Sudden Death in the Young
Is Acute Coronary Thrombosis the Major Precipitating Factor?

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Background Atherosclerotic coronary artery disease, complicated by acute thrombosis, is the usual cause of sudden death in adults. This study addresses the pathology of coronary arteries in sudden death in the young (<35 years old).

Methods and Results Among 200 consecutive cases of sudden death in youth in the Veneto region of Italy, 37 (33 men and 4 women, age 18 to 35 years; mean, 29.4 years) showed obstructive atherosclerotic coronary artery disease in the absence of other cardiac pathologic conditions and causes of death. No patient had previous angina pectoris or myocardial infarction. Cardiac arrest occurred at rest in 30 subjects and was related to effort in 7. A histological study was carried out on the obstructive coronary plaques. Degree of lumen stenosis and extension of lipid core and intimal fibrocellular hyperplasia facing the lumen were calculated morphometrically. Immunohistochemistry and electron microscopy were used to further characterize the plaque cell population. Single-vessel disease was found in 33 patients and triple-vessel disease in 4, with an overall total of 45 obstructive plaques, 34 of which were located in the proximal left anterior descending coronary artery. At histological study, only 10 plaques from 10 patients showed acute thrombosis (occlusive in 5 and subocclusive in 5); the remaining 35 were uncomplicated. Thirty-one plaques were fibrous in nature, while the other 14 were atheromatous. Compared with the atheromatous lesions, the fibrous plaques were rarely complicated by thrombosis (3% versus 64%; P < .001) and distinctly exhibited a fairly well-preserved tunica media (81% versus 21%; P < .001) as well as a stratum of neointimal fibrocellular hyperplasia (68% versus 7%; P < .001), which on immunohistochemistry and electron microscopy appeared to be proliferating smooth muscle cells.

Conclusions In our study population, sudden death was precipitated by acute coronary thrombosis in only 27% of patients with obstructive coronary atherosclerotic plaque. Most of the young victims of sudden death with obstructive coronary atherosclerosis showed single-vessel disease that affected the left anterior descending coronary artery and was due to fibrous plaques with neointimal smooth muscle cell hyperplasia and a preserved tunica media in the absence of acute thrombosis. (Circulation. 1994;90:2315-2323.)

Key Words • atherosclerosis • coronary disease • myocardium • ischemia • death, sudden

Several pathological studies have demonstrated that coronary atherosclerotic disease complicated by thrombosis is the most common morphological substrate of acute coronary events and sudden death in adults. Only a few reports have addressed the pathological lesions of coronary atherosclerosis and the pathophysiological mechanisms of fatal myocardial ischemia in young people. The aim of the present study was to establish the frequency, extent, type, and possible pathophysiology of sudden death in the young due to coronary atherosclerosis.

Methods In the time interval from January 1979 to June 1993, we collected 200 consecutive cases of sudden death in young people within the target project “Juvenile Sudden Death” of the Veneto region, Italy. Sudden death was defined as unexpected death as a result of natural causes within 1 hour of initial symptoms in persons ≤35 years of age; cases of sudden infant death syndrome were excluded from the study.

The Veneto region of northeastern Italy covers an area of 18,368 km² and has a population of 4,380,797 inhabitants, according to the 1991 census; all residents are white, and the population is ethnically homogeneous.

After extracardiac causes of death (15 cerebral and 10 respiratory) were excluded, sudden death was related to the cardiovascular system in 163 cases, whereas it remained unexplained in 12 (6%).

The hearts were fixed in formalin and immediately forwarded to the Institute of Pathological Anatomy of the University of Padua for prompt morphological study. Macroscopic examination included measurement of heart weight and wall thickness, inspection of the coronary arteries and valves, and identification of any myocardial infarcts, scars, or dilatations. The origin and course of the coronary arteries were examined, and the patency of the four major epicardial coronary trunks was analyzed by taking transmural sections at 3-mm intervals. The coronary arterial segments and several transmural blocks of ordinary myocardium from the free walls and septum were processed for histological examination; when deemed necessary, the histology of the conduction system was also studied according to a previously described method.

