Combating the Epidemic of Heart Disease

Daniel Levy, MD

At the beginning of the 20th century, the 3 leading causes of death in the United States were infectious diseases—pneumonia, tuberculosis, and diarrhea—which in combination claimed 539 lives per 100 000.[1] Lurking in the background as the fourth leading cause of death was heart disease (137 deaths per 100 000). But this would change. With life expectancy of only 47 years at the beginning of the century, people did not live long enough for heart disease to claim many lives. Without a means for accurate diagnosis, many deaths from heart disease went unrecognized. With the advent of the electrocardiogram to facilitate the diagnosis of heart disease, antibiotics to treat infectious diseases, and increasing life expectancy, the number and proportion of deaths due to heart disease soared. During the Great Depression, the number of deaths due to heart disease was twice that of the next leading cause of death (pneumonia). In 1945, at the time of President Roosevelt's fatal brain hemorrhage due to decades of uncontrolled hypertension, heart disease accounted for more deaths in the United States than the next 3 causes combined. Deaths due to heart disease peaked in 1968 at 374 per 100 000.

Necropsy studies of soldiers killed in the wars in Korea and Vietnam provided an opportunity to define the prevalence of subclinical coronary atherosclerosis in young people. In 1953 Enos et al[2] described coronary lesions discovered at autopsy in 300 male soldiers (mean age, 22 years) killed in the Korean War. Gross evidence of coronary disease was present in 77% of the decedents: 35% with fibrous thickening, 26% with a coronary artery narrowed by 10% to 49%, and 15% with a coronary occlusion of 50% or more. In 1971, McNamara et al[3] reported evidence of coronary atherosclerosis in 45% of 105 Vietnam War combat deaths (mean age, 22 years), with 5% having severe coronary disease. In their concise descriptive narratives, these studies provided unequivocal evidence of the silent burden of coronary atherosclerosis in young, otherwise healthy adults, and in finding a "reservoir" of carriers of disease, they helped explain the emergence of heart disease as a 20th century epidemic among middle-aged and older adults.

See also p 2577.

In this issue of *JAMA*, Webber and colleagues[4] report on the prevalence of coronary and aortic atherosclerosis in 3832 US service members who died from combat or unintentional injuries from 2001 to 2011 while serving in support of military operations in Iraq or Afghanistan. With a mean age of 27 years, the service members' prevalence of coronary atherosclerosis of any degree was 8.5%, a value considerably lower than reported by Enos et al[2] (77%) and McNamara et al[3] (45%). Minimal, moderate, and severe coronary atherosclerosis were present in only 1.5%, 4.7%, and 2.3% of the recent decedents, respectively. The large sample size of the study provided robust estimates of the low burden of subclinical atherosclerotic disease and permitted an exploration of differences in prevalence of disease across various demographic strata. The prevalence of atherosclerosis increased with age and was greater in those with lower education levels but was not associated with occupation, ethnicity, service branch, or military rank.

Taken together, the reports by Enos et al,[2] McNamara et al,[3] and Webber et al[4] offer cross-sectional perspectives on subclinical atherosclerosis in healthy young military service members, but unlike standardized, population-based, cross-sectional studies (eg, the National Health and Nutrition Examination Survey [NHANES], for example), these studies are not directly comparable and also might not be generalizable to the US population of young adults. Unlike NHANES, the 3 autopsy studies were conducted at irregular intervals and were restricted to military personnel who were likely to be healthier than the US population as a whole. The restrictive criteria used by Webber et al to establish the presence of cardiovascular disease risk factors, along with the "healthy warrior effect," may have resulted in low measures of prevalence of key risk factors. Specifically, the prevalence of obesity (4%), smoking (3%), hypertension (1%), dyslipidemia (0.7%), and impaired fasting glucose (0.2%) were markedly lower than among comparable age groups in the US population[5] or compared with published estimates of risk factor prevalence in the military.[6] The methods used for ascertainment of several risk factors likely underrepresented their true prevalence and limited the authors' ability to draw conclusions about risk factor associations with

Author Affiliation: National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.
Corresponding Author: Daniel Levy, MD, The NHLBI Framingham Heart Study, 73 Mount Wayte, Ste 2, Framingham, MA 01702-5827 (levyd@nhlbi.nih.gov).

atherosclerotic cardiovascular disease. Webber et al found that obesity, hypertension, and dyslipidemia were each associated with approximately a doubling in the prevalence ratios for atherosclerosis. The prevalence ratios, however, may be exaggerated because only the most severe manifestations resulted in an inpatient or multiple outpatient encounters required for the diagnosis of hypertension, dyslipidemia, or diabetes/impaired fasting glucose. Also, cigarette smoking and diabetes/impaired fasting glucose, 2 risk factors well known to be associated with atherosclerotic cardiovascular disease, were not associated with atherosclerosis by autopsy.

However, the autopsy case series offers advantages over other designs for detecting associations of risk factors with pathological changes of atherosclerosis. Because postmortem information was available and because the decedents were selected without regard to the exposures (cardiovascular risk factors) or the outcomes (coronary and aortic atherosclerosis) of interest, the design of the study of Webber et al[4] is unlikely to have introduced systematic biases due to sampling or outcome measurement. Consequently, it is highly likely that the main finding of this study is valid: the prevalence of atherosclerosis in young men today is much lower than the prevalence in the Korean or Vietnam War eras. If these findings are generalizable to the US population as a whole, then the cardiovascular health of the US population may have improved appreciably over the past 6 decades.

