Differences in Muscle Blood Flow in Upper and Lower Extremities of Patients after Correction of Coarctation of the Aorta

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SUMMARY Using the method of $^{133}$Xe clearance we investigated blood flow and calculated vascular resistances simultaneously in the muscles of the upper and lower extremities in 58 patients following successful surgical correction of aortic coarctation carried out at age 11.5 (±2.9) years. The interval from operation to investigation was 11.5 (±4.5) years. Resting and maximal ischemic exercise blood flows in the upper extremity were decreased and the duration of maximal blood flow was shortened. Values recorded from the lower extremities did not differ from normal controls. The difference between upper and lower extremities was statistically significant. Vascular resistance during maximal blood flow was higher in the upper extremities than in the lower. Differences between upper and lower extremities did not change after vasodilation elicited by amyl nitrite. The degree of differences was not dependent upon the age at operation, the age of the patients at investigation, or on the time interval between operation and investigation.

Methods

Before investigation of muscle blood flow the patient rested for 30 min in a supine position, blood pressure cuffs were inflated around both upper arm and upper leg arteries, and pressures were measured on the left upper extremity. Fifty $\mu$Ci of radioactive xenon ($^{133}$Xe) in physiological saline was then injected into the muscles of the extensor group in the right forearm and into the anterior tibial muscle on the right side. The total injected volume was 0.1 ml. The rate of washout of $^{133}$Xe from muscle was simultaneously measured by two scintillation counters (Duovigraph, ACEC) placed on the upper and lower extremities. The scintillation crystals were 5 cm in diameter and had 7 cm cylindrical collimators. The head of the collimator was located at a distance of 10 cm from the site of injection in order to decrease the effect of small changes in position and geometry of the extremity during the investigation. The decrease in radioactivity was recorded by a two-channel direct writer (Recti-Riter, Texas Instruments) on paper moving at a speed of 3.75 cm/min. A pen amplitude of 1 cm represented about 500 imp./sec.

One minute after administration of $^{133}$Xe we started to measure the decrease in radioactivity at rest. After 15 min, the upper arm and upper leg were compressed by inflating the blood pressure cuffs to pressure values at least 20 torr higher than systolic pressures measured for that patient, and the subject was asked to carry out vigorous flexion and extension of the hand and movement of the ankle against a weight of 1 kg, fixed to a specially constructed ergometer. Radioactivity was monitored continuously to be sure total arterial occlusion was present. The rate of exercise was maintained by means of metronome at 60 strokes/min. Exercise was interrupted with the onset of intense ischemic pain in both extremities, usually after 2 to 3 min. We then very rapidly deflated the cuffs and recorded the curves of radioactivity decrease (fig. 1).

After 30 min of rest we again injected $^{133}$Xe into the same muscle regions, as far as possible from the initial injection sites. The collimated probes were located and oriented in such a manner that any residual radioactivity from the first injection would not interfere with the second set of measurements. During the second measurements we did not evaluate resting flow; from the start both extremities were
subjected to an exercise workload under ischemic conditions in the same manner as in the first part of the investigation. At the end of the ischemic workload the patients inhaled 1 ampule (150 mg) of amyl nitrite for 20 sec from an open anesthetic mask. In the course of inhalation we measured on the left upper extremity the decrease in pressure up to the end of the inhalation. At that moment the inflated cuffs were released on the right upper and lower extremities and the rate of washout of $^{133}$Xe from the muscles was investigated in the manner previously described. Investigations were carried out in an air-conditioned room at the environmental temperature ranging from 23 to 25°C.

