Measurement of Arterioles in Coarctation of the Aorta

By Robert C. Painter, M.D., Edgar A. Hines, Jr., M.D., and Jesse E. Edwards, M.D.

In cases of aortic coarctation determinations of the wall-to-lumen ratio were made for the arterioles of the thyroid, pancreas, kidney and periadrenal tissue and compared with those for arterioles from the same organs in control cases. As in primary hypertension, there was, on the average, an increase in the wall-to-lumen ratio in each of the regions studied in the cases of coarctation as compared with the same tissues of the control group. This means that for arterioles of the same wall size the lumen was narrower in the cases of coarctation than in the control cases.

In recent years the possibility of surgical treatment of coarctation of the aorta has stimulated greater interest not only in its early diagnosis but also in its clinical, pathologic, and physiologic characteristics. One of the most universally accepted facts has been the presence of hypertension in the upper extremities and "relative hypotension" in the lower extremities. The present study was undertaken with this premise in mind. The purpose has been to determine the status of the arterioles in coarctation of the aorta and to compare the findings above with those below the site of stenosis.

The background of this study is furnished by the many workers who have described the pathology of the arterioles in essential hypertension. Many of the early investigators^1^-^4^ described various changes (hypertrophy, fibrosis, hyalinization, and so forth) of one or all three divisions of the arteriolar wall, and each investigator felt that a particular specific change was the primary pathologic process. In 1929 Kernohan, Anderson and Keith^5^ reported their findings in 53 cases representing all grades of essential hypertension, in which they studied arteriolar changes in biopsy specimens taken from a pectoralis major muscle. They felt that fundamental structural changes were hypertrophy of the media, with an increased number of cells, proliferation of the endothelial cells occasionally with associated subendothelial proliferation, and hyperplasia with occasional splitting of the internal elastic lamina. In order to express accurately the degree of thickening of the arteriolar wall and the change in size of the lumen, they also made measurements of the walls and lumina of a large number of arterioles and expressed the change in terms of the wall-to-lumen ratio. ("Wall-to-lumen" will hereinafter be referred to as "W/L.") They found the W/L ratio in pectoral muscle of the normal subject to be 1:2. In benign hypertension it was 1:1.4, and in severe benign or early malignant hypertension, 1:1.1.

Subsequently, similar studies were carried out on the kidney,^8^ myocardium,^9^ pancreas, liver, gastrointestinal tract, spleen,^10^ brain,^11^ thyroid,^12^ and skin^13^ of patients with essential hypertension. These investigators obtained results comparable to those of Kernohan and associates and the results were summarized by Kernohan in 1939. He felt that the thickening of the walls of the arterioles was not the cause but the result of hypertension. He concluded that the sequence of events in this pathologic process could be described as follows: (1) work hypertrophy of the musculature of the media occurs, with coincidental hypertrophy of the elastic lamina; (2) when the walls are sufficiently thick to impair nourishment, degeneration follows (the degree of impairment determines whether fibrosis, fatty degeneration, necrosis, or even liquefaction occurs); (3) increase in endothelial cells of the intima and increase in intimal connective tissue occur late and the latter may be actual or apparent, (4) the adventitia is frequently increased in thickness.

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Andrus\textsuperscript{18} has objected to the use of the W/L ratio, saying this is an erroneous measurement. However, Moritz\textsuperscript{19} in a detailed study has discounted his objections and feels that it is an accurate and worth-while determination.

Clinically, the severity of hypertension in coarctation of the aorta is comparable to that occurring in patients with group I and group II essential hypertension. The degree of hypertension seen in patients with group III and group IV essential hypertension does not usually occur in patients with coarctation of the aorta.\textsuperscript{17} Thus arteriolar changes would be expected to be minimal in coarctation as compared with those in the more severe cases of essential hypertension, but any definite and consistent change as compared with those in normal controls can be considered as significant.

Graybiel, Allen and White\textsuperscript{18} studied the arterial vessels in five cases of coarctation of the aorta in which the patients’ ages varied from 20 to 33 years. They determined the W/L ratio of the vessels in the skin from the arm and leg as well as in biopsy specimens from the deltoid and gastrocnemius muscles. They concluded that there was no significant difference between the arterioles of the arm and of the leg in the cases of aortic coarctation which they studied. Although there was occasional slight intimal thickening and slight endothelial proliferation, they felt that the vessels were essentially normal in appearance.

