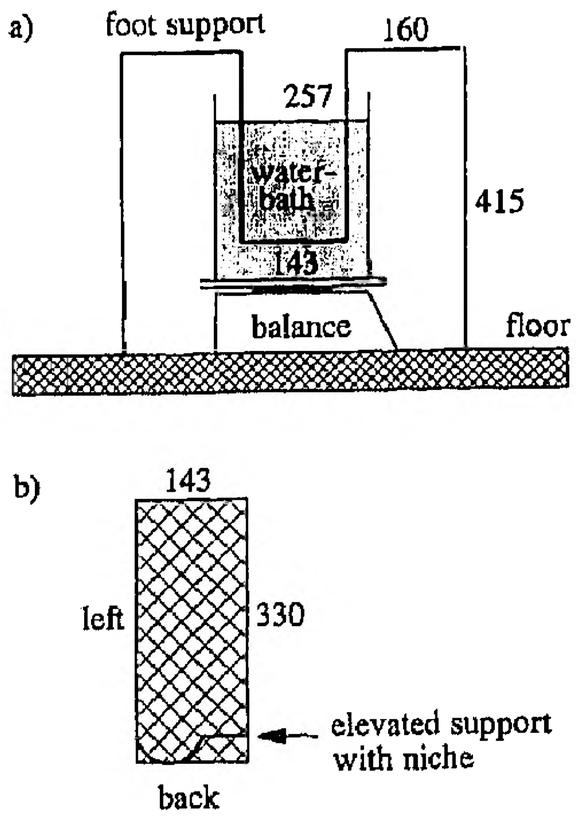
Ankle oedema is a common side effect of antihypertensive treatment with arteriolar vasodilators, particularly with calcium entry blockers (CEB) and potassium channel openers (PCO) such as diazoxide [1]. In the heterogeneous group of CEB, the incidence of oedema formation is higher with dihydropyridines such as nifedipine than with drugs such as verapamil and diltiazem [2]. It is very likely that this difference is related to the higher vascular selectivity and, consequently, the more pronounced vasodilatory effect of dihydropyridines [3]. Oedema formation with vasodilating drugs might be a direct result of vasodilation, but has also been ascribed primarily to renal sodium retention after blood pressure reduction [4]. The latter possibility does not seem to be likely for CEB, which do not cause sodium retention [5,6] but even induce acute natriuresis and diuresis [7]. To elucidate the mechanism of oedema formation, we studied the acute effects of nifedipine, diazoxide and the angiotensin converting enzyme (ACE) inhibitor captopril on foot volume and sodium excretion in healthy sitting volunteers.

Methods

Subjects

Twelve healthy volunteers (10 men and two women), aged 19–33 years, were recruited. All of the participants were free of medication and without signs of venous insufficiency. The two women were not using oral contraceptives. Blood pressures were below 140/90 mmHg (ranges systolic 101–140 and diastolic 60–84) and all of the individuals had a normal height (range 167–192 cm) and body weight (range 49–95 kg). The study protocol was approved by the Sint Radboud Hospital Ethics Committee and all of the volunteers gave their written informed consent to participate in the study.

Fig. 1.



Side view of the foot volume recorder (a) and top view of the immersed bottom of foot support (b). Measures of foot support (in millimetres) are indicated by the numbers. The Perspex water bath measuring 388 mm × 208 mm × 250 mm had a maximal capacity of 20 l. The left foot of the subject is immersed within the water bath and placed on the bottom of the foot support with the heel against the niche in the back.

