Increased Pulse Pressure in Patients with Arteriosclerosis Obliterans of the Lower Limbs

Michel E. Safar, Jean J. Totomoukouo, Risk A. Asmar, and Stéphane M. Laurent

Brachial blood pressure, ankle systolic pressure, calf blood flow before and after postocclusive reactive hyperemia, and treadmill exercise results were determined in 16 patients with arteriosclerosis obliterans disease (AOD) of the lower limbs. These values were compared with values from 16 controls matched for age and sex. For the same mean arterial pressure in controls, pulse pressure was significantly higher and resting calf blood flow, slightly lower in patients with AOD. Resting calf blood flow was positively correlated with mean arterial pressure and pulse pressure in patients with AOD but not in controls. In AOD patients, reduced walking distance was strongly and positively correlated with "vascular bed reserve" expressed as the ratio between peak blood flow after postocclusive reactive hyperemia and resting calf blood flow. Correlation studies indicated that the higher the pulse pressure, the more reduced the walking distance and the more altered the vascular bed reserve. The study provided evidence that: 1) Increased pulse pressure, rather than increased mean arterial pressure, is a characteristic feature of patients with AOD, and 2) the pulsatile component of blood pressure, which reflects the alteration of the buffering function of large arteries, might influence the reductions in walking distance and vascular bed reserve observed in patients with AOD. (Arteriosclerosis 7:232–237, May/June 1987)

In patients with arteriosclerosis obliterans of the lower limbs (AOD), hypertension is frequent. Intra-arterial blood pressure measurements have shown that systolic pressure is predominantly increased, with minimal changes in diastolic and mean arterial pressure. Increased systolic, and hence pulse, pressures have been found to be due to a reduction in arterial compliance and a modification in the timing of reflected waves without major alterations in ventricular ejection and vascular resistance. However, such systemic hemodynamic changes have been poorly related to the most important clinical features of patients with AOD: reduced walking distance and impaired postocclusive reactive hyperemia. In the present investigation, reduced walking distance and postocclusive reactive hyperemia were evaluated by use of noninvasive techniques in patients with AOD. These two parameters may be related to the level of pulse pressure rather than to the level of mean arterial pressure, reflecting the alterations in the buffering function of large arteries of patients with arteriosclerosis obliterans.

Methods

Study Population

A total of 32 subjects were included in the present study: 16 ambulatory patients with AOD and 16 control subjects. All subjects were untreated or had discontinued their therapy at least 4 weeks before the investigation.

The 16 patients with arteriosclerosis obliterans (eight men and eight women) were included by a diagnosis based on their history, results of physical examination, and appropriate noninvasive laboratory investigations including the determination of the ratio of ankle to brachial systolic pressure as described below. All subjects suffered from unilateral intermittent claudication defined as a predominant cramping discomfort in the calf, clearly provoked by walking and relieved after several minutes of rest. The claudication distance varied between 30 and 1000 meters. No subject had rest pain, gangrene, or neurological and locomotor involvement. In all cases, the diagnosis was confirmed by standard arterial angiography. The 16 patients had unilateral stenosis of the iliac and/or femoro-popliteal arteries. Their ages were from 36 to 72 years (mean: 59 ± 3 years) (± 1 SEM); weight was 45 to 100 kg (mean: 67 ± 3 kg); mean height was 1.65 ± 0.01 meter. No patient had clinical symptoms of heart failure or coronary insufficiency. The chest x-ray did not show any pulmonary abnormality; no depression of the ST segment was observed on the electrocardiogram (ECG). No patient had proteinuria, urinary infection, or electrolyte disturbance.
In the 16 control subjects (nine men and seven women), physical examination and standard biological parameters were strictly normal. In all cases, the palpation of the distal arterial pulses was performed at least three times and was strictly normal. In addition, noninvasive hemodynamic tests were within the normal range (i.e., after at least three measurements, the ratio of the ankle to brachial systolic pressure was greater than one). Control subjects were matched for age, weight, and height to the AOD patients. In addition, the controls were chosen to have the same mean arterial pressure (MAP) as patients with AOD. Evaluation of MAP is indicated below. Control subjects were from 47 to 70 years old (mean 56 ± 2 years); weight was between 54 and 80 kg (mean 69 ± 2 kg); and mean height was 1.65 ± 0.01 m.