The study by Webber et al[4] is not well suited to address the root causes of this favorable trend or of the parallel declines in deaths from heart disease in the United States. However, evidence available from other sources indicates that the decline in heart disease mortality is attributable both to advances in treatments for patients with clinical heart disease (ie, secondary prevention) and successful primary prevention strategies resulting in improvements in modifiable cardiovascular disease risk factors in individuals free of heart disease. On balance, primary and secondary prevention strategies are believed to have contributed about equally to national declines in heart disease mortality.[7] Advances in primary (but not secondary) prevention are likely to explain the declines in coronary atherosclerosis across the 3 autopsy studies.[2-4]

During recent decades there have been steady declines in several key cardiovascular disease risk factors in the United States. First, the proportion of individuals who smoked cigarettes declined from about 50% of men and 30% of women in the mid-1960s to about 20% in both sexes in 2010.[5,8] Second, from 1976 to 2008, there were improvements in awareness, treatment, and control rates for hypertension (defined as blood pressure ≥140/90 mm Hg). The proportion of individuals with hypertension aged 18 to 74 years who were treated for hypertension and whose blood pressure was controlled to less than 140/90 mm Hg increased from 10% to 49% over this time period.[5,9] Third, the proportion of men and women with elevated cholesterol levels of 240 mg/dL or greater declined by about 50% in men and women over the same interval.[5,9] In contrast, worrisome upward trends in obesity and diabetes threaten to reverse favorable risk factor trends. From 1976 to 2008, the prevalence of overweight increased for men and women within each racial/ethnic group.[5,10] Today 69% of adults in the United States are overweight or obese.[10] As a consequence of national obesity trends, the prevalence of diabetes is increasing; from 1958 to 2010, the proportion of adults and children in the United States diagnosed with diabetes increased from 1% to 7%.[11]

Autopsy studies have demonstrated that coronary disease begins at a young age. Consequently, primary prevention campaigns to address obesity and related risks should begin in childhood.[12] Declines in cardiovascular disease risk factors have almost certainly contributed to the observed reductions in prevalence of subclinical atherosclerosis, incidence of clinical atherosclerotic disease, and deaths from heart disease. Although age-adjusted heart disease death rates have declined by 72% since their peak during the Vietnam War years, cardiovascular disease remains the leading cause of death in the United States.[5,13] The national battle against heart disease is not over; increasing rates of obesity and diabetes signal a need to engage earlier and with greater intensity in a campaign of preemption and prevention.

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Manifestations of Coronary Atherosclerosis in Young Trauma Victims—An Autopsy Study

ABRAHAM JOSEPH, MD, FACC, DOUGLAS ACKERMAN, MD, J. DAVID TALLEY, MD, FACC, JOHN JOHNSTONE, MD, FACC, JOEL KUPERSMITH, MD, FACC

Louisville, Kentucky

Objectives. **The aim of this study was to look at the prevalence of coronary atherosclerosis, its severity and site of involvement in patients <35 years old who died from noncardiac trauma.**

Background. **Autopsies performed on casualties of the Korean War revealed coronary artery involvement in 77.3% of the hearts studied, and data after the Vietnam War noted the presence of atherosclerosis in 45% of casualties with severe disease in 5%, suggesting a decline in the prevalence of coronary atherosclerosis in young men.**

Methods. **One hundred eleven victims of noncardiac trauma (86.4% white with a mean age of 26 ± 6 years) underwent pathologic examination of their coronary arteries to estimate the presence and severity of coronary atherosclerosis grossly, microscopically and through computerized planimetry. Identified segments of the coronary arteries were sectioned at 3-mm intervals, stained with special stains and after microscopic examination transferred to videotape and digitized to allow estimation of the percent compromise in the lumen area by atherosclerotic plaque.**

Results. **Signs of coronary atherosclerosis were seen in 78.3% of the total study group, with >50% narrowing in 20.7% and >75% narrowing in 9%. No demographic or anatomic features separated the groups with less or more severe involvement of their coronary arteries. Proximal involvement was more common except in the right coronary artery, which was as frequently involved distally.**

Conclusions. **The overall prevalence of coronary atherosclerosis in a young, predominantly male study group was comparable with that noted after the Korean War. Left main or significant two- and three-vessel involvement was noted in 20% of the group studied and emphasizes the need for aggressive risk factor modification in this group.**

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It is well known that coronary atherosclerosis exists in the young. Fatty streaks are present in the aorta of most children >3 years old, increasing rapidly in adolescence (1), with coronary artery involvement beginning about a decade later (2). A number of autopsy studies performed on young soldiers who died from a noncardiac related cause have demonstrated evidence of atherosclerosis ranging from insignificant disease to total occlusion. Although one of the earlier studies performed in 1953 after the Korean War documented an incidence of 77.3% (3–5), later data after the Vietnam conflict showed some degree of coronary atherosclerosis in 45%, with more severe disease in only 5% (6). Although these differences may have been due to a difference in techniques used in identifying the degree of coronary atherosclerosis, the possibility of an actual decline in the incidence of coronary artery disease in the young was raised. Seventeen years have elapsed and we looked at a similar group who died of noncardiac-related causes to study the incidence of coronary artery disease, its severity as related to different age groups, and the site of involvement in the coronary bed.

Methods

Study patients. All hearts of patients aged 14 through 35 years old who underwent autopsy at Humana Hospital University of Louisville were studied. The first 111 hearts to be dissected in serial order were used to obtain data. Historical data with regard to the age, gender and race of the patient, previous medical history, medications and drug habits were noted from the death certificate, where available. Because of difficulty in obtaining risk factor information in this study group, we also examined the risk factor profile in 100 consecutive age-matched patients who were admitted to the Surgical Intensive Care Unit at University Hospital predominantly because of injuries sustained in accidents. A family history of heart disease, smoking, hypertension or diabetes was elicited, and serum cholesterol levels of all patients were examined.

Heart preparation. All hearts were weighed as an index of myocardial hypertrophy. The origin of the coronary arteries in relation to the sinotubular junction and its coexistence with coronary ostial lesions were documented.

Dissection of coronary arteries. To examine the extent of coronary atherosclerosis, the coronary artery tree was di-

From the Cardiovascular Division, Department of Medicine and the Department of Pathology, University of Louisville, Louisville, Kentucky.

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Address for correspondence: Abraham Joseph, MD, Cardiovascular Division, ACB 3rd Floor, 530 South Jackson, Louisville, Kentucky 40292.

