

Sudden cardiac death^{☆,★}

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Abstract

The rate of cardiac deaths that are sudden is approximately 50%, and decreases with age. The causes of sudden cardiac death are diverse, and are a function of age. In children and adolescents, coronary anomalies, hypertrophic cardiomyopathy and myocarditis are frequent substrates for lethal arrhythmias; in adults, coronary atherosclerosis and acquired forms of cardiomyopathy are the most common findings at autopsies of sudden cardiac death. This review focuses on coronary causes of sudden cardiac death, especially congenital coronary artery anomalies, which result in sudden death almost exclusively in adults younger than age 35, and coronary thrombosis. The most lethal coronary artery anomaly is the left coronary artery arising from the right sinus of Valsalva; this anomaly often results in fatal arrhythmias, often with exercise. The right coronary artery arising from the left sinus of Valsalva may also be lethal in adolescents and young adults, but, unlike the anomalous left, is more often an incidental finding at autopsy. Approximately 60% of sudden coronary death is caused by coronary thrombosis, the rest die with severe coronary disease in the absence of thrombosis. The two major substrates of coronary thrombosis are plaque rupture and plaque erosion, and are not only different pathologically, but are seen in patients with divergent risk factor profiles. Plaque rupture is the most common cause of fatal coronary thrombus, and is characterized by necrotic core with a thin fibrous cap, infiltrated by macrophages. The factors that result in plaque instability and rupture are largely unknown, and are under intense scrutiny; morphologic studies have identified serum lipid abnormalities as a key risk factor in the development of plaque rupture. Plaque erosion, in contrast to plaque rupture is seen in younger men and women, is not associated with lipid abnormalities, and does not result from exposure of the lipid core to the lumen. The heterogeneity of the atherosclerotic plaque and the diverse mechanisms of plaque progression and thrombosis have only been relatively recently explored, and are largely elucidated by autopsy studies of victims of sudden coronary death. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Sudden death; Coronary artery; Thrombosis; Coronary anomalies

1. Introduction

Sudden death is reported to occur in 300,000 to 400,000 individuals a year in the USA and is most prevalent from birth to 6 months (sudden infant death syndrome) and between 45 and 75 years. Only 19% of sudden natural deaths in children between 1 and 13 years are cardiac in origin, whereas in the 14–21-year age range, 30% are cardiac [1]. In the adult population, the commonest cause

of sudden death is coronary heart disease. The highest prevalence is seen in those with prior history of cardiac arrest and myocardial infarction, with the risk of sudden death being highest between 6 to 18 months after the event. The incidence of sudden death declines with advancing age. In the Framingham study, 62% of all coronary heart disease deaths were sudden in men aged 45–54 years, whereas in the 55–64- and 65–74-year age groups, the percentage of sudden death fell to 58% and 42%, respectively [2]. The incidence of sudden death is higher in men than women, largely because women are protected from coronary heart disease during the premenopausal years. In the Framingham study there was a 3.8-fold higher incidence of sudden cardiac death in men than women [2]. The excess relative risk in men peaked at 55 to 64 years reflected in a male to female ratio of 6.75:1; this ratio fell to 2.17:1 in the 65–74-year age group. Racial differences in the incidence of sudden cardiac death have also been noted, Blacks having an increased risk as compared to Whites [3] (Table 1).

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Table 1
Population-based incidence of sudden cardiac death, State of Maryland population aged 14–40 years, rate/100,000 per year

	CAD	HTCM CM	ALL SUCD	
Blacks	4.3	0.8	1.7	9.5
Whites	2.3	0.1	0.5	4.2
Black men	5.6	1.0	3.2	14.5
White men	4.0	0.1	0.9	6.8
Black women	1.2	0.6	0.4	5.1
White women	0.6	0.0	0.1	1.6
Population	2.5	0.3	0.8	5.5

CAD=coronary artery disease; HTCM=hypertensive cardiomyopathy; CM=idiopathic cardiomyopathy (including dilated cardiomyopathy and idiopathic left ventricular hypertrophy); SUCD=sudden unexpected cardiac death. Adapted from Ref. [3].