The rate of muscle flow ($Q_M$) was calculated in the following manner:

$$Q_M = \frac{100 \cdot \lambda \cdot \ln 2 \text{ ml/100g/min}}{t-\frac{1}{2}}$$

where $t-\frac{1}{2}$ is the time necessary for a decrease to half of initial values on a semilogarithmic transformed curve. For the calculation of resting blood flow ($Q_{M\text{-rest}}$) we substitute into the equation $t-\frac{1}{2}$ from the resting washout curve; for calculation of maximal flow ($Q_{M\text{ max}}$) we substitute $t-\frac{1}{2}$ read off from the segment of the curve with the greatest slope, recorded during ischemic exercise hyperemia. The coefficient $\lambda$ is taken from the different solubility of xenon in muscle and in blood$^9$:

$$\text{solubility in muscle} \quad \frac{\text{solubility in blood}}{\text{solubility in blood}} = \frac{1.62}{3.75 \text{ Ht} + 1.45 (100-\text{Ht})} = \frac{162}{145 + 2.3 \text{ Ht}},$$

where Ht = hematocrit.

In addition to resting and maximal blood flow rates we derived the duration of maximal flow ($T\cdot Q_{M\text{ max}}$). This is the time interval during which a straight line extension of the maximal rate of fall of the semilogarithmic transformed curve follows exactly the curve. Resistance of the peripheral vascular bed was calculated from values of mean arterial pressure and blood flow:

$$R = \frac{P}{Q_M}$$

where $P$ = mean blood pressure, calculated from systolic (Psy) and diastolic pressures (Pdi) according to the equation:

$$P = P_{di} + (\frac{P_{sy}-P_{di} \cdot 40}{100})$$
For calculation of vascular resistance, one substitutes for $Q_M$ values of resting or maximal flow. Radioactive exposure of the gonads during two injections of $^{133}$Xe, as used in the present experiments, has been calculated as $0.04 \times 10^{-9}$ rad. Lassen reports that this dosage is equivalent to only 1/10,000 of that to which the gonads are exposed during X-ray investigation of the pelvic region.

In all, muscle blood flows were investigated in 58 patients after successful correction of coarctation of the aorta, including 44 males and 14 females. Mean age at investigation was 23.1 (±4.7) years. The operation had been carried out at a mean age of 11.5 (±4.5) years. The mean interval from the operation to the time of investigation was 11.5 (±4.5) years. Results measured in patients in whom coarctation of the aorta had recurred, or hypertension was present, were not included in the investigation.

The measured data were compared with the reference values measured previously in our laboratory with the same methods. The control group consisted of 12 males and eight females, aged 6 to 16 years. It is safe to assume that pathological vascular changes, encountered often in young adults are not yet present in this age group. Mean age of 11.6 years corresponds to the average time interval after the surgical re-establishment of normal hemodynamics in the "post-coarctation" vascular bed in our patients. Resting and maximal muscle blood flow values were at the upper limit of normal values reported for adults. Informed consent with the investigation was obtained in all cases.

Statistical evaluation of significance of differences of mean values was done according to Student's $t$-test. Differences between upper and lower extremities in the same patient and differences between values before and after inhalation of amyl nitrite were evaluated by a paired $t$-test. A computer was used to calculate regression and correlation coefficients.

### Results

#### Resting Muscle Blood Flow

Table 1 shows that after surgical correction of coarctation of the aorta resting muscle blood flow in patients was significantly less in the upper extremity ($P < 0.05$) than in control subjects. Mean values in the lower extremities did not differ from normal reference values. There was a statistically significant difference between the decreased values in the upper extremity and the normal ones in the lower extremity ($P < 0.05$).

### Maximal Muscle Blood Flow

Table 1 indicates that in the upper extremity maximal muscle blood flow was also significantly decreased ($P < 0.05$), whereas in the lower extremity there was no difference from normal control levels. Values measured in the upper extremity were lower than in the lower extremity ($P < 0.001$).

#### Duration of Maximal Flow

Maximal blood flow in the upper extremities lasted a shorter time than in normal controls (table 1) ($P < 0.01$). In the lower extremities values in corrected coarctation patients did not show any significant difference from normal. The difference between the upper and lower extremities was statistically significant ($P < 0.01$).

#### Vascular Resistance

At rest the difference in resistance was not significant (table 2).

Vascular resistances during maximal dilation of the muscle vascular bed, calculated from values of maximal blood flow, in the upper extremity were practically twice those in the lower (table 2) ($P < 0.001$).