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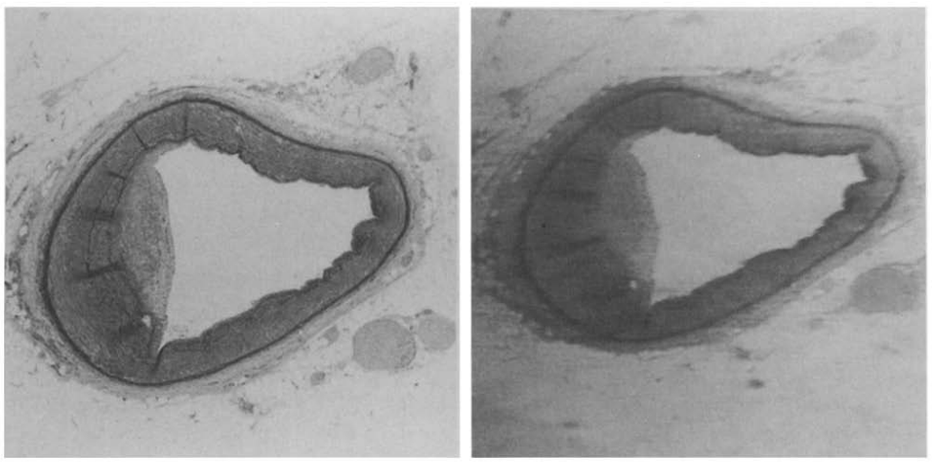

Figure 1. Stained section of the proximal left anterior descending coronary artery showing the internal elastic lamina (left) with a comparison image (right) after transfer to videotape and digitization.

vided into segments according to previously established clinical criteria. The left coronary tree consisted of the left main, left anterior descending and left circumflex coronary arteries. The left anterior descending artery was further subdivided into proximal (before the origin of the first septal perforator) mid and distal segments (distal to the second diagonal branch). The left circumflex coronary artery was divided into proximal (up to the origin of the major marginal branch), mid (the major marginal branch) and distal segments. The right coronary artery was divided into proximal (up to the right ventricular branch), mid (between the right ventricular and acute marginal branches) and distal segments, with the latter segment including the posterior descending and left ventricular branches. The coronary arteries were cross-sectioned at 3-mm intervals from the ostia to the terminal pericardial branches to determine the presence or absence of atherosclerotic plaques and any lumen narrowing. Sections representative of the most involved area in each segment were then processed by dehydration in alcohol, cleared in xylene, fixed in 10% buffered formalin, and embedded in paraffin, with suitable decalcification techniques employed before fixation for those segments of coronary arteries that were calcified.

Grading arterial specimens. After fixation and embedding, the cross sections were stained with hematoxylin-eosin and elastic van Gieson stain. Using high powered microscopy, each section was examined by a pathologist independent of the coroner's office who had no knowledge of clinical or pathologic observations or collection site. Because fatty streaks or diffuse intimal thickening secondary to smooth muscle cell proliferation is not considered to represent a true atherosclerotic change, we did not consider this a sign of early disease. Cross-sectional lumen stenosis was then graded from I to IV. Grade I, using this system, represented 0% to 25% narrowing; grade II, 25% to 50% narrowing; grade III, 50% to 75% narrowing, and grade IV, 75% to 100% narrowing. Although this method of estimating the degree of coronary atherosclerosis has been used in earlier studies, it lacks accuracy and reproducibility. To overcome this limitation, a cardiologist unaware of the visual and microscopic data then used computerized planimetry utilizing a software program (developed by Kontron, MIPRON Image Processing System Bildanalyse GmbH) involving edge detection techniques to estimate the residual circumferential area at the occluded site.

Analysis by computerized planimetry. All cross sections representative of the involved segment of the diseased artery were transferred onto 0.5 in. (1.27 cm) or 0.75 in. (1.91 cm) videotape and involved no distortion of the image (Fig. 1). After initial input of the most involved segment and with the use of a predefined scaling factor, the original lumen area of the segment, as defined by the internal elastic lamina, was obtained in cm^2 (A). The residual circumferential area was then determined after the residual lumen was traced manually (a). The percent compromise in lumen area was then obtained by using the formula $[(A - a)/A] \times 100$ (subtracting the residual lumen area from that enclosed by the internal elastic lamina) (Fig. 2 to 5).

Statistical analyses. Our primary interest was in studying the prevalence of coronary artery disease and comparing this with data obtained after the Korean and Vietnam conflicts. We tested proportional data for significance using the chi-square test and 2×2 contingency tables with the Yates correction. Continuous variables were expressed as mean values ± 1 SD. The unpaired Student t test (two tailed) was used to test the hypotheses that two group means were not different for continuous variables, asserting a difference if p was < 0.05. The chi-square test tested for homogeneity of the study and comparison groups and looked for differences among the groups with different severities of disease. A critical ratio test for equality of two proportions looked for statistically significant differences between the frequency with which different sites in the coronary anatomy were involved for different degrees of disease using 95% confidence limits and the same p value (< 0.05).

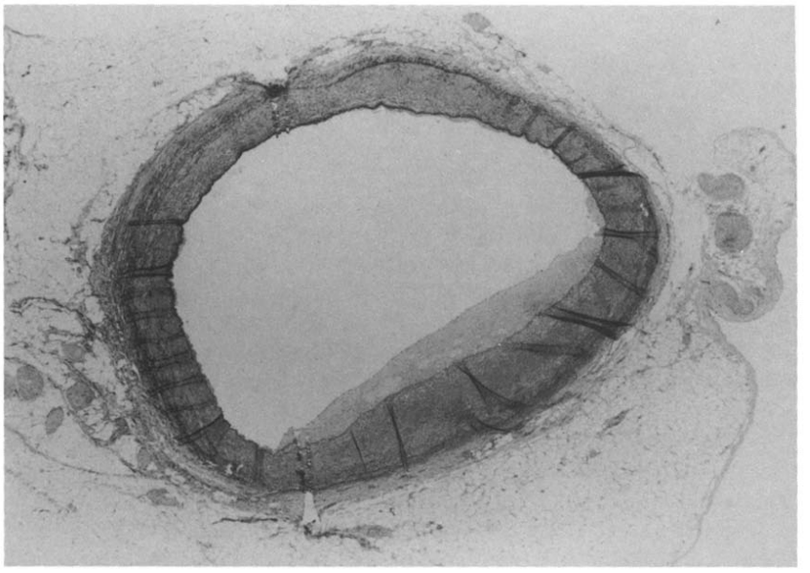

Figure 2. Stained section of the left main coronary artery with the interr. l elastic lamina defined with van Gieson stain and the lumen compromised by early atherosclerotic plaquing (19.0% area narrowing as estimated by planimetry).

