Nephrosclerosis and aortic atherosclerosis from age 6 to 70 years in the United States and Mexico

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Summary. With increasing age, the thoracic aorta shows progressive fibroplastic intimal thickening, which is thought to be pre-atheromatous. A similar progressive intimal thickening in the renal cortical arteries is the distinguishing feature of the nephrosclerosis which underlies essential hypertension. Therefore, the earliest detectable youthful precursors of atherosclerosis and hypertension show strong morphological resemblances to each other. In this study, close statistical associations have been shown between the two types of arterial intimal fibroplasia. Both conditions show similar sigmoid growth curves from ages 6 to 70 years, thereby generating correlations across age groups of $r=0.99$ in New Orleans and $r=0.95$ in Mexico City. Specimens gathered in New Orleans were found to have about 1.4 times greater arterial intimal thickening than specimens from Mexico City, and this excess was seen at all ages in both the aortas and the renal cortical arteries. It seems likely that intimal fibroplasia of arteries is reflecting similar biological principles at all levels of the vascular tree. Whatever etiological factors vary between New Orleans and Mexico City, those factors appear to act directly at a tissue level to promote the early precursors of atherosclerosis and of the nephrosclerosis that underlies hypertension.

Key words: Hypertension – Aging – Arteriolosclerosis – Nephrosclerosis – Atherosclerosis

Introduction

With increasing age, the thoracic aorta shows progressive fibroplastic intimal thickening. The thickness of intima was recently found to be approximately proportional to age, from 15 to 55 years, with an average growth rate of about $6 \mu$m per year; from 55 to 70 years, the growth rate slackened to about $3 \mu$m per year (Tracy et al. 1987b). Small arteries of the renal cortex also show progressive fibroplastic intimal thickening with age, which is readily measured as intimal thickness in proportion to outer diameter ($% \text{OD}$) (Tracy et al. 1988b). In a mixed group of black and white males and females in New Orleans, a growth rate of about 0.25% OD per year was found from 15 to 55 years of age; the growth rate slackened to 0.13% OD per year from 55 to 70 years (Tracy et al. 1990). The similarities in the behavior of these two forms of arterial change with age, along with their morphological resemblances to each other, suggest the possibility of a pathogenetic linkage between them.

Fibroplastic thickening of arterial intima in the renal cortex is one of the defining feature of nephrosclerosis, whereby this condition is distinguished from other renal diseases; it is a feature of nephrosclerosis that relates well to blood pressure in subjects with essential hypertension (Bell 1950; Katafuchi and Takebayashi 1987; Sommers et al. 1958; Tracy and Toca 1974; Tracy et al. 1981, 1988a, b; Ueda et al. 1976; Yamaguchi et al. 1969). Fibroplastic intimal thickening of the aorta is sometimes said to be pre-atheromatous, in that the necrotic core of atherosclerosis is thought to emerge within the fibrotic substrate (Geer and Haust 1972; Ross et al. 1984; Stary 1989; Tracy and Kissling 1985; Tracy et al. 1983, 1987b). These aging changes, seen in two levels of the arterial tree, may constitute early steps that initiate a life-long course of progression toward clinically significant cardiovascular disorders (Freedman et al. 1988; Katafuchi and Takebayashi 1987; McGill 1968; Stary 1989; Tracy et al. 1987b).

An opportunity to examine the statistical associations between aortic and renal arterial fibroplasia further arose in association with studies of coronary heart disease (CHD; Tracy et al. 1983) and of childhood precursors of atherosclerosis (Freedman et al. 1988). Those studies provided samples of aortas and kidneys from a collection of coroners’ autopsies in New Orleans. An opportunity to assess these matters in Mexico City also arose.

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fortuitously. A series of coroners’ autopsies constructed to compare coronary arteries in Mexico with those in New Orleans also provided samples of kidney tissues, but not aortas (Cueto-Garcia et al. 1989). Aortas from Mexico City had, however, been examined in an earlier study, and the data from that source are used here to provide a first look at Mexico for comparison with New Orleans (Tracy et al. 1986; Tracy and Kissling 1988).

The intimal fibroplasia of aorta and of renal cortical arteries have morphological similarities to each other. The present study was undertaken to explore some statistical similarities between the two pathological conditions. Autopsies conducted in a coroner’s service on victims of sudden and violent deaths are often used to obtain a rough idea about the prevailing severities of arterial disorders in the general population (Freeman et al. 1988; McGill 1968; Strong and Restrepo 1978; Vaneeck 1976). The use of this approach here is, therefore, in keeping with established practice.

**Materials and methods**

The 119 cases from the New Orleans CHD series were sampled from those examined at the Orleans Parish Coroner’s Office from June 1979 to August 1980. The objective was to obtain cases of death due to CHD and other cases of death due to non-cardiovascular causes (basal) matched by age, race and sex to the CHD cases. Details are given elsewhere (Tracy et al. 1983). The sample contained 58 white males, 11 white females, 37 black males, and 13 black females; 52 had CHD and 67 had basal causes of death. The diagnosis of CHD was based upon the presence of coronary thrombosis or of arteriosclerotic occlusion of the coronary artery with myocardial scar. Basal cases had no evidence of cardiovascular disease by history or on gross inspection at the time of autopsy. Cases with anatomical evidence of CHD but dying of some other cause, and cases with other cardiovascular disease, such as cerebrovascular or renal disease, were excluded from this series.

