Arteriolar Abnormalities with Chronic Systemic Hypertension

A Quantitative Study

By Richard L. Naeve, M.D.

SUMMARY
A quantitative study of arteriolar structure has been undertaken in 23 individuals with chronic hypertension and 18 normotensive controls. In the hypertensive individuals, some arterioles were found to have an increased, and others a subnormal, mass of medial smooth muscle. Both abnormalities often bear a definite relation to arteriolar sclerotic lesions, those arterioles proximal to sclerotic segments having an increased medial coat and those distal, an atrophic coat. Mean values for mass of arteriolar muscle were often normal in organs of the hypertensive patients. These anatomic features can be correlated with a variety of physiological and clinical observations in the disorder.

Additional Indexing Words:
Arteriolar sclerosis
Vascular resistance
Arteriolar muscle mass

Despite many investigations, the exact vascular abnormalities responsible for increased vascular resistance in individuals with chronic systemic hypertension have never been clarified. The increased resistance apparently lies at the level of arterioles and small arteries, but there is uncertainty about the functional significance of the various structural abnormalities reported in these vessels. Arteriolar sclerosis is probably accelerated in chronic hypertension, but its functional significance has been questioned because various vasodilator stimuli often reduce vascular resistance. Short has even questioned the presence of the accelerated sclerotic process. Folkow has suggested that medial hypertrophy might narrow the arteriolar bed in chronic hypertension, but Short has found such an increase of arteriolar muscle to be absent, at least, in the intestine.

It is difficult to choose between these discordant observations and opinions because so little quantitative data are available on vascular structure in the disorder. To help supply this deficiency, the present study has applied quantitative morphological techniques to the structure of arterioles in individuals with chronic systemic hypertension. Results of the study help assign a functional significance to a number of arteriolar abnormalities which appear in the disorder.

Clinical Data
Data on 23 individuals who died with chronic systemic hypertension are shown in table 1. The youngest was 14 years old; the oldest, 49 years. The cause of the hypertension in 20 of the patients was known. Twelve had some type of chronic renal parenchymatous disease, four had functioning pheochromocytomas, and four had postductal coarctation of the aorta. Blood pressures recorded in table 1 are median values for all those recorded during the last month of life. Heart weights

From the Department of Pathology, The University of Vermont College of Medicine, Burlington, Vermont.

This study was supported by Grant HE-06409-05 from the National Heart Institute, U.S. Public Health Service, and a grant from the Vermont Heart Association.
and myocardial measurements were available in all but three cases. Left ventricular hypertrophy was present in all 20, the left ventricular wall being over 1.5 cm in thickness. All hearts were enlarged, weighing more than 510 g in adult males and 370 g in adult females. Causes of the deaths of the 23 hypertensive patients included uremia, cardiac failure, cerebral hemorrhage, and surgery.

The 18 control subjects used in the study varied in age from 18 to 47 years. All had normal blood pressures, and none had left ventricular walls thicker than 1.4 cm or hearts weighing more than 400 g for males or 315 g for females. Most died as a consequence of trauma or an acute infectious process.

**Methods**

In each case, 1 to 4 blocks of tissue from heart, liver, pancreas, gastrointestinal tract, adrenals, kidneys, and brain were sectioned at 6 μ and stained with hematoxylin and eosin. In some instances, duplicate sections were also stained with Verhoeff's and van Gieson's stains, and at times, elastic tissue stain was added to sections prepared with hematoxylin and eosin. Not all tissues were available in every case.

Previously described methods were used to quantitate structural features of arterioles. To be measured an arteriole had to be between 30 and 100 μ in diameter, be cut in cross section, and have no sclerotic or intimal proliferative lesions. Each arteriole encountered in a section which met these criteria was measured. Excluded were many arterioles less than 30 μ in diameter. Since no generally accepted criteria are available for distinguishing between small arteries and arterioles, we termed all of the measured vessels “arterioles” for the sake of convenience. By using a camera lucida and planimeter under conditions of constant magnification, relative cross-sectional areas of lumen, intima, and media of four to eight arterioles were determined in each organ in each case. The smaller number of vessels was often measured in kidney and pancreas where the severity of arteriolar sclerosis often made it difficult to locate appropriate vessels. By the same quantitative histological methods, cross-sectional areas of individual intimal and medial nuclei were also determined in each vessel. The relative mean areas of individual arteriolar intimal nuclei did not vary significantly within an organ or between hypertensive and control cases so that the total area of these nuclei was used as an internal standard or base line to which other arteriolar measurements could be referred. It should be repeated that no vessels

![Table 1](image-url)
with sclerotic or any type of intimal proliferative lesion were included in these measurements. A careful balance was maintained between the number of arterioles measured in individual organs of hypertensive and normotensive cases.

