Control of Edema in Hypertensive Subjects Treated With Calcium Antagonist (Nifedipine) or Angiotensin-Converting Enzyme Inhibitors With Pycnogenol

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Summary: The presence of edema in different phases and stages of essential hypertension may be due to antihypertensive treatment. Some drugs may cause edema by inducing vasodilatation, increasing the capillary exchange surface and capillary filtration. Pycnogenol has an important anti-edema effect in diabetic microangiopathy and chronic venous insufficiency. This 8-week study evaluated capillary filtration in 2 comparable treatment groups with hypertension treated with a calcium antagonist (nifedipine) or angiotensin-converting enzyme inhibitor to define its efficacy in preventing edema caused by antihypertensives. A significant decrease in filtration was observed in the Pycnogenol groups. Pycnogenol controls this type of edema, it helps to prevent and limit long-term damage in the microcirculation in hypertensive patients, and allows the dose of anti-hypertensive drugs to be reduced in most patients.

Key Words: Hypertension—Pycnogenol—Edema.

The presence of edema in different phases and stages of hypertension may be due both to the disease itself and to treatment. Some antihypertensive drugs may cause important edema by inducing vasodilatation, increasing the number of open capillaries, abnormally increasing the capillary exchange surface, and finally, by enhancing capillary filtration (CF) into the interstitial space. The presence of edema may be an indication of the efficacy of the treatment after vasodilatation, but long-term edema may contribute to a further, progressive deterioration of the microcirculation and increase the damage caused by hypertension itself. Edema may be much more evident and relevant in subjects with associated edema-producing conditions, such as venous disease and diabetes mellitus, which are also causes of edema.

Pycnogenol (Horphag Research Ltd, St Peter Port, Guernsey, UK) is a natural compound that has an important anti-edema effect in several conditions, including diabetic microangiopathy and chronic venous insufficiency.[1-6]

The aim of this 8-week study was the evaluation of CF in subjects with essential hypertension treated with calcium-antagonists or angiotensin-converting enzyme (ACE) inhibitors to evaluate the efficacy of Pycnogenol in preventing edema due to antihypertensive treatment.

PATIENTS AND METHODS

Subjects treated with antihypertensive drugs for essential hypertension and presenting with distal edema (ankle/foot) were included after informed consent. Dietary and salt restriction had been used for at least 6 months. A registry of these patients has been maintained for 10 years within the Vascular Epidemiologic Study in San Valentino.

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Inclusion Criteria

Subjects with edema after treatment with ACE inhibitors or the calcium antagonist nifedipine were selected. Treatment with the antihypertensive drugs remained unchanged during the observation period that followed. Antihypertensive treatment had been used in these patients, without changes in dosage or compound, for at least 4 months. It was not associated with any other treatment.

Hypertension in these subjects, which had been defined as mild-to-moderate, was considered under good control, and the subjects were particularly compliant. The dosage had been individually defined in each subject according to standard indications. The ACE inhibitors used were trandolapril in 10 patients or ramipril in 12 patients. Also, only subjects treated with the calcium antagonist nifedipine were included in the registry.

Exclusion Criteria

Patients with significant, clinical target-organ damage (left ventricle, retina, kidney function) were excluded from the study. Also excluded were patients with diabetes mellitus or any other clinical condition that required pharmacologic treatment.

Treatment

The treatment period with Pycnogenol was 8 weeks. The dosage was 50 mg, 3 times daily versus an equivalent dosage of placebo.

Pycnogenol represents a standardized extract from the bark of the French maritime pine, consisting of a concentrate of polyphenolic substances as procyanidins, catechin, taxifolin, and phenolic acids.[1] Pycnogenol has been shown to improve the microcirculation[2] and to reduce signs and symptoms of chronic venous insufficiency.[3-6] Furthermore, by stimulating endothelial nitric oxide synthesis.[7] Pycnogenol enhances endothelial nitric oxide production and lowers increased blood pressure.[8,9]

The aim of the present study was to investigate whether Pycnogenol would be able to decrease the pathologically enhanced capillary filtration of patients treated with ACE-inhibitors or the calcium antagonist nifedipine by measuring CF with strain-gauge plethysmography,[10-12] with the selective measurement of CF at the foot level as a specific target of the study.

Statistical Analysis

Results were evaluated by using analysis of variance (ANOVA) and Mann-Whitney *U* test.

TABLE 1. Details of the Included Subjects

Treatment	N	Age	M:F
ACE inhibitors			
Pycnogenol	11	47.7 (4)	6:5
Placebo	12	47 (3)	7:5
Nifedipine			
Pycnogenol	16	48 (4)	8:8
Placebo	14	48 (2)	8:6

ACE = angiotensin-converting enzyme.