Table 1 reports the underlying substrates in the 163 cases of sudden death related to the cardiovascular system. Thirty-seven (22.7%) were found to have obstructive atherosclerotic coronary artery disease, ie, at least one major coronary artery with cross-sectional narrowing ≥70%, in the absence of other cardiac pathologic conditions and causes of death.

The obstructed coronary artery segment of these hearts underwent a battery of histological examinations, in parallel with the corresponding tissue segment in 20 hearts from age- and sex-matched subjects who died suddenly of drug abuse or extracardiac causes (“controls”). Serial sections 6 μm thick...
Table 1. Study Project “Juvenile Sudden Death,” Veneto Region, Italy (1979-1993)*

<table>
<thead>
<tr>
<th>Cause</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive coronary atherosclerosis</td>
<td>37</td>
</tr>
<tr>
<td>Right ventricular cardiomyopathy</td>
<td>20</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>17</td>
</tr>
<tr>
<td>Conduction system abnormalities</td>
<td>17</td>
</tr>
<tr>
<td>Congenital coronary anomalies</td>
<td>14</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>12</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>9</td>
</tr>
<tr>
<td>Aortic rupture</td>
<td>9</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>8</td>
</tr>
<tr>
<td>Nonatherosclerotic acquired coronary artery</td>
<td>6</td>
</tr>
<tr>
<td>Postoperative congenital heart disease</td>
<td>5</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary thromboembolism</td>
<td>3</td>
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<tr>
<td>Others</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>163</td>
</tr>
</tbody>
</table>

*Sudden death in young people (≤35 years) related to the cardiovascular system.

were cut and stained with the hematoxylin-eosin, Weigert-van Gieson, and azan techniques. Parallel sections 4 to 5 μm thick were stained with a panel of antibodies using avidin-biotin-peroxidase complex immunohistochemical methods for cell population characterization. Selected coronary plaques were also investigated by transmission electron microscopy.

Plaques were evaluated in terms of site, circumferential distribution (concentric versus eccentric), severity of stenosis, composition (atheromatous versus fibrous), complications (occlusive or nonocclusive mural thrombus), intimal fibrocellular hyperplasia, inflammation, and status of the tunica media.

A plaque was defined as concentric when there was no arch of normal artery wall and eccentric in the presence of an associated arch of normal artery wall. The tunica media underlying the plaque was considered preserved when its thickness was ≥80% of the thickness of the tunica media from the uninvolved wall or from an adjacent, atherosclerosis-free coronary segment. Atheromatous plaques had a central extra-cellular lipid pool area (lipid core) that was separated from the lumen by a cap of fibrous tissue. Fibrous plaques consisted of connective fibrous tissue without a lipid core.

Coronary plaques were defined as complicated when they exhibited acute lesions, such as thrombus and/or hemorrhage. Thrombus was defined as an occlusive or nonocclusive intraluminal aggregate of fibrous strands entrapping platelets, red cells, and leukocytes that was superimposed on the luminal surface or deep into the plaque.

Fibrocellular hyperplasia was defined as a layer of abundant intimal cellularity overlying the plaque and consisting of smooth muscle cells within a loose connective tissue matrix.

Morphometric analysis of the histological sections of obstructed coronary segments was performed with a Kontron Ibas II image analyzer. The degree of stenosis was calculated by comparison of the residual arterial lumen to the area within the internal elastic lamina and was expressed as the percent of cross-sectional narrowing. The extents of lipid core and intimal fibrocellular hyperplasia were measured as the proportion of the total plaque cross-sectional area occupied by extracellular lipid alone and the cellularity overlying the plaque, respectively.

χ² analysis was used to assess different variables. A value of P≤.05 was considered statistically significant.

