Relation of a Postmortem Renal Index of Hypertension to Atherosclerosis and Coronary Artery Size in Young Men and Women

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Abstract—In a cooperative multicenter study, the Pathobiological Determinants of Atherosclerosis in Youth, we measured atherosclerosis of the aorta and right coronary artery (RCA) in 2403 black and white men and women 15 through 34 years of age who died of external causes and were autopsied in forensic laboratories. We measured the diameter of the opened, flattened, and fixed RCA and the diameter, intimal thickness, intimal cross-sectional area, medial thickness, and medial cross-sectional area of the pressure-perfused, fixed left anterior descending (LAD) coronary artery. Using the ratio of intimal thickness to outer diameter of the small renal arteries to predict mean arterial pressure during life, we classified the cases as normotensive (mean arterial pressure $<110$ mm Hg) or hypertensive (mean arterial pressure $\geq 110$ mm Hg). The prevalence of hypertension by age, sex, and race corresponded closely with that measured in a survey of the living population. Hypertension had little or no effect on fatty streaks. Hypertension was associated with more extensive raised lesions in the abdominal aortas and RCAs of blacks $>20$ years of age and in the RCAs of whites $>25$ years of age. At all ages, women had less extensive raised lesions in the RCAs than did men, but the effect of hypertension on raised lesions was similar to that in men. Adjustment for serum lipoprotein cholesterol levels and smoking in a subset of cases yielded results similar to those obtained without adjustment. Hypertension was associated with larger diameters of the RCA and LAD coronary artery and with larger cross-sectional intimal and medial areas of the LAD coronary artery. Hypertension augments atherosclerosis in both men and women primarily by accelerating the conversion of fatty streaks to raised lesions beginning in the third decade of life, and the effect of hypertension increases with age. (Arterioscler Thromb Vasc Biol. 1998;18:1108-1118.)

Key Words: coronary arteries ■ aorta ■ atherosclerosis ■ arterial structure ■ hypertension

We have known for a long time that hypertension is associated with the severity of atherosclerosis and risk of CHD in middle-aged and older adults. Recent angiographic studies, also performed on adults, have shown that hypertension is associated with impaired reactivity of the coronary arteries independently of atherosclerosis. Children, adolescents, and young adults demonstrate a wide range of blood pressures, but it was not known whether elevated blood pressure affected the structure of the coronary arteries or the progression of atherosclerosis in youth.

We addressed these issues in a study of atherosclerosis among young people, 15 through 34 years of age, in the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study. Investigators participating in this multicenter project collected $\sim 3000$ sets of coronary arteries and aortas from young men and women who had died of external causes (accidents, homicides, and suicides) and had been autopsied in forensic laboratories. We measured atherosclerotic lesions in these arteries and measured risk factors in blood and tissue, including blood pressure estimated from the thickness of the intima of small renal arteries. Analysis of data from 1164 men showed that hypertension was associated with more extensive raised lesions, but not fatty streaks, in both the aorta and RCA. The current report is based on about twice the number of cases, includes young women as well as men, and extends the observations to the dimensions of the coronary artery and the coronary artery wall.

Methods

Study Design
Fifteen cooperating centers adopted a Standard Operating Protocol and Manual of Procedures to collect specimens and submit them to...
Subjects

Study subjects were persons 15 through 34 years of age who had died of external causes (accidents, homicides, and suicides) within 72 hours after injury and were autopsied within 48 hours after death in 1 of the cooperating medical examiners’ laboratories. Age and race were obtained from the death certificate. Persons of race other than black or white and those with congenital heart disease, Down syndrome, AIDS, or hepatitis were excluded. From a total of 3210 cases collected between June 1, 1987, and August 31, 1994, we excluded 334 cases because they did not meet the study criteria. Of the 2876 accepted cases, kidney samples were available for 2833 cases. We previously reported large effects of elevated glycohemoglobin on coronary heart disease, and central laboratories.

