Pathophysiology of Sudden Coronary Death in Women
Implications for Prevention
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Despite major progress in detection, prevention, and treatment, coronary artery disease remains the leading cause of death in the world. More than half of all coronary deaths are sudden and unexpected, occurring within 6 hours of the onset of symptoms and usually outside the hospital. Coronary artery disease is by far the most common pathology underlying the 300,000 cases of sudden cardiac death occurring in the United States each year. The insidious nature of sudden cardiac death and the finality of the outcome represent major barriers to development of effective preventive and therapeutic strategies. This is a particular problem in women, in whom the risk of coronary artery disease and of sudden death is lower than in men and in whom the index of suspicion of serious cardiovascular pathology remains low. Data from carefully conducted postmortem studies of victims of sudden cardiac death provide important insights into the pathogenesis of sudden cardiac death and the risk factors that predispose to it.

In a study reported in the current issue of Circulation, Burke et al relate cardiac pathology in 51 female victims of sudden death identified at the Office of the Chief Medical Examiner of the State of Maryland to antecedent symptoms and cardiac risk factors and compare these to findings in 15 female victims of fatal trauma as control subjects. Several striking findings emerge from the study: (1) Of the 36 deaths that were witnessed, only 8 (22%) were preceded by chest pain; 12 (33%) were preceded by other, nonspecific symptoms, including back pain, dizziness, nausea and vomiting, shortness of breath, malaise, fatigue, fever and chills, stomach distension, and tingling of the left shoulder; and 16 (45%) were preceded by no symptoms whatsoever. (2) Only one patient was receiving hormone replacement therapy. (3) Coronary anatomy was different in younger (presumably premenopausal) women, in whom acute coronary thrombosis was most commonly related to plaque erosion versus older (presumably postmenopausal) women in whom plaque rupture or healed myocardial infarction without acute coronary thrombosis was the dominant lesion. (4) Cardiac risk factors differed in the younger versus the older women, with smoking predominant in the younger group and hypercholesterolemia, hypertension, and diabetes in the older.

Thirty of the 51 sudden coronary deaths in the Burke series occurred in women <50 years of age, a surprising finding considering the low incidence of coronary artery disease in this age/sex group. In part this finding reflects, as the authors acknowledge, inherent selection bias as the result of autopsy sampling. More importantly, however, this calls attention to the lethal nature of myocardial infarction in young women. The 26-year follow-up date from the Framingham Heart Study demonstrated that women of all ages have an excess risk over men of death caused by myocardial infarction, with overall case-fatality rates of 32% for women versus 27% for men. Furthermore, case-fatality rates for myocardial infarction in women were higher at either extreme of the age span, reaching 50% in the 35- to 44-year group and 46% in the 75- to 84-year group, far exceeding case-fatality rates for middle-aged women or men of any age. Thus a myocardial infarction is a relatively rare but deadly event in young women.

In the Framingham cohort, women had a lower incidence of sudden coronary death than men, but in two thirds of women who died suddenly, sudden cardiac death was the first clinical manifestation of coronary heart disease. The absence of typical premonitory symptoms of coronary heart disease in women probably denied them the benefit of closer periodic electrocardiographic surveillance and preventive medical interventions that might have been lifesaving.

In the Burke series, women who died before age 50 years of coronary causes were generally free of the risk factors most commonly associated with heart disease in women: Only 20% were hypertensive; mean total cholesterol was 194 mg/dL; HDL cholesterol was 47 mg/dL; and mean glycosylated hemoglobin was 7.1%. These values were similar to those seen in the trauma control subjects. The most common risk factor in this group was cigarette smoking (assessed by postmortem serum thiocyanate level) in 50% of subjects. Not assessed in the Burke study were some of the newer, nontraditional cardiovascular risk factors, including homocysteine levels, clotting factors such as plasminogen activator inhibitor, fibrinogen and von Willebrand factor, lipoprotein [a], and chronic infections. Further study of the newer risk factors in populations may be useful in identifying the population of young women at increased risk for coronary events.

Cigarette smoking is clearly a powerful risk factor for myocardial infarction and sudden cardiac death in women, probably by altering clotting factors and platelet function as well as by accelerating atherosclerosis and stimulating the sympathetic nervous system. In one epidemiologic study, cigarette smoking was the strongest risk factor for sudden

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cardiac death among women; all of those ≤45 years of age who died suddenly were heavy (>1 pack per day) smokers.8 Furthermore, in the Framingham cohort, the strongest predictors of sudden coronary death in women were an increased hematocrit level and a decreased vital capacity.7 Although cigarette smoking was not a significant predictor of sudden unexpected death in this population, the authors raised the possibility that smoking may have acted through hematocrit or some other hematologic mechanism to increase risk.

