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Evaluation of regional haemodynamics and alterations of vascular wall of the lower limbs in hypertensive subjects

A. PINTO*, R. SCAGLIONE, D. GALATI, S. PATERNA, G. PARRINELLO, S. ARNONE AND G. LICATA

Institute of Internal Medicine, University of Palermo, Palermo, Italy
**Institute of General Pathology, University of Catania, Catania, Italy*

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This study was designed to analyse the relationship between arterial hypertension and changes in arterial blood flow and vascular wall damage of the lower limbs in hypertensive patients with various degrees of hypertension.

Six hundred and fifty-four hypertensive patients (421 males and 233 females) aged 35 to 70 years and 88 healthy subjects (63 males and 25 females) aged 39 to 60 years were studied. Strain-gauge plethysmography of the lower limbs was used to calculate arterial calf blood flow (RF), arterial calf blood flow after post-ischaemic hyperaemia (PF), basal and minimal vascular resistances (BVR and MVR), time to reach peak flow (tPF), time until 50% reduction of peak flow ($tT_{\frac{1}{2}}$) and total recovery time (tT).

In 108 (67 males and 41 females) of the hypertensive patients, a morphological study by echo-Doppler duplex scanning of the popliteal artery was performed to measure medial–intimal thickening and popliteal lumen diameter.

Our results indicate that regional haemodynamics of the lower limbs worsened in hypertensives in comparison with control subjects. In addition, the change in peripheral haemodynamics was related to the degree of hypertension. Moreover, medial—intimal thickening was significantly ($P<0.05$) higher in severe hypertensives than mild hypertensives. Popliteal lumen diameter was significantly ($P<0.05$) lower in severe hypertensives than moderate and mild hypertensives. In all these subjects mean blood pressure was correlated directly ($r=0.31$; $P<0.001$) with medial–intimal thickening and inversely ($r=-0.37$; $P<0.001$) with popliteal lumen diameter. Multiple regression analysis indicated that mean blood pressure, age and serum cholesterol were independently correlated to medial–intimal thickening. This relationship was not influenced by the diabetic patients and smokers among the groups.

Our results indicate that hypertension impairs peripheral flow and encourages the development of medial–intimal thickening.

Introduction

Hypertension may promote major changes in regional haemodynamics and in the arterial wall. Some of these may be considered protective and are related to a remodelling of the artery to better withstand the increase in wall tension resulting from high intravascular pressure. However, other responses to vascular injury induced by hypertension might predispose the artery to further adverse consequences[1].

For these reasons some authors have recently hypothesized the common origin of hypertension and atherosclerosis[2,3]. Although hypertension is reported to impair regional haemodynamics and to increase the risk of developing atherosclerotic plaques[4], few studies have been undertaken to analyse the effects of hypertension on regional haemodynamics and the arterial wall of the lower limbs.

The investigation of regional haemodynamics has greatly improved since the introduction of strain gauge plethysmography. This is the only non-invasive method available for the direct measurement of arterial blood flow at rest and after ischaemia, and of vascular wall reactivity, and for the indirect measurement of vascular resistances[5–7].

In addition, several studies have recently stressed the role of echo-Doppler in the detection both of arterial wall and blood flow[7–12]. With these two methods it is possible to follow the development of haemodynamic alterations and to specify the severity of vascular structural damage in relation to the degree of hypertension (mild, moderate and severe)[7,8,11–15]. This study was designed to evaluate the relationship between arterial wall and haemodynamic alterations (arterial calf blood flow, vascular reactivity times and basal and minimal vascular resistances) in patients with essential hypertension.

Subjects and methods

SUBJECTS

Six hundred and fifty-four patients (421 males and 233 females aged 35 to 70 years) with a diagnosis of mild, moderate and severe essential hypertension according to the criteria of the Joint National Committee on detection, evaluation and treatment of high blood pressure were selected over a ten year period (1983–1993)[16]. Normal blood pressure was defined as a systolic blood pressure lower than or equal to 140 mmHg and a

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Correspondence: Professor Antonio Pinto, via Segesta n° 5, 90141 Palermo, Italy.