Consent for this investigation was obtained from the 32 subjects after a detailed description of the procedure. The protocol was approved by the Institut National de la Santé et de la Recherche Médicale (INSERM).

**Hemodynamic Assessment Protocol**

After the patients rested 30 minutes in the supine position, the hemodynamic study was performed in a quiet room with a controlled temperature of 21° to 24°C. The protocol was assessed in the following order: measurement of systemic arterial pressure, determination of the ratio between ankle and brachial systolic pressures by the Doppler technique, and evaluation of calf blood flow by plethysmographic method. In addition, the 16 patients with arteriosclerosis obliterans underwent an exercise treadmill test, which was followed by a second determination of the ratio of ankle to brachial systolic pressures.

**Measurement of Arterial Pressure and Heart Rate**

Arterial pressure was measured according to the American Heart Association Recommendation with a standard mercury sphygmomanometer and by the auscultatory method, on the basis of Korotkoff phases: phase I for the systolic arterial pressure (SAP) and phase V for the diastolic arterial pressure (DAP). MAP was calculated in mm Hg as the diastolic pressure plus one-third pulse pressure (PP). PP was the difference between SAP and DAP. Validation for these calculations had been previously performed in our laboratory, using intra-arterial measurements. Heart rate (beats per minute) was determined on the basis of the ECG recording immediately after the blood pressure determination.

**Brachial and Ankle Systolic Arterial Pressure Measurement**

Brachial and ankle systolic arterial pressures were measured using a pressure cuff of appropriate dimension, a standard mercury sphygmomanometer, and a Doppler probe according to the technique described by Yao et al. Brachial systolic pressure (BSP) was recorded on the basis of the first appearance of an audible sound. Ankle systolic pressure (ASP) was determined by a pressure cuff applied snugly above the malleolus. The cuff was inflated by about 40 to 50 mm Hg above the brachial systolic pressure. The end-point of the systolic pressure was determined by the reappearance of the pulse (a sound audible by Doppler). On the basis of this technique, no limb presented an incompressible arterial syndrome. Three measurements were performed on each limb and were averaged to give the mean value of the ankle systolic pressure. The ASP/BSP ratio was then calculated on the basis of these measurements.

**Measurement of Calf Blood Flow**

The calf blood flow was measured at rest and after ischemia by means of venous occlusion plethysmography as described previously. The subjects dressed in trunks were placed in the prone position. The leg to be examined was placed on a pillow with the calf on a level higher than the heart. In all cases, just before the measurement of blood flow, the circulation of the foot was occluded with a pneumatic cuff placed 15 cm below the knee joint. The gauge was placed at a standard site around the widest part of the calf. A pneumatic cuff was placed around the thigh just above the knee. Resting calf blood flow (RCBF) was measured by inflating the cuff to 60 mm Hg in order to determine the arterial input. Three measurements were performed and the mean value was calculated. Then the cuff was inflated to 250 mm Hg in order to induce ischemia over 3 minutes. Rapid determination of blood flow was carried out during subsequent reactive hyperemia. Thus calf “peak” blood flow (CPBF) was measured. Blood flow was expressed in ml/min/100 ml of tissue. Normal values of the laboratory for RCBF between 50 and 75 years are between 1 and 4 ml/min/100 ml (mean = 2.5 ml/min/100 ml). Intersubject reproducibility was 4 ± 1%. The CPBF/RCBF ratio was then calculated and multiplied by 10 for simplicity. As far as calf blood flow measurements are concerned, there is a well-known problem with attempting venous occlusion on the thigh because of its thickness. Subdiastolic pressures occlude surface veins draining the calf but possibly not deep veins, depending on the dimensions of the thigh and the amount of muscle. On the other hand supradiastolic pressure to occlude the deeper veins can reduce arterial inflow. However, validation of plethysmographic methods have been previously provided by comparison with direct measurements of flow, suggesting that, at least in steady state conditions, the CPBF/RCBF ratio may be a valid parameter.