The Bogalusa heart study is an epidemiological study of cardiovascular risk factors from birth to the age of 26 years (Freedman et al. 1988). Five cross-sectional surveys were conducted, covering more than 8000 subjects in Bogalusa, La. from 1973 to 1985. Of 104 autopsies conducted from 1978 to 1986 in the basis population, 40 supplied adequate samples of both kidney and aorta. Ages at death were 6–25 years. The sample contained 22 white males, 7 white females, 8 black males, and 3 black females. All cases were classed as basal causes of death.

Specimens were collected in 1960–1964 in New Orleans and Mexico City as a part of the International Atherosclerosis Project (IAP) (McGill 1968). Aortas from those sources have been previously described microscopically, and the results have been reported elsewhere (Tracy et al. 1986). Those data are plotted graphically here to allow comparison of results between the two studies. Race, sex, and cause of death composition of the IAP data previously reported were somewhat different from the newly collected data. However, race and sex have proved to have little impact on the current results, and cause of death effects can be judged from the tabulated findings.

A study of coronary atherosclerosis in Mexico City was undertaken in 1988, by assembling a collection of specimens from 111 males dying of violent causes, and transporting them to New Orleans for evaluation (Cueto-Garcia et al. 1989). As a component of this undertaking, samples of kidney tissue were also assembled, and evaluated by the methods described here. These kidney samples have been measured only by observer A. Ages 12–54 years were represented. Microscopy of aortas was not done in this series; rather, data from the IAP series were used in their place.

Samples of kidney tissue were managed as for a routine autopsy without special handling. Bits of tissue cut perpendicular to the capsular surface were fixed and stored in acetate-buffered 10% formaldehyde. Samples were embedded in paraffin, sectioned at 6 μm, and stained with periodic acid-Schiff (PAS)-alcian blue. Generally, a total of 2-4 cm² area of renal cortex were represented in two to six sections of tissue. The method for morphometry of the kidney has been described at length elsewhere (Tracy et al. 1988b) and is summarized here. A microscope with ×10 and ×40 objective lenses and mechanical stage controlled by the left hand was equipped with an eyepiece ruler marked in units equivalent to 10 μm, under the ×10 objective lens. All arterial profiles in the series were examined systematically. The OD of the least axis of the elliptic profile was measured under the ×10 objective lens, excluding the adventitia, and measuring from one outer media to the other. The thicknesses of intima were measured under the ×40 lens, also along the least axis, with the better presented of the two opposite walls (i.e., lacking tangential sectioning, branch ostium, or artifact). If both opposite walls were equally well presented, then an average of the two was used. Vessels with OD less than 80 μm (i.e., arterioles) were excluded because they are often hyalinized, thus obliterating the intima and media. Vessels over 300 μm were excluded because it is impractical to obtain them in sufficient numbers in all specimens. The average ratio of intima to diameter in the “close” level vessels (OD 150–300 μm) is R, and in the “remote” level vessels (OD 80–149 μm) is R; units of measure are %OD. These size ranges are named with respect to the heart. Relative to each other, the remote level vessels are thought to offer greater resistance to blood flow, while the close level vessels have more of a strictly conduit function.

Three instances of diabetic nephropathy were encountered in the New Orleans CHD study. These were retained in the total pool. No chronic pyelonephritis, glomerulonephritis, malignant nephrosclerosis, or conditions other than benign nephrosclerosis were found besides the three diabetics. In Bogalusa and Mexico, no instance was encountered of kidney disease other than nephrosclerosis.

Aortas were opened longitudinally, formalin fixed, and sampled along the left and right lateral walls from the fourth to the twelfth intercostal ostia, as detailed elsewhere (Tracy et al. 1983). Longitudinally oriented segments were decalcified with acetic acid, blocked in paraffin, sectioned at 11 μm, and stained with hematoxylin and eosin. Ink marks were placed on the cover slips at intervals to define 1/20 of the sample length approximately 0.7 cm in most aortas.

Positions affected by atheronecrosis, operationally defined as having cholesterol clefts easily discerned under the 40× objective lens, were marked with black ink; the percentage of the length of the specimen marked positive for atheronecrosis was called . The mean fibroplastic thicknesses of the intima (in micrometers) averaged over the non-necrotic points, were called . Details of these methods are discussed elsewhere (Tracy et al. 1983).

Kidney and aortic sections of the 119 New Orleans CHD cases and 40 Bogalusa Heart Study cases were independently graded by a pathologist (A) and a nonsmtery graduate student (B). The mean values of for observers A and B were 4.5 and 3.9 %OD respectively; the mean values of for observers A and B were 8.6 and 8.7 %OD, showing less grader difference for than for . The correlations between observers were 0.84 and 0.88 for and , respectively, which are not significantly different. The mean values of for observers A and B were 312 and 288 μm respectively; the mean values of for observers A and B were 9.2 and 8.0% of the aortic specimen respectively. The correlations between observers were 0.96 and 0.91 for and , respectively. The readings of the two observers were averaged into a single value for all variables in each case in subsequent analyses. Mexican renal slides, and the aortic slides from the IAP, were evaluated only by observer A.

In order to make age adjustments for , , and , the three variables were related to age (A) by cubic regression equations. In all three situations, the “intercept” term was not significantly