Hypertension and Cerebral Atherosclerosis

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SUMMARY
This study consisted of an analysis of autopsy material from 3,824 persons who were 30 years of age or older in whom the arterial circle of Willis was scored for the severity and extent of atherosclerosis. Several criteria were used for hypertension. These consisted of the heart weight, the clinical diagnosis of hypertension, and the blood pressure. Regardless of which criterion was used, a definite increase in the severity of atherosclerosis of the circle of Willis was noted in the presence of hypertension. The increase was most pronounced when clinical criteria were used.

Additional Indexing Words:
Necropsy study Arteries of Circle of Willis Heart weight Blood pressure

That hypertension is a common antecedent of atherosclerosis and a significant factor in its etiology has been suggested.1-6 There is ample evidence from experimental,7-14 clinical,15-20 and pathological studies21-31 to indicate that hypertension not only accelerates the onset but also accentuates the progress of atherosclerosis.

The present study is based on a series of 5,033 autopsies in which the frequency and severity of atherosclerosis of the circle of Willis have been recorded. These cases were obtained from routine autopsies carried out at the University of Minnesota Hospitals and the Hennepin County General Hospital during 5 years (1961-1966). The autopsy percentages, as determined for 1965, were 84% for the University of Minnesota Hospitals and 70% for the Hennepin County General Hospital. Brain autopsies were obtained in 79% of the autopsied cases. A previous survey of the entire series showed that gross atherosclerotic changes of the cerebral vessels were uncommon in individuals under 30 years of age. Furthermore, few cases of hypertension were found in this age group. The present study, therefore, is limited to the 3,824 persons in this series who were 30 years of age and older. The inherent bias of autopsy data due to selectivity is acknowledged. Our series shows characteristics similar to those reported by others,32,33 namely, younger individuals came to autopsy more frequently than older individuals and

Figure 1
Distribution of heart weights by age and sex.
the autopsy rate for males is slightly higher than that for females.

Method

The arteries of the circle of Willis were examined and scored for the extent and severity of atherosclerosis in accordance with the coding technic of Baker and his associates. In this method 22 sites of the circle of Willis are scored on the basis of 0 to 4 depending upon severity of involvement, the maximum score being 88.* These scores form the basis for the comparisons made in this presentation.

The scoring was done by two investigators. A reliability study on the scoring method was conducted between the two coders on 24 specimens which had been cut at various scoring sites by a pathologist not involved in the study. Each circle of Willis was independently scored twice by the two coders according to a randomized block design with subsampling. The mean difference in scores was not statistically significant (mean difference, 0.8, \( P = 0.15 \)) and the standard deviation for repeated scorings by the same coder was 2.1.

The association between the frequency and severity of cerebral atherosclerosis and hypertension was assessed in relation to three separate criteria: heart weight, clinically diagnosed hypertension, and blood pressure.

Heart Weight

The heart weight has often been used as evidence of hypertension. Arbitrary values for

*This technic takes into consideration the involvement of the vessel wall as well as luminal encroachment. It divides atherosclerosis of the circle of Willis into four groups:

Grade 1+: Opacity involving only a small part of the vessel circumference. No narrowing of the lumen.

Grade 2+: (A) Diffuse thin plaque that does not involve the entire vessel circumference with minimal narrowing of the lumen. (B) Small thick plaque that narrows the lumen less than 25%.

Grade 3+: (A) Diffuse thin plaque involving the entire vessel circumference with mild narrowing of the lumen. (B) A localized thick plaque producing 25 to 50% narrowing of the lumen.

Grade 4+: (A) A thick plaque involving the entire vessel circumference with moderate or marked narrowing of the lumen. (B) A localized thick plaque resulting in more than 50% narrowing of the lumen.

 heavy hearts varying from 300 to 500 g depending on sex have been selected by various investigators. We thought that it would be more appropriate to determine the distribution of heart weights of the study cases in order

![Figure 2](http://circ.ahajournals.org/)

**Figure 2** Distribution of vessel scores by heart weight categories (50th percentiles of total heart weight distributions, see figure 1).