Selected Abbreviations and Acronyms

CHD = coronary heart disease
EEL = external elastic lamina
IEL = internal elastic lamina
LAD = left anterior descending
LV = left ventricle, left ventricular
MAP = mean arterial pressure
NHANES = National Health and Nutrition Survey
PDAY = Pathobiological Determinants of Atherosclerosis in Youth
RCA = right coronary artery
ORO = oil red O

Dissecting and Preserving Arteries

The forensic pathologist and his assistants removed the aorta along with other organs. The PDAY team dissected the aorta from a point 2 cm proximal to the ligamentum arteriosum to a point 2 cm distal from the aortic bifurcation. Branching arteries were severed close to the aortic wall, and adventitial fat was removed by sharp dissection. The PDAY team opened the aorta along a line on the dorsal surface midway between the orifices of the intercostal and lumbar arteries, rinsed the intimal surface with Hanks’ modified balanced salt solution, and flattened it with the adventitial surface downward. The PDAY team then split the aorta longitudinally along a line on the ventral surface that bisected the celiac, superior mesenteric, and inferior mesenteric ostia; prepared the right half for histochemical and chemical analyses; and placed the left half on a piece of cardboard with the adventitia downward. This left half was covered with absorbent cotton and fixed in 10% neutral buffered formalin in a flat pan for 48 hours.

The PDAY team opened the RCA from its origin to the point where it turned downward along the posterior interventricular sulcus with the use of blunt-point microdissecting scissors, dissected it from the heart, removed the epicardial fat, and fixed it in the same manner as the aorta. The left main and LAD coronary arteries were fixed by perfusion with 10% neutral buffered formalin under 100 mm Hg pressure.

The collection centers placed each half aorta and RCA in a plastic bag and shipped accumulated tissues to a central laboratory each week. The central laboratory stained the arteries with Sudan IV and packaged each artery with its identification number in a transparent plastic bag with a slight excess of 10% neutral buffered formalin.

The collection centers wrapped the left main and LAD coronary arteries in absorbent cotton sufficient to split but not compress the arteries, suspended them in a screw-top tube with 1% formalin, and shipped them to a central laboratory each week. The central laboratory removed a 5-mm-long segment of the LAD coronary artery just distal to the origin of the circumflex artery, embedded it in paraffin, and sectioned it at 6 μm. Sections were stained with the Gomori’s trichrome stain. An adjacent proximal block of the fixed LAD coronary artery was sectioned at 20 μm in the frozen state and stained with ORO, counterstained with Lillie’s hematoxylin, and mounted in glycerol jelly.

Height

The length of the cadaver, from the vertex of the cranium to the base of the heel, was measured in units commonly used by the local medical examiner or coroner. The measuring instrument was laid parallel to the body, which was in a supine position and with the inferior extremities extended. Measurements were recorded to the nearest centimeter or one-half inch.

Heart Weight and LV Thickness

The prosector weighed the heart to the nearest gram after removing blood clots and the extraneous proximal aorta and pulmonary vessels. The PDAY team measured the thickness of the LV to the nearest millimeter at its obtuse margin halfway between the mitral valve and apex and also measured the thickness of the right ventricle at the conus, 1 cm from the pulmonary valve.

Grading Arteries

Pathologists, blinded to demographic, clinical, or pathological observations and collection site, evaluated the RCAs and left halves of the aortas. They visually estimated the extent of intimal surface involved with fatty streaks, fibrous plaques, complicated lesions, and calcified lesions by procedures developed in the International Atherosclerosis Project. A fatty streak was a flat or slightly elevated intimal lesion stained by Sudan IV and without other underlying changes. A fibrous plaque was a firm, elevated, intimal lesion, sometimes partially or completely covered by sudanophilic deposits. A complicated lesion was a plaque with hemorrhage, thrombosis, or ulceration. A calcified lesion was an area in which calcium was detectable, either visually or by palpation, and without overlying hemorrhage, ulceration, or thrombus. The sum of the percentages of surface involved with fibrous plaques, complicated lesions, and calcified lesions by gross visual grading was designated “raised lesions.” Most of the raised lesions were fibrous plaques. Consensus grading of lesions was the mean of independent gradings by 3 pathologists. Intraobserver variability was assessed by repeated independent gradings of coded specimens randomly interspersed among new specimens. Agreement among observers was reported previously.