### The Effect of Vasodilation on Muscle Blood Flow and Resistance

In 57 patients vasodilation was produced by inhalation of amyl nitrite resulting in a decrease in mean blood pressure from 106.0 to 89.8 torr ($P < 0.001$).

### Maximal Blood Flow

Table 3 indicates that in the upper and lower extremities this value only slightly decreased during the maximal decrease in systemic pressure (NS). The highly significant

### Table 1. Muscle Blood Flow

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Coarctation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right upper</td>
<td>Right lower</td>
</tr>
<tr>
<td>Blood flow</td>
<td>extremity Mean</td>
<td>extremity Mean</td>
</tr>
<tr>
<td></td>
<td>sd</td>
<td>sd</td>
</tr>
<tr>
<td>Resting (ml/100 g/min)</td>
<td>3.3 (20)</td>
<td>2.4 (51)</td>
</tr>
<tr>
<td>Maximal (ml/100 g/min)</td>
<td>78.8 (20)</td>
<td>56.4 (44)</td>
</tr>
<tr>
<td>Duration of maximal flow (s)</td>
<td>38.9 (20)</td>
<td>28.4 (44)</td>
</tr>
</tbody>
</table>

*Difference from reference value: $P < 0.05$.

**Difference from reference value: $P < 0.01$.**

### Table 2. Vascular Resistance after Correction of Coarctation of the Aorta

<table>
<thead>
<tr>
<th></th>
<th>Extremity (resistance units)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upper</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>Resting Blood Flow</td>
<td>61.1</td>
</tr>
<tr>
<td>Maximal Blood Flow</td>
<td>2.5</td>
</tr>
<tr>
<td>Maximal Blood Flow after Amyl Nitrite</td>
<td>2.0</td>
</tr>
</tbody>
</table>


TABLE 3. Maximal Muscle Blood Flow after Amyl Nitrite

<table>
<thead>
<tr>
<th>Blood flow</th>
<th>Upper Extremity</th>
<th>Lower Extremity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before amylnitrite</td>
<td>After amylnitrite</td>
</tr>
<tr>
<td>Maximal flow (ml/100g/min)</td>
<td>Mean 56.4 (44)</td>
<td>Mean 51.9 (41)</td>
</tr>
<tr>
<td>Duration of maximal flow (s)</td>
<td>Mean 28.4 (44)</td>
<td>Mean 25.8 (41)</td>
</tr>
</tbody>
</table>

*Upper vs lower extremity after amylnitrite.

difference between upper and lower extremities, evident before administration of amylnitrite, persisted (P < 0.001).

Duration of Maximal Blood Flow

This interval remained virtually unchanged in both the upper extremity and the lower extremity after amylnitrite (table 3). The difference between the upper and lower extremities remained highly significant (P < 0.001).

Vascular Resistance during Maximal Blood Flow

Inhalation of amylnitrite did not produce a change either in the upper or the lower extremities (table 2). The difference between the increased values in the upper and the lower values in the lower extremity, measured under normal conditions, persisted during the decrease in perfusion pressure and was highly significant (P < 0.001).

The Relationship of Differences in Muscle Blood Flow and Resistances in Upper and Lower Extremities, to the Time of Operation

Differences between upper and lower extremities in terms of maximal muscle blood flow, duration of maximal flow, and in vascular resistance were correlated with the age of the patients at the time of operation, with the age of patients at the time of investigation, and with the time interval between operation and investigation. In no case did we find a statistically important relationship.

Discussion

These findings have convincingly shown that even some time after successful surgical correction of coarctation of the aorta, we can find significant hemodynamic differences in the vascular beds of the "pre-coarctation area," represented in the present case by the right forearm, and the "post-coarctation bed," represented by the calf musculature of the same side. The decreased muscle blood flow at rest and maximal blood flow in the upper extremity can be explained by a higher vascular resistance in the pre-coarctation region as compared with the post-coarctation vascular bed. The increased vascular resistance in the upper extremity and the normal values in the lower extremity in such patients before operation has been reported on by Patterson.11 Steele12 has argued that increased resistance exists in the entire peripheral vascular bed.