On the other hand, Hines, Farber and Keith,\textsuperscript{19} using the Kernohan criteria and technic, examined biopsy specimens of skin and subcutaneous tissue from the upper part of the arm and from the calf of nine ambulatory patients with coarctation of the aorta. In all cases of coarctation, as compared with the control cases, the thickness of the arteriolar wall was increased relative to the diameter of the lumen. Structural changes consisted of endothelial hyperplasia, proliferation and thickening of the inner elastic lamina, hyperplasia of the nuclear elements in the media, and apparent reduction in the size of the lumen. Not all arterioles were equally affected, although most of them showed some change from normal. Sections of skin from the calf revealed changes of the same degree as those from the arm.

\textbf{Material and Methods}

This study was carried out to determine the changes, if any, in the systemic arterioles in coarctation of the aorta as compared with a control group and to determine particularly what difference might exist between arterioles in the tissues above and those below the site of coarctation. The definition of an arteriole as outlined by Kernohan—namely, those arterial vessels with an outside diameter of 25 to 100 microns—was adhered to. A micrometer eyepiece was used over a high power objective, giving a magnification of 430 times (10 times 43). In figure 1 the external circle represents the external margin of the media of the arteriole while the inner circle represents the boundary of the lumen. The thickness of ab, cd, ef, and gh, respectively, were totaled and divided by four to give the average thickness of the medial and intimal components of the arteriolar wall. This figure was called the “thickness of the wall.” The average value for the diameter of the lumen of the vessel was determined by adding bc and fg and dividing by two. The adventitia was not included in the measurements since this layer varied considerably in thickness. Ten arterioles in each tissue were measured in each case. Each section was examined routinely from left to right. The first 10 arterioles cut at right angles and suitable for measurement were used.

From the measurements obtained the ratio of the thickness of the wall to the diameter of the lumen was calculated for each arteriole and averages of these ratios for each tissue in each case were made. Then, in order that the thickness of the wall would always be represented by “1” in the ratios, the two elements of each ratio were divided by the first element (the thickness of the wall) to obtain the ratio in the form presented in this paper. Thus, for example, if the observed ratio of the thickness of the wall to the diameter of the lumen were 25:50, the two elements of this ratio would be divided by 25 to give the form 1:2 as used in this paper.

The tissues chosen for study were kidney, pancreas,
periadrenal tissue, and thyroid. Each tissue was sectioned and stained with hematoxylin and eosin and with Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain. All measurements were made on the latter sections since elements of the vessel are clearly defined.

**Table 1.**—Average Wall-to-Lumen Ratios in 10 Control Cases

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Average of all controls</th>
<th>Range (average in individual cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>1:1.98</td>
<td>1:1.61—1:2.27</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1:2.68</td>
<td>1:2.16—1:3.54</td>
</tr>
<tr>
<td>Kidney</td>
<td>1:2.66</td>
<td>1:2.11—1:3.71</td>
</tr>
<tr>
<td>Periadrenal</td>
<td>1:2.34</td>
<td>1:1.88—1:3.20</td>
</tr>
</tbody>
</table>

* Ten arterioles were measured in each tissue studied in each case.

**Table 2.**—Average Wall-to-Lumen Ratios in Nine Cases of Aortic Coarctation

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Average of all cases</th>
<th>Range (average in individual cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>1:1.78</td>
<td>1:1.46—1:2.24</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1:2.35</td>
<td>1:1.71—1:3.44</td>
</tr>
<tr>
<td>Kidney</td>
<td>1:2.00</td>
<td>1:1.51—1:2.42</td>
</tr>
<tr>
<td>Periadrenal</td>
<td>1:2.10</td>
<td>1:1.81—1:2.40</td>
</tr>
</tbody>
</table>

* Ten arterioles were measured in each tissue studied in each case except that the thyroid gland was represented by only six cases.