Results

The 37 patients with obstructive atherosclerotic coronary artery disease consisted of 33 men and 4 women (mean, 29.4 years; in every case, sudden death was the first clinical manifestation of coronary artery disease. No patient had a history of angina pectoris or previous myocardial infarction. ECG tracings were available in 24 cases and did not exhibit ischemic changes or evidence of ventricular preexcitation or QT interval prolongation.

At the time of the fatal complication, 30 patients were engaged in a sedentary activity, while the other 7 collapsed during (3 patients) or immediately after (4 patients) severe exertion.

Risk factors for coronary artery disease were ascertained in 10 subjects; family history in 1, smoking in 4, smoking and hypertension in 1, smoking and hypercholesterolemia in 1, diabetes in 1, and obesity in 2. In addition, one subject had undergone mediastinal irradiation for Hodgkin’s disease.

Gross examination ruled out any regional, acute, or healed myocardial infarction. In 33 subjects, only one major coronary trunk was obstructed (single-vessel disease); this was the proximal left anterior descending coronary artery in 30, the left circumflex in 1, the right coronary artery in 1, and the left main coronary artery in 1. The remaining 4 patients showed three-vessel disease. Therefore, 45 obstructive plaques overall were examined histologically. The severity of stenosis of the obstructive plaques varied from 70% to 95% (mean, 79%). Plaques appeared eccentric in 36 obstructive segments and concentric in 9. Fourteen plaques (31%) were atheromatous, with a large lipid core ranging from 28.22% to 47.97% (mean 40.26±3.68%) of the total plaque cross-sectional area; 31 (69%) were fibrous in nature, without a lipid core (Fig 1).

Plaques complicated by thrombosis were found in 10 of 37 patients (27%) and accounted for 22% (10 of 45) of all the obstructive coronary plaques. Acute thrombosis was occlusive in 5 subjects and nonocclusive in 5, and it occurred at the obstructive plaques in each case. The other 27 patients had a total of 35 obstructive, uncomplicated coronary plaques.

A stratum of fibrocellular hyperplasia overlaid 22 obstructive plaques, with an extent ranging from 8.13% to 46.52% (mean 25.60±12.21%) of the total plaque cross-sectional area. At immunohistochemistry (smooth muscle actin antibody) (Fig 2) and electron microscopy (Fig 3), the intimal fibrocellular hyperplasia appeared to be a smooth muscle cell proliferation.

Atheromatous Plaques

Nine of 14 atheromatous plaques (64%) were complicated by acute thrombosis (Fig 4) and showed a lipid core that covered 35.92% of the total plaque cross-sectional area. Ten of 14 plaques (71%) were eccentric, and 11 of 14 (79%) showed some degree of atrophy of the tunica media beneath the plaque. Only one atheromatous plaque, which was complicated by mural thrombosis, showed a fibrous cap superimposed by a stratum of fibrocellular hyperplasia as well as a lymphocytic infiltrate.
**Fibrous Plaques**

Thirty of the 31 fibrous plaques (97%) were not complicated by thrombosis. Fibrous plaques were usually eccentric (26 of 31, 84%) and associated with a preserved tunica media along the entire circumference of the vessel wall (25 of 31, 81%). Evidence of fibrocellular hyperplasia was found in 21 of 31 fibrous plaques (65%), all from patients with single-vessel disease. Lymphocytic inflammatory infiltrates were seen in the adventitial layer in 3 uncomplicated fibrous plaques.
Atheromatous Versus Fibrous Plaques

As shown in Table 2, acute thrombosis occurred significantly more often on atheromatous than fibrous plaques \( (P<.001) \). Moreover, fibrous plaques differed significantly from atheromatous plaques in terms of fibrocellular hyperplasia and preservation of the tunica media \( (P<.001) \). There was no significant difference concerning eccentric shape or inflammatory infiltrate occurrence.

Myocardium

Histological examination of the ventricular myocardium supplied by the obstructed coronary artery revealed signs of hyperacute ischemic damage in each case, consisting of contraction band necrosis (Fig 5) and/or wavy fibers. These ischemic injuries were rarely observed in the adjacent perfusion areas distal to the nonobstructed coronary arteries.