1.1. Causes of sudden cardiac death

The prevalence of sudden death varies with the age of the patient but also by the definition of sudden death. Most of the deaths reported as sudden have occurred outside the hospital or in emergency rooms, reflecting their unexpected nature. Clinicians define sudden cardiac death as natural, nonviolent, unexpected, and occurring within 1 h of the onset of acute symptoms. The World Health Organization defines sudden death as death within 24 h following onset of symptoms [4]. However, this definition includes many cases of well-established acute myocardial infarction, and therefore should not be considered as sudden cardiac deaths. Kuller et al. [5,6] have shown the influence of the definition of sudden death on the incidence of cardiac causes: When

the definition of sudden death was less than 2 h after onset of symptoms, 12% of deaths were sudden and 88% were due to cardiac causes; when applying a symptom duration of less than 24 h, 32% of deaths were sudden but cardiac causes of death fell to 75%. In most of our studies, we have defined sudden cardiac death as natural, nonviolent, unexpected, and witnessed within 6 h of the onset of symptoms from a stable medical condition. For unwitnessed deaths, the definition of sudden death requires that the deceased had been seen in stable condition less than 24 h before being found dead, and any potentially lethal noncardiac cause must be ruled out.

1.2. Definitions

The *cause* of death is defined as the disease or injury initiating the train of events producing death. Cardiac causes of death are generally related to coronary, valvular, or myocardial diseases. Aortic rupture may result in cardiac tamponade and sudden death, and is occasionally considered part of the spectrum of cardiac death, although the underlying cause is vascular, not cardiac. The *manner* of death refers to the circumstances of death, and is classified as natural or violent (unnatural or traumatic). The distinction between natural and accidental iatrogenic deaths may be difficult and somewhat arbitrary. Generally, the death is considered natural if the procedure carries a significant risk of a fatal complication, and the condition is life threatening.

The *mechanism* of death is the terminal physiologic or biochemical disturbance that leads to sudden death. In most

Table 2
Causes and mechanisms of sudden cardiac death

Immediate cause	Underlying causes	Mechanisms
Acute ischemia	Coronary atherosclerosis, nonatherosclerotic coronary diseases, aortic stenosis	Ventricular fibrillation, bradycardia, electromechanical dissociation (usually end stage or postresuscitation)
Infiltrative diseases	Inflammatory (myocarditis), scars (healed infarcts, cardiomyopathy)	Ventricular fibrillation, bradyarrhythmias (uncommon ^a)
Cardiac hypertrophy	Hypertrophic cardiomyopathy, systemic hypertension, idiopathic concentric left ventricular hypertrophy, aortic stenosis	Ventricular fibrillation, bradyarrhythmias (uncommon)
Cardiac dilatation (congestive failure)	Dilated cardiomyopathy, chronic ischemia, systemic hypertension, aortic insufficiency, mitral insufficiency	Ventricular fibrillation, bradyarrhythmias (uncommon)
Cardiac tamponade	Rupture myocardial infarct, aortic rupture	Electromechanical dissociation
Mechanical disruption of cardiac blood flow	Pulmonary embolism, mitral stenosis, left atrial myxoma	Electromechanical dissociation, ventricular fibrillation
Global myocardial hypoxia	Severe ischemic heart disease, aortic stenosis	Baroreflex stimulation with bradyarrhythmias, ventricular tachyarrhythmias
Acute heart failure	Massive myocardial infarct, rupture papillary muscle, acute endocarditis with chordal or leaflet rupture, MVP with chordal rupture	Electromechanical dissociation, ventricular fibrillation
Generalized hypoxia	Pulmonary stenosis, pulmonary hypertension	Bradyarrhythmias
Vasovagal stimulation	Neuromuscular diseases	Baroreflex stimulation with bradycardia
Preexcitation syndrome	Accessory pathways	Atrial fibrillation → ventricular fibrillation
Long QT syndrome	Congenital and acquired states	Ventricular fibrillation (torsades de pointes)
Heart block	AV nodal scarring, inflammation, tumor	Bradycardia → ventricular fibrillation

EMD=electromechanical dissociation; AV=atrioventricular; MVP=mitral valve prolapse.

^a Especially in the presence of infiltrative processes involving the conduction system.

Table 3
Causes of sudden cardiac death in infants and children

Anatomic findings	0–1 year (20 pts)	1–21 years (50 pts)
Coronary artery anomalies	10 (50%)	12 (24%)
Myocarditis	0	14 (28%)
No finding	7 (35%)	10 (20%)
Other findings	2 (10%)	8 (16%)
Hypertrophic cardiomyopathy	1 (5%)	6 (12%)

Adapted from Ref. [7].

cases of cardiac death, the physiologic abnormality is a cardiac arrhythmia, although other mechanisms include acute heart failure and obstruction of blood flow (see Table 2).