TABLE 2. Volumetric Capillary Filtration Measured by Strain-Gauge Plethysmography[a]

Treatment Groups	CF at Conclusion	CF at 8 weeks
ACE-inhibitors		
Pycnogenol	2.43 (0.22)	1.56 (0.23)[b]
Placebo	2.41 (0.2)	2.44 (0.3) NS[c]
Nifedipine		
Pycnogenol	2.52 (0.3)	1.61 (0.2)[b]
Placebo	2.62 (0.2)	2.48 (0.3) NS[c]

CF = capillary filtration; ACE = angiotensin-converting enzyme.

a. Expressed in mL/min per 100 cm^3 of tissue.

b. Differences before–after: significantly different to start, $P < .05$.

c. NS = difference before–after not significant. Significantly different compared with placebo significant ($P < .05$).

RESULTS

The two treatment groups were comparable for age, sex, and other variables. Details of the study subjects are shown in Table 1. All subjects completed the study.

Table 2 and Figure 1 show the changes in CF with treatment. At inclusion CF was abnormally increased in groups treated with nifedipine or ACE inhibitors, without a significant difference between the placebo and Pycnogenol groups. No significant changes in CF were observed with placebo, but a significant decrease in CF, toward normality, was observed in both antihypertensive groups treated with Pycnogenol (Figure 1).

The normal CF value ± SD with strain-gauge plethysmography for subjects of this age averages 1.22 ± 0.2 mL/min (range, 1.11 to 1.29 mL/min) in 100 cm^3 of tissue (Figure 1). No side effects or tolerance problems attributable to Pycnogenol were observed during the study.

These results show that Pycnogenol is very effective even in this difficult clinical condition,

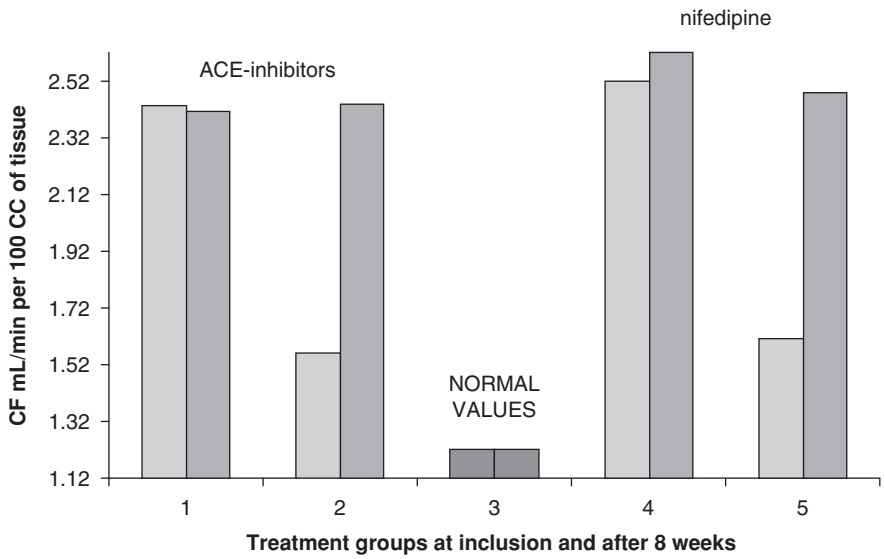

FIG. 1. Variations in capillary filtration (CF) after 8 weeks in the hypertensive treatment groups. Angiotensin-converting enzyme (ACE) inhibitors (left 4 columns), and nifedipine (right 4 columns) with Pycnogenol (grey columns) and placebo (black columns).

in which edema has to be expected in a large percentage of subjects under treatment.

DISCUSSION

In patients with essential hypertension,[13-15,18-20] important changes in microcirculation parameters are a consequence of hypertension, but may also occur as a result of the antihypertensive treatment itself. Skin blood flow and perfusion (evaluated with laser-Doppler flowmetry), transcutaneous measurements of Po_2 and Pco_2, and the measurement of capillary permeability and filtration made before and after treatment with nifedipine[19] have shown the level of microcirculatory alterations.

Before antihypertensive treatment, a significant decrease in skin flow and venoarteriolar response had been observed in hypertensive patients. With antihypertensive treatment (nifedipine), all microcirculatory parameters improved and systolic and diastolic pressures decreased. Capillary filtration was abnormally increased in treated patients in association with the improvement in the microcirculation.[19] The increase in CF in some subjects was much higher than the values observed in normal conditions, and this value induced clinically visible ankle and foot edema.

The importance of abnormalities in the microcirculation of hypertensive subjects is being increasingly recognized. The microvascular changes are a key point in the development of end-organ damage induced by hypertension, including ischemic heart disease.[14,15] At the arteriolar level in the heart and in the whole microcirculation, thickening of the microvascular walls and the progressive, relative narrowing of the lumen eventually produces a level of functional occlusion. The result is a progressive reduction in the number of perfused arterioles or capillaries in most vascular beds, including the coronary circulation. These changes have been seen within the structure and density of the microvascular system at the level of the heart muscle, in the conjunctiva, in the retinas, and in the kidneys.

