Regional Compliance of Brachial Artery and Saline Infusion in Patients with Arteriosclerosis Obliterans

Jaime A. Levenson, Alain C. Simon, Brigitte E. Maarek, Richard J. Gitelman, Jean N. Fiessinger, and Michel E. Safar

Simultaneous brachial artery pressure and blood flow measurements were made in 15 patients with arteriosclerosis of the lower limbs (AOLL) and in controls of the same age and sex. Blood flow was evaluated by a pulsed Doppler device with a double-transducer probe. From analysis of the pressure-flow curves during diastole, regional arterial compliance (RAC) was determined by using as a model of the forearm arterial tree a system of tubes, each with a storage capacity, in series with the arteriolar resistance vessels. In AOLL patients, RAC was significantly reduced (102 ± 13 vs 173 ± 14 × 10⁻⁴ ml/mm Hg, p < 0.01), and systolic pressure was significantly increased. After saline infusion, systolic pressure continued to increase and arterial compliance, to decrease; brachial blood flow did not change. Study of the baroreflex sensitivity in AOLL patients under basal conditions indicated that a higher pulse pressure was required to obtain the same heart rate as in the controls. The study provided evidence that in AOLL patients: 1) compliance was reduced in the brachial artery (a regional circulation with no clinical evidence of arterial occlusion); 2) an increase in systolic pressure resulted from the decreased arterial compliance; and 3) saline infusion exaggerated the observed reduction in arterial compliance and increase in systolic pressure. (Arteriosclerosis 5:80–87, January/February 1985)

For a long time, arteriosclerosis obliterans of the lower limbs has been considered a degenerative disease localized in the lower part of the aorta and its branches. Recently it has been suggested that the disease may have consequences for the whole arterial system, since arterial compliance is reduced in systemic circulation, which causes a predominant increase in systolic pressure. However, several problems remain to be solved in regard to the relationship of these findings to general circulatory dynamics.

First, the arterial compliance of the systemic circulation is the sum of the regional compliance of each part of the arterial tree. Thus, the reduction in systemic compliance could simply reflect a decrease in compliance of the terminal abdominal aorta and its branches. From this point of view, it is extremely important to evaluate compliance in a particular regional circulation where there is no obvious clinical or biological evidence of arterial modification.

Second, the increase in systolic arterial pressure resulting from decreased compliance is a special risk factor in the prognosis of patients with arteriosclerosis obliterans. It has been shown that, in patients over 50 years of age, systolic pressure is a greater independent cardiovascular risk factor than diastolic pressure. Thus, it is extremely important to evaluate the different parameters (such as salt intake) that may influence the level of systolic pressure and arterial compliance in these patients.

In the present study, regional arterial compliance before and after saline infusion was studied in men with arteriosclerosis obliterans of the lower limbs and was compared with that in controls of the same age. For this, we used a new method for evaluating compliance of the brachial artery in humans.
Methods

Study Subjects

The study subjects were 30 men, 15 patients with arteriosclerosis obliterans of the lower limbs and 15 normal controls. The patients' ages ranged from 47 to 69 years (mean, 50 years); the ages of the controls ranged from 40 to 73 years (mean, 55 years). The patients' body weight was 69 ± 2 kg and the controls' weight was 67 ± 3 kg (±1 se). All subjects were hospitalized for 1 week on a 100 mEq/day sodium diet. All treatment was discontinued at least 20 days before the investigation.

The 15 control subjects were not hospitalized for cardiovascular disease. The results of the clinical and biological investigations (serum and urinary electrolytes, serum creatinine, electrocardiogram, and chest x-ray) were normal. The ankle and brachial systolic pressures were measured in basal conditions with the Doppler method. The ankle/arm pressure ratio was always more than 1.0, which excluded peripheral arterial disease.

The 15 patients with arteriosclerosis obliterans suffered from unilateral or predominantly unilateral cramping discomfort in the calf that was provoked by exercise and relieved after several minutes of rest. The claudication distance varied between 50 and 600 m. The diagnosis was based on a thorough clinical examination, which included determinations of brachial and ankle systolic pressures by the Doppler technique. In all cases, the diagnosis was confirmed by arteriography. The 15 patients had bilateral stenosis of the iliac and/or femoral arteries. There was stenosis of the inferior mesenteric artery in three cases.

No patients had clinical symptoms of heart failure or coronary insufficiency. Their right and left blood pressures were symmetrical, and their chest x-rays showed no cardiac enlargement. Electrocardiograms at rest, analyzed according to the criteria of Mason et al., were normal in all cases. Neurological involvements were absent. In all cases, creatinine clearance was equal to or greater than 80 ml/min/1.73 m².