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Table 1 Characteristics of the total population

	Control (A)	Mild HT (B)	Moderate HT (C)	Severe HT (D)	$P<0.05$
M/F	63/25	155/91	142/74	124/68	—
Age (years)	50 ± 10	51 ± 12	50 ± 13·5	53 ± 16	ns
Height (cm)	165 ± 5	166 ± 4	164 ± 5	166 ± 3	ns
Weight (kg)	73 ± 12	74 ± 10	74 ± 9	75 ± 8	ns
SBP (mmHg)	125·2 ± 5·1	160·9 ± 6·27	185·4 ± 8·5	205·5 ± 15·8	*
DBP (mmHg)	74·8 ± 4·1	104·7 ± 5·15	116·2 ± 6·25	130·8 ± 7·75	*
MBP (mmHg)	92·5 ± 3·4	123·6 ± 5·4	140·9 ± 6·5	154·4 ± 10	*
HR (beats . min^{-1})	74 ± 8	76 ± 6·4	76 ± 9	78 ± 12	**

Mild HT, Moderate HT and Severe HT=mild, moderate and severe hypertensives; M/F=males/females; SBP=systolic blood pressure; DBP=diastolic blood pressure; MBP=mean blood pressure; HR=heart rate.
*, A vs B–C–D; B vs C–D; C vs D.
**, A vs D.

diastolic blood pressure lower than or equal to 90 mmHg. Hypertension was defined as systolic blood pressure higher than or equal to 160 mmHg or diastolic blood pressure higher than 90 mmHg. Mild hypertension was defined as diastolic blood pressure higher than 90 and lower than 100 mmHg, moderate hypertension as diastolic blood pressure higher than 100 and lower than 110 mmHg and severe hypertension as diastolic blood pressure higher than 110 mmHg[16]. A full review of medical records was used to support the diagnosis of hypertension and its degree. For this reason, only the medical records containing at least three consecutive measurements of blood pressure were considered for further analysis. Blood pressure was measured in triplicate using a mercury sphygmomanometer after 5 min in a supine position. Phase V of the Korotkoff method was used to measure diastolic blood pressure. Mean blood pressure was calculated by the sum of diastolic blood pressure and one third of pulse pressure; heart rate (beats . min^{-1}) was detected by electrocardiographic tracing. Eighty-eight normotensive healthy subjects (Group A) (63 males and 25 females) aged 39 to 60 years were also studied and acted as controls. All patients were submitted to a non-invasive haemodynamic study of the lower limbs by strain-gauge plethysmography. The 654 hypertensive patients were subdivided into three groups according to the stage of hypertension. Group B included 270 patients with mild hypertension (175 males and 95 females aged 35 to 65 years); group C included 212 patients with moderate hypertension (136 males and 76 females aged 36 to 67 years; group D included 172 patients with severe hypertension (110 males and 62 females aged 38 to 70 years) (Table 1).

METHODS

Strain-gauge plethysmography

This method is based on the principle that variations in mercury column resistance are related to sphygmic changes in the body, as previously described by Whitney[17]. Every change in limb volume corresponds to a modification in the length of the mercury in the tube (strain-gauge) placed around the limb; it determines a signal, which opportunely translated and amplified, is recorded by a polygraph. Flow measurement, taken while the subject is resting, is performed by venous occlusion, using an instantaneous insufflating cuff located higher than the detector (strain-gauge) at a pressure higher than venous pressure (50 mmHg) and lower than diastolic pressure. The resulting compression facilitates arterial inflow, prevents venous downflow, while allowing quantitative analysis of blood to be evaluated. After evaluating resting flow value, ischaemia was then induced by cuff insufflation to a pressure higher than systolic pressure (250–300 mmHg); this was then maintained for 3 min. Measurements taken 5 s after fast decompression of the cuffs may give the post-ischaemic first-flow value; the higher peak after decompression yields the peak flow value. Subsequent recordings were performed every 5–10 s for 5 min to evaluate how long it took for resting conditions to be reinstated. Moreover, with strain-gauge plethysmography it is possible to measure leg systolic pressure, basal and minimal vascular resistances non-invasively[5,6,7,17].