Coronary Artery Morphology in Controls

None of the control hearts exhibited obstructive coronary atherosclerosis. A concentric diffuse intimal thickening was present in all, with an intimal/medial ratio ranging from 0.2 to 2.0. Raised lesions, in the form of fibrous plaques, were seen in 6 subjects and were all located in the proximal tract of the left anterior descending coronary artery; 3 were concentric and 3 eccentric in shape, and they narrowed the lumen from 10% to 50%. A stratum of fibrocellular intimal hyperplasia like that observed in the sudden death cases was not seen in any of these plaques. The tunica media was always regularly preserved, and inflammatory infiltrates were not seen in the adventitia.

Discussion

Coronary artery disease is the most common cause of sudden death in middle-aged and elderly people,\(^1-10,15-17\) In younger subjects, other causes of sudden death have been reported, such as hypertrophic cardiomyopathy,\(^18\) mitral valve prolapse,\(^19\) arrhythmogenic right ventricular cardiomyopathy,\(^20\) and congenital coronary anomalies.\(^21,22\) The pathological findings in our large series indicate, however, that coronary atherosclerosis is an important substrate of sudden cardiac death even in youth \( (\leq 35 \text{ years}) \), since it accounted for nearly one fourth of all the fatal events.

In this study, coronary artery disease exhibited distinctive features in terms of extent, site, and morphology of the obstructive atherosclerotic plaques, as well as the incidence of thrombosis. Moreover, a combination of clinical and pathological observations suggest a peculiar pathogenesis of fatal myocardial ischemia.
A mostly fibrous plaque was located at the proximal anterior descending coronary artery in a 35-year-old man who died suddenly. A, A layer of intimal cell hyperplasia is visible on the luminal side. Azan stain, original magnification ×60. B, Transmission electron microscopy shows two smooth muscle cells, the one on the left with the feature of a foam cell and the one on the right very rich in myofilaments. The cells are enmeshed in an interstitium rich with collagen fibers.

**Extent and Site of Coronary Artery Disease**

In line with previous angiographic and pathological studies in young people, we found a high incidence of single-vessel obstructive coronary artery disease, mostly affecting the proximal left anterior descending coronary artery. This finding probably reflects the "young age" of the coronary artery disease, which only later in life will progress and become a generalized obstructive process; in this context, previous necropsy studies in adult and elderly victims of sudden coronary death showed a high frequency of multivessel coronary artery disease.\(^1\)\(^-\)\(^4\)\(^,\)\(^7\)\(^,\)\(^10\)\(^,\)\(^25\)

A modification in flow dynamics may induce mechanical vessel wall injury and explain the propensity for obstructive plaque localization at the proximal tract of the left anterior descending coronary artery, just below the left main coronary artery bifurcation, where flow velocity is critically reduced and wall shear stress is increased.\(^26\)\(^,\)\(^27\) It is noteworthy that in a recent study on coronary atherosclerosis in a northern Italian population ranging in age from 1 to 20 years, we found that the proximal left anterior descending coronary artery was the segment most prone to the formation of fibrocellular intimal thickenings and early nonobstructive coronary plaques.\(^28\) This observation was recently confirmed by
**FIG 4.** Fresh occlusive thrombosis of the proximal anterior descending coronary artery superimposed by an eccentric atheromatous plaque with a large lipid core in a 33-year-old man who died suddenly. Azan stain, original magnification ×25.