The ratio \( \frac{\text{area of arteriolar media}}{\text{total area of intimal nuclei}} \) was adopted as a measure of the relative area of medial smooth muscle present in individual vessels. A mean ratio was determined for arterioles in each organ in each case. It has been shown experimentally that this ratio is not influenced by moderate distention of the lumina of small arteries and arterioles.\(^9\) The ratio \( \frac{\text{area of arteriolar lumina}}{\text{total area of intimal nuclei}} \) was adopted as a measure of the relative state of dilatation of individual vessels. An increasing luminal size with dilatation is associated with an increasing ratio.

The medial cytoplasmic area of each arteriole was calculated by subtracting the combined area of medial nuclei from the total medial area. The relative cytoplasmic mass of individual muscle cells in a vessel was determined by dividing the medial cytoplasmic area of the vessel by the number of medial nuclei present. A mean value for this determination was calculated for the arterioles in each organ in each case.

An index reflecting the number of medial nuclei present in an arteriole was calculated by dividing the number of medial nuclei in the vessel by the number of intimal nuclei. As with other calculations, a mean value was determined for each organ in each case. Again, it has been shown that this value is not influenced by stretching or distention of small arteries and arterioles.\(^9\)

Vessels measured in the kidney were mainly interlobular arteries; those in the gastrointestinal tract were arterioles in the submucosa, and those in the brain, arterioles in the meninges. Serial sections of multiple organs were also prepared in several cases. Two-dimensional reconstructions of arterioles were prepared from these serial sections by the method of Brewer.\(^10\) The \( t \)-test was used when statistical analysis seemed appropriate.

**Results**

By referring to mean values for individual cases, the muscle mass in arterioles was normal in many of the organs of the hypertensive individuals, especially in those individuals with pheochromocytomas or a coarctation of the aorta (figs. 1 to 4). In the other hypertensive cases, arteriolar muscle mass was usually normal in the gastrointestinal tract, liver, and pancreas but sometimes increased in heart, brain, adrenals, and kidneys (figs. 1 to 4).

Mean values for arteriolar muscle mass give no indication of the discordance for this parameter within individual organs. An analysis of such discordance demonstrates additional abnormalities in the hypertensive cases. The difference between the highest and the lowest

![Graph 1](image1.png)

**Figure 1**

Diastolic blood pressure is plotted against an index of muscle mass in arterioles. C indicates cases of coarctation of the aorta and P cases of pheochromocytoma. Mean values for arteriolar muscle mass in gastrointestinal tract and liver are normal in most of the hypertensive cases.

![Graph 2](image2.png)

**Figure 2**

Diastolic blood pressure is plotted against an index of muscle mass in arterioles. C indicates cases of coarctation of the aorta and P cases of pheochromocytoma. Mean values for arteriolar muscle mass are normal in the pancreas in most of the hypertensive cases.
muscle mass recorded for individual arterioles was calculated for each organ in each individual. A mean value for this difference was then calculated for each organ in the hypertensive individuals as a group and in the normotensives as a group. These mean values were larger in the hypertensive than in the normotensive group indicating a greater variation in arteriolar muscle mass in hypertensive individuals. See "Methods" for explanation of units.

In several organs mean values for number of medial nuclei in arterioles were greater in the hypertensive cases than in the normotensive controls (table 3). Mean values for cytoplasmic mass of individual arteriolar medial muscle cells were similar in hypertensive and control cases (table 3). Again, these mean values do not reflect the increased discordance for these parameters within individual hypertensive cases. In the hypertensive cases arterioles which had an abnormally increased muscle mass almost invariably had values for medial cell number and cytoplasmic mass which were abnormally increased; these latter parameters were usually subnormal in arterioles with a subnormal muscle mass. Thus, some arterioles in hypertensive individuals
have medial hyperplasia and hypertrophy while other arterioles have medial hypoplasia and atrophy.