Foot volume recordings

Apparatus and procedure

Like other methods in use for measuring foot volume, our method uses the principle of water displacement, but records it in a new, indirect and very precise way. As shown in Figure 1a, a Perspex water bath with a maximal capacity of 20 l is placed on a sensitive electronic balance (Mettler PM 34, Mettler Instrumente AG, Greifensee, Switzerland). A specially constructed stainless steel foot support is suspended in the foot-bath, but rests fully on the floor on both sides of the balance. The water bath is filled with tap water until the balance indicates exactly 15 000 g, after which the balance is tared to zero. Subsequent immersion of the foot induces water displacement that is perceived by the balance as an increase in weight, which equals the immersed volume multiplied by the relative weight of water at a specific temperature (0.998 g/ml at 22°C). Stated differently, the balance registers the force necessary to immerse the foot, which depends solely on the volume of the foot (Archimedes principle). In order to reach a fixed and reproducible degree of immersion of the foot and lower leg, a stable chair with adjustable height is used and a rigidly standardized seated position is sought with the thigh horizontal, the lower leg vertical and the left foot resting on the foot support with the heel against the niche in the back and the fore-foot against the left-hand side of the foot support (Fig. 1b). Moreover, to minimize errors caused by different degrees of immersion, three or four successive foot placements and recordings are performed without actually removing the foot from the water bath: if fewer than three recordings are within a 5 g range, the foot is withdrawn and the whole procedure is repeated. Water losses between experiments caused by removal of the foot from the water bath and evaporation are easily corrected for by adding water to the bath until the balance again indicates exactly zero. Thus, the same water level is attained before each measurement. Because the relative volume of water closely approaches unity at room temperature (1.00223 ml/g at 22°C), the simple conversion of 1 g to 1 ml can be used because it systematically underestimates volume by only 0.2%.

Testing of the new method

Before studying drug effects, we tested the accuracy of the filling of the water bath, the reproducibility of the method both for patients and for volunteers and some aspects of the biological variation of foot volume.

Study protocol

The acute effects of the experimental drugs on foot volume and natriuresis were studied on four different days separated by interval periods of at least 3 days. In a randomized, cross-over, open manner all subjects received oral placebo, 20 mg nifedipine (two 10 mg capsules bitten and swallowed), 25 mg captopril (a tablet swallowed) and 150 mg diazoxide (intravenous infusion during 10 min). The volunteers continued their usual diet between experiments.

Subjects were kept fasting during the last 3 h preceding the experiments except for an oral water load of 300 ml taken 2 h before drug administration. After their arrival at the ward, the volunteers were seated in normal office chairs with their feet resting on the ground. This sitting rest was interrupted only for foot volume recordings and for voiding in an adjacent room. After 30 min sitting rest by the subject, baseline levels of blood pressure, heart rate, body weight and foot volume were recorded and baseline blood and urine samples were collected. Thereafter, one of the four experimental drugs was administered and subjects drank 250 ml tap water. An additional 375 ml oral water load was supplied during the next 90 min. Foot volumes, body weights, blood pressures and heart rates were recorded 30, 60, 120 and 180 min after drug administration, whereas blood and urine samples were collected at 60 and 180 min. To reduce the influence of biological variation, subjects were always studied at the same time of the day and baseline foot volume values were recorded after 30 min of sitting rest by the subject. Only left foot volumes were recorded.

Blood pressure and heart rate were recorded in triplicate with a Hawksley random zero mercury sphygmomanometer and by pulse counting, respectively. In blood and urine samples, creatinine, sodium and chloride concentrations were determined by standard (semi)automated techniques. The haemoglobin level was determined using a standard automated technique (H3, Technicon, Tarrytown, New York, USA) and the serum albumin level by using an automated bromine cresol green method.

Table 1 Baseline values before drug administration

	Placebo	Captopril	Diazoxide	Nifedipine	*P*
Body weight (kg)	75.3 ± 3.8	75.4 ± 3.9	75.2 ± 3.8	75.1 ± 3.8	0.09
Systolic blood pressure (mmHg)	106 ± 3	108 ± 2	104 ± 2	105 ± 2	0.46
Diastolic blood pressure (mmHg)	68 ± 2	72 ± 2	68 ± 1	70 ± 2	0.13
Heart rate (beats/min)	66 ± 2	65 ± 2	67 ± 2	68 ± 2	0.27
Foot volume (ml)	1344 ± 44	1335 ± 42	1335 ± 43	1333 ± 42	0.56
Haemoglobin level (mmol/l)	8.4 ± 0.1	8.5 ± 0.2	8.5 ± 0.2	8.5 ± 0.2	0.59
Albumin level (g/l)	48 ± 1	50 ± 1	49 ± 1	50 ± 1	0.24
FE_{Na} (%)	0.6 ± 0.1	0.6 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	0.83
FE_{Cl} (%)	1.3 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.2	0.50

Values are expressed as means ± SEM. Fe_{Na}, fractional excretion of sodium; Fe_{Cl}, fraction excretion of chloride. *P*-values are for comparison of baseline values by repeated-measures analysis of variance.