The protocol was approved by the Institut National de la Santé et de la Recherche Médicale. Informed consent for the investigations was obtained from the patients after a detailed description of the procedure.

Clinical Procedure

For the study of regional arterial compliance, 10 normal subjects and 10 patients with arteriosclerosis obliterans were tested on the third day of hospitalization. Tests were made with subjects in the supine position, without premedication, and after overnight fasting. A transcutaneous catheter was inserted into the brachial artery and connected to a Statham P 23 ID balanced, resistive strain gauge via a short, low-compliance Teflon catheter that was regularly flushed with heparinized Ringer's solution. The frequency response of the system was determined by the transient method, and the response was flat beyond 30 Hz and showed a damped resonant frequency of 50 Hz. The signal was recorded on an Electronics for Medicine recorder; inspection of the oscilloscope permitted selection of a representative pressure pulse for analysis; this was recorded at a paper speed of 100 mm/sec.

The volume of blood flow in the brachial artery was deduced from measurements of blood flow velocity and artery diameter made by a pulsed Doppler velocimeter. Briefly, this apparatus has a double transducer probe and a range-gated time reception system. In the upper left in Figure 1, the two transducers of the probe are shown. These are at a 120° angle, permitting calculation of the incidence angle of the ultrasonic beam and the vessel axis. When blood velocity was the same for each transducer, the ultrasonic beams were both at a 60° angle to the vessel axis.

The apparatus also had an adjustable time reception system, which permitted measurement of the distance between the red cells giving the Doppler signal and the transducer, as well as the width of the measurement volume. The upper right-hand part of Figure 1 shows that the distance from the proximal and distal arterial walls to the transducer can be de-
terminated by progressing step by step (with a step advance of 0.4 mm) across the vessel lumen with the smallest possible measurement volume (0.4 mm). The proximal and distal walls correspond, respectively, to the depth of the first and last Doppler signals received. The internal diameter of the vessel equals the difference between the distance of the distal and proximal walls from the transducer, projected on the vessel section (multiplied by sin 60°, the angle of incidence of the ultrasonic beam).

During the investigation, after the 60° incidence angle had been obtained, the probe was fixed over the course of the artery by a stereotaxic device. Particular care was taken to ensure measurements with the patient's forearm extended supine and supported horizontally at the level of the right atrium. The Doppler velocimeter was coupled to the electrocardiogram, so that the step advance of the measurement volume was related to the R-wave of each electrocardiographic (ECG) complex. Thus, the advance of the measurement volume across the vessel was reflected in the peak velocity profile (see the lower part of Figure 1). The interval between two successive velocity peaks represents the length of the step advance, so that the vessel diameter equaled the number of velocity peaks multiplied by the step advance (0.4 mm) and by sin 60°. Each measurement was repeated at least three times with each transducer, and the artery diameter was taken to be the mean of at least six measurements expressed in centimeters. Reproducibility was 5% ± 2%.

After the internal diameter of the brachial artery had been calculated, the cross-sectional blood-flow velocity was measured by fixing the depth of the measurement volume on the proximal wall and adjusting the width of the measurement volume to the arterial diameter. Representative blood-flow velocity curves were selected and recorded for analysis on an Electronics for Medicine multichannel recorder at a paper speed of 100 mm/sec. The blood-flow velocity was expressed in centimeters per second (cm/sec). The measurements of the brachial artery diameter (D) and the blood-flow velocity (V) enabled determination of the brachial artery blood flow (Q) with the use of a cylindrical model of the artery:

\[ Q = \pi D^2/4V \]  

Analysis of Pressure and Blood-Flow Velocity Curves

Figure 2 shows a simultaneous recording of pressure and blood-flow velocity curves from the brachial artery. For determining blood flow, the internal diameter of the brachial artery was considered constant throughout the cardiac cycle, since the variations in arterial caliber, due to the transmission of the pressure wave were small relative to the diameter itself.11

Thus, the phasic volume flow has the same contour as the flow velocity curve. A typical brachial artery flow velocity contour is illustrated in Figure 2. Peak flow occurred within 0.15 seconds after the onset of systolic flow and was followed by a retrograde flow; a slight dicrotic wave of antegrade flow then ensued, followed by a stable flow (Vd) during the last two-thirds of diastole.12
The value of \( V \) was calculated from the integration of the last part of the diastolic velocity curve, and the mean blood-flow velocity \( (V_m) \) was simultaneously obtained by integration of the whole velocity curve. By determining the \( V \) and \( V_m \) velocities, the diastolic \( (Q_d) \) and the mean \( (Q_m) \) volumes of blood flow were calculated with formula (1). The \( V \) and \( V_m \) velocities were expressed in centimeters per second; the mean of five successive waves was used. Diastolic and mean volume blood flows were expressed in millimeters per minute.

