Plaque Rupture and Sudden Death Related to Exertion in Men With Coronary Artery Disease

Allen P. Burke, MD
Andrew Farb, MD
Gray T. Malcom, PhD
You-hui Liang, MD
John E. Smialek, MD
Renu Virmani, MD

HE HEALTH BENEFITS OF REGULAR exercise are well-known, and an association between exercise and reduced risk of coronary heart disease has been demonstrated.1-4 Proposed beneficial effects of physical activity in reducing cardiac mortality include metabolic influences on risk factors, hematologic variables, direct effects on the myocardium, and indirect effects on mortality risk.5,6 Despite the benefits of exercise, acute exertion may trigger acute cardiac events,7 and emotional and physical stress may trigger acute myocardial infarction.8 It has been theorized, but not demonstrated pathologically, that acute exertion may predispose to sudden coronary events by precipitating rupture of a vulnerable coronary artery plaque. The purpose of this study was to examine the association between acute plaque rupture and exertion-related sudden coronary death in a series of carefully studied autopsy hearts.

METHODS

Hearts from men who died of sudden coronary death were studied in a prospective fashion. These hearts were seen in consultation with the medical examiner in the state of Maryland between January 1994 and May 1997. Coronary artery fixation, cardiac dissection, and tissue sampling were performed as previously described.9 Coronary deaths were defined as natural deaths that occurred without evidence of extracardiac cause of death and in which at least 1 epicardial coronary artery had more than 75% cross-sectional lumen narrowing by ath erosclerotic plaque or plaque with superimposed thrombus. Sudden death was defined as symptoms commencing within 6 hours of death (witnessed arrest) or death occurring within 24 hours after the victim was last seen alive in his normal state of health. Coronary deaths with acute thrombus were further categorized as plaque rupture and plaque...
erosion as previously defined. Healing plaque ruptures were defined as an interruption of the fibrous cap with disorganizing thrombus, generally with proteoglycan and smooth muscle cell–rich intimal proliferation surrounding the area of interruption. Vulnerable plaques were defined as a fibrous cap thinner than 65 µm that was infiltrated by macrophages overlying a necrotic core as previously defined. The maximum and minimum thickness of the fibrous cap overlying the necrotic core at sites of plaque rupture was measured by ocular micrometer to the nearest micrometer. The number of vasa vasorum was quantitated manually with the aid of computerized morphometry on sections stained immunohistochemically for endothelial cells with antibodies against factor VIII–related antigen.

Postmortem evaluation of levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), glycosylated hemoglobin, and thiocyanate as a marker for cigarette smoking and evaluation for hypertension was performed as previously described. In every case, available history was used to corroborate autopsy determination of risk factors. In exertion-related deaths, information from the scene and next of kin was obtained to estimate if the individual performed exercise routinely as part of a regimen (several times per week) or was sedentary. Cases were excluded if there was gross hemolysis or if evaluation of total protein and serum albumin levels indicated hemococoncentration or hemodilution. The body mass index was estimated as weight in kilograms divided by the square of height in meters.

Investigators at the scene of death recorded the circumstances of death, including the decedent’s activity, in each case. In deaths that were not witnessed, the location of the body and clothing were recorded, and an assessment to the probable activity prior to the terminal event was made in each case. The exertional status was defined as rest (patient found in bed, in a reclining position, or apparently ambulating in the performance of day-to-day activities), physical exertion, or emotional stress. Physical exertion was defined as the performance of a sport during or within 1 hour of the cardiac arrest, heavy lifting, strenuous digging or shoveling, or sexual activity. Emotional stress was defined as a witnessed verbal altercation with physical involvement (eg, chasing, hitting, or posturing) occurring within 2 hours of the cardiac event, public speaking, or involvement in another fear-inducing activity (eg, fire fighting).

For univariate analysis, unpaired t tests were used to compare continuous variables of risk factors and other parameters in the exertion group vs the rest group. When these parameters were analyzed for the different groups of exertion, an analysis of variance (ANOVA) was performed with risk factors (independent variable) for multivariate analysis. For multivariate analysis examining the association of risk factors with numbers of vulnerable plaques, for both exertion and traditional risk factors, ANOVA was performed.