1.3. Infants and children

The causes of death vary with the age of the patient. In neonates and infants, a common cause of sudden unexpected death is the sudden infant death syndrome, which has been defined as the sudden death of an infant under 1 year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history. A cardiac cause of sudden infant death syndrome has yet to be established.

Steinberger et al. [7] reported their experience in 20 patients less than 1 year of age dying suddenly (Table 3). In 65% of cases, a cause of death was identified, 80% of which were ectopic aortic origin of one or more coronary arteries. In older infants and young children, up to 75% of sudden unexpected deaths are not attributed to heart disease [8,9]. Up to 50% of cardiac causes in children dying during exercise are idiopathic arrhythmias with apparently normal heart at autopsy [10]. In the 50 cases of sudden cardiac death reported by Steinberger et al. in patients aged 1–20 years, cardiac abnormalities were present in 80% [7]. The most common identifiable cause of sudden death in young children is myocarditis and congenital heart disease, including coronary artery anomalies and hypertrophic cardiomy-

Table 4
Causes of death, ages 14–20

Cause of death	
No finding	18 (30%)
Myocarditis	8 (13%)
Hypertrophic cardiomyopathy	7 (12%)
Anomalous coronary artery	5 (8%)
Complex congenital heart disease	4 (7%)
Atherosclerosis	3 (5%)
Dilated cardiomyopathy	3 (5%)
Floppy mitral valve	3 (5%)
Idiopathic left ventricular hypertrophy	3 (5%)
Aortic dissection	2 (3%)
Kawasaki	2 (3%)
Tunnel coronary artery	1 (3%)
Hypertensive left ventricular hypertrophy	1 (2%)
Totals	60

Adapted from Ref. [11].

opathy. In young patients with known heart disease who are followed in cardiology clinic, causes of sudden death are generally structural.

1.4. Adolescents and adults

In adolescents and young adults, myocarditis, cardiomyopathies (right ventricular dysplasia, hypertrophic and idiopathic left ventricular hypertrophy), and coronary artery anomalies are the most common causes of sudden cardiac death in individuals with structural heart disease [3,11]. In developed countries, coronary atherosclerosis is by far the most common finding in cases of sudden cardiac death in patients over 30–35 years of age (Tables 4–6).

2. Coronary causes of sudden cardiac death

2.1. Coronary atherosclerosis

2.1.1. Epidemiological factors

Coronary atherosclerosis is the overwhelming cause of sudden death in this country in patients older than 35 years. In patients dying of coronary disease, up to 50% of deaths are sudden. The proportion of deaths from ischemic heart disease that are sudden declines with advancing age, because older patients are more likely to die of complications of heart failure, rather than ventricular arrhythmias.

2.1.2. Definition of severe narrowing

Experimental studies in animal models have shown that the critical luminal narrowing is 75% cross-sectional area compromise before flow limitation is severe enough to lead

Table 5
Causes of death, ages 21–30

Cause of death	
Atherosclerosis	64 (28%)
No finding	49 (21%)
Idiopathic left ventricular hypertrophy	27 (12%)
Hypertrophic cardiomyopathy	16 (7%)
Myocarditis	14 (6%)
Anomalous coronary artery	9 (4%)
Dilated cardiomyopathy	7 (3%)
Tunnel	7 (3%)
Aortic dissection	7 (3%)
Rheumatic mitral stenosis	6 (3%)
Complex congenital heart disease	5 (2%)
Hypertensive left ventricular hypertrophy	4 (2%)
Endocarditis	4 (2%)
Sarcoidosis	3 (1%)
Aortic stenosis	3 (1%)
Floppy mitral valve	2 (1%)
Right ventricular cardiomyopathy	2 (1%)
Coronary aneurysm (congenital)	1 (0.4%)
Amyloid	1 (0.4%)
Pericarditis	1 (0.4%)
Totals	229

Adapted from Ref. [11].

