ARTERIOLAR LESIONS IN HYPERTENSION: A STUDY OF 350 CONSECUTIVE CASES TREATED SURGICALLY. AN ESTIMATION OF THE PROGNOSTIC VALUE OF MUSCLE BIOPSY¹

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Since 1933, approximately 900 cases of arterial hypertension have been submitted to supradiaphragmatic splanchnic-section and lower dorsal sympathetic ganglionectomy by M. M. Peet and his associates. Of these, 350 consecutive cases, which were followed for 1 to 7 years after the operation, have been reported on by Peet, Woods, and Braden (1). These authors pointed out that the selection of cases to be submitted to the operation is based on relatively simple requirements. Preferably, the patient should not be over 50 years of age; his renal function should be adequate, as indicated by a urea clearance of at least 40 per cent of normal and a power of concentrating urine above the specific gravity of 1.012 after 18 hours without food or liquids. The blood non-protein nitrogen should be below 45 mgm. per cent; the heart must be compensated. These clinical criteria are designed to determine whether the patient is capable of withstanding a major operative procedure; none of them has proved to be of significant prognostic value beyond the immediate outcome of the operation.

A more direct investigation of the vascular system would probably give data of greater theoretical and practical value in the study of hypertension and, at the same time, might make it possible to differentiate reversible vascular lesions from lesions which have become permanent. Since the increased resistance of the arterioles has been recognized as the main mechanical factor in hypertension, a particular attempt should be made to differentiate between hypertension due to arteriolar spasm and hypertension due to thickening of the arteriolar wall. It is possible that an anatomical thickening of the arteriolar wall is not necessarily an irreversible phenomenon, since a moderate hypertrophy of the muscle fibers in the tunica media

of some arterioles might subside, if the strain due to the high pressure is removed by removing the still predominant spasm.

The vascular system can be investigated by several methods. Some of these are:

1. *The intensity of vasomotor reactions to different stimuli*, such as: (a) The administration of amyl nitrite (2), amytal or sodium nitrite (3). This method has been found unsatisfactory by one of us (4). (b) The changes in blood flow through the extremities following changes in temperature or cocaine block of the vasomotor nerves (5, 6). (c) The cold pressor test recommended by Hines and others (7 to 14) and the breath-holding test or inhalation of carbon dioxide (14, 15). In a series of 22 patients, we have found (21) that the therapeutic results of splanchnicectomy are better in patients who, before the operation, had shown a greater rise in blood pressure during the cold pressor and the breath-holding tests.

2. *The measurement of the effective renal blood flow*. It has been shown that the renal blood flow is reduced in patients with hypertension (16 to 19) although, according to Steinitz (20), this is not a constant finding. Our experience with 22 patients (21), although this is a relatively small series, indicated that the effective renal blood flow in mild cases of hypertension, can be as high as the lowest values found in non-hypertensive subjects, but it is always markedly reduced in the more severe cases. The best therapeutic results have been obtained in cases where the effective renal blood flow was not markedly reduced.

3. *The direct observation of the blood vessels of the eyegrounds*. This has proved of great value in the classification of patients with hypertension and in the prognosis of the disease (22 to 24). Wagener and Keith (23) and Woods and Peet (25) have demonstrated a definite correlation between mortality and the severity of the vascular changes in the fundus.

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4. *The direct observation of the arterioles in tissues obtained by biopsy.* In 1936, Chabanier and his associates (26, 27) published a series of 120 cases of kidney biopsy in nephritic and hypertensive patients and suggested that the observation of the renal arterioles should precede any attempt at surgical denervation of the kidneys, a procedure which they recommend in both types of disease. Gerbi (28), in 1937, came to the same conclusion. Since the surgery involved in renal biopsy is not simple, it cannot be recommended as a routine method of investigation until it can be definitely proven that it furnishes valuable data not otherwise obtainable.

The biopsy of skeletal muscle (pectoralis major or gastrocnemius) is much simpler. This has been performed by a large number of investigators and the general consensus is that in hypertension, there is thickening of the walls of the small arteries, and that in the more severe cases, this is associated with other lesions, such as sclerosis, necrosis, perivascular infiltration, or hyalinization of the endothelium.

The reader will find a comprehensive review of the literature up to 1929 in an article of Kernohan, Anderson, and Keith (29). Since that date, numerous other authors have become interested in the arteriolar changes in hypertension (30 to 38). Using actual measurements of the arterioles, Kernohan, Anderson, and Keith (29) found that in 53 cases of biopsy of the pectoralis major in hypertension, the media was hypertrophied and that in most cases, there was an increase of the nuclear elements. They also found that these lesions were more severe in cases of severe benign, early malignant, or malignant hypertension. These results were confirmed later by Keith, Barker, and Kernohan (39) on a series of 143 patients, and recently, by Heyer and Keeton (40).