Morphometry of Coronary Arteries

The morphometry laboratory scanned 35-mm color transparencies of each Sudan IV–stained RCA at a resolution of 512×256 pixels by 8-bit gray scale through a green filter, stored the image on a DEC MicroVAX II computer, and displayed it on a Gould Vicom IP9527 image processing system. The operator manually identified fiducial points, consisting of pairs of points 1 cm apart along the outer edges of the opened and flattened vessel. Using these points, we measured the width of the opened and flattened RCA in the digitized images at 1-cm intervals, beginning 1 cm from the proximal end. Because there were a number of irregular cuts at the origin of the RCA and because many arteries were not >5 cm long, we used only the measurements
Arteries in Hypertensive Youth

at 2, 3, and 4 cm from the proximal end. Assuming that the artery was circular in cross section, we computed the approximate diameter from the width measurements. The mean diameter decreased 8% over this 2-cm interval. Because analysis of the diameter at 2, 3, and 4 cm yielded similar results concerning the effects of hypertension, we present the results of the mean diameter over this entire interval.

The morphometry laboratory scanned the trichrome- and ORO-stained sections of the LAD coronary artery at a resolution of 1024×1024 pixels by 24-bit full color with the use of an Eikonix 78/99 digital scanner and stored and displayed the image on the same system used for the gross images of the RCA. On each image, the operator manually identified the luminal border, the IEL, and the EEL. If the IEL or EEL was broken, the operator drew a smooth curve between the visible ends. The operator then measured the length of the EEL; the cross-sectional areas of the intima and media; and the minimum, maximum, and mean thicknesses of the intima and media. Because some sections of the artery wall were flattened transversely during histological processing, we assumed that the EEL was a circle and calculated the LAD coronary artery diameter and total artery cross-sectional area from the length of the EEL. We computed the cross-sectional area of the lumen by subtracting the measured intimal and medial areas from the calculated arterial cross-sectional area.

Dissecting, Preserving, and Processing Kidney Tissue

The PDAY technicians stripped the kidneys of the capsule and perirenal fat and bisected them. One section that included the cortex and medulla from each kidney was fixed in 10% neutral buffered formalin and shipped to the central laboratory. At the central laboratory, blocks perpendicular to the capsular surface were embedded in Paraplast, sectioned at 6 μm, and stained with periodic acid–Schiff–Alcian blue. The 2 sections represented 2 to 4 cm² of cross-sectional area of the renal cortex.

Classification of Hypertension Status

We measured arterial changes associated with hypertension in histological sections of kidney by a method developed by Tracy et al. The grader used a microscope equipped with 10× and 40× objective lenses and an eyepiece ruler marked in units corresponding to 10 μm under the 10× objective lens. The grader measured the outer diameter, from 1 outer media to the other, of the least axis of the elliptical profile of all arterial profiles with outer diameters of 80 to 300 μm. The grader then measured the thickness of the intima, also along the least axis, under the 40× lens. The measurement was made in the better presented of the 2 opposite walls; if both were equally well presented, a mean of the 2 was used. One observer measured an average of 36.8 arteries per case (range, 6 to 60). We grouped the measurements into those derived from arteries with outer diameters of 80 through 149 μm (arteries remote from the heart) and those derived from arteries with outer diameters of 150 through 300 μm (arteries more proximal to the heart). We calculated a renal measure of hypertension by dividing the mean thickness of the intima by the mean outer diameter of the artery separately for the measurements made on the smaller (remote) arteries and the measurements made on the larger (proximal) arteries.

We classified each case as normotensive or hypertensive by an algorithm that predicts MAP from the renal measure of hypertension and age. (A typographic error in the published equation was corrected by changing the sign for 1 coefficient from positive to negative.) Because young women have lower blood pressures than do young men with similar renal measure of hypertension values, a small adjustment was added to the MAP of women to apply the algorithm to them. The adjusted value was obtained by comparing average blood pressures of young men and women as measured in living populations.

The normotensive category included cases with a predicted MAP <110 mm Hg; hypertensive, those with a predicted MAP ≥110 mm Hg. These cutoffs were selected on the basis of analysis of lengthy lifetime records of blood pressure measurements in persons whose kidneys were examined after autopsy. The cutoffs were similar, but not identical, to MAPs computed from systolic and diastolic pressures that have been used as cutoffs in epidemiological surveys. For example, a frequently used definition of borderline hypertension as a systolic blood pressure between 140 and 160 mm Hg and a diastolic blood pressure between 90 and 95 mm Hg yields a lower limit for computed MAP (sum of the systolic plus twice the diastolic divided by 3) of 107 mm Hg; in contrast, a definition of hypertension as a systolic blood pressure >160 mm Hg and a diastolic blood pressure >95 mm Hg yields a limit for computed MAP of 117 mm Hg. Agreement within and among observers was reported previously.