Using a Periflow 4 Janssen the following haemodynamic parameters were detected: arterial calf blood flow at rest (RF) (ml . min^{-1} . 100 g tissue^{-1}); arterial calf blood flow after post-ischaemic hyperaemia (PF) (ml . min^{-1} . 100 g tissue^{-1}); basal and minimal vascular resistances (BVR and MVR) arbitrary units were obtained as follows: mean blood pressure divided by resting and peak flow; time to reach peak flow (tPf) (s); time to 50% reduction of peak flow ($tT\frac{1}{2}$) (s); total recovery time (tT).

This method is currently utilized in our laboratory with good reproducibility[6,7].

Echo-Doppler duplex scanning

This method utilises B-mode echotomography in combination with a pulsed or continuous wave Doppler; in this way it is possible to obtain both detailed vascular images and accurate measurements of vessel diameter

Table 2 Haemodynamics of the lower limbs in the total population

	Control (A)	Mild HT (B)	Moderate HT (C)	Severe HT(D)	$P<0.05$
RF (ml . min^{-1})	3·98 ± 0·9	4·15 ± 2·12	3·09 ± 1·67	2·94 ± 2·08	***
PF (ml . min^{-1})	25·11 ± 5·4	24·15 ± 2·12	20·93 ± 9·11	12·01 ± 7·88	**
tPF (s)	3·0 ± 0·3	3·3 ± 0·5	4·0 ± 1·5	5·5 ± 1·0	*
tT_1^1 (s)	9·0 ± 4·5	12·5 ± 6·0	19·5 ± 8·5	22·5 ± 7·5	*
tT^2 (s)	65 ± 15	85 ± 10	95 ± 25	115 ± 35	*
RVB (AU)	25·24 ± 5·9	27·4 ± 4·33	42·56 ± 13·4	51·4 ± 18·22	**
RVM (AU)	3·68 ± 0·91	6·12 ± 3·4	7·06 ± 4·21	11·95 ± 4·89F	*

Mild HT, Moderate HT and Severe HT=mild, moderate and severe hypertensives; RF=rest flow; PF=peak flow; tPF=time to rice peak flow; tT_1^1=time until 50% reduction of peak flow; tT=total recovery time; RVB=basal vascular resistances; RVB=minimal vascular resistances.
*A vs B–C–D; B vs C–D; C vs D.
**A vs C–D; B vs C–D; C vs D.
***A vs C–D; B vs C–D.

and haemodynamic changes. To detect the popliteal artery we usually employ a 5 MHz probe because it gives a good resolution of the more profound artery[7,8–12]. In our laboratory echo-Doppler duplex scanning has shown an intra-observer variability of 5·9%[7,8].

In 108 (67 males and 41 females) of the 654 hypertensives medial–intimal thickening of the popliteal artery occurred. Thickening was considered to have taken place if it was equal to or lower than 0·5 mm. The lumen diameter (in mm) of the popliteal artery was measured with a Sonedap 40 echographic instrument. The popliteal artery was scanned longitudinally, using the best images for determination, to visualize the I-M complex on the far wall of the artery. Medial–intimal thickening and the popliteal lumen diameter were measured from frozen images of the artery (10 to 20 mm proximal to the bifurcation) by two observers independently. Areas of calcified plaque or calcified wall were not measured. Each subject was scanned for 20 min and an additional 20 min was used to take the measurements. The hypertensive patients were further subdivided into three groups: subgroup 1 included 38 patients with mild hypertension (23 males and 15 females aged 35 to 65 years); subgroup 2 included 36 patients with moderate hypertension (21 males and 15 females aged 36 to 67 years); subgroup 3 included 34 patients with severe hypertension (23 males and 11 females aged 38 to 70 years). In addition, serum total cholesterol, triglyceride levels, smoking habits and the presence of diabetes mellitus were also evaluated. Subjects were considered to be smokers if they currently smoked five cigarettes a day, or had stopped smoking only 6 months before the study.

Prevalent diabetes mellitus was defined as a fasting glucose ≥ 140 mg . dl^{-1}, a non-fasting glucose ≥ 200 mg . dl^{-1} and/or a history of/or treatment for diabetes[18].

