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Relationship of Ischemic Heart Disease to Sudden Death

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ABSTRACT: A clinicopathological synthesis is presented of the relationship of ischemic heart disease to sudden cardiac death. The immediate pathophysiological process responsible for sudden cardiac death is a lethal arrhythmia, usually ventricular fibrillation. Although significant coronary atherosclerosis is present in most cases of naturally occurring sudden death, available evidence indicates that several mechanisms can be operative in the pathogenesis of the fatal event. These are (1) acute myocardial infarction in a minority of cases; (2) myocardial ischemia, without infarction, which is initiated either by (a) an exertion-induced increase in myocardial oxygen demand or (b) an acute coronary event often involving plaque degeneration and platelet aggregation; and (3) a primary arrhythmia, usually resulting from altered electrical conduction in the setting of a previous myocardial infarction.

KEYWORDS: pathology and biology, symposium, cardiovascular system, ischemic heart disease, sudden death

Determination of the mechanism of sudden death is a major issue in forensic medicine. Through his experience, logical analysis, and articulate presentations, Dr. Charles S. Petty has provided considerable insight into the various ways that sudden death can result from natural disease, violent injury, and the interaction of the two processes. We salute him as an inspirational teacher and esteemed colleague [*1,2*].

Sudden death can result from a number of different disease processes, including entities as diverse as massive pulmonary thromboembolism and hypertrophic cardiomyopathy [*3*]. Nevertheless, it is clear that a large majority of the cases of naturally occurring sudden death have coronary atherosclerosis as the underlying pathology and, therefore, that ischemic heart disease is the leading cause of sudden death [*4,5*]. However, there has been considerable uncertainty and controversy regarding the pathophysiological mechanisms responsible for sudden cardiac death. Ischemic heart disease has diverse clinical and pathological manifestations [*6–8*]. The purpose of this presentation is to synthesize available information regarding the pathobiology of ischemic heart disease with particular emphasis on potential mechanisms of sudden cardiac death.

Clinical Studies

Sudden cardiac death is generally recognized as death occurring within seconds, minutues, or hours after the onset of an acute event of cardiac origin and, typically, prior

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to hospitalization [*4,5*]. Clinical studies, including community-based programs, have clearly established that ventricular fibrillation is the usual pathophysiological mechanism responsible for the cardiac arrest [*9–15*]. These studies have also shown that most patients resuscitated from sudden cardiac death do not develop diagnostic evidence of myocardial infarction [*9–15*].

Autopsy Studies

Autopsy studies have provided important information regarding sudden cardiac death [*16–20*]. The majority of cases exhibit significant coronary atherosclerosis, defined as luminal narrowing of at least one coronary artery by at least 75% of the luminal area (50% of luminal diameter) (Table 1). Significant numbers of cases also exhibit scars indicative of previous myocardial infarction. Only a minority show evidence of an acute myocardial infarction. However, multifocal contraction band lesions are frequent. These lesions are indicative of acute myocardial injury, which can have a variety of causes, including excess catecholamine stimulation and ischemia. The incidence of acute thrombosis varies but involves a minority of cases in most series. The relatively high incidence reported by Davies and Thomas [*19*] may be related to the patient population studied or to the techniques used to examine the coronary arteries.

TABLE 1—*Cardiac pathological findings in three series of subjects with sudden cardiac death.*

	Reichenbach et al. [*16,17*]	Baroldi et al. [*18*]	Davies and Thomas [*19*]
Number of patients[a]	87	208	100
Coronary disease[b]			
Mild to moderate	7 (8%)	28 (13%)	0
Severe	80 (92%)	180 (87%)	100 (100%)
Old subtotal or complete occlusion of one or more vessels	51 (59%)	75 (34%)	ND
Acute thrombus	9 (10%)	54 (25%)[c]	74 (74%)[d]
Myocardial infarcts			
No old or recent infarct or fibrosis	29 (33%)	30 (15%)	ND
Healing or old infarct or fibrosis	58 (67%)	175 (85%)	ND
Recent infarct	4 (5%)	35 (17%)	ND
Multifocal muscle cell injury with contraction bands	44/50 (88%)	178 (86%)	ND

[a]Most subjects had a witnessed death within minutes to 2 h of sudden collapse.

[b]Severe atherosclerosis involving one or more coronary arteries is based on evidence of a reduction in the luminal area of >75% (Reichenbach et al.) or the luminal diameter of >50% (Baroldi et al.). Old subtotal or complete occlusion is based on evidence of a reduction in the luminal area or diameter of >90%.

[c]Baroldi et al. found 32 cases (15%) with acute occlusive thrombi and an additional 22 (10%) with acute, nonocclusive, mural thrombi.