We analyzed the relation of hypertension classification to atherosclerotic lesions by using renal measure of hypertension values derived from proximal and remote arteries separately. The results were similar; therefore, we present only the results based on measurements of the smaller remote arteries.

Statistical Methods

We analyzed by ANOVA the associations of hypertension, sex, race, and 5-year age group with percent intimal surface area involved with lesions, heart weight, heart weight-height ratio, ventricle thicknesses, RCA diameter, and LAD measurements (diameter, cross-sectional area, intimal cross-sectional area and thickness, medial cross-sectional area and thickness, total wall cross-sectional area and thickness, ORO-positive area, and percent of intimal area that was ORO-positive). The linear model included the main effects of hypertension, sex, race, and 5-year age group and all 2-factor interactions. We applied a logit transformation to the proportion of surface area involved with lesions and to the proportion of intimal area that was ORO-positive. A small constant (0.001) was added to avoid the logarithm of zero. We applied a logarithmic transformation to the heart weight, heart weight-height ratio, ventricle thickness, and LAD coronary artery measurements. The prevalence of cases classified as hypertensive was analyzed using logistic regression.

Prevalence of Hypertension

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence of Hypertension</strong></td>
</tr>
<tr>
<td>Table 1 shows the prevalence of hypertension by sex, race, and 5-year age groups. Hypertension was more frequent in men than women ($P=0.0001$) and was more frequent in blacks than whites ($P=0.0002$). Prevalence changed with age ($P=0.0304$). There was no interaction between sex and race, sex and age, or race and age in their effects on the prevalence of hypertension.</td>
</tr>
<tr>
<td>Figure 1 compares the prevalence of hypertension in PDAY cases with the prevalence observed in the 1976 to 1980 National Health and Nutrition Survey (NHANES II) by sex, race, and age. The PDAY and NHANES II prevalence rates were significantly different in 2 of the groups (black men 18 to 24, $P=0.0125$; white men 25 to 34, $P=0.0267$), but the discrepancies were in opposite directions.</td>
</tr>
<tr>
<td>The prevalence of hypertension in cases with missing glycohemoglobin was not significantly different from the prevalence in cases with normal glycohemoglobin. The prevalence of hypertension was higher in cases with elevated (≥8%) glycohemoglobin than in cases with normal glycohemoglobin (hypertension prevalence with elevated glycohemoglobin, 23.4%; with normal glycohemoglobin, 15.3%; $P=0.0660$), but the differences in prevalence did not vary significantly with sex, race, or age. In all subsequent analyses, we excluded cases with elevated or missing glycohemoglobin values.</td>
</tr>
</tbody>
</table>
Effects of Hypertension on Atherosclerosis

**Thoracic Aorta**
Hypertension did not affect the extent of fatty streaks, nor were there interactions of hypertension with sex, race, or age. Hypertension was associated with more extensive raised lesions ($P = 0.0239$). The effect of hypertension on raised lesions was greater in women than men (interaction of sex and hypertension, $P = 0.0592$) and was greater in blacks than whites (interaction of race and hypertension, $P = 0.0013$). The effect of hypertension increased with age (interaction of age and hypertension, $P = 0.0009$; results not shown).

**Abdominal Aorta**
Hypertensive women had less extensive fatty streaks than did normotensive women, whereas hypertensive men had similar involvement (interaction of hypertension and sex, $P = 0.0608$; Figure 2).

Black hypertensives had more extensive raised lesions than did black normotensives, whereas there was little effect of hypertension in whites (interaction of race and hypertension, $P = 0.0006$; Figure 3). The effect of hypertension on raised

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**TABLE 1. Prevalence of Hypertension by Sex, Race, and 5-Year Age Group**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Race</th>
<th>Age, y</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number</td>
<td>Percent</td>
</tr>
<tr>
<td>Male</td>
<td>White</td>
<td>15–19</td>
<td>170</td>
<td>81.7</td>
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<tr>
<td></td>
<td></td>
<td>20–24</td>
<td>223</td>
<td>89.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25–29</td>
<td>253</td>
<td>85.5</td>
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<td></td>
<td></td>
<td>30–34</td>
<td>205</td>
<td>82.7</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>15–19</td>
<td>200</td>
<td>78.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20–24</td>
<td>280</td>
<td>83.3</td>
</tr>
<tr>
<td></td>
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<td>25–29</td>
<td>261</td>
<td>80.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–34</td>
<td>177</td>
<td>77.3</td>
</tr>
<tr>
<td>Female</td>
<td>White</td>
<td>15–19</td>
<td>69</td>
<td>94.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20–24</td>
<td>92</td>
<td>95.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25–29</td>
<td>95</td>
<td>91.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–34</td>
<td>84</td>
<td>93.3</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>15–19</td>
<td>59</td>
<td>89.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20–24</td>
<td>71</td>
<td>93.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25–29</td>
<td>81</td>
<td>83.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–34</td>
<td>73</td>
<td>84.9</td>
</tr>
</tbody>
</table>