Table 6
Causes of death, ages 31–40

Cause of death	n (%)
Atherosclerosis	258 (60%)
No finding	38 (9%)
Hypertensive left ventricular hypertrophy	26 (6%)
Idiopathic left ventricular hypertrophy	18 (4%)
Dilated cardiomyopathy	16 (4%)
Hypertrophic cardiomyopathy	13 (3%)
Myocarditis	12 (3%)
Sarcoidosis	10 (2%)
Aortic stenosis	9 (2%)
Aortic dissection	8 (2%)
Endocarditis	6 (1%)
Floppy mitral valve	6 (1%)
Tunnel coronary artery	3 (1%)
Right ventricular dysplasia	3 (1%)
Rheumatic mitral stenosis	3 (1%)
Anomalous coronary artery	2 (0.5%)
Coronary artery dissection	2 (4%)
Congenital heart disease	1 (2%)
Lipomatous hypertrophy, atrial septum	1 (2%)
Totals	432

Adapted from Ref. [11].

to myocardial ischemia. Based on autopsy studies on the degree of luminal narrowing of coronary arteries in patients dying suddenly to other patients dying of other causes, it has been determined that greater or equal to 75% cross-sectional luminal narrowing is a useful figure for separating critical stenosis that may result in acute myocardial ischemia, from noncritical stenoses [12,13]. However, it is not surprising that many cases of more severe narrowing are incidental findings at autopsy. Of 124 men aged 50–69 years with traumatic or natural noncoronary deaths, the incidence of severe one-vessel disease was 10%, two-vessel disease 3%, and three-vessel disease 1% [13]. Therefore, any decision that death is due to coronary atherosclerosis, especially in the presence of a stable plaque, must be supported by rigorous exclusion of other noncardiac causes of death.

2.1.3. Extent of disease in coronary sudden death

In our experience with out-of-hospital sudden coronary deaths, the proportion of hearts with one-vessel disease (single coronary artery cross-sectional lumen area narrowed $\geq 75\%$ by atherosclerotic plaque) is 44%, two-vessel disease 32%, three-vessel disease in 22%, and four-vessel disease in 1% [14]. In other series of sudden death, in which there are a large number of hospital-based deaths, the proportion of one-vessel disease is as low as 16%, with 27% two-vessel disease, 47% three-vessel disease, and 10% four-vessel disease [15]. In the series of sudden coronary death reported by Thomas et al. [16], one-vessel disease was found in 26% of cases, with 39% having two-vessel disease and 33% three-vessel disease. In the absence of hypertension, the heart weight increases in cases of sudden death as the number of severely narrowed epicardial arteries increases [17].

In our series, the culprit lesion (area of maximal stenosis or that of acute thrombus) was found in the left anterior

descending in 40%, the right coronary in 29%, the left circumflex in 18%, the left obtuse marginal in 5%, left diagonal in 2%, left main in 2%, posterior descending in 2%, and ramus intermedius in 2% of cases of sudden coronary death [14].

2.2. Coronary plaque morphology in sudden cardiac death

2.2.1. Incidence of luminal thrombi

The frequency of coronary thrombosis in sudden coronary death varies from 20% to 70% [14,18,19]. This large range is in large part due to the population studied. The time interval between onset of symptoms and death, the presence of acute myocardial infarction, and the type of prodromal symptom (stable angina, unstable angina, no apparent symptoms) all affect the incidence of thrombi in coronary sudden cardiac death. Thrombi are quite common in coronary sudden death associated with acute myocardial infarction; the incidence of thrombi in sudden death with acute infarcts is generally accepted to be 70–80% in angiographic and autopsy studies [20,21]. The incidence of coronary thrombi in “instantaneous” sudden death occurring in the absence of any chest pain or clinical prodrome ranges from negligible to 50% [15,22,23], suggesting that the terminal arrhythmias may be precipitated by cardiac hypertrophy or healed infarcts. The incidence of acute thrombi in sudden coronary death in patients with systemic hypertension is significantly lower than normotensives, introducing a further factor influencing the frequency of thrombosis in sudden coronary death [17]. Plaque erosion in the absence of plaque fissuring is an important cause of coronary thrombosis in atherosclerotic sudden coronary death, and may be pathogenetically distinct from plaque rupture [24] (Fig. 1).

2.2.2. Incidence of stable plaques

In approximately 40% of cases of coronary sudden death, there are no plaque disruptions identified, despite careful postmortem evaluation with angiography, perfusion fixation, and serial sectioning. The mechanism of ventricular arrhythmias in these cases is uncertain; however, healed myocardial infarction is present in 20% of cases dying with severe coronary and in the rest (20%) the mechanism of death is unknown. Others have suggested cardiac hypertrophy either from systemic hypertension or chronic ischemia. Also at the time of death there may have been coronary artery spasm, which according to us cannot be diagnosed at autopsy. In such cases, noncoronary causes of sudden cardiac death should be carefully excluded, because stable plaques resulting in critical narrowing are common incidental findings. Deep plaque hemorrhage without intraplaque thrombus or plaque fissure is currently considered a form of stable plaque, and is often an incidental finding at autopsy.