**Exercise Protocol**

Patients with AOD were then tested for their ability to walk a distance. This test used a treadmill at a speed of 3 km/h and a 10% inclination according to classical methods. Electrocardiogram monitoring was performed with 12 leads. After the pain-free walking distance, the initial walking distance (IWD) was determined as the distance to the first sensation of pain, ache, cramp, or severe fatigue. The patient was then encouraged to continue the exercise until he had to stop because of maximal increasing pain. The beginning of the exercise to this last point was considered as the maximal walking distance (MWD). All patients had to be able to walk on the treadmill for at least 30 meters for the MWD, and for less than 1000 meters for the MWD. They underwent the treadmill test on at least three visits. Patients studied included only those who showed a stable
walking distance, i.e., when the three MWD varied less than 25%. IWD and MWD were the mean values of the measurements at the three visits. No patient had chest pains or a significant positive ST segment depression at ECG monitoring during or after exercise. BSP, ASP, and heart rate were measured immediately after the end of the treadmill test as described elsewhere.6-13

Statistical Analysis
Mean ± 1 standard error of the mean, correlation coefficient, and variance analysis were calculated by standard statistical methods.14 Differences in means between control subjects and patients with AOD were assessed by Student’s t test. The effect of exercise in AOD was assessed by the paired t test. A p value of less than 0.05 was accepted as being statistically significant.

Results
Systemic Hemodynamics at Rest
Although mean arterial pressure was quite similar in the two populations, systolic arterial pressure was slightly higher and diastolic arterial pressure, slightly lower in patients with AOD (Table 1). Heart rate was similar in the two populations. Pulse pressure was significantly higher in patients with AOD than in control subjects (68 ± 6 mm Hg versus 50 ± 2; p < 0.01).

Pulse pressure and mean arterial pressure were significantly correlated in both populations. Figure 1 shows that, at any given value of mean arterial pressure, pulse pressure was higher in patients with AOD than in controls.

Regional Hemodynamics at Rest
At rest, ankle systolic pressure was significantly lower in patients with AOD than in control subjects (73 ± 6 mm Hg versus 155 ± 5 mm Hg; p < 0.001) (Table 2). The ASP/BSP ratio was significantly different between the two groups of subjects (0.50 ± 0.05 versus 1.10 ± 0.01; p < 0.001).

Resting calf blood flow (RCBF) was significantly reduced in patients with AOD (1.96 ± 0.25 versus 2.79 ± 0.27 ml/min/100 ml) (p < 0.05) but remained within the normal values of our laboratory (see above). In patients with AOD, RCFB was significantly and positively correlated with mean arterial pressure (r = +0.66; p < 0.01) and with pulse pressure (r = +0.61; p < 0.01) (Figure 2). In control subjects, no significant correlations were observed between RCFB and mean arterial pressure (r = 0.39) or pulse pressure (r = 0.10).

Calf Peak Blood Flow
CPBF was significantly lower in patients with AOD than in control subjects (5.75 ± 0.35 versus 25.96 ± 1.85 ml/min/100 ml; p < 0.001) (Table 2). There was a significant correlation between CPBF and the ASP/BSP ratio (r = +0.60; p < 0.01) in patients with AOD. No significant correlation was observed between these two parameters in control subjects (r = -0.30).

The CPBF/RCBF ratio was significantly reduced in patients with AOD (34.7 ± 3.7 versus 101 ± 8.2; p < 0.001) (Table 2). The ratio was significantly correlated with the pulse pressure (r = +0.61; p < 0.01) (Figure 2). In control subjects, no significant correlations were observed between RCFB and mean arterial pressure (r = 0.39) or pulse pressure (r = 0.10).

Table 1. Systemic Hemodynamic Parameters in Resting Patients with Arteriosclerosis Obliterans Disease of the Lower Limbs

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control subjects (n = 16)</th>
<th>AOD patients (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>140 ± 4</td>
<td>148 ± 6</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>89 ± 3</td>
<td>81 ± 2</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>107 ± 3</td>
<td>104 ± 4</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>50 ± 2</td>
<td>68 ± 6*</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>75 ± 2</td>
<td>71 ± 3</td>
</tr>
</tbody>
</table>

Values are mean ± 1 SE. *p < 0.01.