Resistance in the forearm did not fall to normal values even with maximal dilation of the muscle vascular bed produced by muscle exercise during ischemia. In the lower extremity resistance values during maximal dilation corresponded to values presented elsewhere in the literature.13 Resistances during maximal dilation in the upper extremities in these patients corresponded to values measured in hypertensive subjects.14 Experimental studies in spontaneously hypertensive rats and observations in humans with hypertension have shown that the cause of the increased resistance in the peripheral vascular bed is an increased ratio between the width of the vascular wall and the diameter of the vascular lumen.14-17 The media of arterioles increases in size and the structure of the muscular wall changes.18-20 The differences between muscle flow and resistance in upper and lower extremities and the duration of increased resistance during maximal flow all suggest that the vascular bed of the upper extremities of these postsurgical patients behaves in a manner similar to that in hypertensive patients.

Immediately after surgical reconstruction of the aorta in coarctation, pressure in the pre-coarctation portion of the peripheral vascular bed decreases sharply.21 This is followed by yet a further decrease in pressure. In some patients, however, the hypertension does not decrease, or in some cases with normal blood pressure preoperatively, hypertension begins to develop in the postoperative period. In the present series of 65 patients, hypertension was demonstrated in three, i.e., in 4.6%.22 The trend of changes in muscle blood flow in two of three hypertensive patients was the same as that found in the entire group.

The pathogenesis of hypertension in successfully operated cases of coarctation of the aorta has not yet been clearly explained. All mechanisms which can come into play in explaining the origin of essential hypertension have been cited as causes: genetically conditioned changes,14, 23-24 humoral factors,23, 26 reflex neural mechanisms,26-28 disturbances of central nervous centers,29, 30 chemical changes in the arteriolar wall.21 Our findings of pathological hemodynamics in the pre-coarctation vascular bed offers a further possible explanation of hypertension after surgical correction of coarctation. If a considerable part of the peripheral vascular bed has a pathologically increased resistance, a generalized increase in blood pressure can easily result from factors which, under normal conditions, would not produce any change in blood pressure.

In essential hypertension it is possible that changes in vascular resistance and blood flow similar to those occurring in the upper extremities of patients after surgical correction of aortic coarctation can also develop from other causes which change the character of circulation in a manner similar to that produced by coarctation. These changes in hemodynamics can be found in a number of pathological
states which result in a hyperkinetic circulation, but also in "normal" stress situations and during severe muscular exercise.

There is no doubt that the length of time this abnormal hemodynamic state has been present in a patient affects the development of demonstrable changes in vascular resistance. In coarctation of the aorta abnormal hemodynamics in the two different segments of the circulation are present from birth, and in the present group of patients lasted for a mean period of 11.5 years. Since we were unable to find a relationship between age at operation and the degree of differences in flow and resistance in upper and lower extremities, and these changes were demonstrated in patients operated from age 5 at the minimum, damage to vessels probably starts at a very early age. Experimental data from spontaneously hypertensive rats are in agreement with this view. Long term medical therapy of hypertension, or surgical intervention at an early stage of the disease prevents the development of structural changes in arteries, whereas delayed initiation of therapy had a less convincing effect. Nevertheless, even in the latter case the structural state of the vessels improved.15, 18, 22, 23

The decrease in maximal blood flow and the higher resistance in the upper extremity as compared with the lower remains highly significant even when blood pressure is decreased following amyl nitrite. Administration of amyl nitrite, which has a very marked dilatation effect on arterioles, demonstrated that muscle work during ischemia attains maximal values of local vasodilation. At the same time the drug study confirmed the assumption that the mechanism in the increased resistance in the pre-coarctation portion of the vascular bed was not functional. An anatomical basis appears to be a more likely explanation.

In patients following surgical correction of coarctation, we have found a significant shortening of the time of duration of maximal blood flow after work under conditions of ischemia in the upper extremity. We do not know the mechanisms for this.

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