Statistical analysis

Differences between all groups were evaluated by one-way analysis of variance and Newman-Keuls post hoc test. Comparison of the percentage of diabetic patients and smoking subjects among all the groups were analysed by the Chi-square test. Linear regression analysis was used to calculate coefficients of correlation between mean blood pressure, medial–intimal thickening and the lumen diameter of the popliteal artery. Multiple regression analysis was used to ascertain whether the mean blood pressure was independently correlated with medial–intimal thickening and the popliteal lumen diameter. Independent variables in the multiple regression analysis was mean blood pressure, age, gender, serum cholesterol, diabetes and smoking habits. A $P<0.05$ was considered statistically significant. All the results were expressed as mean value ± standard deviation.

Results

TOTAL POPULATION

All the groups were comparable with regard to age, gender and height. Systolic, diastolic and mean blood pressure were obviously significantly ($P<0.05$) higher in the hypertensive groups than in controls. Only in severe hypertensives was heart rate higher than controls; it did not change at all in the other groups (Table 1).

PERIPHERAL HAEMODYNAMICS

Rest flow (ml . min^{-1} . 100 g muscle tissue^{-1})

Arterial blood flow at rest was significantly lower ($P<0.05$) in moderate and severe hypertensives than in mild hypertensives and controls. However, no difference was observed in arterial rest flow between moderate and severe hypertensives (Table 2).

Peak flow (ml . min^{-1} . 100 g muscle tissue^{-1})

Post-ischaemic arterial blood flow of the lower limbs was significantly ($P<0.05$) lower in severe hypertensives than controls and moderate and mild hypertensives, and significantly lower in moderate hypertensives than

Table 3 Characteristics and percentage of diabetics and smokers in the morphologic study

	Mild HT Group 1	Moderate HT Group 2	Severe HT Group 3	$P<0.05$
Number	38	36	34	—
M/F	23/15	21/15	23/11	—
Age (years)	49 ± 13	50 ± 12	54 ± 13	ns
Height (cm)	166 ± 5	164 ± 4	165 ± 4	ns
Weight (kg)	71 ± 8	73 ± 7	74 ± 5	ns
SBP (mmHg)	161·5 ± 8·8	180·9 ± 10·05	201·95 ± 18·05	*
DBP (mmHg)	105·2 ± 6·35	115·2 ± 7·15	132·8 ± 8·80	*
MBP (mmHg)	123·5 ± 5·14	138·9 ± 6·09	153·0 ± 9·34	*
HR (beats . min^{-1})	77·5 ± 7·01	78·2 ± 8·75	79·9 ± 6·25	ns
				χ^2-test
Diabetic patients	10 (26·5%)	7 (19·5%)	7 (20·5%)	ns
Smoking patients	6 (15·8%)	11 (30·6%)	15 (44·1%)	ns

Mild HT, Moderate HT and Severe HT=mild, moderate and severe hypertensives; M/F=males/females; SBP=systolic blood pressure; DBP=diastolic blood pressure; MBP=mean blood pressure; HR=heart rate.
*, 1 vs 2–3; 2 vs 3.
**, 1 vs 2–3.

controls and mild hypertensives. No significant change in peak flow was observed between mild hypertensives and controls (Table 2).

Basal vascular resistance (arbitrary units)

Basal vascular resistance was significantly ($P<0.05$) higher in severe hypertensives than controls and moderate and mild hypertensives and significantly higher in moderate hypertensives than controls and mild hypertensives. No significant changes in basal vascular resistance was observed between mild hypertensives and controls (Table 2).

Minimal vascular resistances (arbitrary units)

Minimal vascular resistances were significantly ($P<0.05$) higher in all the hypertensive groups than controls. In addition, they were significantly ($P<0.05$) higher in severe hypertensives than moderate and mild hypertensives and in moderate hypertensives than mild hypertensives (Table 2).

Arterial wall reactivity times (tPF-$tT\frac{1}{2}$-tT s)

Indirect expression of arterial wall reactivity times progressively worsened in all the groups. In particular, they were significantly ($P<0.05$) higher in severe hypertensives than in moderate and mild hypertensives and in moderate hypertensives than mild hypertensives (Table 2).