Table 2. Regional Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control subjects (n = 16)</th>
<th>AOD patients (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle systolic pressure (mm Hg)</td>
<td>155 ± 5</td>
<td>73 ± 6*</td>
</tr>
<tr>
<td>Ankle systolic pressure/brachial systolic pressure</td>
<td>1.10 ± 0.01</td>
<td>0.50 ± 0.05*</td>
</tr>
<tr>
<td>Resting calf blood flow (ml/min/100 ml)</td>
<td>2.79 ± 0.27</td>
<td>1.96 ± 0.25†</td>
</tr>
<tr>
<td>Calf peak blood flow (ml/min/100 ml)</td>
<td>25.96 ± 1.85</td>
<td>5.75 ± 0.35*</td>
</tr>
<tr>
<td>CPBF/RCBF × 10†</td>
<td>101.0 ± 8.2</td>
<td>34.7 ± 3.7*</td>
</tr>
</tbody>
</table>

Values are mean ± 1 SE. *p < 0.001, †p < 0.05. ‡Arbitrary unit.
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Figure 2. Relationships between resting calf blood flow and mean arterial pressure (A) and pulse pressure (B) in patients with arteriosclerosis obliterans of the lower limbs.

ASP/BSP ratio in patients with AOD (r = 0.72; p < 0.001) but not in controls (r = 0.11). Figure 3 shows the correlations between the CPBF/RCBF ratio with mean arterial pressure (A) and pulse pressure (B). The ratio was negatively and significantly correlated with pulse pressure in controls (r = −0.52; p < 0.05), in patients with AOD (r = −0.80; p < 0.001) and in the whole population (r = −0.76; p < 0.001). No comparable results were obtained with mean arterial pressure (Figure 3).

Hemodynamic Effects of Exercise Test in Patients with AOD

After the exercise treadmill test, brachial systolic pressure increased significantly from 149 ± 7 to 164 ± 7 mm Hg (p < 0.01) and heart rate from 71 ± 3 to 118 ± 4 beats/minutes (p < 0.001), whereas ankle systolic pressure decreased significantly from 73 ± 6 to 46 ± 9 mm Hg (p < 0.001) and the ASP/BSP ratio, from 0.50 ± 0.05 to 0.29 ± 0.06 (p < 0.001).

The initial walking distance was 111 ± 20 meters and the maximum walking distance was 334 ± 66 meters. MWD was negatively correlated with pulse pressure (r = −0.58; p < 0.02) (Figure 4) but not with mean arterial pressure (r = −0.29). MWD was positively and significantly correlated with the CPBF/RCBF ratio (r = + 0.72, p < 0.005).

Discussion

In previous studies, increased pulse pressure was noticed in patients with AOD in comparison with age- and...
sex-matched normal subjects. However, mean arterial pressure was slightly different in the two populations, suggesting that hyperpulsatility in patients with AOD might be the simple consequence of the elevation in mean arterial pressure. Indeed, the two parameters are usually strongly and positively correlated. In the present investigation, patients with AOD were compared with controls of similar age, sex, and mean arterial pressure. In that condition, misleading interactions between pulse pressure and mean pressure at rest could be easily ruled out.

In the present investigation, resting calf blood flow remained within the normal range of our laboratory. However, in comparison with controls matched for the same mean arterial pressure, the value was slightly reduced. Moreover, in patients with AOD, resting calf blood flow was positively related to mean arterial pressure (Figure 2), a finding which is important to discuss. It is well accepted that the hemodynamic changes of the diseased lower limb in patients with AOD result from the association of two major resistances in series, the stenosis and the arterioles, rather than predominantly the downstream arterioles as is normally the case. Clearly, flow is determined by the driving pressure across these two resistances, the systemic arterial pressure of which is an important component. In such conditions, it seems likely that elevated systemic arterial pressure in patients with AOD contributes to the maintenance of an adequate perfusion of the lower limbs, causing a positive correlation of resting calf blood flow both with mean arterial pressure and with pulse pressure (Figure 2).