2.2.3. Incidence of plaque fissures

In most cases of sudden coronary death with plaque fissures, there are superimposed thrombi [25]. Plaque dis-

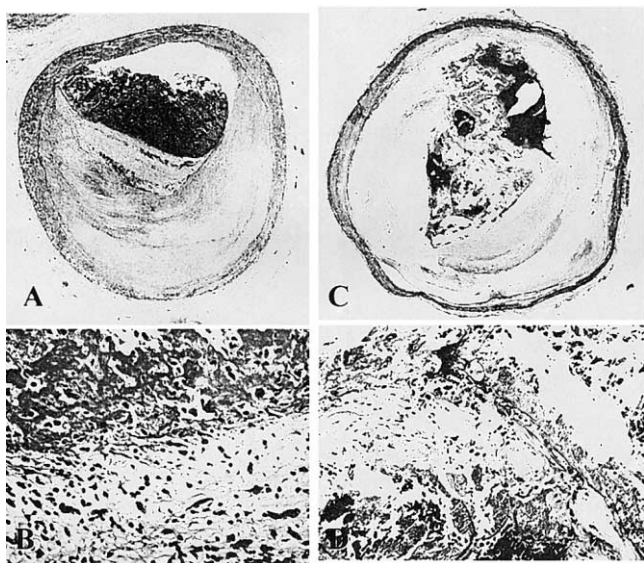


Fig. 1. (A) A cross section of the left anterior descending coronary artery in a woman who died suddenly. Note that there is an eccentric plaque, with nonocclusive luminal thrombus (Movat pentachrome). (B) A higher magnification of (A) demonstrates the surface erosion, without disruption of the fibrous cap. There is smooth muscle cell proliferation in a proteoglycan rich matrix (hematoxylin eosin). (C) Plaque rupture demonstrates a thin cap (center), with necrotic core with intraplaque hemorrhage (top) in continuity with the lumen, which is nearly filled with thrombus (Movat pentachrome). (D) A Higher magnification of (C) demonstrates the thin fibrous cap, which is interrupted and surrounded by platelet fibrin thrombus (Movat pentachrome).

ruption in the absence of luminal thrombus occurs in 3–20% of cases of sudden coronary death [14,21,25,26], and presumably contributes to acute ventricular ischemia secondary to sudden coronary narrowing. However, plaque fissures with intraplaque thrombi have been described as incidental findings in up to 9% of hearts in patients with severe coronary artery atherosclerosis [13]. In contrast, plaque fissures with luminal thrombus are found almost exclusively in patients dying from complications of coronary artery disease.

2.3. Incidence of myocardial infarction

The likelihood of discovering an acute infarction in autopsied cases of sudden coronary death is over 50% in hospital-based studies of sudden death [19,20]. In out-of-hospital deaths, and cases of instantaneous sudden death with no symptoms or symptoms lasting less than 1 h, acute infarcts are unusual, and found in less than 25% of cases [14,15,18].

The incidence of healed infarcts in out-of-hospital sudden coronary deaths is greater than that of acute infarcts. We found an acute myocardial infarction in only 21% of sudden coronary deaths, including 11% with both acute and healed infarcts. Healed infarcts in the absence of acute infarction are found in 41% and no infarct in 38% of sudden coronary deaths [14]. In hearts with acute myocardial infarction, the

infarcts are transmural and grossly identifiable in approximately 50% of cases, and subendocardial and identified only by histologic examination in the remainder.

2.4. Types of coronary thrombus: rupture and erosion

Until recently it was reported that symptomatic thrombotic coronary artery disease was caused solely from rupture of a thin fibrous cap [20,21]. We have recently reported that thrombi in sudden coronary death may occur from three distinctly differently plaque morphologies [27]. The two most common lesions that account for 95% of all thrombi are plaque rupture (60%) and plaque erosion (35%); least frequent is the ruptured calcified nodule (5%). Plaque erosion is seen in younger individuals and is the most common form of thrombus in premenopausal women. In contrast to rupture, erosions are less often calcified, more often nonocclusive, and more often eccentric [24] (Fig. 1).