[d]Davies and Thomas found acute lesions in 95% of the 100 cases; these consisted of some combination of plaque fissures (93 cases), major occlusive intraluminal thrombi (44 cases), minor (mural) intraluminal thrombi (30 cases), and intraintimal thrombi (21 cases).

Clinicopathological Correlation

The available clinical and pathological data indicate that several mechanisms may be operative in the pathogenesis of sudden cardiac death (Fig. 1). These include (1) acute myocardial infarction, (2) myocardial ischemia without infarction, and (3) a primary arrhythmia (Table 2) [*3–5,9–20*].

It is now clear that a lethal arrhythmia leading to sudden cardiac death can occur in the absence of acute myocardial ischemia [*4,13,14*]. This phenomenon is referred to as a primary arrhythmia. Electrophysiological studies have shown that myocardial scarring can be associated with altered electrical conduction, which can predispose the subject to ventricular fibrillation without a new episode of myocardial ischemia. This mechanism may be operative in subjects dying suddenly with evidence of a previous myocardial infarction. Primary arrhythmias also can occur in the absence of coronary atherosclerosis. The best recognized examples of this phenomenon are the prolonged Q-T interval syndromes. In other cases, anatomically detectable alterations of the conduction system may be involved.

Many cases of sudden cardiac death are initiated by acute myocardial ischemia [*3–5, 9–20*]. A minority, approximately 20 to 30%, of cases of sudden cardiac death can be attributed to acute myocardial infarction, and many of these cases show an acute coronary thrombotic occlusion as a causative factor. Myocardial ischemia also can be induced by increased myocardial oxygen demand in the presence of coronary atherosclerosis. This mechanism appears operative in cases of sudden death associated with jogging and other forms of exercise. Uncertainty has existed regarding the mechanism of the many cases

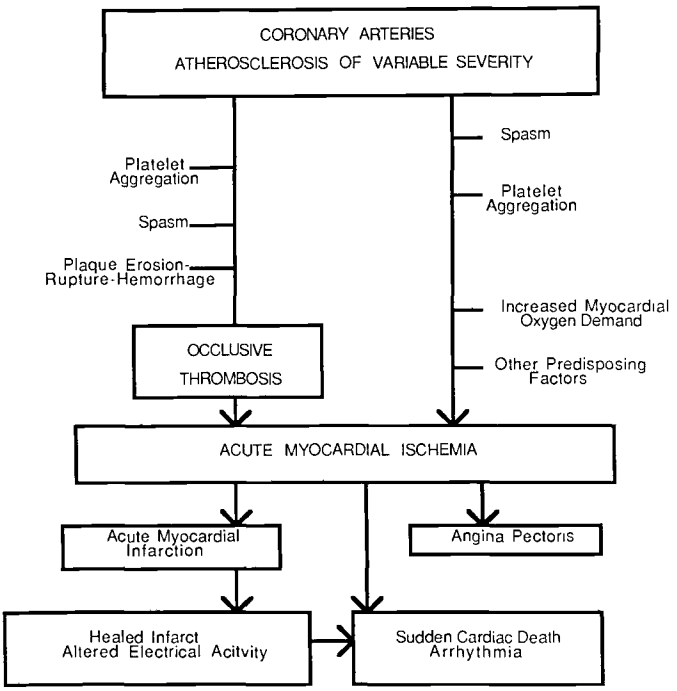

FIG. 1—*Mechanisms operative in the pathogenesis of ischemic heart disease. (Reproduced in modified form with permission from Buja, L. M., et al.,* Archives of Pathology and Laboratory Medicine, *Vol. 105, 1981, pp. 221–226. Copyright 1981, American Medical Association.)*

TABLE 2—*Mechanisms of sudden cardiac death.*[a]

	Myocardial Infarction	Myocardial Ischemia	Primary Rhythm Disturbance
Percentage of sudden cardiac deaths	20 to 30	uncertain	uncertain
Autopsy findings	coronary artery disease, frequently with acute coronary artery occlusion	coronary artery disease, with variable incidence of acute coronary artery injury and thrombi	coronary artery disease; hypertrophic cardiomyopathy; apparently normal heart in a small percentage of cases
Duration of warning symptoms prior to collapse	minutes to hours	minutes	seconds or no warning at all
Long-term prognosis after successful resuscitation	relatively good	relatively good	poor

[a]Adapted from Eisenberg, M. S., et al., "Sudden Cardiac Death," *Scientific American*, Vol. 254, No. 5, May, 1986, pp. 37–43. Used with permission of Scientific American, Inc.

of sudden cardiac death with coronary atherosclerosis in the absence of an acute myocardial infarction or exertion-induced ischemia. Some of these cases may involve a primary arrhythmia. However, many such cases probably involve an acute episode of myocardial ischemia. Increasing evidence points to subtle alterations of the coronary arteries as the mechanism of ischemia-induced ventricular fibrillation, whether or not an acute myocardial infarction occurs.