Fractional sodium and chloride excretions (FE_{Na} and FE_{Cl}) were calculated using the formula

$$FE_x = (U_x/P_x) \times (P_{creat}/U_{creat}) \times 100\%$$

with U_x and P_x representing the urinary and plasma concentrations.

Statistical analysis

Statistics were performed with SAS (Statistical Analysis System) software (SAS Institute Inc., Cary, North Carolina, USA). Coefficients of variation for reproducibility were calculated by one-way analysis of variance [8]. Repeated-measures analysis of variance was used to compare baseline values, whereas Wilcoxons rank sum test was used to compare the effects of the experimental drugs with those of placebo. Percentage changes from baseline values were used for these pairwise comparisons. $P<0.05$ was considered statistically significant. Results are presented as means ± SEM.

Results

Accuracy of foot volume recordings

Refilling the water bath

Because the balance is also used to control the filling of the water bath, replacing the water induced only minor errors: the recorded volume of a standard measure varied only slightly during 10 fillings of the water bath (coefficient of variation 0.09%, mean volume 1111 ml).

Reproducibility

Three successive recordings were performed within approximately 5 min in 27 volunteers and 22 patients. Between recordings, the foot was withdrawn from the water bath and dried carefully. The water lost by removal of the foot was replaced before the next recording, as indicated earlier. In this test, foot volume recordings proved to be highly reproducible in volunteers (coefficient of variation 0.32%, mean volume 1234 ml) and also in patients (coefficient of variation 0.28%, mean volume 1292 ml).

Biological variation

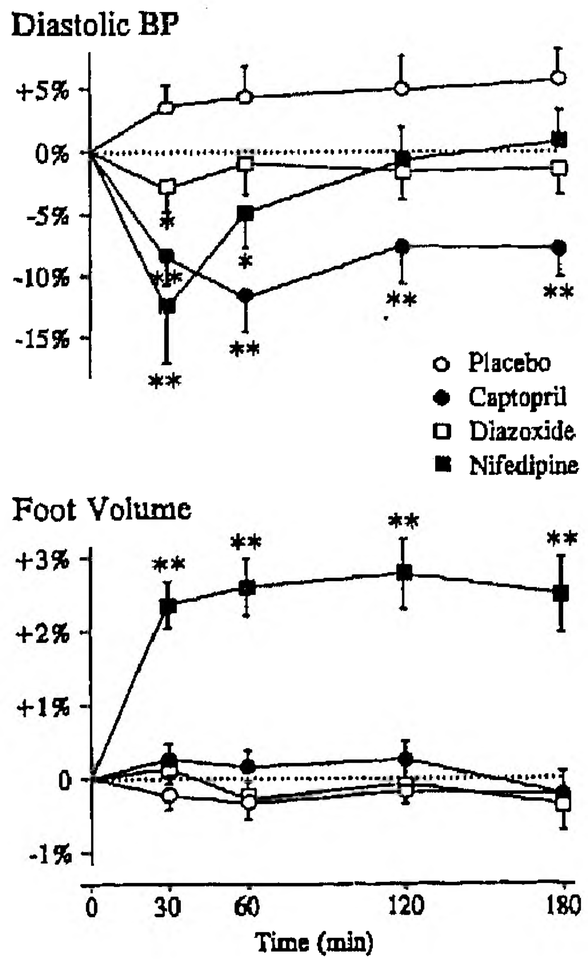
Fifteen minutes of sedentary rest by the subject corresponded to an increase in foot volume by 1.0 ± 0.2% ($P<0.01$, n = 9). During the course of a usual week day, the foot volume of healthy students also increased by 1.2 ± 0.5% ($P<0.05$, n = 12).