RESULTS
A total of 141 hearts were studied. One hundred thirteen cases, comprising the earliest two thirds of the current cases, have been published previously but without data regarding activity at death or medication use. The mean (SD) age of all men was 51 (11) years. There were 106 whites, 34 blacks, and 1 Asian. The deaths were witnessed in 90 cases and not witnessed in 51 cases. The deaths were categorized into 2 groups: exertion (n = 25) and rest (n = 116) (Table 1).

Exertion-Related Deaths
Fourteen of the 25 deaths related to exertion occurred in previously sedentary men who were engaged in sudden strenuous activity: carrying heavy objects (unloading a truck [2], moving heavy furniture [2], pushing a car [1]; lawn mowing [2]; having sexual intercourse [2]; ditch digging [1]; playing basketball [2]; bicycling [1]; and shoveling snow [1]. In 4 men, death occurred during physical

Table 1. Activity at Death, Risk Factors, and Incidence of Plaque Rupture

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Exertion</th>
<th></th>
<th>Rest</th>
<th></th>
<th></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Physical</td>
<td>Emotional</td>
<td>Total</td>
<td>Awake</td>
<td>Asleep</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>(n = 18)</td>
<td>(n = 7)</td>
<td>(n = 25)</td>
<td>(n = 96)</td>
<td>(n = 20)</td>
<td>(n = 116)</td>
</tr>
<tr>
<td>Age, y</td>
<td>48 (8)</td>
<td>53 (11)</td>
<td>49 (9)</td>
<td>51 (10)</td>
<td>54 (13)</td>
<td>51 (11)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 (5)</td>
<td>31 (6)</td>
<td>29 (5)</td>
<td>28 (6)</td>
<td>27 (6)</td>
<td>28 (6)</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>6.67 (1.60)</td>
<td>6.41 (1.03)</td>
<td>6.59 (1.45)</td>
<td>5.97 (1.62)</td>
<td>6.02 (1.60)</td>
<td>5.97 (1.60)</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>258 (62)</td>
<td>248 (40)</td>
<td>255 (56)</td>
<td>231 (63)</td>
<td>233 (62)</td>
<td>231 (62)</td>
</tr>
<tr>
<td>TC/HDL-C ratio</td>
<td>0.03 (0.38)</td>
<td>0.85 (0.25)</td>
<td>0.95 (0.38)</td>
<td>1.06 (0.52)</td>
<td>1.14 (0.52)</td>
<td>1.08 (0.52)</td>
</tr>
<tr>
<td>Mean glycosylated hemoglobin, %</td>
<td>7.5</td>
<td>6.9</td>
<td>7.1</td>
<td>7.3</td>
<td>8.3</td>
<td>7.5</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>56</td>
<td>43</td>
<td>52</td>
<td>58</td>
<td>68</td>
<td>59</td>
</tr>
<tr>
<td>Plaque rupture, No. (%)</td>
<td>13 (72)</td>
<td>4 (24)</td>
<td>17 (68)</td>
<td>25 (26)</td>
<td>2 (11)</td>
<td>27 (23)</td>
</tr>
</tbody>
</table>

*BMI indicates body mass index; TC, total cholesterol; and HDL-C, high-density lipoprotein cholesterol. Data are presented as mean (SD) unless indicated otherwise.
activity that had been performed on a regular basis: swimming (1), exercising on a stationary cross-country ski machine (1), and running (2). Seven of the 25 exertion deaths occurred during emotional exertion: verbal presentations before an audience (2), verbal and physical altercation (3), court appearance (1), and fire-fighting (1).

**Nonexertional Deaths**

Of the 116 nonexertional deaths, 62 occurred at home, 13 while driving, 4 in hotel rooms, 26 at work, and 11 outdoors. Of the 62 men who died at home, 20 died apparently while sleeping, 5 died while in the bedroom watching television, 3 died in the kitchen, 26 died in the living room or family room, and 8 died in a workshop or the basement. The 13 automobile drivers who died suddenly were involved in automobile crashes. However, there were no cases of significant trauma at the time of the cardiac arrest, and all but 1 police report excluded any possibility of near collision with another automobile or possible “road rage” or other inciting event. In most of these cases, witnesses or passengers indicated that the driver had an apparent “heart attack.” In 1 driving case, the driver lost control of the vehicle after slumping at the wheel and sideswiped another car before landing in a ditch. The 4 men who died in hotel rooms were found alone and apparently had been involved in sedentary activities. The 26 men who died while at work were involved in nonstrenuous activities or activities that were repetitive in nature and did not involve lifting heavy objects. The 11 men who died while outdoors were performing various activities not related to exercise, heavy labor, or lifting but were walking in the yard or toward a car or a bus, eating, leaving a meeting place or entertainment area, or walking by the roadside.

