Systemic Arterial Compliance in Patients with Arteriosclerosis Obliterans of the Lower Limbs

Observations on the Effect of Intravenous Propranolol

Jaime A. Levenson, Alain C. Simon, Jean N. Fiessinger, Michel E. Safar, Gerard M. London, and Edouard M. Housset

Hemodynamic parameters and systemic arterial compliance were measured in patients with arteriosclerosis obliterans of the lower limbs before and after acute administration of propranolol. Arterial compliance was evaluated from a simple viscoelastic model, enabling the calculation of diastolic drainage and diastolic blood flow as indices of the reservoir role of the large arteries in overall circulation. In comparing basal conditions with normal subjects of the same age, patients with arteriosclerosis obliterans exhibited a significant decrease in arterial compliance ($p < 0.01$) and heart rate ($p < 0.02$) with a significant increase in systolic pressure ($p < 0.001$). Diastolic drainage was increased ($p < 0.01$) and was positively correlated with diastolic time ($r = 0.73, p < 0.001$). Diastolic blood flow remained within normal ranges ($52 \pm 2$ vs $49 \pm 3$ ml/m$^2$/sec). After acute propranolol intravenous administration, heart rate and stroke volume decreased ($p < 0.001$), while total peripheral resistance increased ($p < 0.001$). Systemic arterial compliance and diastolic blood flow significantly decreased ($p < 0.01$). The study provided evidence that in patients with arteriosclerosis obliterans, the diastolic blood flow was maintained in basal conditions despite the observed reduction in arterial compliance, and that intravenous propranolol administration decreased systemic arterial compliance and diastolic blood flow.

(Arteriosclerosis 2:266-271, May/June 1982)

Arteriosclerosis of the lower limbs is usually considered a degenerative disease localized in the lower part of the aorta and its branches. However, lesions of a significant part of the large artery system, such as arteriosclerosis obliterans of the lower limbs, may have general consequences on circulatory dynamics. Indeed, the large arteries act as a reservoir that stores blood during cardiac ejection and releases it during diastole, enabling the intermittent cardiac output to be converted to a steady flow through the capillaries. Recently available methods have been proposed to quantitatively estimate the reservoir role of large arteries in humans. They include evaluation of systemic arterial compliance from a simple viscoelastic model of the entire arterial tree and calculation of diastolic drainage of blood by the large arteries and diastolic blood flow through the capillaries. In this study, hemodynamic investigation including these latter arterial parameters was performed in patients with arteriosclerosis obliterans of the lower limbs in static basal conditions. We also tested the effects on large artery function of intravenous administration of propranolol, a drug well known to reduce cardiac output in acute conditions.
Methods

Study Subjects

The study subjects were 35 men: 21 patients with arteriosclerosis obliterans of the lower limbs and 14 normal controls. The patients' ages ranged from 33 to 67 years; ages of the controls ranged from 35 to 70 years. Morphologic characteristics are indicated in table 1. 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 reason for the hospitalization of the 14 control subjects was not cardiovascular disease. The results of the clinical and biological investigations were normal, including serum and urinary electrolytes, serum creatinine, electrocardiogram, and chest x-ray. The ankle and brachial systolic pressures were measured in basal conditions with the Doppler method. The ankle-arm pressure ratio was constantly greater than 1.0, excluding peripheral arterial disease.

The 21 patients with arteriosclerosis obliterans suffered from unilateral or predominantly unilateral clamping discomfort in the calf, clearly provoked by exercise and relieved after several minutes of rest. The claudication distance varied between 60 and 700 m. The diagnosis was based on a thorough clinical examination, including determinations of brachial and ankle systolic pressures by the Doppler technique. In all cases, the diagnosis was confirmed by arteriography. The 21 patients had bilateral stenosis of the iliac and/or femoral arteries. Stenosis of the inferior mesenteric artery existed in two cases.

None of the 21 patients had clinical symptoms of heart failure or coronary insufficiency. Their chest x-rays did not show 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 Sante et de la Recherche Medicale. Informed consent for the investigations was obtained from the patients after a detailed description of the procedure.

Table 1. Clinical Parameters

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Patients with arteriosclerosis obliterans of the lower limbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>51 ± 2</td>
<td>53 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66 ± 3</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.74 ± 0.04</td>
<td>1.79 ± 0.03</td>
</tr>
</tbody>
</table>

Values are ± 1 standard error of the mean.

Hemodynamic Parameters

The hemodynamic study was performed without premedication, after overnight fasting, on Day 3 of hospitalization. With the subject in the supine position, transthepiate catheters were inserted into the right and left antecubital veins, one for the injection of indocyanine green and the other for drug administration. The investigation began at least 30 minutes after insertion of the catheters.