In regard to the pressure curve, Figure 2 clearly shows that the pressure decline was monoeponential in the last two-thirds of diastole, as shown elsewhere. Calculations similar to those used for the velocity curve were made from the pressure curve, enabling calculation of the mean diastolic arterial pressure and the mean arterial pressure (MAP).

**Arterial Model**

The arterial system of the forearm was conceived as a system of interconnected tubes with a storage capacity. Blood entry into the system was phasic, while outflow at the other end was approximately constant and Poisseuillean due to the arteriolar resistances of the forearm. The Windkessel property of the system assumes that there is a constant linear resistance of the forearm. The Windkessel property of the system, so that Equation (3) becomes:

\[
d/dt = C \cdot dp/dt
\]

(2)

in which \( C \) represents the compliance of the model.

Such an approach requires that all pressure changes within the system be simultaneous. Thus, inflow \( (Q_i) \), outflow \( (Q_o) \), and pressure \( (P) \) are related so that:

\[
Q_i - Q_o = C \cdot dp/dt
\]

(3)

Since outflow is Poisseuillean, \( Q_o \) represents the ratio between the pressure and the resistance \( (R) \) of the system, so that Equation (3) becomes:

\[
Q_i = P/R + C \cdot dp/dt
\]

(4)

\( Q_i \) is not phasic during diastole, but is a constant plateau \( (Q_o) \); thus, the solution of Equation (4) during diastole is a monoeponential function of time:

\[
P = R \cdot Q_o - (R \cdot Q_o - P_o) \cdot e^{-t/RC}
\]

(5)

in which \( t \) is the time during diastole and \( P_o \) represents the pressure at the onset of the diastolic pressure decay.

This exponential decline of pressure during diastole fits with the monoeponential pressure decay in the last part of diastole (Figure 2). Moreover, Equation (5) predicts that: 1) the value of pressure extrapolated from the exponential diastolic pressure curve at infinite time \( (P \rightarrow \infty) \) (see the bottom of Figure 2) equals the product of \( R \cdot Q_o \); and 2) the slope \( (a) \) of the exponential diastolic pressure decay equals the reciprocal of the product \( R \cdot C \), so that the compliance \( (C) \) of the arterial model, which represents the regional arterial compliance \( (RAC) \), is calculated as:

\[
RAC = 1/\alpha R
\]

(6)

**Evaluation of Regional Arterial Compliance**

The RAC was evaluated according to Equation (6). Arterial resistance \( (R) \) was calculated as the ratio between the MAP and the mean volume blood flow in the brachial artery \( (Q_m) \), and expressed as \( 10^{-4} \) ml/mm Hg. The exponential slope \( (\alpha) \) of the diastolic pressure decay was measured by exponential correlation vs time of the difference between the diastolic pressure at any moment of diastole and the \( P \) value (Figure 2 bottom). The \( P \rightarrow \infty \) value is calculated as follows:

\[
P = R \cdot Q_o = MAP \cdot Q_d/Q_m = MAP \cdot V_d/V_m
\]

(7)

To take into account only the low frequency components of pressure and to exclude the reflection wave just after the dicrotic notch, our analysis was limited to the last two-thirds of the diastolic pressure segment (Figure 2 bottom). Measurements and calculations were made on five successive pressure and velocity curves using an analogue-to-digital converter. Regional arterial compliance was the mean value of these five determinations and was expressed as \( 10^{-4} \) ml/mm Hg. Reproducibility was 5% ± 3%.

**Saline Infusion**

In the 10 patients with arteriosclerosis obliterans, measurements were performed before and 120 minutes after isotonic saline infusion given at a rate of 17 ml/min by a Harvard pump. Saline infusion was also performed in six normal subjects of the same mean age.