Role of Acute Coronary Alterations

The development of secondary changes (complications) in coronary atherosclerotic lesions is directly linked to the development of clinical manifestations of acute ischemic heart disease, including unstable angina pectoris, acute myocardial infarction, and sudden cardiac death (Figs. 1–4) [*6–8,21–30*]. Considerable evidence indicates that the critical factors in the initiation of acute coronary lesions are (*a*) an episode of endothelial injury, usually of the denuding type and (*b*) platelet aggregation, which is triggered by the endothelial injury. The consequences of the platelet aggregation are both mechanical, as a result of an acute further reduction in luminal size, and functional, related to the sudden narrowing of the vessel (spasm) due to release of vasoactive products from the platelets. Potential outcomes of this process range from spontaneous resolution to occlusive thrombosis. Other cases of acute myocardial ischemia may be initiated by coronary vasospasm induced by poorly defined mechanisms other than platelet aggregation [*2,30*].

Most coronary thrombi are associated with significant, anatomically demonstrable alterations of the vessel wall (Fig. 3). These alterations are characterized by fissuring, ulceration, or rupture of the luminal surface of the plaque and are often associated with major hemorrhage into the plaque. Following disruption of the plaque surface, thrombi may form within the intima as well as in the lumen. The mechanisms responsible for

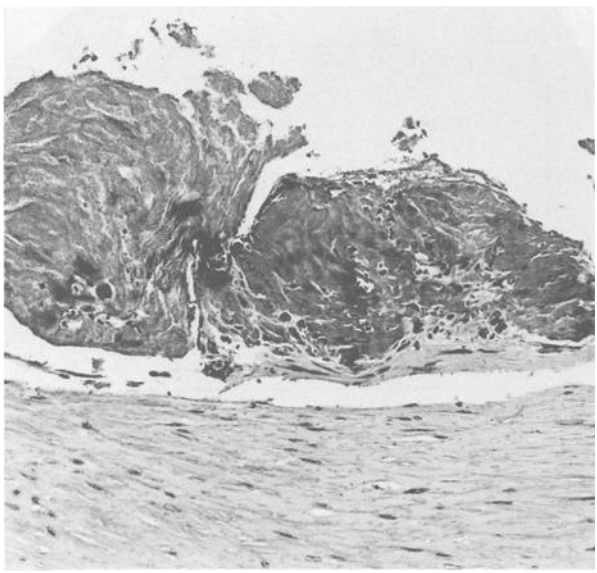

FIG. 2—*New and organizing platelet thrombi on the intimal surface of a coronary plaque from a patient with a history of unstable angina pectoris who died suddenly (hematoxylin and eosin stain, ×143). (Reproduced with permission from Willerson, J. T., Hillis, L. D., and Buja, L. M.,* Ischemic Heart Disease: Clinical and Pathophysiological Aspects, *Raven Press, New York, 1982.)*

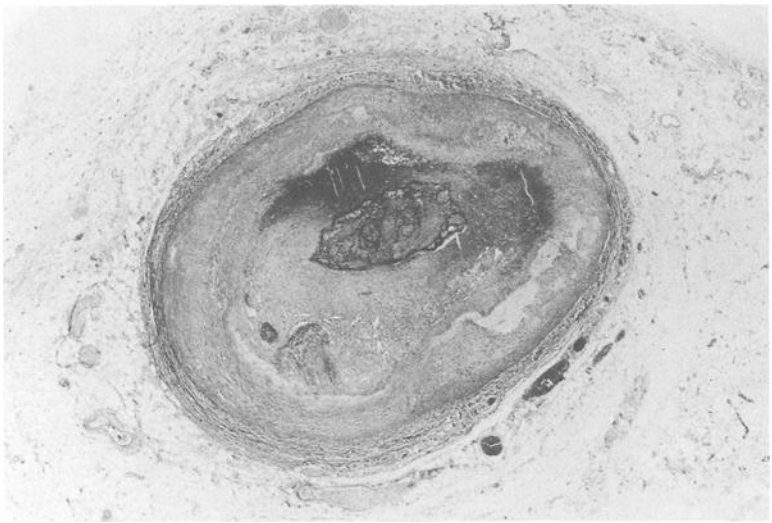

FIG. 3—*Coronary luminal thrombosis associated with plaque erosion and hemorrhage (hematoxylin and eosin stain, ×10). (Reproduced with permission from Willerson, J. T., Hillis, L. D., and Buja, L. M.,* Ischemic Heart Disease: Clinical and Pathophysiological Aspects, *Raven Press, New York, 1982.)*