Results

The hearts of 111 consecutive trauma victims 14- to 35-years old who were examined at autopsy between 1988 and 1989 were studied for evidence of coronary artery disease. The study group was predominantly male (95 [85.5%]) and white (96 [86.4%]). There were 13 black patients (11 male, 2 female) and two male Hispanic patients. The average age for the male patients was 25.6 ± 5.4 years, and the average age of the female patients was 25.6 ± 6.1 years. The age and gender distribution of the study group are represented in Figure 6. The predominant causes of death were gunshot wounds (28.8%) and motor vehicle accidents (23.4%). Other causes included death from hanging, drug or alcohol intoxication, drowning and smoke inhalation. In no instance was the final cause of death related to a cardiac cause.

The average age of the 100 trauma victims admitted to the intensive care unit at University Hospital was 26 ± 4.1 years. They were also predominantly male (81%) and white (75%), with an average body surface area of 1.88 m^2. Although the majority were smokers (68%), there was a smaller incidence of family history of coronary artery disease (15%) and hypertension (6%). Five patients had a serum cholesterol level >200 mg/dl (Fig. 7). Except for being more predominantly white (86.4% vs. 75%, $p < 0.05$), the study group did not differ from the comparison group with respect to gender ($p = 0.478$), age ($p = 0.613$) or body surface area ($p = 0.33$) (Table 1).

Coronary atherosclerosis related to body mass index. Using the body mass index or Quetelet index (kg/m^2), which is a better measure of obesity than percent body fat and has

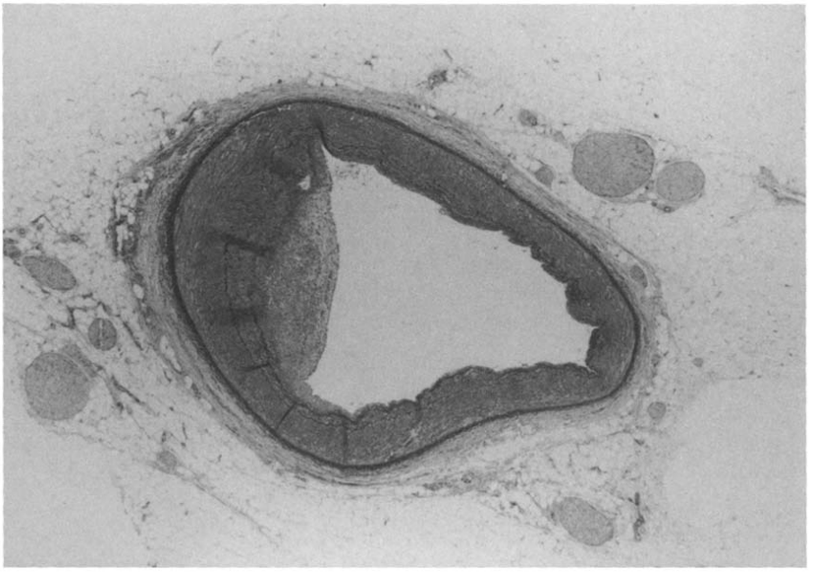

Figure 3. Stained section of the left anterior descending coronary artery in a 27-year old female trauma victim from the current study (estimated area narrowing 23.2%).

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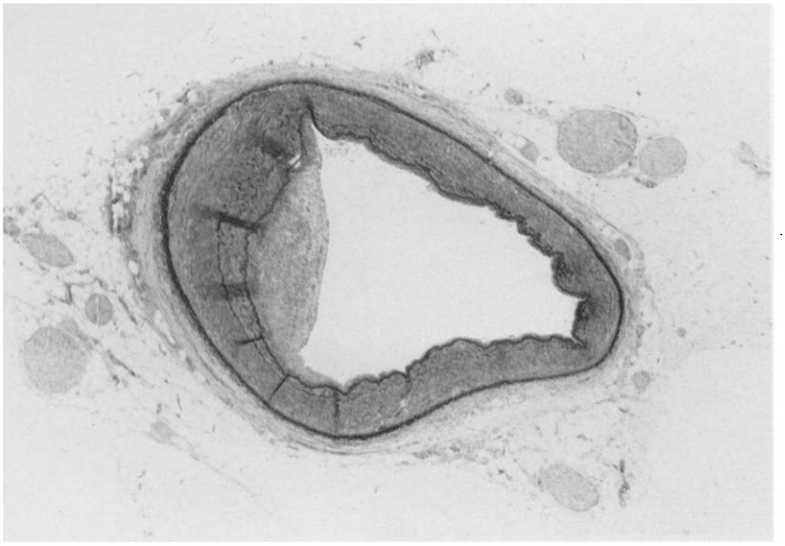

Figure 4. Original lumen of the vessel as defined by the internal elastic lamina and highlighted (A, see text).

been linked to cardiovascular mortality (7), 44 of the 111 patients were noted to have a body mass index >25 (upper limit of normal), with 10 having an index >30 (associated with excess mortality). Although a body mass index >30 by itself could not predict the presence or absence of underlying coronary artery involvement (see Fig. 8), of the 10 victims with a body mass index >30, 8 showed evidence of coronary atherosclerosis.

Gross morphology. The average heart weight was 340.1 ± 67.9 g (range 205 to 520). When corrected for body surface area, the mean heart weight was 200.29 ± 69.9 g/m^2 for male patients and 168.95 ± 54.4 g/m^2 for female patients. The foramen ovale was patent in 28 hearts studied and closed in the rest. The right coronary system was dominant in 77 (69.3%), the left coronary system in 8 (7.2%), with a codominant system in the remaining 26 (23.4%). In the majority (68 [61.2%]), the origin of the coronary arteries was below the sinotubular junction.