**Estimation of Baroreflex Sensitivity**

The sensitivity of the baroreflex was determined by the technique of Smyth et al. in five normal subjects and five patients of the same age with arteriosclerosis obliterans. These patients were not the same ones who participated in the study of regional compliance. After puncture of the brachial artery, several bolus intravenous injections of 50 to 200 \( \mu \)g phenylephrine were given to induce a transient rise in arterial pressure by 20 to 40 mm Hg. The systolic blood pressure of each beat was plotted against the second RR interval (in milliseconds) following it. Plotting was started 10 beats after the end of injection until just after the peak systolic pressure; RR intervals during inspiration were not included in order to reduce the effects of sinus arrhythmia. The linear
relations between the RR intervals and the systolic blood pressure were observed, and the RR systolic pressure correlations with a p value of less than 0.02 were discounted. The reflex sensitivity was expressed as the slope of the regression line (milliseconds increase in RR interval per mm Hg rise in systolic blood pressure). The mean value of two or three slopes was used as an estimate of sensitivity. To study the potential enhancement of the baroreflex sensitivity, the study was performed before and after intravenous administration of ouabain (0.25 mg) in the five patients with arteriosclerosis obliterans.

**Statistical Evaluation**

Means and standard errors of the mean were calculated according to standard statistical methods. Differences in means were assessed by Student’s t test. A p value of less than 0.05 was considered statistically significant.

**Results**

**Brachial Hemodynamics at Rest**

In comparison with the control subjects, patients with arteriosclerosis obliterans of the lower limbs had an increase in systolic (p < 0.01) and mean (p < 0.05) arterial pressures, although their diastolic pressure remained within the normal range (Table 1). Their heart rate was slightly reduced (p < 0.05). Their brachial artery diameter, brachial blood flow, and vascular resistance did not differ from those of controls. Regional arterial compliance was significantly reduced: 102 ± 3 vs 173 ± 14 ml/mm Hg (p < 0.01). Figure 3 shows that seven of the 10 patients were below the lower limit of normal values. Figure 4 indicates that at the same level of MAP as controls, patients' arterial compliance remained significantly reduced (p < 0.01).

Table 2 shows that in comparison with normal subjects of the same age, patients with arteriosclerosis obliterans had a curve relating systolic pressure to RR interval after phenylephrine that showed higher values of basal systolic pressure. The slope of this curve was also slightly increased. No change in the slope was observed in patients with arteriosclerosis obliterans after injection of ouabain.
**Hemodynamic Effects of Saline Infusion**

In patients with arteriosclerosis obliterans of the lower limbs (Table 3), saline infusion induced a significant increase in systolic pressure ($p < 0.02$) and MAP ($p < 0.05$) but no significant changes in diastolic pressure, heart rate, brachial artery diameter, or brachial blood flow. Resistance increased slightly ($p < 0.05$) and compliance decreased markedly from $102 \pm 13$ to $73 \pm 12 \times 10^{-4}$ ml/mm Hg ($p < 0.01$).

In normal subjects, the increase in systolic (131 ± 6 vs 124 ± 4 mm Hg) and diastolic (80 ± 5 vs 74 ± 2 mm Hg) pressure after saline infusion was not significant. Heart rate and brachial hemodynamics did not change. Figure 5 indicates that the increase in systolic pressure was significantly higher ($p < 0.05$) in patients with arteriosclerosis obliterans than in normal subjects.

**Discussion**

A simple first-order viscoelastic model was used to study the arterial tree of the forearm. The classic equation of this model, i.e., Equation (2), relates proportional change in pressure and volume per unit of time, which requires that all pressure changes in the capacitance part of the system be simultaneous. This is the case when the model is restricted to the last part of diastole, where low frequencies of the impedance spectrum predominate.

**Table 2. Baroreflex Sensitivity in Five Patients with Arteriosclerosis Obliterans**

<table>
<thead>
<tr>
<th>Normal subjects (n = 5)</th>
<th>Before ouabain (msec/mm Hg)</th>
<th>After ouabain (msec/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.70</td>
<td>8.30</td>
<td>8.10</td>
</tr>
<tr>
<td>3.40</td>
<td>12.40</td>
<td>13.10</td>
</tr>
<tr>
<td>6.50</td>
<td>9.00</td>
<td>9.50</td>
</tr>
<tr>
<td>11.60</td>
<td>15.20</td>
<td>17.00</td>
</tr>
<tr>
<td>8.50</td>
<td>5.30</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Mean ± SEM

| 7.74 ± 3.0            | 10.02 ± 3.8                 | 9.1 ± 3.3                  |