Arterial pressure was recorded on a Thomson Telco apparatus via a metallic No. 18 hypodermic needle inserted into a brachial artery. The needle was connected to a Statham P 23 db balanced resistive strain gauge via a special low compliance, short (10 cm) Teflon catheter regularly flushed with heparinized Ringer's fluid. No significant distortion existed in the recorded signal. The system was checked with both time and frequency-domain measurements and showed a flat response beyond 80 Hz. Inspection of recorded curves on the oscilloscope over about 1 minute of time permitted representative pressure pulse to be selected for analysis.

Cardiac index was determined in triplicate by the indocyanine green dye-dilution technique, using a Waters cuvette and densitometer, as previously described. It was expressed in ml/min/m² after correction for body surface area. Stroke index was the ratio between cardiac index and heart rate. Total peripheral resistances (TPR) were calculated as the ratio between mean arterial pressure (MAP) and cardiac index (CI) according to the formula:

\[ TPR = \frac{MAP}{CI} \times 80. \] (1)

From a rapid recording (100 mm/sec) of the arterial pressure pulse wave, left ventricular ejection time (LVET) and diastolic and cardiac times were measured. For the determination of LVET, the onset of the measurement was the foot of the diastolic pressure curve. This was defined by extrapolating the wave front downward and finding the intersection of this line with a straight line extrapolation of the last part of the diastolic curve. The endpoint of the ejection time was the nadir of the incisura. Cardiac time was measured from foot-to-foot pressure wave and diastolic time as the difference between cardiac time and LVET. The measurements from 10 consecutive pulsations were averaged. Diastolic time, cardiac time, and LVET were expressed in milliseconds. Left ventricular ejection rate index was the ratio between stroke index (SI) and LVET.

Determination of Systemic Arterial Compliance

The method used to determine systemic arterial compliance has been validated and described in detail in normal and hypertensive humans. Briefly, the entire arterial tree is treated as a simple first-order model associating in series a capacitive part representing the aorta and the large arteries and a resistive part representing the arterioles. Such a model stores a fraction of cardiac ejection during
systole and releases it during diastole throughout the peripheral resistances. The equation of the discharge of the model during diastole is obtained from the electrical analog, the RC model which includes a capacitive element (C), and a resistive element (R) in series. Such a discharge has two fundamental characteristics: 1) it is monoexponential as a function of time, and 2) the time constant (τ) of the system (i.e., the reciprocal of the exponential discharge slope) equals the product of the capacitance (C) and the resistance (R), according to the equation:

$$\tau = R \times C. \quad (2)$$

This equation enables calculation of the compliance of the model (i.e., the systemic arterial compliance of the aorta and the large arteries) as the ratio between the time constant of the exponential pressure decay during diastole (τ), and the resistance of the entire arterial tree, assimilated to the total peripheral resistance (TPR).

Validation of the model requires verification of the monoexponential form of the pressure decay during diastole and demonstration of a proportional relationship through zero, according to Equation 2, between the time constant of the diastolic pressure decay and the total peripheral resistance. The monoexponential decay of pressure during diastole, an important point extensively discussed elsewhere, is verified in each patient of this study. Moreover, similarity of monoexponential diastolic pressure wave form in brachial artery and aorta from the point of view of the approximations involved in the calculation is a well-established point in the literature, enabling determination of the systemic arterial compliance from the brachial artery. The second point of proportional relationship between the diastolic pressure decline time constant and the total peripheral resistance was verified in the patients of our study ($r = 0.80$).

In practice, simultaneous measurement of TPR and τ were necessary to determine systemic arterial compliance according to Equation 2. Total peripheral resistances were calculated as above, but were expressed in mm Hg/ml · sec · m$^2$. Determination of the time constant τ of the diastolic pressure decline was made by semilogarithmically correlating pressure time during diastole; in order to exclude the dicrotic wave just after the measurement and to analyze only the low frequencies of the impedance spectrum, only the last two-thirds of the diastolic portion was correlated. For this, the pulse pressure curve was recorded at a speed of 100 mm/sec, and the last two-thirds of the diastolic portion was sampled at 25 msec intervals. The individual values of blood pressure were plotted against time on semilogarithmic paper. The correlation coefficient and the slope of the regression line were calculated. The reciprocal value of the slope, or time constant (τ) of the system, was expressed in seconds and used as an evaluation of the steepness of the diastolic decay. Blood pressure was recorded just before and immediately after three cardiac output determinations, enabling three values of compliance to be calculated. Arterial compliance was the mean of the three values. The reproducibility of the method was 5% ± 2%.