Although the effect of arteriosclerosis obliterans on resting blood flow is important, it is clear that the limiting influence of the disease will occur at elevated flow rates, i.e., during exercise and postocclusive reactive hyperemia, because the pressure drop caused by the stenosis increases with increasing flow. Under conditions of exercise in which maximum blood flow is required, vascular reserve is reduced in patients with AOD, causing a decrease in walking distance.

In the present investigation, this problem was studied using two classical methods which require methodologic comments: 1) plethysmographic measurements immediately following postocclusive hyperemia and 2) exercise testing involving brachial versus ankle systolic pressure measurements. As far as the former is concerned, it is important to recall that the recovery is exponential with the major fall in flow occurring in the first few seconds. Therefore, it may be difficult to observe peak values using the slow plethysmographic technique. Nevertheless, because of low peak values, one may get much closer to a true peak flow in the diseased leg than in the normal one. However, as a result, differences between controls and AOD patients are minimized, suggesting that the evaluations of the CPBF/RCBF ratio could be an adequate index in clinical practice. Similar observations could be made about the timing of brachial versus ankle systolic pressure measurements during rapid recovery following treadmill exercise. Since the effect of exercise on the percentage fall of ankle systolic pressure versus time may be different in AOD patients according to the topography of occlusions, the ASP/BSP ratio was used in the present study as a semiquantitative index to evaluate the degree of exercise testing and was not taken into consideration for correlation studies.

Within the limitations of the methodology, a strong positive correlation between walking distance and vascular bed reserve was observed in patients with AOD as expressed by the CPBF/RCBF ratio (Figure 4). However, the dominant findings of the study were the relationships observed between pulse pressure on one hand, and walking distance and the CPBF/RCBF ratio on the other hand: the higher the pulse pressure, the more reduced the walking distance and the more altered the CPBF/RCBF ratio (Figures 3 and 4). The reasons for such relationships remain difficult to explain. Exercise in humans not only produces arteriolar vasodilatation but also modifies the dampening function of large arteries; thus there is an increase in pulse wave velocity and a decrease in arterial compliance.

**Figure 4.** The relationship in AOD patients between maximal walking distance and the ratio between calf peak flow and resting calf blood flow (CPBF/RCBF ratio) (A) and between walking distance and pulse pressure (B) (semi-logarithmic scale).
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Since arterial compliance is reduced at rest in patients with AOD,2-4 it seems likely that the buffering function of large vessels is altered during exercise. Interestingly, walking distance and the CPBF/RCBF ratio were poorly correlated with mean arterial pressure in patients with AOD, a finding which contrasts with the strong correlations observed with pulse pressure.

In a previous study on patients with AOD and unilateral intermittent claudication, Lorentsen19 observed that systemic systolic and diastolic pressures increased to significantly higher levels during exercise with the diseased limbs than during exercise with the nondiseased limbs. Furthermore, after the first minutes of recovery following exercise, the systemic systolic pressure (and not the diastolic pressure) in the diseased limbs stayed higher than the pressure measured at rest immediately before exercise. Like the present observations, such findings point to the role for modification of the pulse pressure during exercise, the systemic systolic pressure (and not the diastolic pressure) in the diseased limbs stayed higher than the pressure measured at rest immediately before exercise and suggest that active contraction of muscle cells under ischemic conditions might cause the stimulation of local receptors involving generalized circulatory pressor reflexes19,20 with dominant influence on large vessels and blood pressure.

In conclusion, the present study has shown that increased pulse pressure is a characteristic feature of patients with AOD, as a consequence of the reduction in arterial compliance and distensibility. During exercise, increased pulse pressure contributes greatly to the reduction in walking distance and vascular bed reserve through alterations in the buffering function of large arteries. Further studies are needed to evaluate the complex interrelationships between systemic pressure and lower limb performance in patients with AOD, with a view to possible treatment for hypertension.

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References


Index Terms: arteriosclerosis obliterans • arterial compliance • pulse pressure • hypertension
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