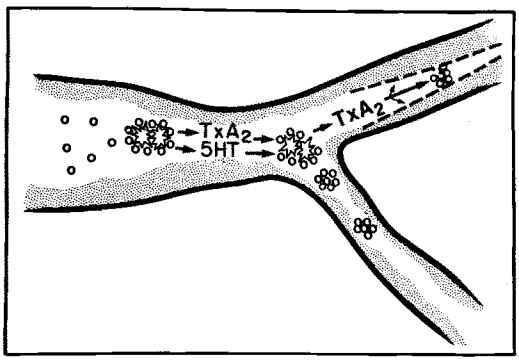

FIG. 4—*Schematic diagram indicating the possible mechanisms by which endothelial injury promotes platelet aggregation and decreased coronary blood flow. Aggregating platelets* (stars) *release thromboxane A_2 (Tx A_2) and serotonin (5HT) at sites of coronary artery stenosis and endothelial injury. These mediators cause further platelet aggregation at that site and, downstream, dynamic coronary vasoconstriction, and partial or total coronary artery thrombosis. Absence or reductions in endothelially derived relaxing factor (EDRF), prostacyclin (PGI_2), and tissue plasminogen-activating factor (tPA) at vascular sites with endothelial injury probably contribute to the development of vasoconstriction and thrombosis. Activated platelets also release platelet-derived growth factor (PDGF), which stimulates smooth muscle proliferation. This is a likely mechanism of intimal proliferation following vessel wall injury. (Reproduced with permission from the American College of Cardiology and from Willerson, J. T., et al.,* Journal of the American College of Cardiology, *Vol. 8, 1986, pp. 245–250.)*

these changes require further study and elucidation. Hemodynamic trauma probably plays a role; vasospasm may be operative in some cases. It is also possible that accumulation of toxic substances due to necrosis in the plaque core leads to progressive injury and degeneration of the fibrous capsule of the plaque, thereby increasing susceptibility to hemodynamic injury.

A likely scenario for frank plaque rupture is as follows [*21*]: after endothelial and subendothelial injury, the luminal surface of the plaque becomes increasingly permeable. Accumulation of plasma within the plaque leads to an increase in intraplaque pressure. Subsequently, erythrocytes leak into the plaque. This accentuates the increase in intraplaque pressure and eventually leads to rupture of the plaque from within, as indicated by the outwardly directed flaps of the ruptured plaque. Exposure of the blood to the thrombogenic plaque contents leads to thrombus formation both in the arterial lumen and in the plaque. Fissuring of the plaque can lead to intraplaque and luminal thrombosis without plaque hemorrhage [*19,20,22*].

An alternative theory for plaque hemorrhage and rupture is that the hemorrhage is derived from intraplaque vessels that form during vascularization of plaques. It has been argued that significant bleeding from these vessels is not possible because the pressure in the coronary lumen would greatly exceed the pressure within the thin-walled extensions of the vasa vasorum. However, it is possible that, with a stenotic lesion, the pressure drop across the lesion would be such that intraluminal pressure could fall to the point that bleeding from intraplaque vessels could occur.

A dog model of coronary stenosis with endothelial injury has been used to study the interaction between platelets and the vessel wall in the genesis of acute ischemic heart disease [*25–28*]. In this model, coronary stenosis with endothelial injury results in fluctuations in coronary blood flow, termed cyclic blood flow variations, which are characterized by transient episodes of little or no flow, followed by sudden restoration of flow. It has been shown that these flow alterations are due to recurrent episodes of platelet aggregation and dislodgement at the site of coronary stenosis and injury. Neutrophils also accumulate on and in the injured vessel wall. It has also been shown that the platelet release products, thromboxane A_2 and serotonin, are major mediators of this process (Fig. 4). The process can be ameliorated by treatment with thromboxane synthetase inhibitors, thromboxane receptor antagonists, and serotonin receptor antagonists [*25–28*]. There is evidence in humans that similar mechanisms are involved in unstable angina pectoris. Increased thromboxane levels across the coronary bed, as well as excess amounts of thromboxane degradation products, have been documented in patients with unstable angina [*23,24,29*].

There is evidence that a significant number of subjects with sudden cardiac death may have experienced symptoms consistent with unstable angina pectoris prior to their sudden death [*20*]. There also is evidence that acute coronary injury, manifested by often subtle anatomic alterations of the coronary arteries, is responsible for many cases of sudden cardiac death due to ischemic heart disease [*19*]. Clinical and experimental studies support an important role for acute coronary alterations in the pathogenesis of most cases of acute ischemic heart disease [*2,6–8,21–30*].

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