**Calculated Diastolic Drainage and Diastolic Blood Flow**

Diastolic drainage represents the amount of blood that is stored in the large arteries during diastole, according to the Windkessel model. The diastolic pressure gradient is (Ps-Pd) mm Hg, where Ps is the end-systolic pressure and Pd, the end-diastolic pressure. Assuming a linear pressure-volume relationship between the two pressures, we can calculate diastolic drainage (DD ml/m$^2$) as follows:

$$DD = C \times (Ps-Pd), \quad (3)$$

where C is arterial compliance (ml/mm Hg/m$^2$).

Diastolic blood flow, the ratio between diastolic drainage and diastolic time, represents the amount of blood drainage per unit of time through the peripheral vessels during diastole and is expressed in ml/sec/m$^2$.

**Administration of Propranolol**

In 10 patients with arteriosclerosis obliterans of the lower limbs, hemodynamic parameters were measured before and 10 minutes after bolus intravenous administration of 0.2 mg/kg of d-l propranolol, a dosage known to produce an effective total beta-blockade.

**Statistical Methods**

Means, standard errors of the mean, and correlation coefficients were calculated according to standard statistical methods. Regression analyses were performed using the least squares method. Differences in means were assessed by the Student's $t$ test. A $p$ value of less than 0.05 was accepted as being statistically significant.

**Results**

**Central Hemodynamics**

Table 2 shows that all 21 patients with arteriosclerosis obliterans of the lower limbs had a diastolic pressure less than 90 mm Hg. Systolic pressure was significantly increased ($p < 0.001$), as was the diastolic pressure gradient (Ps-Pd) ($p < 0.001$). Heart rate was significantly reduced ($p < 0.02$), due to an increase in diastolic time ($p < 0.02$) and in LVET ($p < 0.02$). The CI, SI, left ventricular ejection rate index, and TPR were within normal ranges or slightly increased.

**Arterial Parameters**

In comparison with normal subjects (table 3), patients with arteriosclerosis obliterans of the lower
Table 2. Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients with arteriosclerosis obliterans of the lower limbs</th>
<th>Normal subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>146 ± 5*</td>
<td>124 ± 3</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>65 ± 2</td>
<td>70 ± 1</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>92 ± 3</td>
<td>88 ± 2</td>
</tr>
<tr>
<td>Diastolic pressure gradient (mm Hg)</td>
<td>31 ± 1*</td>
<td>22 ± 2</td>
</tr>
<tr>
<td>Heart rate (b/min)</td>
<td>66 ± 3†</td>
<td>76 ± 2</td>
</tr>
<tr>
<td>Left ventricular ejection time (msec)</td>
<td>332 ± 7*</td>
<td>302 ± 6</td>
</tr>
<tr>
<td>Diastolic time (msec)</td>
<td>603 ± 34†</td>
<td>486 ± 20</td>
</tr>
<tr>
<td>Cardiac index (ml/mm/m²)</td>
<td>3,311 ± 124</td>
<td>3,322 ± 131</td>
</tr>
<tr>
<td>Stroke index (ml/m²)</td>
<td>48 ± 1†</td>
<td>44 ± 2</td>
</tr>
<tr>
<td>Stroke index/ left ventricular ejection time ratio (ml/m²/sec)</td>
<td>0.154 ± 0.003</td>
<td>0.146 ± 0.005</td>
</tr>
<tr>
<td>Total peripheral resistance (dynes/sec · cm⁻⁵ · m²)</td>
<td>2,275 ± 105</td>
<td>2,104 ± 100</td>
</tr>
</tbody>
</table>

Values are means ± 1 standard error of the mean.

*p < 0.001, †p < 0.05, ‡p < 0.05.

The major contribution of this study is the finding of reduced systemic arterial compliance in patients with arteriosclerosis obliterans of the lower limbs. Better interpretation of this result requires a stricter definition of systemic arterial compliance. It was calculated here from a model of the whole arterial tree and thus represents the compliant part of the entire arterial system (i.e., actually the aorta and the large arteries). Moreover, use of the simple first-order model, previously validated in normal and hypertensive humans, remains valid for patients with arteriosclero-

Acute Administration of Propranolol

Figure 3 shows the percent changes in hemodynamic parameters after the administration of propranolol. Blood pressure did not change significantly, but diastolic pressure gradient increased (32 ± 4 vs 40 ± 5, p < 0.05). The SI and heart rate significantly decreased (p < 0.01), while TPR increased (p < 0.01). Both systemic arterial compliance and diastolic blood flow significantly decreased (p < 0.01), with no change in the diastolic drainage. Before and after propranolol administration, diastolic blood flow was strongly positively correlated with CI (r = 0.81, p < 0.001).

Discussion

Figure 1. Systemic arterial compliance in patients with arteriosclerosis obliterans of the lower limbs and in controls. Asterisk (*) indicates that p < 0.01.