MORPHOLOGICAL PARAMETERS

One hundred and eight of 654 hypertensive patients were also submitted to echo-Doppler duplex scanning to evaluate the change in the arterial wall. These subjects were comparable with regard to age, gender, height, weight, heart rate and triglycerides. In addition, no significant differences were found as regards smoking habits or the percentage of diabetic patients (Table 3). On the contrary, total serum cholesterol levels were significantly ($P<0.05$) higher in severe hypertensive subjects than in mild hypertensives.

Medial–intimal thickening and lumen diameter of popliteal artery (mm)

The medial–intimal thickening of the popliteal artery was 0·75 ± 0·44 mm in mild hypertensives, 0·94 ± 0·58 mm in moderate hypertensives and 1·25 ± 0·65 mm in severe hypertensives. These values were significantly ($P<0.05$) lower in severe than in moderate and mild hypertensives and in moderate than mild hypertensives. The popliteal lumen diameter was 4·44 ± 0·44 mm in mild hypertensives, 4·25 ± 0·58 mm in moderate hypertensives and 3·91 ± 0·65 mm in severe hypertensives. These values were significant ($P<0.05$) lower in severe hypertensives than moderate and mild hypertensives.

In all these subjects mean blood pressure correlated directly ($r=0.31$; $P<0.001$) with medial–intimal thickening and inversely with popliteal lumen diameter ($r=-0.37$; $P<0.001$) (Fig. 1). Multiple regression analysis indicated that mean blood pressure, age and serum cholesterol were independently correlated to medial–intimal thickening.

Discussion

It is known that essential hypertension in humans is characteristically associated with increased peripheral vascular resistances[13,15,19,20]. Moreover Eagan[21] and co-workers reported that hypertension was related to an altered relationship between blood flow and resistance. Other studies have reported an altered function not only of the resistive vessels but also of the large arterial vessels, with a significant reduction of the compliance of the latter[22–24].