Pathologic grading of extent and site of coronary atherosclerosis. Of the 111 hearts studied, 40 (36.0%) had coronary beds free of coronary artery disease as assessed using only visual criteria. With microscopy and planimetry, only 24 hearts manifested intimal hyperplasia alone or no signs of atherosclerosis for an overall incidence of early or progressing atherosclerosis in the remaining 87 (78.3%). Early signs of involvement (20%–50% area narrowing) in any of the coronary arteries was seen in 64 hearts (57.6%), with more severe involvement (>50% narrowing) in the remaining hearts (23 [20.7%] of 111). Among the male patients (95 of 111), the coronary arteries were noted to be involved in 72 hearts for an overall incidence of 75.8%. This incidence was significantly higher than the 45% incidence obtained from

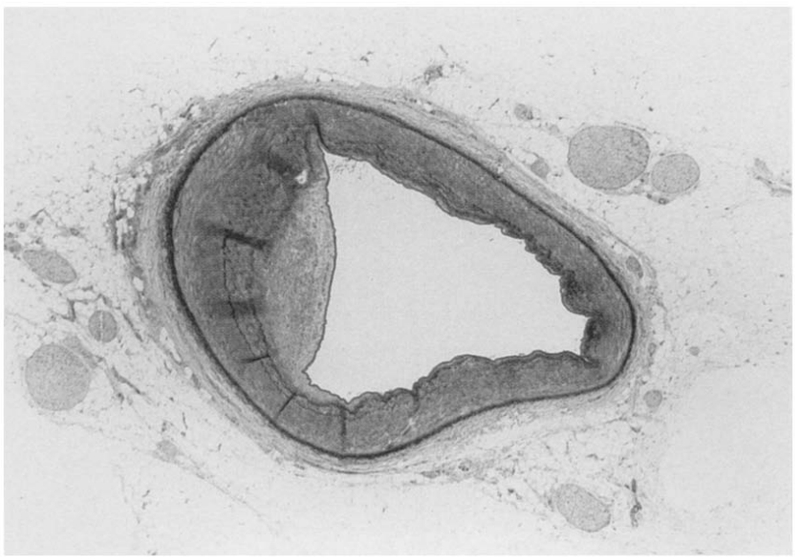

Figure 5. Residual lumen contoured for planimetry and highlighted (a). Percent narrowing obtained by [(A − a)/A] × 100 (see text).

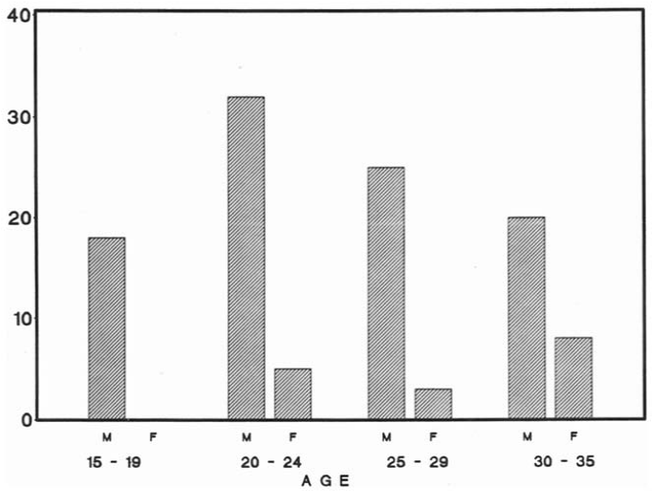

Figure 6. Age (year) and gender of the 111 trauma victims in the current study whose coronary arteries were evaluated for atherosclerosis. Values on the vertical axis represent number of victims. F = female; M = male.

Vietnam War casualties ($p < 0.001$, with 95% confidence limits of 0.707 and 0.860) (Table 2).

Site of involvement. Involvement of the left main coronary artery was noted in 14 hearts, with narrowing >50% in 6. One male patient (32 years old) and one female patient (33 years old) had >90% stenoses involving this vessel.

Although the proximal segments of the coronary arteries were more commonly involved than the mid or distal segments, this observation was less true of the right coronary artery, where the distal portion of the vessel often appeared to be as frequently involved. Fifty-four individual hearts exhibited narrowing in the proximal left anterior descending artery and circumflex coronary arteries, with distal involvement noted in only four and three hearts, respectively ($p <$ 0.001). In contrast, although proximal involvement of the right coronary artery was noted in 33 hearts, the mid-right coronary artery was involved in 2 hearts, and the distal right coronary artery in 25 hearts ($p = 0.144$) (Fig. 9).

Table 1. Demographics of Comparison Versus Study Groups

	Comparison Group*	Study Group
Male/female	81/19 (81.0)	95/16 (85.5)
Age (yr)	26.0 ± 4.1	25.6 ± 5.5
(White race/other)	75/25 (75.0)†	96/15 (86.4)†
BSA (m^2)	1.88 ± 0.7	1.80 ± 0.5

*100 age-matched trauma victims admitted to the surgical intensive care unit during the same period as the study group. †$p < 0.05$. No other differences between groups were significant. Values are expressed as number (%) of patients or mean value ± SD. BSA = body surface area.

Incidence of severe coronary atherosclerosis (>50% narrowing). As assessed by an index of >50% circumferential area narrowing as a sign of significant atherosclerosis, the hearts of 23 patients showed involvement, with signs of single-vessel disease in 11, of two-vessel disease in 7 and of three-vessel disease in 3. The age range of this group ranged from 16 to 35 years (mean 27.6 ± 5.4). They were predominantly male (20 of 23) and white (21 of 23). Body surface area ranged from 1.7 to 2.5 m^2 (mean 1.9 ± 0.5). Heart weight, when corrected for body surface area, averaged 208.4 ± 78.1 g/m^2 (normal, 250 to 300 g for women and 300 to 350 g for men). There were no significant differences between this group and the rest with less severe disease with respect to age, gender, race, body surface area or heart weight (Table 3). The preferential involvement of the proximal segments of the major coronary arteries was again noted, 11 involving the left anterior descending (10 of 11 proximal), 12 the left circumflex (11 of 12 proximal) and 10 the right coronary artery (7 proximal, 1 mid and 2 distal)

Figure 7. Risk factor data in 100 trauma victims who survived. Values on the vertical axis are in percent. Chol >200 = cholesterol >200 mg/dl; DM = diabetes mellitus; FAM Hx = family history of heart disease; HTN = hypertension; other abbreviations as in Figure 6.