**Risk Factors**

The characteristics of the study subjects are shown in Table 1. There were no significant differences between men whose deaths occurred during exertion vs those at rest in age, body mass index, or levels of TC or HDL-C. The mean (SD) TC/HDL-S ratio was 8.2 (3.0) in the exertion group vs 6.2 (2.7) in the rest group ($P = .002$). There were no significant differences in other risk factors between men with sudden death occurring during exertion vs rest. The number of presumed cigarette smokers was 69 (59%) of 116 men in the rest group and 13 (52%) of 25 men in the exertion group ($P = .50$). There were 31 men with hypertension in the rest group and 7 with hypertension in the exertion group ($P > .99$). The mean (SD) glycosylated hemoglobin reading was 7.5% (2.6%) in the rest group and 7.1% (1.5%) in the exertion group ($P = .43$).

**Medication Use**

Five (20%) of 25 men who died during exertion and 40 (34%) of 116 men who died at rest were taking 1 or more prescription medications. These included antibiotics (6 at rest, 2 exertion), allopurinol (2 at rest), angiotensin-converting enzyme inhibitors (11 at rest, 2 exertion), benzodiazepines (5 at rest), β-blockers (9 at rest), calcium channel blockers (6 at rest, 1 exertion), psychotropic drugs (10 at rest, 1 exertion), diuretics (2 at rest), diuretics (11 at rest, 2 exertion), oral hypoglycemics (10 at rest, 3 exertion), nitroglycerin (2 at rest), and simvastatin (3 at rest). Three (12%) of 25 men who died during exertion and 22 (19%) of 116 men who died at rest were taking over-the-counter medications, including aspirin (6 at rest, 2 exertion), bronchodilating inhalants (3 at rest), nonsteroidal anti-inflammatory (9 at rest, 3 exertion), acetaminophen (9 at rest, 2 exertion), and antihistamines (9 at rest).

**Cardiac Findings**

The mean (SD) heart weight in the exertion group was 518 (122) g and 496 (114) g in the rest group ($P = .42$). Histologically manifest acute infarcts were present in 15 (13%) of 116 hearts in the rest group and 0 of 25 hearts in the exertion group ($P = .07$). The culprit plaque in the 25 hearts in the exertion group was acute plaque rupture in 17, healing plaque rupture in 0, stable plaque in 6, and plaque erosion in 2. In the 116 hearts in the rest group, the culprit plaque was acute plaque rupture in 27, healing plaque rupture in 5, stable plaque in 60, and plaque erosion in 24. The proportion of acute plaque ruptures in the rest group (23%) compared with the exertion group (68%) was significantly different ($P < .001$, Fisher exact test). The proportion of abnormal cholesterol values was highest in the plaque rupture exertion group, followed by men dying at rest with plaque rupture, at exertion with stable plaque or healing plaque ruptures, and at rest with stable plaque.

In multivariate analysis, using plaque rupture as a dependent variable and including all men who died suddenly, plaque rupture was associated with exertion ($z = 3.1$, $P = .002$) and the TC/HDL-C ratio ($z = 3.1$, $P = .002$). Other risk factors, including smoking, glycosylated hemoglobin level, and hypertension, were not associated with plaque rupture in this multivariate analysis ($P > .10$).

The mean (SD) number of vulnerable plaques in the coronary arteries of each heart in the exertion group was 1.6 (1.5) and in the rest group was 0.9 (1.2) ($P = .03$). By ANOVA, the mean number of vulnerable plaques in each heart was associated with the TC/HDL-C ratio ($P = .006$), independent of age, body mass index, smoking, glycosylated hemoglobin level, and hypertension ($P > .10$). When exertion was included in the analysis, both exertion ($P = .02$) and the TC/HDL-C ratio ($P = .04$) were associated with vulnerable plaques.