Drug effects

Two subjects were not able to empty their bladders at the requested time on one or more occasions, implying that comparisons of fractional excretions should be restricted to the remaining 10 subjects. Baseline levels of all measured parameters were comparable on the four experimental days (Table 1).

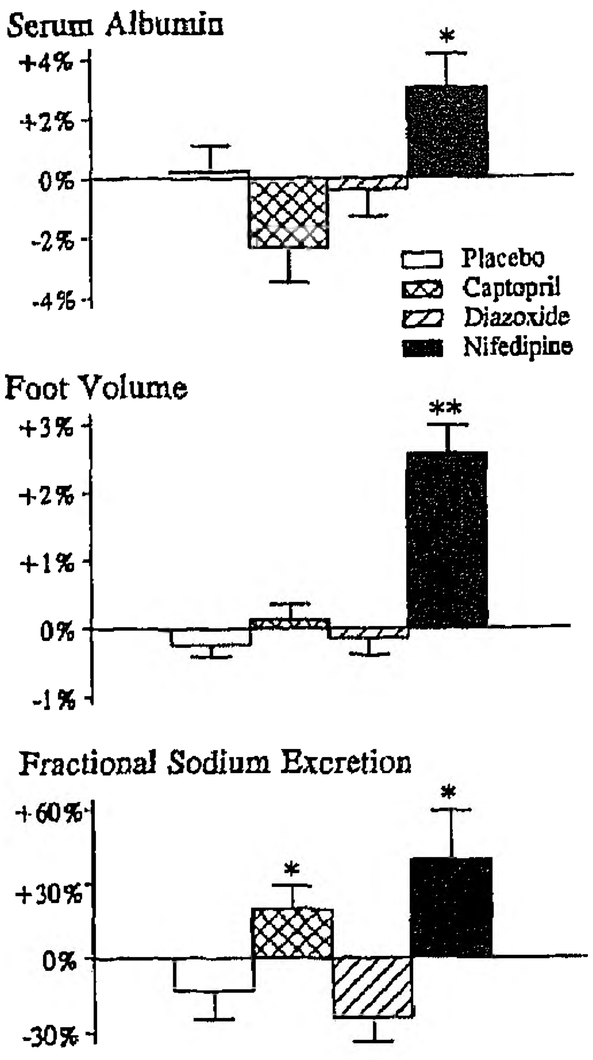
In these healthy volunteers, only administration of captopril decreased the systolic blood pressure (by 5 ± 2% versus 0 ± 1% with placebo, $P<0.05$). All of the active drugs decreased the diastolic blood pressure, with captopril and nifedipine having a clearly more pronounced effect (Fig. 2). Administration neither of diazoxide nor of cap-

Fig. 2.



Relative changes in diastolic blood pressure (BP) and foot volume after administration of placebo, 20 mg nifedipine, 25 mg captopril and 150 mg intravenous diazoxide. *$P<0.05$, **$P<0.01$, versus placebo (Wilcoxons rank sum test). Error bars indicate SEM.

Fig. 3.



Mean relative changes in serum albumin level, foot volume and fractional sodium excretion (FE_{Na}) after administration of placebo, 20 nifedipine, 25 mg captopril and 150 mg intravenous diazoxide. *$P<0.05$, versus placebo (Wilcoxons rank sum test). Error bars indicate SEM.

topril had an effect on the heart rate ($-2 \pm 2\%$ and $+1 \pm 2\%$, respectively) whereas nifedipine increased it by $7 \pm 3\%$ ($1 \pm 2\%$ decrease with placebo, $P<0.05$).

The foot volume remained stable on placebo days and was changed neither by captopril nor by diazoxide administration (Figs 2, 3). In contrast, the foot volume increased rapidly with nifedipine administration and remained increased until the end of the experiment 3 h after drug administration (mean increase $2.6 \pm 0.4\%$, $P<0.01$, Figs 2, 3). None of the subjects developed visible oedema during this short period.