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to determine heart weight criteria for hypertension. The cumulative distributions by 10-g intervals were computed for each 10-year age and sex group. The 25th, 50th (median), and 75th percentiles were plotted at the midpoints of the age intervals, and the lines connecting equal percentile points represent percentile curves over age. The curves are presented in figure 1 for males and females. The number of cases on which the analysis was based are given in table 1. The correlations of heart weight and body weight and of heart weight and body height were investigated by age and sex and were found to be too weak to warrant any adjustment of heart weights for either or both of these variables.*

Instead of using a fixed heart weight value for the separation of cases into hypertensive and normotensive categories, it was decided to divide the cases into groups of equal size, one group with "light" heart weights and one group with "heavy" heart weights. This was accomplished by using the median heart weight value for each age and sex group as the division point. A comparison of the vessel scores between these two heart weight categories would indicate if, in general, heavier heart weights are associated with increased cerebral atherosclerosis. A second group of heart weights by a separation at the 75th percentiles was used for a comparison between the vessel scores of the 25% of cases with very heavy heart weights and the vessel scores of the cases with heart weights below the 75th percentiles, that is, with low or medium heart weights.

The distributions of circle of Willis scores were obtained for each heart weight category, by age and sex, and are shown in terms of percentile curves in figures 2 and 3. The curves in figure 2 are for the groups defined by separation at the medians, and those in figure 3 are for the groups obtained by separation at the 75th percentiles of the heart weight distributions. A general sex difference, as discussed elsewhere,35 was manifested by an earlier onset of detectable cerebral atherosclerosis in males than in females and by higher vessel scores in younger males com-

*The linear regressions of heart weight on body weight, on body height, and on weight and height together were obtained for each sex and 10-year age group. The reduction in sum of squares for residual variation in heart weight varied over age and sex groups from 1% to 20% when regression on body weight was considered. Regression on body height yielded reductions of 0 to 6%, and the multiple regression on weight and height led to reductions of 1% to 22%. The largest reductions of 20% with regression on weight alone and of 22% with regression on weight and height were found in the female age group of 60 to 69 years. In this group the following values were found for the standard deviation of heart weight:

Heart weight: $sd = 117$ g.
Heart weight/body weight: $sd = 105$ g.
Heart weight/body weight and height: $sd = 104$ g.

Other than linear relationships may possibly yield better results but were not investigated at this time.

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pared to those for females of the same age; a reversed sex difference in severity of cerebral atherosclerosis can be observed in the oldest age group.

The cases in which the heart weights were heavier show consistently higher circle of Willis scores than those with lighter heart weights at all ages. Except for the females grouped by the 75th percentile, where the largest difference is found in the seventh decade, the maximum differences in median scores of 9 or 10 points occur in the eighth decade. The curves for the heavy heart weight group in figure 3 are not as smooth as those in figure 2 because they are based on only one half of the number of cases categorized as having heavy heart weights in figure 2. However, a general comparison between the two sets of curves for a given sex reveals similar differences in vessel scores regardless of which division points for heart weights are used.

In both figures it is apparent that a few males with heavy heart weights have high vessel scores in the sixth and seventh decade, as indicated by the spread between the 75th percentiles. This difference disappears completely in the oldest male age group where the 75th percentiles of vessel scores are identical for all heart weight categories. On the other hand, in this oldest age group a considerable difference is found between the lower vessel scores of the two heart weight categories, as represented by the 25th percentiles. No such consistent differences between percentiles of vessel scores are found in the curves for

females, where all percentile curves seem to increase at approximately equal rates.

Clinical Hypertension

A comparison of vessel scores in hypertensive and nonhypertensive cases would directly demonstrate a possible association between hypertension and severe cerebral atherosclerosis. For the identification of hypertensive individuals we accepted the recorded clinical diagnosis of the disease. There were 645 patients of age 30 years and older, with a diagnosis of hypertension, and their distribution by age and sex is given in table 2.