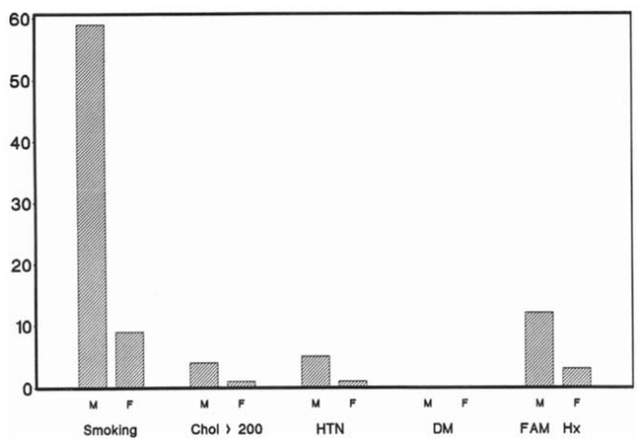

Figure 8. Prevalence of coronary atherosclerosis (CAS) as related to body mass index (BMI). Values on the vertical axis represent number of victims.

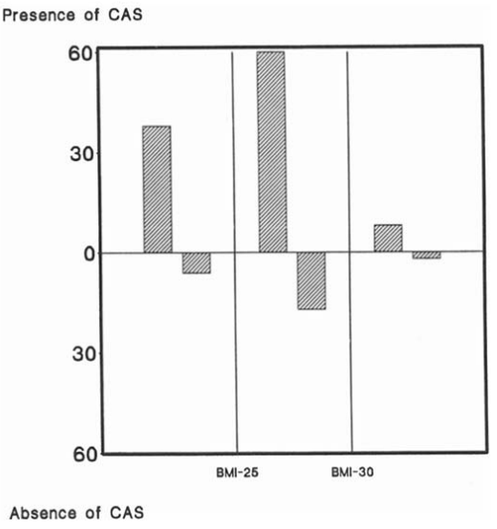

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Table 2. Incidence of Coronary Atherosclerosis in Male Trauma Victims

Study Group	No.	Mean Age (yr)	Incidence	CSA (%) >50%	CSA (%) 75% to 90%
Enos et al. (5) (Korean War)	300	22.1	77.3	—	—
Virmani et al. (4) (Korean War)	94	20.5	56.0	19.0%	6.4%
McNamara et al. (6) (Vietnam War) (86.6% white)	105	22.1	45.0	—	5.0%
University of Louisville (present study) (86.4% white)	95	25.6	75.8	21.0%	9.0%

CSA = cross-sectional area narrowing.

(Fig. 10). The overall incidence of severe coronary artery disease (between 75% and 90% area narrowing) in the male patients was 9.0% and not significantly different from that in earlier studies (6.4% for the Korean War casualties, $p = 0.66$, and 5% after the Vietnam War, $p = 0.33$). Lesions >50% in area narrowing were noted in the left main coronary artery in seven hearts.

No total occlusions were seen and ostial disease was rare. Visual estimation of lesions noted at the time of autopsy was often inaccurate when compared with subsequent microscopic and planimetric examination. Although the more severe lesions were often close to actual values, assessment of less severe lesions was frequently underestimated.

Figure 9. Prevalence of coronary atherosclerosis by site. The left anterior descending (LAD) and left circumflex (Cx) arteries were more often involved proximally unlike the right coronary artery (RCA), which was equally involved in both proximal (P) and distal (D) segments. Values on the vertical axis represent number of involved hearts. LM = left main coronary artery.

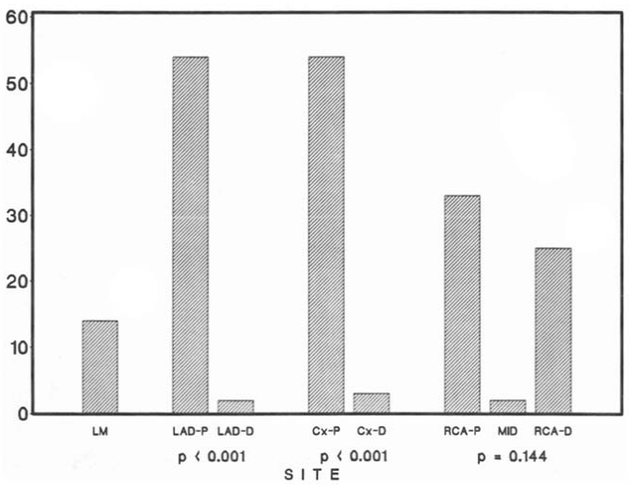


Table 3. Demographics of Groups With Mild and Significant Disease*

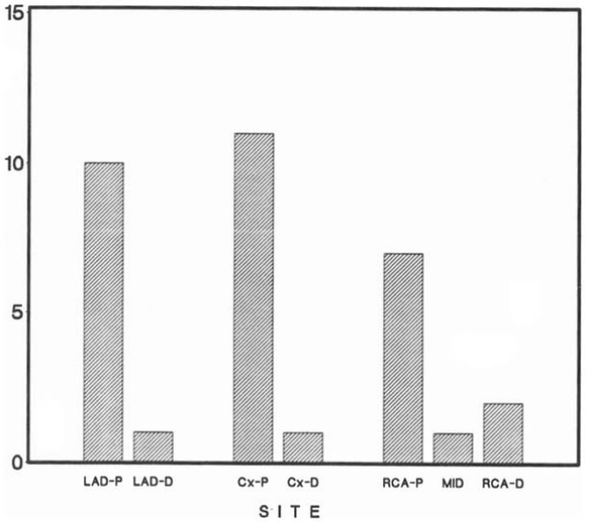
	<50% CSA Narrowing (n = 64)	>50% CSA Narrowing (n = 23)
Male/female	53/11 (82.8% M)	20/3 (86.9% M)
Age (yr)	25.6 ± 5.5	27.6 ± 5.4
White race/other	55/9 (85.9% W)	21/2 (91.1% W)
BSA (m^2)	1.8 ± 0.5	1.9 ± 0.5
Heart weight (g/m^2)	188.94 ± 67.9	208.36 ± 78.1

*There were no significant differences between groups. M = male; W = white; other abbreviations as in Tables 1 and 2.