an autopsy study from Kentucky in trauma victims <35 years old.29

**Morphology of Coronary Plaques and Occurrence of Thrombosis**

In most of the young victims of sudden coronary death, we found that the obstructive plaques were fibrous in nature, with a stratum of smooth muscle cell hyperplasia occupying up to 46% of the total plaque cross-sectional area. Although some workers postulated the nonatherosclerotic nature of these proliferative intimal lesions, there is growing evidence that fibrocellular plaques represent an early stage of mature atheromatous plaques.30-32 Only a few other investigations have addressed the composition of atherosclerotic plaques in juvenile fatal coronary artery disease.1,12,24 Our findings are in agreement with the recent study of Dollar et al,12 which showed that a combination of cellular and dense fibrous tissue was the major component of significantly narrowed plaques in young women (<40 years) with fatal coronary artery disease. These workers suggested that the large amount of cellular fibrous tissue characterized "young atherosclerotic plaques that developed rapidly". Our present finding of a stratum of intimal smooth muscle cell hyperplasia overlying the fibrous plaque is consistent with the morphological pattern of actively and rapidly progressing atherosclerosis in response to vessel wall injury such as that occurring in patients undergoing heart transplantation, percutaneous coronary angioplasty, coronary vein graft bypass, and chest irradiation (syndromes of "accelerated atherosclerosis").31 Histopathological studies of coronary artery disease in human cardiac allografts demonstrated that accelerated coronary artery disease begins as an intimal thickening due to smooth muscle cell proliferation and fibrosis and with

<p>| Table 2. Comparison Between Atheromatous and Fibrous Plaques According to Occurrence of Thrombosis, Fibrocellular Intimal Hyperplasia, and Other Morphological Features |
|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Atheromatous Plaques, N (%)</th>
<th>Fibrous Plaques, N (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no.</td>
<td>14</td>
<td>31</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>9 (64)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Eccentric shape</td>
<td>10 (71)</td>
<td>26 (84)</td>
</tr>
<tr>
<td>Fibrocellular intimal hyperplasia</td>
<td>1 (7)</td>
<td>21 (68)</td>
</tr>
<tr>
<td>Preserved tunica media</td>
<td>3 (21)</td>
<td>25 (81)</td>
</tr>
<tr>
<td>Inflammatory infiltrates</td>
<td>1 (7)</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

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time progresses to mature atheromatous lesions by accumulating intracellular and extracellular lipid.32

Acute thrombosis was found in only 22% of our obstructive plaques, a much lower frequency than that observed in adult series. In the study by Davies et al.10 73.3% of the plaques from adult victims of sudden coronary death were complicated by thrombosis. This discrepancy may be explained by the different populations examined and the peculiar composition of the obstructive coronary plaques. Our patients constituted a homogeneous group of young victims of sudden coronary death with no clinical history or necropsy evidence of acute or previous myocardial infarction. Kragel et al.33 recently observed that the frequency of acute coronary lesions was significantly lower in patients with unstable angina or sudden death not complicated by acute myocardial infarction than in patients with myocardial infarction; moreover, severely narrowed plaques in the acute myocardial infarction group contained significantly more pultaceous debris (atheromatous plaques) and less cellular fibrous tissue. We found a statistically significant difference in thrombosis occurrence between atheromatous and fibrous plaques (64% versus 3%, P<.001), and these results are in keeping with the well-established fact that coronary thrombosis is precipitated by the fissuring of lipid-rich atherosclerotic plaques.34-36 The mean extent of the lipid core in the atheromatous coronary lesions complicated by thrombosis was about 40% of the total plaque area, a figure very similar to that recently reported by Davies et al.37 in human aortic plaques undergoing ulceration and thrombosis. The low frequency of coronary thrombosis in our series might be related to the high prevalence of poorly thrombogenic fibrous plaques.

Limitations of the Study

The following limitations of the present study should be addressed. Our morphometric measurements of stenosis were based on formalin-fixed coronary arteries, which were not perfused at postmortem. Since coronary arteries were not fixed in distension and therefore collapsed, the degree of stenosis might have been overstimated. Collapse, in particular, is a problem in young individuals with pliable elastic vessels. Moreover, one should be aware that the postmortem observation of an obstructive plaque does not necessarily imply a flow-limiting coronary lesion in vivo. The term "obstructive" plaque, used here to indicate a cross-sectional area narrowing ≥70%, should be considered simply a histologically high-degree stenosis and not necessarily a "critical" lesion.