In the 44 hearts with acute plaque rupture, the site of rupture (shoulder region, mid cap, circumferential) could be determined in 36 cases, and in 8 cases the destruction was too great to determine the exact site of plaque rupture. The 36 cases included 20 men who died while at rest and 16 men who died during exertion. Of these 20 rest cases, the site of plaque rupture was the shoulder region in 13 (FIGURE 1), mid cap in 6, and circumferential in 1. Of these 16 exertion cases, the site of plaque rupture was the shoulder region in 4 and mid cap in 12 (FIGURE 2). Excluding the plaque ruptures with circumferential or destroyed rupture sites, the proportion of shoulder ruptures was greater in rest cases.
(13/20 [65%]) vs exertion cases (4/16 [25%]) (P = .02). The mean (SD) percentage of luminal narrowing at the site of plaque rupture was 69% (11%) in the rest group and 70% (13%) in the exertion group (P = .75) (FIGURE 3). The mean (SD) minimum thickness of the fibrous cap in plaque ruptures associated with exertion was 5.6 (3.8) µm, vs 9.9 (6.7) µm in cases of plaque ruptures associated with deaths not related to exertion (P = .05). There was no difference in the maximal thickness of the fibrous cap (mean [SD], 27.9 [21.2] µm, exertion, vs 30.8 [11.2] µm, rest; P = .65). The mean (SD) number of intraplaque vasa vasorum at the site of plaque rupture was 40 (20) in the exertion group and 25 (17) in the rest group (P = .03). Hemorrhages into plaque (including those at a rupture site) occurred in 18 (72%) of 25 hearts from men who died during exertion and 47 (41%) of 116 hearts from men who died while at rest (P = .007).

**Table 2.** Cholesterol Values and Culprit Plaques Stratified by Exertion*

<table>
<thead>
<tr>
<th></th>
<th>Exertion (n = 25)</th>
<th>Rest (n = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plaque Rupture</td>
<td>Plaque Erosion</td>
</tr>
<tr>
<td></td>
<td>(n = 17)</td>
<td>(n = 2)</td>
</tr>
<tr>
<td>TC, mean (SD)</td>
<td>6.80 (1.03)</td>
<td>4.94 (1.73)</td>
</tr>
<tr>
<td>mg/dL</td>
<td>263 (40)</td>
<td>191 (67)</td>
</tr>
<tr>
<td>TC/HDL-C ratio,</td>
<td>8.8 (2.6)†</td>
<td>4.5 (1.1)</td>
</tr>
<tr>
<td>mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated TC, %‡</td>
<td>93</td>
<td>50</td>
</tr>
<tr>
<td>Elevated TC/HDL-C C</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>ratio, %§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated TC level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or TC/HDL-C ratio,</td>
<td></td>
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</tr>
<tr>
<td>%‰</td>
<td>100</td>
<td>50</td>
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<tr>
<td></td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>67</td>
</tr>
</tbody>
</table>

*TC indicates total cholesterol; HDL-C, high-density lipoprotein cholesterol.
†Both exertion and elevated TC/HDL-C ratio were independently associated with plaque rupture by multivariate analysis (see “Results” section).
‡Men with a TC level exceeding 5.43 mmol/L (210 mg/dL).
§Men with a TC/HDL-C ratio exceeding 5.0.

**Figure 1.** Plaque Rupture at the Shoulder Region of the Fibrous Cap

A 60-year-old man was found dead in bed. Left, The site of rupture is present at the junction of the fibrous cap with the mildly thickened intima of the relatively normal arterial wall (shoulder region) (arrows) (Movat pentachrome, original magnification ×15). Right, A higher magnification of the shoulder area showing rupture site and overlying thrombus (Movat pentachrome, original magnification ×30).

**COMMENT**

Circadian variation in sympathetic activity, vascular reactivity, and platelet aggregability, as well as physical and emotional stress, may precipitate acute coronary events.12,13 The vulnerability of the underlying plaque probably affects the likelihood of such triggers to cause acute coronary events.14 The current study demonstrates that the mechanism of sudden death in the majority of men who experienced sudden death during physical or emotional exertion is plaque rupture, compared with a minority of sudden deaths in resting men. The number of vulnerable plaques in the men whose deaths were associated with physical or emotional stress is greater than in men dying at rest from coronary disease, corroborating the view that plaque vulnerability is important in exertion-related sudden death.