The percentiles for the distribution of vessel scores for hypertensives and nonhypertensives are shown in figure 4. It is evident that hypertensives have a much higher degree of

Table 2

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Males</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>No hypertension</td>
<td>Hypertension</td>
<td>No hypertension</td>
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<td></td>
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<td>30-39</td>
<td>23</td>
<td>161</td>
<td>17</td>
<td>131</td>
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<td>40-49</td>
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<td>301</td>
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<td>458</td>
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<td>33</td>
<td>81</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>356</td>
<td>1985</td>
<td>289</td>
<td>1204</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4

Distribution of vessel scores for cases clinically diagnosed as hypertensive and nonhypertensive.
cerebral atherosclerosis than persons without this disease. More than 25% of hypertensive males have vessel scores over 20 points as early as the beginning of the fifth decade. The largest difference between median vessel scores for the two male diagnostic groups occurs at age 60 to 69, and has a value of 22 points. Expressed differently, in the older age groups, a given median vessel score is reached by the hypertensive males when they are 20 or more years younger than it is attained by the nonhypertensive males. The maximum difference in median vessel scores for females is also found in the seventh decade. With a value of 13 points, it is considerably smaller than that for males. The largest age difference for a given median vessel score is 15 years for females, and this value is observed between the ages of 50 and 55 for hypertensives and the ages of 65 and 70 for nonhypertensives.

**Figure 5**

*Distributions of systolic and diastolic blood pressure by age and sex.*

**Figure 6**

*Distribution of mean blood pressure by age and sex.*

**Blood Pressure**

Despite certain inherent weaknesses in the use of blood pressure measurements in a retrospective study, the data were nevertheless analyzed for the relationship between cerebral atherosclerosis and different levels of blood pressure. The recorded blood pressure represented the highest systolic and diastolic readings found in the patient's chart. The distributions of these systolic and diastolic measurements were determined for intervals of 5 mm of mercury and the percentile curves, similar to those used in the heart weight analysis, are presented in figure 5; figure 6

**Table 3**

*Number of Cases with Recorded Blood Pressure*

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>114</td>
<td>106</td>
</tr>
<tr>
<td>40-49</td>
<td>183</td>
<td>201</td>
</tr>
<tr>
<td>50-59</td>
<td>340</td>
<td>253</td>
</tr>
<tr>
<td>60-69</td>
<td>385</td>
<td>255</td>
</tr>
<tr>
<td>70-79</td>
<td>411</td>
<td>226</td>
</tr>
<tr>
<td>80+</td>
<td>164</td>
<td>98</td>
</tr>
<tr>
<td>Total</td>
<td>1597</td>
<td>1139</td>
</tr>
</tbody>
</table>

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shows the distributions for mean blood pressure (the arithmetic mean of the systolic and the diastolic measurement for each patient). The number of cases for which data were available is given in table 3.

Again the 50th and the 75th percentiles for each age and sex group were used to divide the cases into "high" level and "low" level groups for systolic and diastolic blood pressure, as well as for mean blood pressure. The distributions of vessel scores were nearly similar for the groups of a given level determined by the same percentile division points. This is not surprising because it can be assumed that a considerable number of patients with high level systolic blood pressure are also included in the high level diastolic group. However, there seems to be a slight trend for males with a high level of systolic blood pressure to have higher vessel scores than the males with a high level of diastolic blood pressure, particularly in the age group of 60 to 69. For a comparison of average vessel scores among groups, the median vessel scores are shown in figure 7.

In view of the similarity between the distributions of vessel scores for the systolic and the diastolic groups, it seemed appropriate to base a more detailed comparison of circle of Willis scores on the percentile points of the distribution of mean blood pressure. The corresponding percentile curves for the vessel scores are presented in figures 8 and 9. The cases with high level mean blood pressure show considerably more cerebral atherosclerosis than the low level group, particularly when only the upper quartile is separated from the remainder of the cases. When the 50th percentile of mean blood pressure is considered as division point, the maximum difference in median vessel scores between high and low level groups is found in the eighth decade with values of 14.5 points for the males and 10.5 points for the females. In the case of a separation at the 75th percentiles of
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Percentiles at given age

- Mean BP < 50th percentile
- Mean BP ≥ 50th percentile

**Males**

<table>
<thead>
<tr>
<th>Vessel Score</th>
<th>25th percentile</th>
<th>50th percentile</th>
<th>75th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in Years</td>
<td>30</td>
<td>40</td>
<td>50</td>
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</tbody>
</table>

**Females**

<table>
<thead>
<tr>
<th>Vessel Score</th>
<th>25th percentile</th>
<th>50th percentile</th>
<th>75th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in Years</td>
<td>30</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>

**Figure 8**

Distribution of vessel scores by mean blood pressure categories (75th percentile of total mean blood pressure distribution, see figure 6).

mean blood pressure, the two curves for median vessel scores show the largest spread of 17 points for the males and 14 points for the females one decade earlier.