Sex, $P = 0.0001$; race, $P = 0.0002$; age, $P = 0.0304$; sex $\times$ race, $P = 0.2108$; sex $\times$ age, $P = 0.2942$; and race $\times$ age, $P = 0.8468$.

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**Figure 1.** Prevalence of hypertension by age, race, and sex in NHANES II compared with prevalence in the current study. Vertical and horizontal bars represent SEs. White men 18 to 24 are represented by ▼; white men 25 to 34, ◇; white women 18 to 24, ○; white women 25 to 34, □; black men 18 to 24, ▼; black men 25 to 34, ◇; black women, 18 to 24, ●; and black women 25 to 34, ■.

**Figure 2.** Extent of fatty streaks in abdominal aorta by age, race, sex, and hypertension. There was no effect of hypertension on fatty streaks in men, and hypertensive women had less extensive fatty streaks. White bar indicates normotensive; black bar, hypertensive; ▼, SE.
lesions increased with age (interaction of age and hypertension, \( P = 0.0051 \)).

RCA

Hypertension did not affect fatty streaks in men, but hypertensive women had less extensive fatty streaks than did normotensive women (Figure 4) (interaction of hypertension and sex, \( P = 0.0749 \)). There were no interactions of hypertension with race or age.

Hypertension increased the extent of raised lesions (\( P = 0.0253 \)), and the effect increased with age (interaction of age and hypertension, \( P = 0.0012 \); Figure 5). There was no interaction of hypertension with sex (\( P = 0.3266 \)). The effect of hypertension was slightly, but not significantly, greater in blacks than whites (interaction of race and hypertension, \( P = 0.1240 \)). Raised lesions in both normotensive and hypertensive women lagged \( \sim 5 \) years behind those in normotensive and hypertensive men, respectively.

We examined a subset of cases in which serum lipoprotein cholesterol and thiocyanate (an indicator of smoking) levels were measured.\(^{18}\) Adjustment for VLDL+LDL and HDL cholesterol levels and smoking status yielded similar results for the effects of hypertension (results not shown).

Hypertension Effect on Heart Weight and Ventricular Thickness

Figure 6 shows the heart weight by age, sex, and hypertension. There was an interaction of age and hypertension (\( P = 0.0012 \)). In the 15- to 19-year age group, hypertensive individuals had lower heart weights than did normotensive individuals (\( P = 0.0015 \)). In contrast, hypertensive individuals \( > \) age 20 had higher heart weights than did normotensive individuals (\( P = 0.0312 \)). Similar relationships resulted when the heart weight-height ratio was compared; among persons 15 to 19 years, hypertensives had lower ratios than did normotensives; in contrast, among persons 20 years and above, hypertensives had higher ratios (results not shown). Hypertension did not affect the thickness of the right ventricle or LV (results not shown).

Hypertension Effect on Coronary Artery Diameter

Hypertension was associated with a greater mean diameter (measured on the opened and flattened artery) of the RCA

Figure 3. Extent of raised lesions in abdominal aorta by age, race, sex, and hypertension. Hypertension was associated with more extensive raised lesions in blacks, and the effect of hypertension increased with age; there was no effect of hypertension in whites. See Figure 2 legend for explanation of bars.

Figure 4. Extent of fatty streaks in the RCA by age, race, sex, and hypertension. There was no effect of hypertension on fatty streaks in men, but hypertensive women had less extensive fatty streaks than did normotensive women. See Figure 2 legend for explanation of bars.