On the other hand, Andrus (41) states that there was a greater amount of fibrous tissue in the wall of the arterioles in hypertensive than in non-hypertensive patients of the same age group, but it was not possible to distinguish between hypertensive and normal subjects merely by examining the arterioles of the pectoral muscles. He did not, however, measure the thickness of the wall. Moritz and Oldt (42) came to the same conclusion. Keith, Wagener, and Barker (22)

and Wagener and Keith (23) also state that there is no definite correlation between the findings in the arterioles of the muscles and the changes in the fundi or the severity of the disease; however, the arterioles of muscle obtained by biopsy in 65 cases of severe hypertension were altered more severely than those obtained in cases of benign hypertension.

There is general agreement on the fact that hypertension is associated with a certain degree of alteration of the arterioles, although the extent to which these lesions correlate with other symptoms and with the severity of the disease is still unknown. Nor are data available in the literature on the relationship between lesions of the arterioles in the muscle and results of therapy, although the most severe changes in the arterioles have been found in cases of malignant hypertension (31, 33, 35, 37), making the ultimate prognosis serious.

The purpose of our study was to correlate the degree of thickening of the arteriolar wall in the skeletal muscle with other symptoms of hypertension and with the therapeutic results. We were also interested in investigating the prognostic value of muscle biopsy and the advisability of performing such a biopsy before advising surgical treatment.

It has not been possible to repeat the muscle biopsy after treatment in the series of cases presented in this paper.

METHODS

Our series includes 350 patients with arterial hypertension, treated by supradiaphragmatic splanchnicectomy and resection of the 10th, 11th, and 12th thoracic sympathetic ganglia. The clinical and laboratory methods of study of the patients and the results of treatment have been reported by Peet, Woods, and Braden (1). Of the 350 patients, approximately 65 per cent have been re-examined postoperatively in the clinics of the University Hospital and 34 per cent have had acceptable data forwarded by their local physician or hospital. Only 4 patients (1 per cent) have not furnished sufficient information. The data were collected from 9 months to 7 years after the operation.

At the time of operation, a biopsy of 4 different pieces of intercostal muscle was collected, allowed to cool to room temperature, fixed in 10 per cent formalin, and imbedded in paraffin. The sections were stained with hematoxylin and eosin. Each section was searched for arterioles of 25 to 150 microns of total diameter, cut transversely so that they would appear with perfectly round margins. The thickness of the wall, at 4 diametrically

TABLE I

W/L	0.5 to 0.75	0.76 to 1.0	1.01 to 1.25	1.26 to 1.5	1.51 +
Males (<i>per cent</i>)	42	36	49	53	48
Females (<i>per cent</i>)	58	64	51	47	52
Total number	12	63	111	90	74

opposite points, was measured by means of an ocular micrometer and the width of the lumen at 2 diameters perpendicular to each other. Only the media and intima of each vessel were measured, since in most cases, it is difficult to see the outer limit of the adventitia. This is especially true in the arterioles of hypertensive patients where there are sometimes perivascular infiltrations of lymphocytes. At least 5 arterioles were measured for each patient, and in most cases, we were able to measure 7 or 8 vessels and, not infrequently, 10. The 4 measurements of the wall and the 2 measurements of the lumen of each arteriole were averaged and the ratio of the thickness of the wall to the diameter of the lumen (wall/lumen ratio or W/L) was computed. The ratios were then averaged for each patient. The results were tabulated on statistical cards, together with the other data obtained in each patient, and statistics were mechanically compiled. The statistical significance of the results was then studied by the Chi square method.³

All the measurements of the arterioles were made by the same person, who had no knowledge of the results of the clinical studies. The objection may be raised that the active contraction of the arterioles might vary from case to case and that the fixation of the muscle in formalin might occur at a different phase of this contraction, thus making the measurements of arterioles in different patients not comparable. This objection, however, does not have the support of the experimental evidence. Moritz and Oldt (42) have shown that if biopsies of skeletal muscle are taken from a dog in normal condition and again at the peak of the hypertensive crisis produced by an injection of adrenalin or at the peak of the hypotensive crisis produced by nitroglycerin, there is no variation in the mean external diameter, mean internal diameter, and mean wall to lumen ratio of the arterioles. It would seem likely, therefore, that in the process of collecting the specimen of muscle, any spasm which might have existed in the arterioles disappears and only permanent anatomical lesions remain; these are probably irreversible lesions, not sensitive to therapy. We assume this to be true in attempting to explain the results of our investigation.