Table 3. Arterial Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients with arteriosclerosis obliterans of the lower limbs</th>
<th>Normal subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arterial compliance (ml/mm/m²)</td>
<td>0.88 ± 0.03*</td>
<td>1.06 ± 0.06</td>
</tr>
<tr>
<td>Diastolic drainage (ml/m²)</td>
<td>31 ± 1*</td>
<td>24 ± 1</td>
</tr>
<tr>
<td>Diastolic drainage/stroke index ratio</td>
<td>61 ± 2†</td>
<td>55 ± 2</td>
</tr>
<tr>
<td>Diastolic blood flow (ml/sec/m²)</td>
<td>52 ± 2</td>
<td>49 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± 1 standard error of the mean.

*p < 0.01, †p < 0.05.
and controls. Because of the viscoelastic properties of large arteries, the diminution of compliance could reflect the decrease in arterial distensibility that occurs with increase in pressure level. However, such a possibility is not likely, since diastolic or mean arterial pressure is the same in patients with arteriosclerosis obliterans of the lower limbs and in controls. In contrast, systolic arterial pressure is significantly higher in patients with arteriosclerosis obliterans of the lower limbs only as a consequence of the reduced systemic arterial compliance in these patients. Thus, since pressure would seem to have a minimal effect on arterial compliance, it is probable that the decreased systemic arterial compliance is due to arteriosclerosis disease itself. In such a mechanism, the reduction in arterial reservoir volume related to the occlusions may play a role, since arterial compliance expresses both the wall distensibility and the volume of the aorta and large arteries. This reduction in the arterial volume is clearly shown on the arteriograms of each patient, where arteriosclerosis lesions strongly diminish the lumen of the lower aorta and its branches.

Since systemic arterial compliance is a property of the large arteries, which store a part of the cardiac ejection during systole and release it during diastole, this stored fraction of stroke volume (diastolic drainage) is a good expression of the arterial reservoir role. Diastolic drainage was calculated classically as the product of the systemic arterial compliance and the pressure gradient during diastole. In patients

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**Figure 2.** Positive correlation between diastolic drainage and diastolic time in the overall population (normal subjects plus patients with arteriosclerosis obliterans of the lower limbs). Note that normal subjects and patients are on the same line. Open circles = patients; black circles = normal subjects.

**Figure 3.** Percentage changes in the hemodynamic parameters after intravenous injection of propranolol in 10 patients with arteriosclerosis obliterans of the lower limbs. Double asterisk (**) indicates that $p < 0.01$. SAP = systolic arterial pressure, DAP = diastolic arterial pressure, HR = heart rate, SI = stroke index, TPR = total peripheral resistance, SAC = systemic arterial compliance, DD = diastolic drainage, DBF = diastolic blood flow.
with arteriosclerosis obliterans of the lower limbs, the
diastolic drainage was increased, in spite of the re-
duced arterial compliance, because of the strong
elevation of the diastolic pressure gradient. The
presence of arterial occlusions in the lower part of
the body could play a role by bringing the site of
reflection of the pressure wave closer to the
heart. This increase in diastolic drainage does
not lead to a parallel increase in diastolic blood flow,
since the diastolic time markedly lengthened. Such a
possibility agrees with the finding of a linear positive
correlation between diastolic drainage and diastolic
time in the overall population in which the constant
slope represents the diastolic blood flow.

Dynamic response to acute intravenous proprano-
lol injection was tested in patients with arteriosclero-
sis obliterans. The observed decrease in cardiac out-
put and increased TPR were classical with
the more striking result was a significant reduction in
diastolic drainage, in spite of the re-
duction in TPR (figure 3) may also reflect this
vasoconstriction in the arterioles, as has been indicated
by the regional vascular effects of intraarteri-
ally administered propranolol in humans. Another
result of acute propranolol administration is the re-
duction in diastolic blood flow. Such a reduction
could be a consequence of the decreased systemic
arterial compliance; when the arterial wall is more
rigid, the diastolic drainage would be expected to
decrease during diastole. However, the reduction in
diastolic drainage is only slight because of the in-
crease in the diastolic pressure gradient. Thus, the
reduction in diastolic blood flow appears mainly as a
reflection of reduced cardiac output, rather than
some peripheral mechanism. This demonstrates the
important role of the heart in the central hemody-
namic equilibrium in patients with arteriosclerosis
obliterans of the lower limbs.

Acknowledgments

We thank Christine Duval and Anne Dunajev for their excellent assistance.

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Index Terms: arteriosclerosis obliterans of the lower limbs • arterial compliance • propranolol

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doi: 10.1161/01.ATV.2.3.266

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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