Figure 5. Extent of raised lesions in the RCA by age, race, sex, and hypertension. Hypertension increased the extent of raised lesions in both whites and blacks and in men and women. Effect of hypertension increased with age. See Figure 2 legend for explanation of bars.
Hypertension was also associated with a greater mean diameter (computed from the length of the EEL measured in the cross-section of the perfused, fixed specimen) of the LAD coronary artery ($P=0.0005$; Figure 8). The effect of hypertension was greater among women than among men (interaction of sex and hypertension, $P=0.0193$) but was similar in blacks and whites (interaction of race and hypertension, $P=0.7339$) and in all age groups (interaction of age and hypertension, $P=0.5353$).

Hypertension Effect on Area and Thickness of LAD Coronary Artery Intima
Hypertension was associated with a slightly larger intimal area of the LAD coronary artery ($P=0.0810$; Figure 9), and the effect was similar in both races and both sexes. There was no effect of hypertension on mean, maximum, or minimum intimal thickness (results not shown).

Hypertension Effect on Area and Thickness of LAD Coronary Artery Media
Hypertension was associated with a larger cross-sectional medial area of the LAD coronary artery ($P=0.0105$; Figure 10) but not with any difference in mean, maximum, or minimum medial thickness (results not shown).

Hypertension Effect on LAD Coronary Artery Total Wall Area
The cross-sectional total wall area was larger in hypertensive men and women than in normotensive men and women at all ages ($P=0.0367$; results not shown). The effect of hypertension on total wall area represents the combined effect of hypertension on the intimal area (Figure 9) plus its effect on the medial area (Figure 10). Hypertension did not affect the mean, minimum, or maximum wall thickness (results not shown).
Hypertension Effect on Lumen Area

Hypertension was associated with a larger lumen area of the LAD coronary artery (Figure 11) in women but not in men (interaction of sex and hypertension, \( P = 0.0019 \)).

Hypertension did not affect the ratio of intimal area to potential arterial lumen (area enclosed within the IEL, ie, “stenosis”; \( P = 0.7004 \), results not shown); but there was a trend, not statistically significant (interaction of sex and hypertension, \( P = 0.1056 \)), for the ratio to be greater in hypertensive men than in normotensive men, whereas the reverse was true in women. This trend was consistent with the greater effect of hypertension on the LAD coronary artery diameter in women than in men (Figures 7 and 8).

Hypertension Effect on ORO-Stained Intimal Area

Hypertension was associated with a larger cross-sectional intimal area stained with ORO (\( P = 0.0795 \)) in both sexes and both races (results not shown). When expressed as a percent of intimal area stained with ORO, the effect of hypertension was not significant (\( P = 0.1630 \)).

Relation of LAD Variables to RCA Gross Lesions

All measures of intimal involvement in cross sections of the LAD coronary artery were positively correlated with the percentage of surface involved with fatty streaks and raised lesions in the RCA. The correlations were stronger with raised lesions (Table 2).

<table>
<thead>
<tr>
<th>LAD Coronary Artery</th>
<th>RCA, % Surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intimal Cross Section</td>
<td>Fatty Streaks</td>
</tr>
<tr>
<td>Area, ( \text{mm}^2 )</td>
<td>0.163</td>
</tr>
<tr>
<td>Mean thickness, mm</td>
<td>0.193</td>
</tr>
<tr>
<td>Maximum thickness, mm</td>
<td>0.173</td>
</tr>
<tr>
<td>ORO area, ( \text{mm}^2 )</td>
<td>0.246</td>
</tr>
</tbody>
</table>

*All coefficients are significantly different from zero (\( P < 0.0001 \)).
Discussion

Summary of Results
Between the ages of 15 and 19 years, hypertension, as indicated by the intimal thickness of small renal arteries, does not affect raised lesions of the abdominal aorta or the RCA. Between ages 20 and 34 years, hypertension is associated with more extensive raised lesions in the abdominal aorta of blacks and with raised lesions of the RCA in both blacks and whites. The effect of hypertension increases with age. Hypertension affects raised lesions similarly in women and men.

Hypertension is associated with a larger diameter of the RCA and LAD coronary artery and with greater intimal and medial cross-sectional areas of the LAD coronary artery between the ages of 15 and 34 years. The greater cross-sectional areas of the intima and media are due to the larger diameter of the artery and not to a greater thickness of either the intima or media.

Validity of Hypertension Assessment
Despite the differences in populations, time at which observations were made, and methods of assessing hypertension, the prevalence rates reported by NHANES II17 are remarkably similar to those reported here. The greater heart weight and greater coronary artery diameter in cases classified as hypertensive also support the validity of this method of assessing hypertension.