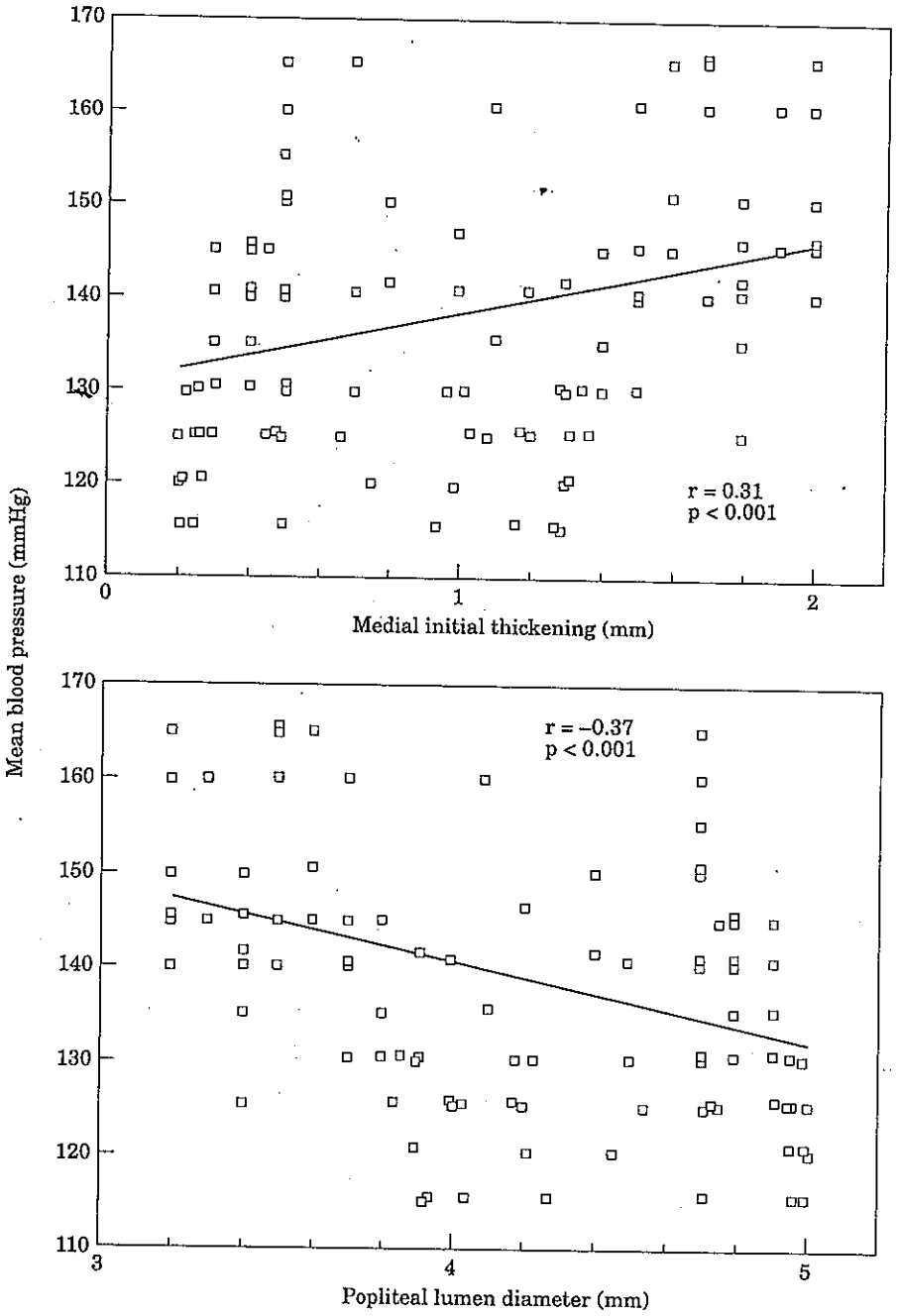

Figure 1 Correlation between mean blood pressure, medial–intimal thickness and popliteal lumen diameter in 108 hypertensive subjects.

In the present study, we have confirmed the progressive worsening of the regional haemodynamics of the lower limbs in the patients with arterial hypertension.

In particular, our study indicates that the maximal capacity of vasodilatation of the circulatory bed in hypertensive patients is impaired proportionally to the severity of hypertension; this is supported by the fact that basal and minimal vascular resistances increased in parallel to the rise in medial–intimal thickening of the artery and to the changes in the measurement of vascular wall reactivity.

These alterations relate to the arteriolar–capillary wall damage (hypertrophy, medial–intimal hyperplasia, functional defect in the relaxation processes of the vascular muscle cells)[25–29]. Although we indirectly evaluated the arterioles, our results suggest that in 108 of 654 patients medial–intimal thickening of the popliteal artery also occurred in mild hypertensive patients. However, this alteration is more evident in moderate and severe hypertensives who usually have impaired arterial calf flow. This finding might be supported by the direct correlation found between mean blood pressure and medial–intimal

thickening; this indicates that the severity of the hypertension may have a bearing on the arterial lesion. This is further supported by multiple regression analysis, which indicated that mean blood pressure is one of the best predictors of medial–intimal thickening of the popliteal artery. The decrease in the lumen diameter of the popliteal artery related to the degree of hypertension does not seem to impinge on the flow of the lower limbs of our patients. Both these findings (medial–intimal thickening and popliteal lumen diameter) might be considered an adaptative phenomenon to the hypertensive stage rather than an early atherosclerotic lesion.

Data on alterations in large calibre arteries induced by hypertension are more recent[1,30,31]. Our results show that hypertension can promote specific organ damage, facilitating worsening of the vascular system. It probably occurs because of the strong pressure which is put on the haematic flow[1]. However, the alterations in vascular wall of the lower limbs might be due to concomitant diseases i.e. diabetes, hypercholesterolemia or to the differing number of smokers in the three groups of hypertensives. In view of this, the percentage of diabetic patients and smokers among mild, moderate and severe hypertensives were similar. Serum cholesterol levels were instead significantly higher in severe hypertensives than mild hypertensives. This indicates that in our subjects hypertension rather than diabetes or smoking impairs peripheral flow and aids in the development of medial–intimal thickening. However, further data have to be provided to explain the mechanisms responsible for the altered blood flow and the change in the arterial wall associated with hypertension.

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