Discussion

Previous studies. It has consistently been assumed that the incidence of coronary atherosclerosis, as evaluated from necropsy studies, increases in severity with advancing age (8–10). A restudy of the problem by one group of investigators (11) in 100 consecutive men did not demonstrate a linear increase in the incidence with age but did show that the process increased rapidly in the 30- to 49-year age period, reaching a maximum in the 50- to 59-year age group and thereafter remaining at a fairly constant level. In examining the incidence of coronary artery disease in the young, Monckeberg (12) reported examining the coronary arteries in 140 combat soldiers who died from injuries sustained in World War I. The soldiers had a mean age of 27.7 years, and 65 (46.4%) of the 140 had increased atherosclerotic plaque in the coronary arteries. French and Dock (13), in studying the hearts of 80 young soldiers 20 to 36 years old who died of sudden cardiac death noted that the basis for coronary

Figure 10. Prevalence of severe coronary atherosclerosis (>50% area narrowing) and site of involvement. The proximal segments of all three coronary arteries were more frequently involved than the mid or distal segments. Values on the vertical axis represent number of involved hearts. Abbreviations as in Figure 9.



occlusion was arteriosclerosis in all cases. Myocardial scars, indicative of earlier insults, were noted in 59%, with recent infarction in 19%. More recent studies examining the incidence of coronary artery disease in the young were published in 1953 by Enos et al. (5), who reported their findings in 300 autopsies on United States service personnel who died in battle during the Korean War. The mean age was 22.1 years, and 77.3% of the hearts had some evidence of coronary atherosclerosis, with findings ranging from mere fibrous thickening to total occlusions. Lumen narrowing was estimated visually with no actual measurements being made, and disease was most often found at bifurcation points.

Investigators at the Louisiana State University School of Medicine (14) in their study of coronary atherosclerosis evaluated grossly the extent of atherosclerotic lesions in the coronary arteries obtained from 548 hospital and medicolegal autopsies performed on patients 1 to 69 years old. They found that white men <40 years old had a higher prevalence and greater extent of all types of lesions. Their data thus supported the hypothesis that coronary atherosclerosis was the most significant determinant of cardiovascular mortality in their study group and that coronary artery lesions developed early in life, at least 20 years before the onset of clinically manifest disease.

McNamara et al. (6) used postmortem coronary angiography and dissection of the coronary arteries to study atherosclerosis in 105 soldiers killed in Vietnam in 1971. Although these investigators used plaque size to estimate the extent of disease, they found evidence of coronary atherosclerosis in only 45% of hearts, with 5% of hearts exhibiting severe coronary atherosclerosis. They suggested that the difference between their findings and those of the Korean War study were possibly due to differences in the methods used to study the degree of lumen compromise. Concluding that the observed decrease in the incidence of coronary atherosclerosis in young men was significant, this appeared to correlate with the noted decrease in the incidence of myocardial infarctions since the 1960s.

To confirm the findings from the Korean War, Virmani et al. (4) restudied the hearts of 94 separate victims, this time using computerized planimetry to determine the true area of the artery, thereby eliminating errors that may have been caused by compression and collapse. The mean age of this group was 20.5 years, and six (6.4%) had evidence of severe atherosclerosis (75% to 90% lumen narrowing), with microscopic evidence of atherosclerosis in 56%. The investigators observed that, although these studies could reflect a meaningful downward trend in the incidence of coronary artery disease, an autopsy study of the incidence and severity of coronary atherosclerosis in trauma victims needed to be conducted.

Risk factors for coronary atherosclerosis. These descriptive studies of the natural history of atherosclerosis stimulated investigations of the relation between risk factors and atherosclerotic lesions. Epidemiologic studies, including the Framingham study (15), were able to predict most of the potential victims of cardiovascular disease years before they became ill. An increase in total to high density lipoprotein cholesterol ratio, hypertension, cigarette smoking, excess weight, elevated blood sugar levels, lack of exercise, stress, electrocardiographic (ECG) abnormalities and other factors were associated with the development of these diseases. Numerous other studies (16–18) have since confirmed these findings and the fact that lowering these risk factors reduces the subsequent rate of coronary heart disease, stroke and other cardiovascular disease (19). The more recent report from the PDAY Research Group (20), which examined serum low density and high density lipoprotein cholesterol concentrations in an autopsy series, also appeared to confirm that these factors and smoking were important determinants of the early stages of atherosclerosis in the young.

We examined the coronary anatomy of young patients because of the rising incidence of clinically significant coronary artery disease we were seeing at our center in this age group. None of the victims in the present study had died a cardiac death or were receiving any cardiac medications. A comparable group admitted during the same period included a majority of smokers (68%), and a smaller proportion (15%) with a family history of heart disease. Hypercholesterolemia was seen infrequently (5%) and hypertension was noted in 6%. Although the body mass index (an indicator of obesity and cardiovascular mortality) was within normal limits in the majority of the patients who had undergone autopsy, 8 of the 10 who were significantly overweight had signs of coronary artery involvement.

Limitations of autopsy studies. *Effects of fixation and processing on tissues.* All autopsy studies are hampered by experimental difficulties and limitations of postmortem assessment of human coronary artery size and lumen narrowing with the differential effects of tissue fixation and processing on vessels. There is very little evidence, however, to suggest that the ratio diameter of lesion to residual lumen can be significantly altered by postmortem changes (21). The histologic examination of 3-mm cross sections of coronary arteries perpendicular to the long axis of the vessel allows a calculation of the length and degree of a stenosis that is satisfactory and acceptable for comparative studies (22). By staining the internal elastic lamina, deriving the areas enclosed by this and the residual lumen, postmortem collapse of the arteries that had not been injected before formaldehyde fixation was offset (4). Siegel et al. (23) studied 61 coronary artery segments to evaluate the potential effects of tissue fixation and processing on postmortem histologic measurements using planimetry to see if this could explain some of the discrepancies between arteriographic and necropsy examination. In vessels with minimal narrowing, fixation and processing resulted in a decrease in total cross-sectional area narrowing, whereas absolute wall area (total cross-sectional area minus lumen cross-sectional area) did not change. Effectively lumen cross-sectional area decreased from 47.6 ± 8.5% to 36.2 ± 7% after processing. In vessels with moderate to severe atherosclerosis, the total

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cross-sectional area and wall area decreased with no change in lumen area. As a result, the percent cross-sectional area in vessels increased from 21.1 ± 10.1% before fixation to 28.7 ± 9.7% after processing. Our methods of identifying the degree of coronary vessel involvement began by identifying the internal elastic lamina as the initial lumen with the residual lumen expressed as a percent of this value, thereby avoiding the effects of fixation and processing on the entire thickness of the vessel wall.