The fractional sodium excretion gradually decreased with administration of placebo and diazoxide (Fig. 3). In contrast, both captopril and nifedipine administration induced an increase in natriuresis. Changes in FE_{Cl} paralleled the changes in FE_{Na}. Administration of the three active drugs changed neither the serum sodium level nor the urine volume during the 3 h after drug administration (data not shown).

The only significant change in body weight was a minimal decrease with captopril administration (by $0.1 \pm 0.1\%$ versus a $0.1 \pm 0.1\%$ increase with placebo, $P<0.05$). The haemoglobin level decreased slightly on placebo days (by $1.1 \pm 0.6\%$) and comparable changes were observed with diazoxide and captopril administration ($0.4 \pm 0.6\%$ and $0.1 \pm 0.5\%$ decreases, respectively). Only nifedipine administration induced a significant, albeit small, increase in haemoglobin level (by $1.7 \pm 0.7\%$, $P<0.01$, versus placebo). Similar changes in serum albumin level were observed (Fig. 3).

Discussion

With our new, simple and accurate method for recording foot volume we could demonstrate that administration of the CEB nifedipine acutely increases sodium excretion and at the same time induces an increase in foot volume in healthy sitting volunteers. The increase in foot volume thus cannot be ascribed to sodium retention. This indicates that administration of nifedipine induces a rapid increase of volume in the hanging legs by local changes in the peripheral vessels. Our data are thus in accord with observations in isolated and denervated cat skeletal muscles, in which local intra-arterial infusion of different types of CEB induced an acute increase of transcapillary fluid filtration and interfered with the increase in vascular resistance which normally protects capillaries against an orthostatic load [9]. Also in humans, systemic administration of a dihydropyridine CEB increased transcapillary fluid filtration in the forearm [10], which could have been caused by an increase in intracapillary hydrostatic pressure after preferential dilation of small precapillary arterioles by CEB [11,12]. However, experiments in bilaterally nephrectomized rats suggested that dihydropyridine CEB increase capillary permeability, because nicardipine induced extravasation of Evans blue dye into skeletal muscle and acutely increased haematocrit levels more than it did those of serum protein [13]. However, our data do not support such an increase in capillary permeability because nifedipine induced a larger rise in the albumin level than it did of the haematocrit level. It is noteworthy that a larger rise in serum albumin level corresponds to transudation because the albumin level is measured in plasma and that of haematocrit in whole blood.

Infusion of the PCO diazoxide did not cause an increase in foot volume. This difference with nifedipine is rather unexpected, because CEB and PCO dilate the same precapillary arterioles [12,14]. It might indicate that different mechanisms underlie oedema formation with CEB and PCO, but our data do not allow firm conclusions to be drawn because the dose of diazoxide used hardly changed the blood pressure and did not induce reflex tachycardia. It is hence not likely that we attained comparable degrees of peripheral vasodilation with nifedipine and diazoxide.

The ACE inhibitor captopril did not change foot volume, in accord with the fact that these drugs do not cause oedema [15]. ACE inhibitors probably do not increase hydrostatic pressure in the capillaries because of preferential dilation of larger arterioles [16].

Because only the acute effects of these vasodilators were studied, we should consider the possibility that their chronic effects are quite different. In the case of PCO, sodium retention with an increase in body weight and oedema formation is frequently observed [4]. In contrast, sodium balance studies after initiation [17] or discontinuation [18] of CEB treatment indicate a long-term reduction in the sodium balance. Thus it is not likely that oedema during chronic use of CEB is caused by sodium retention. Indeed, we have observed several patients who developed oedema during CEB administration and had a simultaneous reduction in body weight.

In conclusion, the parallel increases in foot volume and sodium excretion with nifedipine treatment support the hypothesis that ankle oedema with dihydropyridine CEB is a local phenomenon and a direct consequence of peripheral vasodilation in the hanging legs. The mechanism of oedema formation with PCO remains to be elucidated.

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