Inhaled cigarette smoke has a variety of effects on clotting factors and platelet function that could predispose to acute coronary events. Data from Framingham have shown significantly higher fibrinogen levels in the smoking than in the nonsmoking population, and fibrinogen levels are an independent risk factor for coronary artery disease.8 Smokers also have increased platelet aggregation and prolonged clotting times.9 Furthermore, and most importantly, cigarette smoking appears to damage the endothelium, decreasing prostacyclin synthesis and/or release, thus favoring platelet aggregation and thrombosis.10

The most common lesion found in cigarette smokers in the Burke study was plaque erosion. The average age of the 18 women with plaque erosion was 45 years, and 14 of the 18 (78%) were smokers. Eroded coronary artery plaques that were rich in smooth muscle cells and proteoglycans but lacked a superficial lipid core and had not ruptured into the lumen were recently described by this group in victims of sudden cardiac death.11 Eroded plaques accounted for 44% of a series of 50 consecutive cases of sudden death caused by coronary thrombosis.11 In all cases, thrombi were adherent to the eroded plaque. Patients with plaque erosion were younger (44 versus 53 years) and more likely to be women (50% versus 18%) than those with plaque rupture and had less luminal narrowing and plaque calcification (23% versus 69%). Smooth muscle cells predominated in the eroded plaques, whereas lipid-laden macrophages, T-cells, and HLA-DR-positive cells (marker of cell activation) were present in large numbers at the luminal surface in the vicinity of the rupture site in ruptured plaques. The finding of more cellular fibrous tissue and less dense calcified fibrous tissue in coronary lesions in women is consistent with earlier findings in both native and coronary arteries and saphenous vein grafts of women compared with men.12 Cellular fibrous plaques are associated with an earlier stage of atherosclerosis than dense, hypercellular, lipid-laden plaques, consistent with the concept that atherosclerotic plaque formation is delayed in women by 10 to 20 years, presumably because of the protective effects of ovarian hormones.

Eroded plaques have an irregular surface and lack a protective covering of endothelial cells. The authors postulated that endothelial injury leads to platelet deposition followed by smooth muscle cell proliferation and extracellular matrix synthesis within the plaque. Procoagulant proteoglycans within the plaque, in addition to endothelial dysfunction/denudation and, particularly in smokers, activated platelets and circulating clotting factors, would increase the risk of arterial thrombosis. Further study is needed to identify the specific factors that predispose to plaque erosion.

Coronary lesions in the older (postmenopausal and not hormone replaced) women in the Burke study more closely resembled those usually reported in men, for example, plaque rupture. Rupture of lipid-laden plaques is the most common cause of acute coronary thrombosis and associated clinical events, including unstable angina, acute myocardial infarction, and sudden cardiac death.13 Atherosclerotic plaques that are vulnerable to rupture contain a dense infiltrate of lipid-laden macrophages and lymphocytes within a fibrous cap that overlies an acellular mass of lipids. Thinning and disruption of the fibrous cap caused by release of metalloproteases from activated macrophages within the plaque and/or other factors can lead to plaque rupture and generation of a thrombogenic surface that may form the nidus of an occlusive clot. Hypercholesterolemia (mean total cholesterol, 270 mg/dL) was the predominant risk factor in women with plaque rupture. Recent clinical trials have shown that women as well as men who have hypercholesterolemia and/or have had previous coronary events benefit from aggressive cholesterol lowering, presumably by removing cholesterol from lipid-laden plaques and reducing the probability of rupture.

Eighteen (35%) hearts in the Burke study showed evidence of healed myocardial infarctions with stable plaques. Half of these women were hypertensive, and the mean glycosylated hemoglobin in this group was 10.2%, suggesting a high prevalence of diabetes. These findings are consistent with epidemiologic and clinical trial evidence that elevated systolic and diastolic blood pressures are independent risk factors for acute coronary events and cardiovascular mortality rates in women. Successful antihypertensive treatment reduces the risk of major cardiovascular events in women as well as men.14

Diabetes is a more important risk factor for coronary heart disease in women than in men, negating much of the protective effects of female sex.15 The Nurses’ Health Study showed that maturity-onset diabetes was associated with a threefold to sevenfold increase in risk of a cardiovascular event, and 14-year follow-up data from the Rancho Bernardo Study showed a strong relation between fasting plasma glucose levels and coronary heart disease mortality rates in women. The relative hazard of ischemic heart disease death in diabetic subjects versus nondiabetic subjects was 1.7 in men and 3.3 in women after adjusting for age, systolic blood pressure, cholesterol, body mass index, and cigarette smoking, by use of the Cox regression model. Thus diabetes imposes a greater risk of heart disease in women than in men, and the sex difference is independent of other cardiovascular risk factors,15 although both men and women with diabetes tend to be more hyperlipidemic, more hypertensive, and more obese than nondiabetic subjects. The mechanisms by which diabetes accelerates the natural history of vascular disease are poorly understood and probably do not relate to hyperglycemia per se. Further study is urgently needed in this area.

Finally, it is remarkable that only one patient in the Burke study was receiving hormone replacement therapy. Ovarian hormones are not a panacea, as clearly evidenced by the appearance of fatal coronary artery disease in women in the premenopausal age group. Nevertheless, overwhelming epidemiologic evidence indicates that ovarian hormones, particu-
ularly estrogen, protect against both atherosclerosis and coronary events, which are related to thrombus formation as well as atherosclerosis per se.\textsuperscript{16,17} The vasoprotective effects of estrogen are numerous, including stimulation of endothelial repair in damaged vessels, restoration of endothelium-dependent vasomotor mechanisms, termination of lipid peroxidation, inhibition of platelet adhesion, lipid lowering, inhibition of clotting factor synthesis, and many others.\textsuperscript{18,19} Even while controlled clinical trials are ongoing to more precisely delineate the benefits and risks of hormone replacement therapy, it is important to exploit the known benefits of these agents in protecting women from coronary artery disease–related death.

References

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