Fig. 2. Arterioles of the thyroid. The sections are stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain. The average external diameter of each arteriole measures 50 microns (×1,175). (a) A normal thyroid arteriole with wide lumen and narrow media in a control case (subject aged 17 years). (b) An arteriole in the thyroid of patient aged 12 years of the coarctation group. There is medial hypertrophy with decrease in size of the lumen. Endothelial hyperplasia and a tortuous internal elastic lamina are evident.

Connective tissue appears bright red, muscle yellow, and elastic tissue a deep purplish blue.

Controls were chosen from necropsy cases in which death occurred accidentally or as a result of a rapidly progressive brain tumor. In none of these cases had there been coincidental cardiovascular or renal disease, and the blood pressure had been within normal limits. There were 10 control cases. Five of these were in the age group 10 to 19 years and the remaining five were in the age group 20 to 29 years.

Nine cases of coarctation were included in the study. The ages varied from 7 to 28 years. Of the cases in which the ages were less than 20 years, in one the age was 7 years and in the other four it ranged from 12 to 19 years. The remaining four cases fell into the age group 20 to 29 years. No cases...
of coarctation of the aorta with co-existing bacterial endocarditis were included.

Results
In the cases of coarctation a wide variation in W/L ratio, as well as apparent changes, was observed from arteriole to arteriole in each tissue as well as from case to case. There did not appear to be any consistent differences in the two age groups.

A summary of the average figures for the W/L ratio for each tissue in the 10 control cases

Fig. 3. Periadrenal arterioles. The sections are stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain. The average external diameter of each arteriole measures 75.3 microns (×1,175). (a) An arteriole in the periadrenal tissue in a control case (subject aged 12 years). The media is thin with a wide lumen. (b) A periadrenal arteriole of a patient aged 7 years, of the coarctation group. There are medial hypertrophy, narrowing of the lumen, and thickening of the internal elastic lamina.

is given in table 1. Tissue from the pancreas and kidney and periadrenal tissue were available in all of the nine cases of coarctation. However, thyroid tissue was obtained in only six cases. The average figures for the W/L ratio for each tissue in the nine cases of coarctation are recorded in table 2.

On the average, medial muscular hypertrophy with decrease in the luminal diameter and intimal proliferation were more common in the coarctation group than among the controls (figs. 2 and 3); however, the average measurements in the coarctation group fell within the range of the control group, except in the case of the kidney. Accentuation and thickening of the internal elastic lamina were seen occasionally in the coarctation group.

Comment
Generally, in coarctation of the aorta the thickness of the wall of systemic arterioles increases relative to the diameter of the lumen. This change is most commonly associated with medial hypertrophy and narrowing of the lumen. Furthermore, these changes occur in the tissues below the coarctation as well as those above. The picture is similar in every way to those arteriolar changes occurring in essential hypertension of comparable degree as described by many authors.

These findings would seem to substantiate the theory that a generalized arteriolar hypertonia with resultant increase in peripheral resistance above and below the coarctation occurs in coarctation of the aorta. The high incidence of elevation of diastolic blood pressure in the
lower extremities, even though the systolic blood pressure may be low, has been pointed out by Steele and others, and in addition the resting blood flow in the upper and lower extremities has been found to be essentially normal in cases of coarctation of the aorta as compared with normal controls. While Graybiel and associates in their study found no difference in the vessels above and below the site of coarctation, no control group was reported in their paper. More recently the work done by Hines, Farber and Keith, previously cited, would appear to be parallel and consistent with the results of the study presented here.

Conclusions

1. When the arterioles of the thyroid, pancreas, kidney and periadrenal tissue in cases of coarctation of the aorta were compared with the arterioles of corresponding tissues in control cases, generally it was found that the thickness of the arteriolar wall in cases of coarctation was increased relative to the diameter of the lumen.

2. Hypertrophy of the media, narrowing of the lumen, and apparent endothelial proliferation were the most common changes demonstrable.

3. Thickening of the internal elastic lamina was a less frequent change.

4. Not all arterioles were equally affected in each case.

5. There was no consistent difference between the age groups studied.

References


4 Jones, L.: Quoted by Kernohan, J. W., Anderson, E. W. and Keith, N. M.

5 Fahr, T.: Quoted by Kernohan, J. W., Anderson, E. W. and Keith, N. M.


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