Arteriolar sclerotic lesions were also studied and an attempt was made to relate them to abnormalities in arteriolar muscle mass. The most common arteriolar sclerotic lesion consisted of a subendothelial accumulation of homogeneous, acidophilic material, a process long known as hyalination.\(^6\) It was found in arterioles of both normotensive and hypertensive individuals but was more frequent and severe in the hypertensives. In the hypertensive group, such lesions were most common in the kidney, pancreas, and adrenals, less common in the brain, gastrointestinal tract, and liver, and rare in the heart.

In frequency and severity these lesions were about the same in all the various types of hypertension listed in table 1 except for cases of coarctation of the aorta in which lesions were less frequent in organs served by branches of the aorta below the coarctation.

A second common lesion was characterized by proliferation of cells inside the internal elastic lamina of arterioles. Many of these proliferating elements appeared to be smooth muscle cells but others resembled endothelial cells. This lesion appeared in all of the organs of the hypertensive individuals except the heart; it was relatively rare in normotensive individuals. In the cases of hypertension, it was most common in the kidneys,

**Table 3**

<table>
<thead>
<tr>
<th>Number of Medial Nuclei, Cytoplasm per Medial Muscle Cell and Degree of Dilatation of the Arterioles in Various Organs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEART</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>Medial nuclei in arterioles</strong> (Number of medial nuclei) (Number of intimal nuclei)</td>
</tr>
<tr>
<td>Normotensive controls</td>
</tr>
<tr>
<td>Hypertensive patients</td>
</tr>
<tr>
<td>P values (t-test)</td>
</tr>
<tr>
<td>Cytoplasm per medial muscle cell in arterioles</td>
</tr>
<tr>
<td>Normotensive controls</td>
</tr>
<tr>
<td>Hypertensive patients</td>
</tr>
<tr>
<td>P values (t-test)</td>
</tr>
<tr>
<td><strong>Degree of dilatation of arterioles</strong> (Area arteriolar lumen) (Area intimal nuclei)</td>
</tr>
<tr>
<td>Normotensive controls</td>
</tr>
<tr>
<td>Hypertensive patients</td>
</tr>
<tr>
<td>P values (t-test)</td>
</tr>
</tbody>
</table>

*All values are in arbitrary units. Each is a mean value for all arteriolar measurements in an organ for hypertensive cases as a group and for normotensive individuals as a group. In several organs, mean values for number of arteriolar medial nuclei are greater in hypertensive than in normotensive cases. In contrast, mean values for cytoplasmic mass of individual medial muscle cells are similar in the two groups. Values for arteriolar dilatation are similar in the two groups with the possible exception of the kidney and heart where arterioles are somewhat more contracted in the hypertensive than in the normotensive cases."
Figure 5

Reconstruction from serial sections of an arteriole with a sclerotic segment (case 5, table 1). The dotted area designates that portion of the arteriolar wall which is sclerotic. In shaded areas the media is comprised of smooth muscle. Labeled lines show levels at which sections in figures 6 to 9 were taken.

usually being located in arterioles greater than 40μ in diameter.

Both of the aforementioned lesions were sometimes associated with the appearance of small amounts of collagen in an arteriolar media. More commonly, elastic laminal fibers showed an abnormal proliferation and evidences of swelling and disruption. Fibrinoid necrosis was visible in rare arterioles in several of the cases.

The longitudinal distribution of the arteriolar sclerotic lesions could often be correlated with abnormalities in arteriolar muscle mass. Serial sections revealed that both the hyaline and proliferative types of arteriolar sclerosis were highly variable and intermittent in their distribution, normal arteriolar segments being interspersed between sclerotic segments. Arterioles proximal to these sclerotic segments usually had a greater muscle mass than did distal arterioles (figs. 5 to 9). A progressive decrease in arteriolar muscle mass could often be found after each segment of a succession of arteriolar sclerotic lesions; arterioles proximal to such a series of lesions often had hyperplastic and hypertrophied media while those distal had little or no smooth muscle in their media (figs. 5 to 9).

It is important to note, however, that such sclerotic lesions are not the only cause of abnormal variations in muscle mass from one segment of an arteriole to another. Such variations were also found in the hearts of hypertensive individuals in whom arteriolar sclerotic lesions were uncommon (table 2).