³ The Chi square method evaluates the statistical probability, *P*, that the correlation studied might be due to chance, and therefore, not significant. When *P* is less than 0.05, the correlation is "significant"; when *P* is less than 0.01, the correlation is "highly significant"; when *P* is higher than 0.05 the correlation, very likely, is due to chance, and, therefore, cannot be considered significant (43).

Thirty-six individuals with normal blood pressure were studied. Their age was comparable to that of the hypertensive patients, varying between 18 and 61 years. They were selected according to the same criterion, namely the absence of acute renal disease or cardiac decompensation.

RESULTS

A. Preoperative studies

1. *Age and sex.* There were 165 males and 185 females; the age distribution is given in Table II.

2. *Distribution of preoperative blood pressure levels.* The distribution of preoperative blood pressure levels is given in Table III.

3. *Preoperative classification of the eyegrounds.* The Keith-Wagener classification at time of operation is given in Table IV.

4. *Distribution of wall/lumen ratios (W/L).* W/L of the arterioles in the skeletal muscle of hypertensive patients varied between 0.551 and 3.740 (average 1.822) and was much higher than W/L found in the normal individuals (0.318 to 0.868, average 0.598). The following values for normals were found in the literature: Kernohan, Anderson, and Keith (29), 0.371 to 0.589 (average 0.5); Moritz and Oldt (42), 0.4 to 0.715 (average 0.527); Odel (35), 0.368 to 0.565 (average 0.508); Heyer and Keeton (40), 0.456 to 0.529 (average 0.493).⁴ The consistency of these results is remarkable.

Figure 1 shows the distribution curve of the wall/lumen ratios in our patients. The curve has the shape of a relatively steep bell, as there were only 12 patients (3.4 per cent) with W/L below 0.75, and relatively few patients (74 or 21.2 per cent) with a very severe thickening of the arterioles, as indicated by a W/L of 1.50 or more; the great majority of the patients (264 or 75.4 per cent) had ratios between 0.75 and 1.50. As can be seen from the values given above, there is practically no overlapping between the distribution curves of W/L in normal subjects, and that of hypertensive patients, a fact pointed out also by Heyer and Keeton (40). The distribution curve suggested that the patients be divided into 5 classes according to the values of the wall/lumen ratio. The classes, indicated by the vertical lines in Fig-

⁴ These values were computed from the fractions indicated in the author's papers.

FIG. 1

Vertical lines indicate the 5 classes in which the patients have been divided.

ure 1, have been used throughout the work and are on the abscissa of all figures.

For statistical purposes, it would have been advisable to group patients of Classes 1 and 2 together, since Class 1 contains only 12 patients. We preferred, however, to consider the patients in Class 1 separately, since they had a W/L comparable to that of non-hypertensive individuals.

5. *Wall/lumen ratio and sex.* There was no significant correlation between W/L and sex of the patient (Table I), males and females being approximately in the same proportion in each class.

6. *Wall/lumen ratio and age.* In view of the relationship between age and arteriosclerosis, it was necessary to study the W/L ratio in different age groups. This was done and the results (Figure 2 and Table II) indicate that there is no significant correlation between age and arteriolar lesions.⁵ These results can be explained by the fact that the arteriosclerosis which appears in normal individuals as they grow old, is probably of a different nature from the arteriolosclerosis of hypertension, the former being mainly characterized by degeneration of the intima of the larger vessels, the latter by hypertrophy of the media of the arterioles. It is also possible that high blood pressure *per se* might accelerate the normal process of

the vascular disease to such an extent as to make comparatively insignificant the slower process of aging. A significant correlation might exist between W/L and the duration of the disease; this however could not be established with accuracy in our patients. Since no correlation exists between W/L and age and sex, it was not necessary to divide our patients according to these 2 factors, which would have resulted in groups too small to be statistically significant.

7. *Wall/lumen ratio and blood pressure.* The percentage of patients with high systolic and diastolic blood pressures becomes higher as W/L increases (Figure 3A and 3B), and, concurrently, the average W/L increases as the blood pressure increases (Table III). The only exceptions are the patients with a systolic blood pressure of more than 270 mm. Hg; however, only 7 patients are included in this group. This correlation is statis-

TABLE II
Average wall/lumen ratio according to age at time of operation

Age	W/L	Number of patients	Per cent
10 to 19	1.398	3	0.8
20 to 29	1.127	21	6.0
30 to 39	1.314	90	26.7
40 to 49	1.311	174	49.8
50 to 59	1.297	61	17.4
63	1.107	1	0.3
Total		350	100.0

⁵ P = approximately 0.5.

FIG. 2. NO SIGNIFICANT CORRELATION EXISTS BETWEEN AGE AND W/L

tically highly significant.⁶ The distribution of the values of pulse pressure among the 5 classes of patients with increasing W/L is not uniform (Figure 4A). Statistical studies show that any correlation would have small probability of being significant.⁷ However, when the inverse correlation was studied, it was found that the average of W/L increases steadily as the pulse pressure becomes higher (Table III).