Effects of systemic intravascular distending pressures. There are concerns that the lack of an intravascular distending pressure to systemic pressures when examining for coronary artery disease at autopsy will result in the plaque falsely appearing to represent a greater portion of the vessel circumference and lumen area because of the collapse of the elastic fibers in the vessel wall and the relative rigidity of the plaque material (6). The Korean War autopsy data involved gross and microscopic examination of the coronary artery tree, with no separation of fibrous thickening from actual plaque involvement and no injection techniques. The 105 autopsies performed on the Vietnam War victims used postmortem angiography, with X-ray films made of the coronary artery after the injection of 5 ml of diatrizoate sodium (Hypaque) to standard intravascular distending pressures. The severity of atherosclerosis was judged based on plaque size and extent of vessel involvement with no estimation of lumen compromise. When the mechanical properties of the vessel wall were studied in the rabbit aorta by Wolinsky and Glagov (24), they demonstrated that aortic radius increased, whereas wall thickness decreased as intraluminal distending pressure increased from 5 to 80 mm Hg with little change in vessel dimensions above physiologic diastolic pressures. However, postmortem coronary angiograms have never been found to accurately depict the degree of coronary artery narrowing. Gray et al. (25) perfused the coronary artery tree in 15 patients using barium sulfate-agar at a constant pressure of 150 mm Hg to equilibrium and compared his findings to serial histologic sections of the coronary arteries. In 36 of the 44 coronary arterial segments narrowed >33% of their original area, the postmortem angiogram underestimated the degree of narrowing, and in 20 of the 36 the degree of underestimation was severe. Eusterman et al. (26) compared the degree of narrowing in 479 coronary artery segments from 50 hearts by postmortem angiogram with that found by gross examination. In 73 segments with nonfocal narrowing >5 mm long, the postmortem angiogram underestimated the degree of lumen narrowing in 53 (73%). In 74% of the segments with focal narrowing, when narrowing was underestimated, the error was >50%. Thus perfusion pressure techniques, when used to study coronary arteries at autopsy, appear to underestimate the severity of coronary stenoses, especially when focal, possibly because intravascular pressure distends a weakened sclerotic wall, resulting in the appearance of a less severely involved vessel. The use of this technique may have been responsible for the lower incidence of coronary artery involvement noted in studies performed on servicemen after the Vietnam War.

Underestimation of severity of disease by coronary angiography. Numerous studies have compared coronary arteriography with the severity of coronary artery disease found at autopsy. Kemp et al. (27) examined 131 major coronary arteries in 29 patients and concluded that the degree of coronary narrowing was underestimated angiographically in 16 vessels and was functionally significant in only 3. Vlodaver et al. (28) noted underestimation of lumen narrowing in 44 (33%) of 134 coronary artery segments studied. Others (21,29,30) have confirmed such underestimation, although its frequency and severity have varied, with the widest discrepancy noted in the more severe lesions. Reasons for this underestimation include the number of radiographic views chosen; the projections used; the quality of the arteriogram; diffuse involvement, which makes it less likely to find a normal segment for comparison, and the morphologic nature of the lesion, whether eccentric or concentric. Moreover, a coronary angiographic lesion that occupies <1% of the frame (ideally it should occupy ≥85%) provides less accuracy than an image of a cross-sectional area photomicrograph for estimating the degree of cross-sectional area narrowing (29). Therefore, although coronary angiographic findings continue to remain the standard for assessing the presence and severity of occlusive coronary artery disease and have correlated closely enough that differences from the actual condition have been clinically unimportant in most studies (29–31), underestimating the degree of involvement may occur for the reasons cited.

Comments on results. Our incidence of early or progressive atherosclerosis (75.8% in male patients, 78.3% overall) is similar to that found at autopsy in Korean War service personnel although it is significantly higher than that observed in the Vietnam War casualties, perhaps for reasons related to the methodology used to assess coronary artery involvement. Our study group was older (mean age 25.6 ± 5.5 years) than that of the groups studied after both the Korean and Vietnam conflicts, in which the mean age was 22.1 years but otherwise demographically similar by race and gender. Involvement of the left main coronary artery was seen in 14 hearts (12.6%), with >90% involvement in 2 hearts. As described in earlier studies (11), the proximal segments of both the left anterior descending and left circumflex arteries appear to be more often involved than the distal vessel before the branching points of either the diagonal or marginal branches. In contrast, the right coronary artery was involved distally as frequently as it was proximally, a difference that may have importance clinically when dealing with coronary artery disease in the young. Although multivessel disease was seen in only 10 hearts, the lesions were often significant with >50% narrowing. No demographic features separated this group from those with less severe disease.

Conclusions. The following conclusions can be drawn from the present study:

1. The overall prevalence of coronary atherosclerosis in a group 14 to 35 years old who died from noncardiac causes was comparable with that noted after the Korean War (78.3%). Narrowing >50% was seen in about 20.7%, with lesions >75% in 9.0%.
2. The major risk factors in a comparable group were smoking and a family history of coronary artery disease. Although extreme obesity was more frequently associated with signs of coronary atherosclerosis than was normal weight, there was no correlation between atherosclerosis and body mass index.
3. Left main or significant two- and three-vessel disease was present in ≈20% of the study group. This subgroup would be at significant risk for a cardiac event at a young age.

Implications for prevention of coronary atherosclerosis in the young. An estimated 1.25 million acute myocardial infarctions occur annually in the U.S., resulting in 553,000 deaths (32). Differences in methodology have made it impractical to assess whether differences in the incidence of coronary artery disease in the young represent a real decrease in coronary atherosclerosis. Although one study (33,34) did show an apparent reduction in cardiovascular deaths in young white men between 1969 and 1978, it is not certain whether this reduction was due to a decrease in the incidence of the underlying atherosclerotic lesions or to better treatment of changes that cause the terminal occlusive episode. Continued surveillance of the extent of atherosclerotic lesions measured at autopsy may be an effective indicator of secular trends in coronary heart disease. Our study further confirms that the disease process begins early in life, and preventive measures designed to retard the progression of atherosclerosis should be directed toward the young for maximal benefit.

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