Coronary Artery Disease in Young Adults*

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To Thee It Shall Descend With Better Quiet
—From Act IV, Scene III, Henry IV, Part II, by William Shakespeare

Coronary artery disease (CAD) is a devastating disease precisely because an otherwise healthy person in the prime of life may die or become disabled without warning. When the afflicted individual is under the age of 40, the tragic consequences for family, friends, and occupation are particularly catastrophic and unexpected. Fortunately, the incidence of myocardial infarction (MI) and symptomatic CAD in young adults is low; most studies show that only about 3% of all CAD cases occur in this age range (1).

The fact that clinically manifest CAD in the young adult is relatively uncommon implies that these patients are atypical of the general population. It must be noted, however, that those patients who come to medical attention owing to symptomatic disease may well represent the “tip of the iceberg” when considering manifest and subclinical disease together. Because young, asymptomatic patients typically do not undergo medical investigations leading to the serendipitous discovery of CAD, the true prevalence of the disease has been grossly underestimated. Indeed, when a rigorous intravascular ultrasound-based investigation was undertaken in a cohort of recently transplanted hearts (mean donor age 33.4 ± 13.2 years) by Tuzcu et al. (2), the prevalence of disease was >50%, with one in six teenagers manifesting coronary lesions.

Many early studies (3) evaluating these patients labeled them as having “premature” CAD, but it is now better understood as a rapidly progressive form of the disease (4–6). Subsequently, this subgroup has been the subject of numerous observational series seeking to identify what sets them apart (7). It is well recognized that these patients are mainly male and have several coronary risk factors, but this is a statement easily made of many older CAD patients as well (8,9).

RISK FACTORS

Cigarette smoking has been the single factor most strongly associated with CAD in the young adult. Kannel et al. (10) found in patients included in the Framingham Heart Study, the relative risk for CAD was about three times higher in smokers age 35 to 44, compared to nonsmokers. Repeated exposure to cigarettes and the resulting frequent catecholamine surges damage endothelial cells, leading to dysfunction and injury of the vascular intima. Cocaine, especially taken in combination with tobacco or as concentrated cocaine hydrochloride base (“crack”), is especially likely to produce spasm, plaque rupture, and thrombosis by a similar mechanism but with greater intensity. Coronary vasospasm may occur in angiographically normal coronary arteries even in the absence of stimulants or sympathomimetic agents. Several cases have been reported of acute MI in young patients with acute ethanol intoxication and no evidence of CAD by intravascular ultrasound. Although the precise pathogenetic mechanism remains elusive in these cases, disrupted coronary vasomotor tone with resultant vasospasm is strongly suspected (11).

Diabetes and hyperlipidemia are also frequently present in young CAD patients. Whereas the importance of these factors in the pathogenesis of CAD and their powerful relationship to rapid disease progression is well documented (12,13), their importance in this population is not characterized in detail. Although markedly elevated levels of total cholesterol, low-density lipoproteins, and triglycerides are found in some young CAD patients, few studies have systematically analyzed the lipid panels of this population of patients. Isser et al. (14) found significant elevation of triglycerides and lipoprotein (a) (Lp[a]) levels and depression of high-density lipoprotein (HDL) cholesterol in young patients presenting with their first MI, compared with age- and gender-matched controls. Interestingly, there was also noted to be strong familial clustering of Lp(a) elevation in the asymptomatic first-degree relatives of these patients. Similarly, although insulin-dependent diabetics are at high risk for CAD, diabetes is found in only about 15% to 20% of all young CAD patients. Even less well studied in this regard is the relative risk posed by atherogenic subfractions of low- and high-density lipoproteins, hyperhomocysteinemia, elevated fibrinogen, and abnormal blood viscosity. Recent data (15) suggest that elevated homocysteine and elevated Lp(a) are independent risk factors for the development of CAD in young men; however, these two factors appear to interact in a synergistic fashion to confer risk in young women.

Young women with CAD comprise an especially interesting group given the protective effect of estrogen, but which factors are predictive in this distinctly unusual cohort is poorly understood (1). Anecdotal cases suggest that diabetes in women may have a more powerful role than in men. Women who smoke have a quantitatively similar risk...
as men (16), but more than five times the risk of nonsmoking women (17). Smoking in combination with oral contraceptives poses a 13-fold increase in CAD mortality (18). Truncal obesity and increased body mass index (BMI) have recently been proposed as potential independent risk factors, particularly in young women with CAD. In one cohort of young CAD patients (19), the addition of the logarithmically transformed BMI to the Framingham risk score yielded a substantial increase in predictive power for CAD as assessed by the detection of coronary artery calcification. Augmentation in the area under the receiver-operating characteristic curve was more pronounced in women, but incorporation of BMI data was found useful across the entire study population as well. Other cases of plaque rupture are typically ascribed to spasm, spontaneous coronary dissection, or trauma without overt recognition of subclinical CAD. Patients with hypercoagulable states and certain connective tissue or collagen vascular disorders comprise a population also at high risk for early ischemic events.

Family history is a factor known to be present in many of these patients and probably represents a combination of risk factors that are genetically determined. These include diabetes, lipid and thrombotic disorders, as well as a behavioral predisposition to smoking. A growing body of evidence, for example, shows that specific lipid abnormalities may be genetically transmitted to the offspring of patients with severe CAD. Uiterwaal et al. (20) found lower levels of HDL$_3$ cholesterol and apolipoprotein A2 in male children of CAD patients. Similar but more modest trends were also identified in the female children of these patients.