The mean age of the five normal subjects was 43 ± 3 years and that of the five arteriosclerosis obliterans patients was 47 ± 3 years. The basal systolic pressure was higher in patients with arteriosclerosis obliterans (see Table 1).
decreased arterial compliance in patients with arteriosclerosis obliterans is extremely relevant. Clearly, the slight increase in MAP observed in our patients was due to a predominant increase in systolic pressure, as previously reported. Since arterial compliance is considered one of the determinant factors of systolic pressure, the decrease in regional arterial compliance may be responsible for the increase in systolic pressure of the brachial arterial. Thus, the increase in systolic pressure in patients with arteriosclerosis obliterans is not only a manifestation of increased stiffness of the major arteries (the thoracic and abdominal aorta) but also of the smaller arteries, such as the brachial artery. Evidence for this has also been suggested by the study of the effects of nitroglycerine; the increase in arterial compliance due to nitroglycerine may cause a selective decrease in systolic pressure with no change in diastolic pressure when dosage is low.

In this study, the role of the reduced compliance on systolic pressure was partly confirmed by the effect of saline infusion. During the investigation, no change in blood flow occurred in patients with arteriosclerosis obliterans, but resistance slightly increased and arterial compliance significantly decreased. Diastolic pressure increased similarly in patients and in controls. In patients with arteriosclerosis obliterans, the slight increase in MAP with saline was predominantly due to a significant increase in systolic pressure. Thus, it seems likely that the increase in systolic pressure was caused by the significant reduction in arterial compliance. Such a response to saline infusion is difficult to explain. It is well known that sodium causes a greater increase in blood pressure (mainly in systolic pressure) in older subjects. However, in the present investigation, patients and controls were the same age, so this factor cannot explain the greater increase in systolic pressure observed in arteriosclerosis patients. Since sodium intake may influence the response of the sympathetic nervous system, it seems possible that a neurogenic-mediated mechanism could play a role. Indeed, it has been shown in patients with arteriosclerosis obliterans that decreased arterial compliance is exaggerated by beta-blockade.

Within the limits of the present investigation, it is difficult to assess the basis for an alteration in the autonomic system of patients with arteriosclerosis obliterans. One of the more surprising findings of this study was the observation of a slight, but significant, decrease in heart rate, as already reported. Since age or previous treatment could not explain this relative bradycardia, two possibilities remained to be explored: this could be due to an alteration in the intrinsic pacing function of the heart, or to a baroreflex-

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Before saline</th>
<th>After saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>151 ± 7</td>
<td>174 ± 5†</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>69 ± 3</td>
<td>78 ± 4</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>100 ± 4</td>
<td>114 ± 4*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>65 ± 2</td>
<td>64 ± 3</td>
</tr>
<tr>
<td>Brachial artery diameter (cm)</td>
<td>0.452 ± 0.021</td>
<td>0.456 ± 0.019</td>
</tr>
<tr>
<td>Blood flow velocity (cm/sec)</td>
<td>10.7 ± 10</td>
<td>8.9 ± 1.2</td>
</tr>
<tr>
<td>Brachial blood flow (ml/min)</td>
<td>100 ± 13</td>
<td>83 ± 9</td>
</tr>
<tr>
<td>Regional vascular resistance (mm Hg/ml/sec)</td>
<td>74 ± 13</td>
<td>93 ± 13*</td>
</tr>
<tr>
<td>Regional arterial compliance (10^-4 ml/mm Hg)</td>
<td>102 ± 13</td>
<td>73 ± 12‡</td>
</tr>
</tbody>
</table>

± 1 standard error of the mean.

*p < 0.05.
†p < 0.02.
‡p < 0.01.
mediated mechanism related to the observed arterial findings (reduced compliance and increased systolic pressure). To test the latter hypothesis, baroreflex mechanisms were evaluated according to the method of Smyth et al. Clearly, the curve relating systolic pressure to the RR interval after phenylephrine was reset, so that a higher stretch was required in patients with arteriosclerosis obliterans, which suggests a complex disturbance in the baroreflex control of heart rate. Such observations are compatible with a disturbance of the autonomic nervous system as a secondary effect of reduced arterial distensibility.

In conclusion, the present study has shown that patients with arteriosclerosis of the lower limbs have a decrease in arterial compliance in regional circulations where no clinical symptoms of peripheral arterial disease can be observed. The decrease in compliance is responsible for an increased systolic pressure that is exaggerated after saline administration. The mechanism of the response to saline is unknown but could involve adaptive modifications of the autonomic nervous system.

References

Index Terms: arteriosclerosis obliterans of lower limb • arterial compliance • systolic hypertension • saline infusion
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