Hypertension and Atherosclerosis
Results from these 1824 men and 579 women confirm and extend the previous results based on data for 1164 men8 and are consistent with findings from the limited number of cases examined in the Bogalusa Heart Study, in which blood pressure was measured before death.19,20 The effect of hypertension on atherosclerosis is principally to accelerate the formation of raised lesions rather than fatty streaks. The excess of raised lesions begins to appear at ~25 years of age (Figures 3 and 5). Furthermore, the multiplicative effect of hypertension on raised lesions (ie, the ratio of the extent of raised lesions in hypertensive persons to the extent in normotensive persons) increases with age (significant interaction of age and hypertension). By the beginning of the fourth decade, hypertensive subjects have approximately double the cross-sectional areas of the intima and media in cases classified as hypertensive as do normotensive subjects.

These results do not provide information about physiological mechanisms by which hypertension produces this effect, but they indicate that the search for mechanisms should focus on those involved in the progression of fatty streaks to raised lesions.

Interaction of Hypertension With Sex
The lesser extent of fatty streaks in the abdominal aortas and RCAs of hypertensive women compared with that in normotensive women (Figures 2 and 4) may be accounted for by the greater extent of raised lesions in hypertensive women in the 30- to 34-year age group (Figures 3 and 5), but raised lesions do not explain the differences in fatty streaks in younger age groups. Although the excess of fatty streaks in normotensive women was statistically significant in both arteries (interaction of hypertension and sex, \(P=0.0608\) for abdominal aorta; \(P=0.0749\) for RCA), the number of young hypertensive women was small (Table 1), and we do not believe that this unexpected result should be considered conclusive.

The multiplicative effect (see above) of hypertension on raised lesions in the abdominal aorta and RCA is similar in women and men (Figures 3 and 5; interaction of sex and hypertension was not significant). In the abdominal aorta, the extent of raised lesions is similar in men and women. In the RCA by age 30 to 34 years, hypertensive women have about the same extent of raised lesions as do normotensive men and about half the extent of raised lesions as do hypertensive men. Thus, the protection from advanced atherosclerosis enjoyed by women does not attenuate the effect of hypertension. The effects of hypertension on raised lesions in young men and women parallel closely the effects of hypertension on CHD events among middle-aged and elderly men and women.21-23 CHD events in adult men were about twice as high in hypertensive as in normotensive men and about twice as high in hypertensive as in normotensive women; events in hypertensive men and in normotensive men were each about twice as high as those in hypertensive women and in normotensive women, respectively.

Interaction of Hypertension With Race
The higher frequency of hypertension in blacks than in whites is well established11 and is again demonstrated in these cases (Table 1). The multiplicative effect of hypertension on raised lesions in the RCA of blacks is similar to that in whites (Figure 5; interaction of race and hypertension is not significant), but the multiplicative effect of hypertension on raised lesions of the abdominal aorta is much greater in blacks, both men and women, than in whites (Figure 3; interaction of race and hypertension, \(P=0.0006\)). Smoking selectively affects raised lesions of the abdominal aorta, but the prevalence of smoking in these cases is lower in blacks than in whites,18 a difference that would produce the opposite effect. We examined the effects of hypertension in PDAY cases for which smoking status was ascertained and found that hypertension had the same effect on abdominal aortic raised lesions in smokers and nonsmokers.

Categories 441 to 448 (“Other diseases of arteries, arterioles, and capillaries”) of the US Mortality Statistics include aortic aneurysm and peripheral arterial disease. Mortality rates for these categories in 199024 were higher in white men and women than in black men and women. An extensive literature search disclosed no more detailed data comparing the incidence, prevalence, or mortality related to atherosclerosis of the abdominal aorta among blacks and whites. This topic deserves further exploration.

Validity of Coronary Artery Size Measurements in Postmortem Arteries
Dodge et al25 measured the diameters of coronary arteries free of atherosclerotic lesions from angiograms in 60 men and 10 women (mean age, 45 years), all of whom were normotensive. In men, the lumen of the proximal LAD coronary artery measured 3.6 or 3.8 mm in diameter, depending on whether the right or left artery was dominant. Our measurement of the
lumen diameter of the pressure-perfused and fixed LAD coronary artery (computed from the cross-sectional area of the lumen, assuming it was circular) of normotensive 30- to 34-year-old men was 3.0 (SE, 0.05) mm. It was not feasible to assess right or left dominance.