Hyperacute ischemic myocardial damage (contraction band necrosis and wavy fibers) is not a specific marker of acute myocardial ischemia, since it may evolve during cardiopulmonary resuscitation and is frequently also present in noncardiac sudden death. However, the observation of abundant contraction band necrosis in the myocardium supplied by the obstructive coronary segment compared with its negligible presence in the adjacent perfusion areas distal to the nonobstructive arteries constitutes further evidence that an ischemic mechanism was involved.

A proper control group should have included obstructive coronary plaques of similar size from young persons dying of noncoronary causes, to see whether fibrocellular hyperplasia is a distinctive plaque feature of sudden ischemic death victims. Among the 20 control cases in the present study, only 5 had coronary atherosclerotic...
plaques, and none of these were obstructive or had evidence of superimposed fibrocellular hyperplasia.

One may wonder whether some of our patients without coronary thrombotic occlusion may have died with, rather than of, coronary atherosclerosis. According to Davis et al,10 subjects who died suddenly and who have demonstrable high-grade coronary artery stenosis and no other cause of death revealed by a detailed autopsy can reasonably be regarded as having died of ischemic heart disease.

Possible Mechanisms of Fatal Myocardial Ischemia

In the absence of a coronary thrombosis to account for a "mechanical" coronary occlusion, the pathophysiology explaining the fatal ischemic attack and sudden death is intriguing. It is noteworthy that most of our patients died suddenly, during a sedentary activity, and the fatal event apparently was not preceded by any cause that might have increased the basal metabolic demands of the myocardium. In addition, none had a clinical history or necropsy evidence of previous myocardial infarction, which thus reasonably excludes a primary fatal arrhythmia arising within a scar, a frequent finding in sudden coronary death in adults.10,38

The absence of angina pectoris and ECG-documented ischemic changes in the history of the patients suggests that the obstructive coronary plaques observed at histology might not have been flow-limiting in vivo, and thus the intervention of other factors might have been required to induce the acute myocardial ischemia. Coronary vasospasm is a potential trigger of transient myocardial ischemia,39,40 which, in turn, may precipitate fatal ventricular arrhythmias.41 Smooth muscle cell hyperplasia was recently described as a distinctive feature in coronary plaques retrieved by directional atherectomy from patients with unstable angina and was advanced as an alternative mechanism to thrombus formation in precipitating myocardial ischemia at rest.42 In addition, another study on atherectomy coronary specimens disclosed that "unstable" lesions have a higher degree of cellularity than "stable" lesions, thus suggesting that a proliferative phase characterizes a coronary plaque with clinical evidence of recent instability.43 In two previously described patients with variant angina who died suddenly of ECG-documented ischemia-induced ventricular fibrillation, we found single-vessel disease in the left anterior descending coronary artery that consisted of a fibrous plaque not complicated by thrombosis, a fairly well-preserved tunica media, and a distinct stratum of intimal smooth muscle cell hyperplasia.44 Similarly, in the present study, most of the fibrous plaques exhibited a normal tunica media and a layer of intimal fibrocellular hyperplasia in the absence of thrombosis. We suggest that these two features may represent the potential substrate accounting for coronary hypervasoreactivity. The normally thick tunica media is anatomic prerequisite for preserved vaso-motor reactivity in the atherosclerotic coronary artery.45 Constrictive coronary hyperreactivity accompanies both experimental46-48 and clinical49-53 "accelerated atherosclerosis", which shows many similarities to the smooth muscle cell hyperplasia overlying the fibrous plaques observed in our study. Crucial biological events, such as the release of vasoactive and mitogen factors, may interact and may explain both accelerated atherogenesis and abnormal vasomotion in precipitating sudden death in the young.

Acknowledgments

This study was supported by the Juvenile Sudden Death Research Project, Veneto Region, Venice, and by the National Council for Research, Target Project FAT.M.A., Rome, Italy.

References


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_Circulation_. 1994;90:2315-2323
doi: 10.1161/01.CIR.90.5.2315

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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