8. *Wall/lumen ratio and eyegrounds.* (Figure 5A.) With the exception of Class 1, which includes only 12 patients, the number of cases with severe damage to the eyegrounds, such as angiospasm or papilledema (Keith-Wagener Groups 3 and 4), increases uniformly as W/L increases; the number of patients with normal eyegrounds or with mild lesions (Keith-Wagener Groups 1 and 2) decreases. The correlation is highly significant.⁸ The inverse relation is also true (Table IV), the average value of W/L is greater in the

groups of patients who have more severe damage to the eyegrounds. This is not surprising when one considers that the arterioles of the eyegrounds, on which the classification of Keith and Wagener is mainly based, are in many respects comparable to the arterioles examined in the skeletal muscle. On the other hand, Figure 5A indicates that severe eyeground changes (Groups 3 and 4) are common in all classes, including the class with normal W/L.

This fact is also borne out by the comparison between Figure 5A and Table IV. One hundred and seventy-nine patients are included in the first three classes of W/L (0.5 to 1.25 in Figure 5A); of these only 104 having comparable W/L values (Table IV) have normal eyegrounds or mild pathologic changes (Keith-Wagener Groups 1 and 2), leaving 75 patients with severe lesions (Keith-Wagener Groups 3 and 4). This suggests that the correlation between W/L and eyeground changes might not be as clear as the statistical studies would indicate.

9. *Wall/lumen ratio and cardiac function.* There is no significant correlation between W/L

⁶ Systolic: $P < 0.01$; Diastolic: $P > 0.01$.

⁷ $P > 0.2$.

⁸ $P < 0.01$.

TABLE III
Average wall/lumen ratio according to
preoperative blood pressure

Blood pressure	W/L	Number of patients	Per cent
<i>mm. Hg</i>			
1. Systolic			
140 to 179	1.073	15	4.3
180 to 209	1.183	110	31.4
210 to 239	1.331	150	42.9
240 to 269	1.430	68	19.4
270+	1.213	7	2.0
Total		350	100.0
2. Diastolic			
90 to 109	1.145	21	6.0
110 to 124	1.168	98	28.0
125 to 139	1.277	104	29.8
140 to 154	1.290	85	24.2
155+	1.554	42	12.0
Total		350	100.0
3. Pulse			
30 to 44	1.189	4	1.1
45 to 64	1.271	53	15.2
65 to 84	1.276	127	36.4
85 to 104	1.307	117	33.3
105+	1.420	49	14.0
Total		350	100.0

and enlargement of the heart (Figure 6A and Table VA).⁹ The size of the heart, however, was determined by orthodiagram and teleoroentgenogram, which are not very accurate methods. Furthermore, it is possible that the enlargement of the heart, which is a consequence of long lasting hypertension, might not become apparent by x-ray examination, until long after more sensitive methods, such as the measurement of W/L, the observation of the eyegrounds, the measurement of the blood pressure, or the electrocardiogram, have shown definite signs of abnormality. As a matter of fact, the correlation between W/L and alteration of the electrocardiogram is highly significant (Figure 6C and Table VB).¹⁰

10. *Wall/lumen ratio and renal function.* The correlation between W/L and urea clearance (Figure 7A) is not considered significant.¹¹ However, the average W/L is somewhat higher in the group of patients with reduced urea clearance than in the patients with normal urea clearance (Table VIA). On the other hand, a large number of patients with reduced power of concentrating urine have a higher W/L (Figure 7C) and the average W/L

is higher in patients with abnormally low power of concentration (Table VIB).¹²

In summary, we can state that patients with a greater degree of arteriolosclerosis also show more severe symptoms. In most cases, this correlation is highly significant; it is believed, therefore, that the determination of W/L of the arterioles is of considerable value in judging the severity of the hypertensive disease.

B. Postoperative studies¹³

Of the patients with adequate postoperative data, 51.4 per cent had a significant reduction in blood pressure (1). Approximately one-half of these had pressures reduced to normal or mark-

¹² $P < 0.01$.

¹³ The criteria used to evaluate the results of the operation have been set forth by Peet, Woods, and Braden (1). "Significant reduction in blood pressure is considered as a drop of 80 mm. systolic and 15 mm. diastolic, or more from the preoperative level. The blood pressure value given for each postoperative check-up is the arithmetical average of all readings by the Departments of Medicine and Neurosurgery. No pressure is considered significantly reduced unless both the systolic and the diastolic were lowered. Marked reduction in blood pressure is considered as a drop of 80 mm. systolic and 25 mm. diastolic, or more. Reduction of blood pressure to normal is considered as a drop to, or lower than, 130 mm. systolic and 90 mm. diastolic for patients up to the age of 40. After the age of 40 the drop must be to, or lower than, 150 mm. systolic and 100 mm. diastolic.