2.5. Risk factors and sudden coronary death

Traditional risk factors have been correlated to the type of thrombus observed in sudden coronary death in men and women. In 113 men, we determined the risk factors at autopsy by biochemical analysis of serum for total cholesterol (TC), HDL-C, TC/HDL ratio, and serum thiocyanate, a surrogate marker for smoking. Red cell glycosylated hemoglobin was used to determine the presence of glucose intolerance. We observed that risk factors were present in 96.5% of sudden coronary death. Smoking was a predictor of acute thrombosis regardless of etiology, and plaque rupture correlated with high total cholesterol, low HDL-cholesterol, and a high TC/HDL-cholesterol ratio [28]. We also observed that as the cholesterol rose so did the incidence of vulnerable plaque increase [28].

In women, we have observed that plaque erosion is highly correlated with smoking and is mostly seen in women <50 years. In contrast, plaque rupture is more frequent in women >50 years and correlated with elevated total cholesterol [29]. Vulnerable plaques are more frequently seen in women >50 years than <50 years. Stable plaque with healed myocardial infarction is seen more frequently in women with $\geq 10\%$ glycohemoglobin [29].

The associations demonstrate that the morphologic heterogeneity of coronary atherothrombosis has an underlying pathogenetic basis. The fact that plaque erosion is not associated with elevated levels of cholesterol may explain why some individuals with normal lipid profiles suffer from severe coronary disease. The precise risk factor related to plaque erosion still remains elusive, but unpublished data suggest that thrombotic factors, in addition to vasospasm, may be important. Cigarette smoking appears to increase the likelihood of fatal thrombosis, regardless of etiology. It remains to be seen if newer risk factors, including homocysteine and polymorphisms for hemostatic

factors are associated specifically with one form of thrombosis or another.

3. Coronary artery anomalies

Coronary artery anomalies are rare and are found in 0.3% of autopsies and 1.4% by coronary angiography [30]. Although many anomalies identified by angiography (81%) consist of minor variations in the location of the coronary origin however, some anomalies have been associated with morbidity and mortality. The high-risk anomalies consist of mainly four types: (I) anomalous origin of one or more coronary arteries arising from the pulmonary trunk; (II) anomalous origin of one or more coronary arteries from aorta; (III) single coronary ostium from the aorta; and (IV) hypoplastic coronary arteries (Table 7).

3.1. Pathophysiology

Anomalous coronary arteries are believed to cause myocardial ischemia due to reduced regional blood flow. Each anomaly differs in its mechanism of ischemia [31–34]. Origin of one or more arteries from the pulmonary trunk

result in marked intercoronary shunting and regional ischemia, which is the result of coronary steal. This can lead to acute, chronic, and inducible ischemia.

Anomalous origin of the coronary artery from the aorta includes ostial-valve-like ridges, acute angulation of the origin of the coronary artery with the aorta, with or without left or right coronary artery arising from the opposite sinus of Valsalva can lead to a decrease in coronary flow reserve. Myocardial ischemia may also occur from the anomalous coronary vessel coursing between cardiac structures (for example, between the aorta and pulmonary trunk) potentially leading to vascular compression or kinking. The importance of slit-like orifice and acute-angle take-off is suggested by several observations including (1) their frequent pathologic description in patients dying suddenly in the setting of anomalous coronary arteries; (2) the prevalence of abnormalities of the proximal coronary artery is increased three- to fourfold in cases of sudden cardiac death of unknown cause, even in the absence of a coronary artery anomaly; and (3) surgical revision of the coronary artery ostium can result in relief of symptoms, as reported in a surgical series of eight cases of anomalous right coronary artery with slit-like orifice. Also, the extent of myocardium supplied by the anomalous artery is another variable that may determine the lethality of the anomaly.

In general, coronary artery anomalies may present with symptoms that include angina, shortness of breath, and syncope. More severe presentations include the clinical syndromes of myocardial infarction, congestive heart failure, or sudden cardiac death [31–34]. Overall, symptoms are present in approximately 1/3 of patients. The frequency of symptoms is somewhat related to the extent of myocardium at risk.