Perhaps of equal interest is the lack of a strong association of other traditional risk factors to CAD in the young. Hypertension and lack of exercise are both firmly established risk factors for CAD in general, but they appear to contribute only marginally in this population. Undoubtedly, accounting for the surprising absence of a powerful influence of these factors in this population is important in fully comprehending the pathogenesis of CAD in young adults.

Almost entirely unexplored are the roles of emotional distress, anger, and sudden or extreme physical exertion. In a subgroup analysis of the Coronary Artery Risk Development in Young Adults (CARDIA) study (21), high objective hostility scores were associated with the presence of coronary artery calcification. This intriguing data suggests the possible involvement of risk factors that are often not considered in typical risk-stratification schemes. Considering the occasional involvement of these factors in older CAD patients, their involvement in this group should be further elucidated. Similarly understudied is the role of inflammation, either measured by systemic inflammatory markers such as high sensitivity C-reactive protein, or manifest as frank vasculitis. Because chlamydia, mycoplasma, and H. pylori are often thought of as having a pathogenetic role in CAD, this population would seem to be an ideal group to study for the presence of recent infections. We recently observed a young man with an acute MI who exhibited acute and six-month titers strongly suggesting a mycoplasma infection at the time of his acute infarct. Emotional stress and smoking were also present. He has had no recurrent CAD events after three years of follow-up.

**EXTENT OF ATHEROSCLEROSIS AND PROGNOSIS**

Numerous studies (4–7) have demonstrated the surprisingly good prognosis up to three years after diagnosis of CAD in the young adult. Patients who undergo coronary angiography soon after acute MI typically have less extensive CAD and higher ejection fractions than older MI patients (7). They have fewer comorbidities, are less disabled by recurrent angina and heart failure, and are more likely to return to work. Presentation with symptomatic CAD but without an acute infarction is uncommon, perhaps not surprisingly given the likelihood of overlooking the diagnosis in young patients with chest pain (7).

Klein et al. (7) theorized that two distinct populations exist. The more common subgroup is characterized by single-vessel, and often single-stenosis, disease, presumably related to acute plaque rupture, with an excellent three-year outcome. The favorable prognosis was believed to be related to preserved left ventricular function without multivessel involvement. The less common group has extensive three-vessel CAD with “galloping” progression unrestrained by coronary artery bypass graft surgery (CABG) and preventive measures. However, an attractive explanation for this dichotomy was unclear at the time this hypothesis was proposed, because once plaque rupture occurs, that individual's propensity to form vulnerable plaque is unquestionable.

**CURRENT STUDY**

In this issue of the *Journal*, Cole et al. (22) from Emory University in Atlanta, Georgia, report on the 15-year follow-up of 843 patients who had angiographically documented CAD under age 40. Both in terms of length of follow-up and sample size, this is by far the largest observational series ever published. The investigators found diabetes and smoking to be predictive of mortality, along with prior MI and heart failure. The latter two variables are not surprising, but the independent impact on outcome of these two risk factors surely has a deeper pathogenetic meaning. Furthermore, the investigators show that, contrary to previous studies, the 15-year outcome is not favorable—a 30% mortality overall is found. Interestingly, those treated medically, in contradistinction to those receiving early revascularization with percutaneous coronary intervention or CABG, had a worse outcome. It remains unclear, however, to what extent this finding is reflective of selection bias related to extent and severity of disease. The fact that angina class (at time of presentation) and number of vessels diseased at index catheterization were not predictive of long-term outcome is inconclusive, for it is the speed of
disease progression over this long time frame, rather than initial findings, which would be the most crucial variable.

The revascularization strategy analysis is important and unique, and it adds a great deal to our understanding. However, this analysis only evaluated mortality as an end point. Further studies should consider repeat MI, heart failure, repeat revascularization, and recurrent chest pain/hospital admission. Further, an assessment of disease progression is key.

PATHOGENETIC MECHANISMS

Clearly, this is a fascinating patient group with an important story to tell, but we are just beginning to listen carefully enough to hear. The existing observational data allow a modification of the earlier hypothesis. The two subgroup categorizations remain valid, but the interplay with risk factors can now be better sketched into the picture.

In young patients with a single culprit lesion, and among most women (especially those with dissection or coronary spasm), a plaque rupture on a previously nonsignificant vulnerable plaque is usually the mechanism of acute presentation. Such cases are likely related to acute physical and/or emotional stress, resulting in enhanced coronary shear forces. If these patients do not alter their lifestyles, CAD progression at an earlier age than usual will result, but it may be avoided by following established preventive measures. This group has a substantial vasospastic component superimposed on a genetic predisposition to vulnerable plaque production.

Conversely, a second group is comprised of those with diabetes and others who present with established multivessel disease (including those related to lipid abnormalities). These patients are most likely to have rapid progression of a more typical form of CAD. They will experience only short-term benefit from revascularization, unless very aggressive control over risk factors is strictly adhered to.

The interaction between a genetic propensity to form vulnerable plaque combined with acute stress and/or an active infectious/inflammatory process needs further study. If we can better identify and characterize the mechanism of disease in this population, our understanding of CAD in more typical cases will be vastly improved.

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