"Changes in ocular fundi are evaluated by the Department of Ophthalmology. Improvement of the pathologic vessel changes, of the number of hemorrhages and exudates, of angiospasm and of papilledema is noted only when the change is beyond dispute. All fundi with equivocal changes are regarded as unchanged. In addition the Keith-Wagener classification is used.

"Urine concentration is regarded as normal if the patient is able to concentrate to a specific gravity of 1.029 or higher after thirty-eight hours without water, on a dry diet. During the past years, because of inconvenience to the patient, a short concentration test has been substituted in which normal value is considered to be 1.026 following 18 hours without food or fluids. In both tests used, a change in specific gravity of three points or more is deemed necessary in order to be considered significant.

"Urea clearance is considered normal if the values of the test averaged 75% or higher. A change of 15% is considered significant.

"Cardiac size is determined by the teleoroentgenogram. Fifteen per cent above the predicted normal cardiac area is taken as evidence of enlargement. A change of 10% or more is considered significant. All teleoroentgeno-

⁹ $P > 0.7$.

¹⁰ $P < 0.01$.

¹¹ $P > 0.05$.

FIG. 3. CORRELATION BETWEEN W/L AND BLOOD PRESSURE

edly reduced. Improvement in ophthalmic, cardiac, and renal symptoms varied from 45 to 70 per cent of the cases studied. The operative mortality was 3.15 per cent; 86.6 per cent of the patients had postoperative relief of subjective symptoms, espe-

graphic measurements have been checked by orthodiagram.

"Electrocardiograms are evaluated by the cardiologists on the degree of axis deviation and T-wave changes. Each postoperative reading has been compared with the one taken preoperatively."

cially headache; 81.3 per cent had improvement or complete relief of incapacitation. Subjective symptoms and incapacitation, however, are not considered in this paper.

To study the prognostic value of the preoperative muscle biopsy for the treatment of hypertension by supradiaphragmatic splanchnicectomy, we have correlated W/L with the postoperative changes in symptoms. It must be emphasized that no data have been included in this study unless obtained at least 9 months after operation and

PULSE PRESSURE

that a large number of patients have been followed with repeated examinations for as long as 7 years.

1. Wall/lumen and reduction in blood pressure.

(a) Systolic and diastolic blood pressure. The number of patients who had a significant drop in systolic and diastolic blood pressure, following operation, is greater among those who, preoperatively, had a relatively mild degree of arteriosclerosis, as indicated by a low W/L. As the value of the ratio increases, the number of patients improved decreases rapidly. This is particularly true for the patients whose blood pressure was markedly reduced or reduced to normal (Figure 3C). The correlation shown in Figure 3C is statistically highly significant.¹⁴

It is possible that in the first class hypertension was due, almost exclusively, to a spasm of the arterioles which did not show in the microscopic sections and disappeared after operation; in the latter class, on the contrary, hypertension was most likely due to an irreversible thickening of the arteriolar wall.

(b) Pulse pressure. Approximately the same results were obtained correlating W/L to the post-

operative drop in pulse pressure (Figure 4B). There too, statistical computations indicate that the correlation is highly significant.¹⁵

2. Wall/lumen ratio and improvement of the eyegrounds. The correlation between W/L and improvement of the eyegrounds is also significant, the number of patients improved being higher among those with a low ratio, low among those with a high ratio (Figure 5B).¹⁶ Also the average ratio is lower among the patients who have been improved than among the others (Table VII).

3. Wall/lumen ratio and improvement of the

TABLE IV

Average wall/lumen ratio according to preoperative classification of eyegrounds

Keith-Wagener group	W/L	Number of patients	Per cent
Normal	1.143	12	3.5
Group 1	1.153	14	4.1
Group 2	1.265	78	22.7
Group 3	1.289	145	42.3
Group 4	1.383	94	27.4
Total		343	100.0

¹⁵ $P < 0.01$.

¹⁶ $P < 0.02$.

¹⁴ $P < 0.01$.

KEITH - WAGENER CLASSIFICATION OF EYEGROUNDS

cardiac function. Although there was no significant correlation between W/L and the heart size before the operation, the number of patients who, after operation, had a reduction of cardiac enlargement was inversely proportional to their W/L (Figure 6B and Table VIIIA).¹⁷

However, no significant correlation was found between W/L and the number of patients who had an improvement of the electrocardiogram (Figure 6D and Table VIIIB).¹⁸

TABLE V

Average wall/lumen ratio according to preoperative cardiac status

A. Heart size	W/L	Number of patients	Per cent
Normal	1.232	108	51.2
Increased	1.316	103	48.8
Total		211	100.0

B. Electrocardiogram	W/L	Number of patients	Per cent
Normal	1.163	85	38.8
Abnormal	1.378	134	61.2
Total		219	100.0

¹⁷ $P < 0.01$.¹⁸ $P > 0.05$.