The mechanism of plaque disruption likely involves both apoptotic and necrotic mechanisms of cell death.15-17 Biomechanical factors affecting plaque rupture include circumferential stress,18 which has been calculated to be greatest at the junction of the cap with the normal wall (shoulder region).19 The thinness of the fibrous cap is the physical measurement that appears to promote the greatest vulnerability to rupture.20,21 At the cellular level, the amount of free cholesterol and the degree of macrophage infiltration are associated with cap weakness and rupture,22 which may be related...
to elaboration of matrix metalloproteases degrading collagen.\textsuperscript{23-25}

We have previously demonstrated that the numbers of vulnerable plaques in men dying suddenly with severe coronary disease are increased in men who are hypercholesterolemic and that plaque rupture occurs more frequently in men who are dyslipidemic.\textsuperscript{9} The current study indicates that acute exertion is an additional independent risk factor for plaque rupture in men, presumably by disruption of a vulnerable plaque. Therefore, we suggest that acute exertion should be added as a potential risk factor for plaque rupture, along with elevated serum cholesterol level. The mechanism of plaque rupture, as triggered by exertion, was not investigated fully in the current study. However, the finding that the fibrous cap is thinner at sites of rupture in exertion-related deaths suggests that biomechanical forces play a role. Contrary to what may be expected given mechanical calculations showing that plaque weakness is greatest at the shoulder region because it is the point of greatest stress,\textsuperscript{18,19,26} our data indicate that exertion-related plaque rupture is more frequent in the center of the plaque. This finding agrees with data showing that thinness is a more important determinant of plaque instability than the circumferential site along the plaque’s cap,\textsuperscript{30} suggesting that circulating catecholamines and vasomotor fluctuations may trigger some cases of plaque rupture.

Microfill injections of coronary arteries demonstrate a positive correlation between plaque size and neocapillaries in and around the plaque.\textsuperscript{27,28} The presence of increased numbers of vasa vasorum in plaques that rupture during exertion also points to a possible pathway of plaque rupture. Rupture of vasa vasorum may increase intraplaque mass and pressure, weakening the fibrous cap and leading to rupture and luminal thrombus.\textsuperscript{28} Alternatively, increased vascularity within the plaque may reflect elaboration of growth factors or angiogenetic factors that may be expressed in parallel with metalloproteases. Data on increased plaque hemorrhages in the exertion-related deaths in this study support a direct role of vasa vasorum rupture in the pathogenesis of plaque rupture.

The current study has several limitations. The study population was limited to autopsy cases of sudden coronary death, and the precise state of physical conditioning was not known in all cases. However, the association between acute exertion and plaque rupture suggests that a proportion of sudden deaths in middle-aged men may be decreased if the potential danger of acute exertion in hypercholesterolemic men is avoided. To this end, it would seem prudent to incorporate serum cholesterol reduction as an integral component of an exercise program in those men with elevated serum cholesterol.

**Figure 2. Plaque Rupture at the Center of the Fibrous Cap**

A 38-year-old man collapsed suddenly during an altercation. Left, The rupture site is toward the center of the fibrous cap (arrows) (Movat pentachrome, original magnification ×15). Right, A higher magnification demonstrating rupture site with acute thrombus. Note areas of thinning of fibrous cap (arrowheads) (Movat pentachrome, original magnification ×45).

**Figure 3. Effect of Exertion on Plaque Morphology**

Plaque rupture with exertion (left) is characterized by a relatively thin fibrous cap, relatively numerous vasa vasorum, and rupture in the mid cap. In comparison, a plaque rupture at rest is depicted (right). Th indicates thrombus; HP, hemorrhage into plaque; and L, lumen.
PLAQUE RUPTURES AND SUDDEN DEATH

In conclusion, in men with severe coronary artery disease who die suddenly, acute exertion appears to be an independent risk factor for plaque rupture, presumably by disruption of a vulnerable plaque.

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REFERENCES