Table 7

Relative frequency of potentially serious coronary artery anomalies in angiography and pathology series

Anomaly	Autopsy frequency (<i>n</i> =242) (age, mean, range)	% Sudden death (<i>n</i> =78) (32%)
I. Anomalous origin of		
≥ 1 CA from pulmonary trunk		
A. LMCA or LAD from PT	15.3% [2 (3 days to 17 years)]	38%
B. Both CAs from PT	1.2% [3 days (1 to 7 days)]	100%
C. RCA from PT	0.4% [34 years]	0
II. Anomalous origin of		
≥ 1 CA from aorta		
A. LMCA and RCA from R Ao sinus	20.2% [30 (2 to 87 years)]	57%
B. RCA and LMCA from L Ao sinus	21.5% [39 (0 to 82 years)]	25%
C. LCx and RCA from R Ao sinus	8.7% [49 (20 to 80 years)]	10%
D. RCA and/or LMCA from posterior Ao sinus	7.0% [39 (1 to 69 years)]	29%
E. RCA and LAD from R Ao sinus	0.4% [20 years]	100%
III. Single CA ostium from aorta		
A. Single RCA ostium	9.1%	18%
B. Single LCA ostium	9.1%	9%
IV. Hypoplastic CAs	5.4% [20 (1–69 years)]	38%
V. CA fistula	1.6% [2 (1 day to 7 years)]	25%

3.2. High-risk coronary anomalies

The clinicopathologic records of 242 patients with isolated coronary artery anomalies were reviewed at the AFIP. Cardiac death occurred in 142 patients (59%); 78 (32%) of these deaths occurred suddenly. Of the sudden deaths 45% occurred during exercise.

3.2.1. Left main and right coronary artery from the opposite aortic sinus

The most frequent cause of sudden death was seen in left main coronary artery from the right coronary sinus. In the majority of cases, the anomalous vessel courses between the aorta and pulmonary trunk (67%), with the remainder usually coursing posterior to the aorta. Equally frequent but less likely to be fatal is when the right coronary artery arises from the left coronary sinus. At first, this was thought to be benign anomaly. However, accumulating reports have now clearly associated this anomaly with sudden cardiac death. Sudden death is observed in approximately 25% of cases, with roughly half of these in association with exercise.

3.2.2. Origin of the left main coronary artery from the pulmonary trunk

This anomaly has been frequently reported (over 500 cases, incidence approximately 1/300,000), and is the most common anomaly involving a coronary artery arising from the pulmonary trunk. This anomaly is very commonly fatal, including a predominance of death during early childhood from myocardial ischemia and systolic dysfunction resulting in congestive heart failure and sudden death. When the left main coronary artery arises from pulmonary trunk, the most common site of origin (95%) is the left pulmonary sinus. The wall of the left main coronary artery is vein-like, and extensive collateral vessels arise from the right coronary artery. The heart is enlarged and there is extensive scarring of the anterolateral papillary muscle. Compensatory hypertrophy is observed in the posterobasal portion of the left ventricle. Endocardial fibrosis may be prominent in older children.

3.2.3. Single coronary artery

The coronary circulation may be entirely supplied by a single coronary artery arising from either the right, left or posterior aortic sinus. The course of the coronary arteries can be highly variable, with 23 different courses described by Roberts and Shirani [32]. Several classification schemes have been proposed, using either subgroups based on the site of origin and course of the anomalous vessel or descriptive anatomic terminology. In a compilation of 142 cases, there was an approximately equal distribution between origin from the right and left coronary sinus [33]. Since the publication of this large series, there have been numerous additional smaller series of this anomaly. Single coronary artery can be associated with sudden death (6 of 44 cases (14%) in the AFIP series), with a greater incidence of sudden death when the single coronary artery arises from the right aortic sinus. (Of note, a single coronary artery may also arise from the posterior aortic sinus.) Associated anomalies of the heart and great vessels were seen in 68% of patients under the age of 20, and included transposition of the great vessels, and bicuspid aortic valve. In comparison, few of the adult cases (6%) had other associated congenital heart defects.

3.2.4. Hypoplastic coronary arteries

Hypoplastic coronary arteries (the condition when neither the right nor the left circumflex coronary artery goes beyond the lateral border of the heart) were diagnosed in 13 patients. Five patients (38%) died suddenly; three of these deaths were related to exercise. Cardiac death occurred in four other patients, as a result of coronary atherosclerosis in three and of aortic stenosis in one.

3.2.5. Comparison of patients ≤ 30 and > 30 years

The majority of cases of origin of the left main artery from the right coronary sinus were observed in young patients; otherwise, anomalies were equally distributed

among ≤ 30 and > 30 years old. In general, lethal coronary artery anomalies present under the age of 35–40 years; after this age, coronary artery anomalies found at autopsy are usually incidental findings [34].

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