4. *Wall/lumen ratio and improvement of the renal function.* As there was no significant correlation between urea clearance and W/L before treatment, it is doubtful whether such correlation existed after splanchicectomy (Figure 7B¹⁹ and Table IXA). On the contrary, the number of patients who had an improvement in the power of concentrating urine was greater among those who had a low W/L (Figure 7D).²⁰ There were no significant differences between the average W/L

TABLE VI

Average wall/lumen ratio according to preoperative renal function

A. Urea clearance	W/L	Number of patients	Per cent
Normal	1.211	191	56.8
Reduced	1.342	146	43.2
Total		337	100.0

B. Urine concentration	W/L	Number of patients	Per cent
Normal	1.115	56	16.8
Reduced	1.343	277	83.2
Total		333	100.0

¹⁹ $P > 0.05$.²⁰ $P < 0.01$.

FIG. 6. CORRELATION BETWEEN W/L AND CARDIAC STATUS

of improved and non-improved patients (Table IXB).

5. *Wall/lumen ratio and mortality.* Six years after the first patient had been operated upon, a

total of 107 patients (30.6 per cent) had died. Eleven deaths (3.15 per cent of the 350 patients treated) were due directly to the operation; 78 deaths (22.5 per cent) were due to hypertension

FIG. 7. CORRELATION BETWEEN W/L AND RENAL FUNCTION

(cardiac or renal failure, cerebral accidents, etc.), and 18 deaths (5.15 per cent) to other causes. The correlation between mortality and W/L is striking (Table X): ²¹ of the 78 patients who died

²¹ $P < 0.01$.

of hypertension, 2 (1.9 per cent) had a W/L of 0.5 to 0.75; 8 (7.5 per cent), a W/L of 0.76 to 1.0; 13 (12.1 per cent), a ratio of 1.01 to 1.25; 25 (23.4 per cent), a W/L of 1.26 to 1.50; and 30 (28 per cent), a ratio of 1.51 or more, indi-

PERCENTAGE OF MORTALITY DUE TO HYPERTENSION
ACCORDING TO WALL/LUMEN RATIO IN 350
PATIENTS TREATED SURGICALLY

FIG. 8. CORRELATION BETWEEN W/L AND MORTALITY

cating marked thickening of the vessel walls. The same striking correlation exists between W/L and operative mortality, which is zero for the patients with normal or slightly damaged arterioles and rises gradually to 7.5 per cent for the patients with more severe arteriosclerosis. After 6 years, only approximately 10 to 15 per cent of the pa-

tients included in the first three W/L classes were dead, whereas the mortality rises to 29 per cent for the patients in Class 4, and to 50 per cent for the patients in Class 5 with more severe arteriolar lesions (Figure 8).

The results of this study can be summarized by saying that a good correlation exists between W/L of the arterioles of the skeletal muscle and the level of systolic, diastolic, and pulse pressure, mortality and, possibly, vascular lesions in the eyegrounds. Some degree of correlation exists between W/L and cardiac enlargement, electrocardiogram, and power of concentrating urine, whereas no significant correlation exists between W/L and sex, urea clearance, or age of the patient at the time the biopsy was made (Table XI).

TABLE VII
Average wall/lumen ratio according to changes in eyegrounds after operation

Eyegrounds	W/L	Number of patients	Per cent
Improved	1.201	147	66.5
Unchanged	1.399	64	29.0
Worse	1.361	10	4.5
Total		221	100.0

TABLE VIII
Average wall/lumen ratio according to changes in cardiac status after operation

A. Heart size	W/L	Number of patients	Per cent
Decreased	1.286	82	78.8
Unchanged	1.317	16	15.4
Increased	1.435	6	5.8
Total		104	100.0
B. Electrocardiogram	W/L	Number of patients	Per cent
Improved	1.255	92	72.5
Unchanged	1.255	30	23.6
Worse	1.253	5	3.9
Total		127	100.0

TABLE IX
Average wall/lumen ratio according to changes in renal function after operation

A. Urea clearance	W/L	Number of patients	Per cent
Improved	1.210	132	72.5
Unchanged	1.352	30	16.5
Worse	1.173	20	11.0
Total		182	100.0
B. Urine concentration	W/L	Number of patients	Per cent
Improved	1.185	99	47.4
Unchanged	1.181	72	34.4
Worse	1.185	38	18.2
Total		209	100.0