**Discussion**

The results of our study as well as many reports in the literature suggest that a strong association exists between hypertension and cerebral atherosclerosis. We recognize that other variables could be operational in increasing cerebral atherosclerosis, and it would be of interest to intercorrelate hypertension and other risk factors such as serum lipids and uric acid. Unfortunately, in a retrospective autopsy study, laboratory data are often missing, and even when available the reliability of these data, obtained from different laboratories at various times, would be questionable.

The three-way relationship of cerebral atherosclerosis, obesity, and hypertension is the subject of an investigation currently in progress. In a preliminary analysis the cases for which body height and weight measurements were available were categorized into three groups by ponderal index. The heaviest showed only a very slight trend toward higher vessel scores when clinically diagnosed hypertensives were excluded. The trend by relative weight was even weaker among the hyperten-

**Figure 9**

Distribution of vessel scores by mean blood pressure categories (75th percentile of total mean blood pressure distribution, see figure 6).
sive cases. Within each of the three weight groups the differences in vessel scores between hypertensives and nonhypertensives were large, comparable to those found when body weight was not taken into account. These preliminary results seem to indicate that the great increase in cerebral atherosclerosis in the presence of hypertension is independent of increased body weight.

Although the vessel scores are consistently higher in the hypertensives than in the normotensives, the observed differences vary in magnitude depending on what criterion was used for hypertension. The increase in cerebral atherosclerosis is much more pronounced when the clinical diagnosis of hypertension is considered than when heart weight, as indirect evidence of the disease, is used. For this reason, an investigation of the relationship between vessel scores and heart weight among the cases of clinically diagnosed hypertension was made. These cases were subdivided into a light heart weight group and a heavy heart weight group by means of the 50th and 75th percentiles of the total heart weight distributions. In every age and sex group far more than one half of the hypertensives had heart weights above the median; this clearly indicates that these individuals have higher average heart weights than the nonhypertensives. Some sample sizes in the resulting subgroups were rather small; hence, only the median vessel scores are presented in figure 10. The median curves indicate that hypertensives with light heart weights have approximately the same, or even higher, average vessel scores than those with heavy heart weights.

Figure 10

Average vessel scores in cases of clinically diagnosed hypertension by heart weight. Heart weight categories were determined by percentiles of total heart weight distributions.

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heart weights. In the hypertensives, therefore, high vessel scores are not always associated with heavy heart weights. An additional investigation revealed that some individuals with heavy heart weights were not hypertensive and had low vessel scores. These findings would account for the smaller differences in cerebral atherosclerosis when heart weight was used as a criterion as compared to the large differences found when the clinical diagnosis was used as a criterion.

When hypertension was defined by the 75th percentiles of the mean blood pressure, the curves for vessel scores resembled strongly those found for the clinically diagnosed hypertensives and nonhypertensives in the females, but not in the males. The curves for males with high level mean blood pressure are somewhat lower than those for the group with diagnosed hypertension. The sample sizes for this group with a high level of blood pressure are slightly larger (440 males and 307 females) than the number of clinically diagnosed hypertensives (table 2; 356 males and 289 females), particularly for the males. The possible inclusion of some normotensives with transitory hypertension into the high level mean blood pressure group may have lowered the scores for this group as a whole.

Of interest is the increasing disparity with increasing age in the extent of cerebral atherosclerosis between males with clinically diagnosed hypertension and those without hypertension. One may speculate that in older subjects a longer duration of hypertensive disease led to a greater severity of cerebral atherosclerosis. In the females, on the other hand, the effect of prolonged hypertension may be counteracted by some sex-specific factors.

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