The proximal segments of RCAs of men measured 2.8 or 3.9 mm in diameter, depending on right or left dominance. Our measurement of the diameter of the RCA (computed from the width of the opened, flattened, and fixed artery, assuming it was circular) of normotensive 30- to 34-year-old men was 2.4 (SE, 0.03) mm.

The arteries of normotensive women measured in angiograms were 9% smaller than those of men. In PDAY cases, the diameter of the LAD coronary arteries of women averaged 13.6% less, and the diameter of the RCAs of women averaged 15.8% less, than those of men.

In 16 middle-aged men and women with no risk factors for CHD and no coronary atherosclerosis, the mean diameter of the proximal LAD coronary artery measured by intravascular ultrasound was 4.2 mm and of the midportion of the LAD coronary artery, 3.5 mm. The measures were 10% less during diastole than during systole.

Because arteries are likely to collapse after death and because fixation causes tissues to shrink, possibly more in the unperfused RCAs than in the pressure-perfused LAD coronary arteries, these measures of postmortem-fixed tissues are smaller than corresponding measures during life. However, they probably reflect accurately the differences in coronary artery dimensions during life. Furthermore, our oldest age group was younger than the subjects studied during life.

Hypertension and Coronary Artery Size

Echocardiographic studies of the carotid artery have shown that its diameter is increased in hypertension. Three comparisons of coronary artery reactivity in hypertensive subjects with that in normotensive subjects showed a trend for coronary artery diameter in hypertensives to be greater in the basal state, but the numbers of subjects in each study were not large enough for the trend to be statistically significant.

The coronary arteries of hypertensive subjects showed loss of coronary vasodilator reserve, even when myocardial mass was not increased; loss of flow-dependent dilatation; either impaired vasodilator response to acetylcholine or vasoconstriction in response to acetylcholine; and depressed bioavailability of NO.

The current findings show that hypertension is associated with a larger RCA (Figure 7), a larger LAD coronary artery (Figure 8), a larger LAD intimal cross-sectional area (Figure 9), and a larger LAD medial cross-sectional area (Figure 10). The lumen is not enlarged in hypertensive men but is enlarged in hypertensive women (Figure 11; interaction of sex and hypertension, P = 0.0019). These effects of hypertension on coronary artery size are consistent with many other observations from humans and experimental animals showing that hypertension alters the structure and composition of large elastic and muscular arteries and also increases arterial stiffness.

Coronary artery distention is consistent with the increased arterial stiffness observed with hypertension. A 10-mm Hg difference in blood pressure was also associated with increased stiffness of the carotid arteries of 13-year-old children. Results reported here show that enlargement of the coronary artery begins at least by 15 to 19 years of age (Figures 7 through 10), and possibly earlier, before cardiac hypertrophy occurs (Figure 6) and before there is an effect of hypertension on raised lesions (Figure 5).

Limitations of this Study

The selection of cases entered into this study was influenced by policies of the medical examiner or coroner, local laws, and other circumstances that influenced which deaths were autopsied and which could be used for research. Societal factors and individual characteristics that influence vulnerability to homicide, suicide, and accidents also affected inclusion in this study. Previous analyses of these cases have shown consistent associations of atherosclerosis with risk factors across cause of death categories. Therefore, despite the potentially biased sample, we conclude that the effects of hypertension on arterial structure and atherosclerotic lesions represent those that exist in the living population of young persons.

Implications for Clinical and Public Health Medicine

Hypertension begins to affect coronary artery structure during the teenage years, nearly a decade before hypertension begins to affect the advanced lesions of atherosclerosis. These changes indicate that the altered reactivity of coronary arteries demonstrated in older hypertensive persons probably is also present in young persons. Although we doubt that anyone would recommend antihypertensive drug therapy for moderately elevated blood pressure in teenagers or young adults, these results strengthen the case for control of elevated blood pressure in youth by hygienic measures (weight control, physical activity, and salt restriction) as a long-range strategy for preventing irreversible coronary artery changes, retarding the progression of atherosclerosis, and deferring the onset of clinically manifest CHD.


Relation of a Postmortem Renal Index of Hypertension to Atherosclerosis and Coronary Artery Size in Young Men and Women

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