TABLE X
Mortality rate according to wall/lumen ratio

W/L	Death due to hypertension		Operative mortality		Death due to other causes		Total	
	number	per cent	number	per cent	number	per cent	number	per cent
0.5 to 0.75	2	1.9	0	0			2	1.9
0.76 to 1.0	8	7.5	0	0			8	7.5
1.01 to 1.25	13	12.1	1	0.93			14	13.03
1.26 to 1.50	25	23.4	2	1.87			27	25.27
1.51+	30	28.0	8	7.50			38	35.50
All classes					18	16.8	18	16.88
Total	78	72.9	11	10.30	18	16.8	107	100.00

When a significant correlation exists between W/L and preoperative symptoms, there is also a significant correlation with the improvement of the same symptoms after splanchnicectomy. As a matter of fact, in some cases, such as pulse pressure and heart size, the correlation, which was not very significant before treatment, became highly significant with the postoperative changes.

The arterioles of the skeletal muscle represent a very large fraction of the whole arterial tree and, although an increased resistance uniformly distributed throughout these arterioles could probably alone produce an increase in blood pressure, we felt it advisable to compare the lesions found in the muscle to those found in the arterioles of other organs. This was done, especially in view of the importance of the renal vessels in hypertension and of the emphasis placed in the past on the increased resistance in the blood vessels of the splanchnic area. W/L of the arterioles of the central nervous system, heart, gastrointestinal tract, liver, pancreas, adrenals, spleen, and kidneys was measured in 20 patients whose death was due to hypertension or chronic nephritis and compared to the W/L of the arterioles of the diaphragm and the intercostal muscle. Fourteen cases had essential hypertension and in 6 cases, hypertension was secondary to chronic glomerulonephritis. All hypertensive patients had an increased value of W/L and, as a rule, the thickness of the arteriolar wall was more pronounced in patients with essential hypertension than in patients with chronic glomerular nephritis and secondary hypertension. In both groups, however, W/L in the skeletal muscle was not very different from the average W/L of other organs, thus indicating that the muscle biopsy gives a fair picture of the arteriolar system as a whole (Table XII).

DISCUSSION

The degree of arteriolar thickening can be considered a measure of the peripheral resistance. Thus, we can explain the correlation between W/L, preoperative level, and postoperative changes in blood pressure. In a series of 22 cases, it was previously found (19) that there was a correlation not only between the arterioles in the skeletal muscle and the eyegrounds, the blood pressure, and the vasomotor reactions, but also between these symptoms and blood flow through the kidney. Blood pressure, condition of the arterioles, renal blood flow, and vasomotor reactions are all factors directly affected by the vascular disease itself, and this quite possibly explains why the correlation between these primary symptoms is much more significant than between damage to the arterioles and cardiac and renal symptoms, which are secondary to the vascular disease. As a matter of fact, human and experimental hypertension can exist without alterations of the electrocardiogram or the renal excretory functions, and the enlargement of the heart does not ordinarily appear in the early stages of the disease.

The fact that the therapeutic results are much better in patients whose vessels appeared normal or only slightly damaged than in patients with marked arteriolosclerosis indicates that splanchnicectomy probably acts by removing the spasm of the arterioles. We have previously given evidence

TABLE XI
Correlation between W/L ratio and other symptoms in 350 patients with hypertension

Highly significant	Significant	Non-significant
Systolic blood pressure	Cardiac enlargement	Age
Diastolic blood pressure	Electrocardiogram	Sex
Pulse pressure	Urine concentration	Urea clearance
Eyegrounds		
Operative mortality		
Total mortality		