In most hypertensive patients, an increase in blood pressure produces a rise in resistance in the microcirculation, leading to further elevation of blood pressure. New techniques for exploring the coronary microcirculation have shown that microvascular damage results in reductions of coronary vasodilator reserve, which may be considered an important predictor of clinical deterioration and death. With new studies showing that impairment of microcirculation occurs early in patients with hypertension, there is a need for new therapeutic perspectives in hypertension, concentrating treatment on preventing or reversing changes in the microcirculation of target organs. Insufficient blood flow through end-resistance arteries leads, in time, to severe symptoms associated with peripheral vascular disease.[13-15]

Impaired microcirculatory vasodilatation and adaptation to functional conditions occurs in several types of vascular diseases, including peripheral vascular disease, diabetes mellitus, hypercholesterolemia, hypertension, chronic renal failure, abdominal aortic aneurysms, and venous insufficiency. The development of edema, while the microcirculation improves, represents an important negative effect that may also cause further target organ damage in selected subjects.[16] It is possible, that the extrafiltration of fluids, particularly water and light proteins into the extracapillary compartments, increases the relative concentration of coagulation factors in the blood and alters the viscosity and microdynamics of the blood. The blood viscosity profile and the influence of plasmatic (fibrinogen) and cellular (erythrocyte aggregation) factors in hypertensive patients[16] are altered and may contribute to hypertensive microangiopathy.

Calcium-channel antagonist drugs are widely prescribed against angina and hypertension.[17-19] An important, limiting side effect is edema, which can make heart failure worse. Nifedipine, a calcium-channel antagonist, increases vascular permeability in rat skeletal muscle and skin when injected locally.[18] The injection of nifedipine increased local plasma leakage, and vascular labeling techniques using light microscopy, electron microscopy, and microanalysis show that the microvascular site of leakage is not the capillary but the postcapillary venule of 12 to 36 μm in diameter. In healthy subjects, these vessels control the edema response to inflammation. Therefore, nifedipine acts within the microcirculation by increasing the permeability of the postcapillary venule. As a final event, edema is present at several levels, including in the retinas, the feet, and the coronary circulation, among others.

It is possible that these alterations may be reduced by anti-edema agents that maintain the water in the capillary bed, obstructing the passage of an excess of extra-filtration and, therefore, the genesis of edema.[18-20]

By laser-Doppler flowmetry,[6] in association with other noninvasive microcirculatory techniques such as transcutaneous P_{O_2} and P_{CO_2} and CF measurements it is possible to define 2 major types of microangiopathy:

- Low perfusion microangiopathy (LPM) is observed in peripheral vascular disease, essential hypertension, and Raynaud disease, among others.[21-23]
- High perfusion microangiopathy (HPM) is observed in venous hypertensive microangiopathy, reperfusion microangiopathy, mountain sickness, and diabetic microangiopathy.

In all these conditions, there is an increased skin flux, decreased venoarteriolar response, and increased capillary filtration leading to edema formation. In HPM, elastic compression and drugs acting on capillary filtration effectively reduce skin flux and the increased capillary leakage and edema formation in the lower limbs. In all HPM conditions, edema is the hallmark and the edema observed in antihypertensive treatment also can be considered a type of HPM that benefits by an edema-controlling treatment such as Pycnogenol. It can be actually considered a type of reperfusion microangiopathy.[23]

Specific studies on nifedipine also define this problem. Ankle edema is a common side effect of treatment.[17,19] After 4 weeks of nifedipine therapy, the microcirculation on the dorsum of the foot was measured using laser-Doppler. In treatment patients, there was a significant decrease in venoarteriolar response, which may explain the presence of edema because this response controls the presence of edema in the limbs.[19]

CONCLUSION

The microcirculatory changes observed in hypertensive subjects may be reversed by antihypertensive treatment with the result of another abnormal situation that leads to increased capillary flow, abnormal perfusion, and eventually, a large increase in filtration.

Edema is therefore very common in hypertensive patients under treatment: As many as 35% of treated patients may have some degree of edema. This study indicates that Pycnogenol controls this frequent type of edema and may help to prevent and limit long-term damage in the microcirculation in hypertensive patients.

Treatment with Pycnogenol, in addition to antihypertensive therapy, offers another advantage other than reducing a significant side effect: In a previous study, the dose of the antihypertensive drug nifedipine could be reduced because of the anti-hypertensive effect of Pycnogenol.[9]

Pycnogenol is safe and well tolerated, and thus, this natural extract is an important therapeutic option to reduce the dose of antihypertensive

treatment, improve microcirculation, and also reduce side effects.

Another important observation in the present study was the significant decrease in cough, an other adverse effect of ACE inhibitors, in the group of patients using Pycnogenol; however this will require a separate evaluation.

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