Mean values for degree of arteriolar dilatation showed little difference between hyper-

Figure 6

Section through arteriole reconstructed in figure 5, level A. The arteriole has a relatively normal muscular wall; there are no sclerotic lesions. Hematoxylin-eosin and elastic stains; ×910.
tensive and normotensive persons with the possible exception of the kidney and heart in which the arterioles in the hypertensive individuals were somewhat more contracted than comparable vessels in the normotensive controls (table 3).

Discussion

The present study demonstrates a variety of abnormalities in the arterioles of individuals with chronic systemic hypertension. In such individuals some arterioles have an increased, and others a subnormal, mass of medial smooth muscle. Both abnormalities often bear a definite relationship to sclerotic lesions, those arterioles proximal to sclerotic segments having an increased medial coat and those distal, an atrophic coat. This muscular pattern suggests that the sclerotic segments are the site of increased resistance to blood flow and that pressures proximal to the sclerotic segments are higher than are pressures distal to the abnormal segments. A similar pattern has often been observed in the pulmonary circuit where sclerotic segments are sites of increased resistance and

Figure 7
Section through arteriole reconstructed in figure 5, level B. On the right side, the arteriolar wall has a normal muscular media while on the left side it is sclerotic. Hematoxylin-eosin and elastic stains; ×910.

Figure 8
Section through arteriole reconstructed in figure 5, level C. The left side of the arteriolar wall is sclerotic. On the right the arteriole is branching into a smaller arteriole whose wall is virtually without smooth muscle. Hematoxylin-eosin and elastic stains; ×910.

Circulation, Volume XXXV, April 1967
are responsible for decreases in pressure and muscle mass in distal arteries.\textsuperscript{11} It is also important to note that there are abnormally increased variations in muscle mass from segment to segment in arterioles where no interposed sclerotic lesions are found, especially in the heart. This suggests that not all arteriolar smooth muscle cells have the same amplitude of response to the vasoconstrictor stimuli responsible for the hypertension.

The variety and distribution of the aforementioned vascular lesions also help to explain certain clinical features associated with chronic hypertension. Various vasodilator stimuli can often reduce the high vascular resistance associated with such hypertension, but this resistance cannot usually be reduced to the minimal level achieved by similar vasodilator stimuli in normotensive subjects.\textsuperscript{1,3,12} In hypertensive individuals, arterioles with hyperplastic and hypertrophied media are appropriate sites for reduction of smooth muscle tone by vasodilator stimuli whereas such stimuli probably have little effect on arteriolar segments which are sclerotic. Such a mixture of muscular and sclerotic lesions might also explain certain other hemodynamic disturbances which follow use of vasodilator agents in chronically hypertensive individuals. Although blood flow to vital organs is often unchanged in such individuals, there is evidence that blood flow within certain organs may be redistributed following use of vasodilators, that is, glomerular filtration may be reduced and mental and motor disability may appear. It is suggested that reduction of vascular tone by vasodilator agents without change in regional blood flow might increase flow through arteriolar segments having medial muscle hyperplasia and hypertrophy as the principal structural abnormalities while perfusion might be significantly reduced through sclerotic arteriolar segments. Such a redistribution of blood flow would also help explain the micro-infarcts which develop in organs of some chronically hypertensive individuals following a period of reduced arterial pressure.

The aforementioned lesions are not the only abnormalities which may increase vascular resistance in individuals with chronic hypertension. Even small arteries and arterioles without sclerotic lesions may have a reduced distensibility according to Short.\textsuperscript{7} There is
also evidence that these small vessels may have increased reactivity to vasoconstrictor stimuli but this latter point is still the subject of controversy.\textsuperscript{7,13-16} In the wide variety of case types selected for the current study, it is also possible that such factors as hyper- 
volemia, increased cardiac output, and altered salt and water distribution played some role in the hypertension.\textsuperscript{16}

Acknowledgment

The author is grateful for the valuable advice of Dr. Simon Koletsky, Western Reserve University, Cleveland, Ohio, and for the technical assistance of Mrs. Bertha Pornelos and Mrs. Julie Nichols.

References

Arteriolar Abnormalities with Chronic Systemic Hypertension: A Quantitative Study
RICHARD L. NAEYE

_Circulation_. 1967;35:662-670
doi: 10.1161/01.CIR.35.4.662

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1967 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/35/4/662

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/