TABLE XII
Wall/lumen ratio of muscle biopsy, diaphragm, and other organs

Patient	Cause of death	Muscle biopsy	Diaphragm	Heart	Kidney	Liver	Spleen	Pancreas	G. I. tract	Adrenals	Central nervous system	Average
1	Hypertension	1.818		1.141	1.528	1.535	1.310	1.268	1.488	1.807	0.836	1.311
2	Hypertension	2.008		1.033	2.099	1.478	2.264	1.570	1.515	1.040	0.892	1.382
3	Hypertension	1.705		0.637	1.611	2.288	2.928	0.771	1.350	1.019	0.574	1.285
4	Hypertension	1.625		1.146	1.053	1.464	1.983	1.317	1.304	1.383	1.322	1.378
5	Hypertension	1.157		1.782	1.706	3.074		1.601	1.512		1.630	1.723
6	Hypertension	1.546		1.475	1.799	1.008	2.204	2.237	1.412	1.152	0.913	1.303
7	Hypertension	1.410		1.105	3.036	1.139	1.478	0.715	0.970	1.474	0.661	1.209
8	Hypertension	1.270		1.818		1.429	1.336		1.143		1.279	1.296
9	Hypertension	1.794		1.004	1.460	1.708	2.418	1.014	1.164	1.374	0.773	1.312
10	Hypertension		1.114	1.664	1.403	1.357	1.638	0.957	1.025	1.198	0.958	1.156
11	Hypertension		0.866	0.774	0.975	0.959	1.567	0.717	0.619	0.463	0.650	0.843
12	Hypertension		1.290	1.207	1.728	1.810	1.641	1.202	1.185	1.276	0.869	1.283
13	Hypertension		0.929	1.138	1.240	1.241	1.554	1.141	1.065	0.923	0.910	1.127
14	Hypertension		1.361	0.997	1.555	1.430	1.052	0.938	1.105	1.295	0.647	1.153
Average	Hypertension	1.593		1.112	1.209	1.627	1.572	1.188	1.211	1.200	0.994	1.283
15	Chr. nephritis			1.031	0.665	1.095	1.091	0.807	1.277	0.820	0.809	1.085
16	Chr. nephritis			0.828	1.188	1.311	0.958	1.554	0.917	0.857	0.921	1.013
17	Chr. nephritis			1.443	1.014	1.841	0.932	1.318	0.859	0.855	0.935	1.125
18	Chr. nephritis			0.558	0.975	1.135	1.121	1.401	0.724	1.207	0.392	0.928
19	Chr. nephritis			1.174	0.896	0.668	1.262	1.655	0.777	1.097	0.786	1.026
20	Chr. nephritis			0.818	0.714	1.235	1.115	1.675	0.612	0.948	0.622	0.958
Average	Chr. nephritis			0.975	0.909	1.214	1.080	1.521	0.799	0.967	0.925	1.023

that, in certain cases, the operation may relieve the spasm of the renal arterioles (21). It is possible that by interrupting the pathway of vasoconstrictor stimuli, the renal circulation might improve; the production of hypertensive substances would then cease, the spasm of the arterioles throughout the body disappear, and the blood pressure decrease significantly or return to normal. If the arteriolar lesions have become irreversible, splanchnicectomy does not lower the blood pressure.

The absence of a significant correlation between W/L and age of the patient shows that the influence of the disease itself on the blood vessels is an overwhelming factor compared to the normal process of arteriosclerosis. The absence of a significant correlation between W/L, sex and age adds to the statistical significance of the other correlations studied. The similarity between the value of W/L in the skeletal muscle and the average value of W/L in other organs indicates that the muscle arterioles are representative of the arteriolar system. These results are not in agreement with the findings of Fishberg (38), who states that the lesions of arteriolosclerosis in the skeletal muscle are found only rarely and then to an insignificant extent. Fishberg, however, refers to lesions of the degenerative and sclerotic type,

which are not frequent in essential hypertension; he did not measure the hypertrophy of the wall of the arterioles, which was the only sign of damage in the majority of our patients. Murphy and Grill (31), Scott, Seecof, and Hill (44), and Heyer and Keeton (40) showed that in a large percentage of hypertensive patients, there is a moderate to severe thickening of the arteriolar wall in muscle biopsies, which is in agreement with our findings.

SUMMARY

The ratio of the thickness of the wall to the diameter of the lumen (W/L) of the arterioles in skeletal muscle was computed from data obtained by direct measurement of the blood vessels in biopsy material. Three hundred and fifty consecutive cases of arterial hypertension were studied. All the patients were subsequently submitted to supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy and followed for 9 months to 7 years after the operation. The degree of thickening of the arteriolar wall was compared to the severity of other signs and symptoms and to the therapeutic results. Patients with more severe thickening of the arteriolar wall had more severe symptoms, showed poorer therapeutic results and greater mortality. The correlation is

particularly significant between arteriosclerosis and other evidence of damage to the vascular system, such as the elevation of the blood pressure. The results show that the determination of W/L in skeletal muscle adds very significant information to the clinical and pathological picture of hypertension. It is important in the prognosis of the disease. The results are in agreement with the hypothesis that the surgical treatment of hypertension described here gives better results when hypertension is due to a spasm of the arterioles or to a mild, reversible degree of hypertrophy of the muscle fibers in the media, and not when severe permanent anatomical lesions have transformed the majority of the arterioles into narrow and rigid tubes.

It is suggested that the study of hypertensive patients should include, whenever possible, the determination of the intensity of the vasomotor reactions, the measurement of the effective renal blood flow by diodrast clearance (45), the observation of the blood vessels of the eyegrounds, and the determination of the wall/lumen ratio of the arterioles in muscle biopsies. This direct investigation of the vascular system is at least as important as the examination of the heart and of the renal function, which reveals the extent of the damage produced by hypertension to vital organs and functions, rather than the severity of the disease itself and the extent to which vascular lesions have become irreversible.

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