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Original research article

Drowning and sudden cardiac death

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Abstract

Sudden cardiac death describes the unexpected natural death from a cardiac cause within a short time period, generally, ≤1 hour from the onset of symptoms, in a person without any prior condition that would appear fatal.[1,2] Such a rapid death is often attributed to a cardiac arrhythmia, but with the advent of monitoring capabilities from implantable cardioverter-defibrillators (ICDs), it is now well recognized that classifications based on clinical circumstances can be misleading and often impossible, because 40% of sudden deaths can be unwitnessed.[3] Only an ECG or a ventricular electrogram recorded from an implanted device at the time of death can provide definitive information about an arrhythmia. Prodromal symptoms are often nonspecific, and even those taken to indicate ischemia (chest pain), a tachyarrhythmia (palpitations), or congestive heart failure symptoms (dys- pnea) can only be considered suggestive. For these reasons, total mortality, rather than classifications of cardiac and arrhythmic mortality, should be used as primary objectives for many outcome studies.

Introduction

Magnitude of the Problem

Sudden cardiac death accounts for 300 000 to 400 000 deaths annually in the India, depending on the definition used [1, 2]. When restricted to death <2 hours from the onset of symptoms, 12% of all natural deaths were classified as sudden in one study, and 88% of those were due to cardiac disease [1]. Sudden cardiac death is the most common and oftenthe first manifestation of coronary heart disease and is responsible for ≈50% of the mortality from cardiovascular disease in the India. Inless-developed countries, sudden cardiac death rates parallel the rates of ischemic heart disease as a whole and therefore are lower. Several population-based studies have documenteda 15% to 19% decline in the incidence of sudden cardiac deaths caused by coronary heart disease since the early 1980s.However, the increasing incidence of congestive heart failuremay halt this decline in the future [4].

Figure 1 places the problem into perspective by expressing the incidence of sudden cardiac death in different subgroups at varying risk while indicating the overall number of events per year for each. Thus, if one considers an overall incidence in the adult population of only 0.1% to 0.2% per year, when applied to the entire Indian population, that accounts for more than 300 000 events per year. In contrast, although ≈33% of patients in the convalescent phase after a large myocardial infarction experience sudden cardiac death in the year there- after, overall, they account for a small number of the total sudden cardiac deaths per year. The use of interventions that limit infarct size, such as thrombolytic agents, has reduced this number still further. These factors have an impact on the effects of therapeutic interventions because, although it is relatively easy to identify patients in the small high-risk subgroups and then to possibly prevent or reverse a ventricular tachyarrhythmia, the overall impact on the total number of sudden cardiac deaths will be small. It becomes obvious that, to significantly reduce the incidence of sudden cardiac death, more specific markers are needed for the general population to identify large numbers in subgroups that ac- count for a bigger percentage of the more than 300 000 who die suddenly. The present risk factors (see below) generally identify the risk of developing the structural heart disease underlying sudden cardiac death rather than the proximate precipitator of the event. Because the risk of sudden cardiac death does not necessarily equate with the risk of developing structural heart disease, these risk factors have limited ability in identifying specific individuals at risk for sudden cardiac death. Nevertheless, their control, with concomitant reduction in death from coronary artery disease, is probably at least in part responsible for the reduction in overall sudden cardiac death. Figure 1B shows idealized curves of survival from sudden cardiac death for a population free of major cardio- vascular events versus a population that has survived a major cardiovascular event. After an initial high attrition rate for the high-risk group in the first 6 to 18 months, the curves then become parallel, illustrating the modulating effects of time on the incidence of sudden cardiac death. Ultimately, risk stratification will be important only if it can be coupled with a therapeutic intervention that reduces the risk of dying.

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Risk Factors of Sudden Cardiac Death

Influence of Age, Race, and Sex

Because up to 80% of individuals who suffer sudden cardiac death have coronary heart disease, the epidemiology of sudden cardiac death to a great extent parallels that of coronary heart disease. As such, the incidence of sudden cardiac death increases with age in both men and women, because the prevalence of ischemic

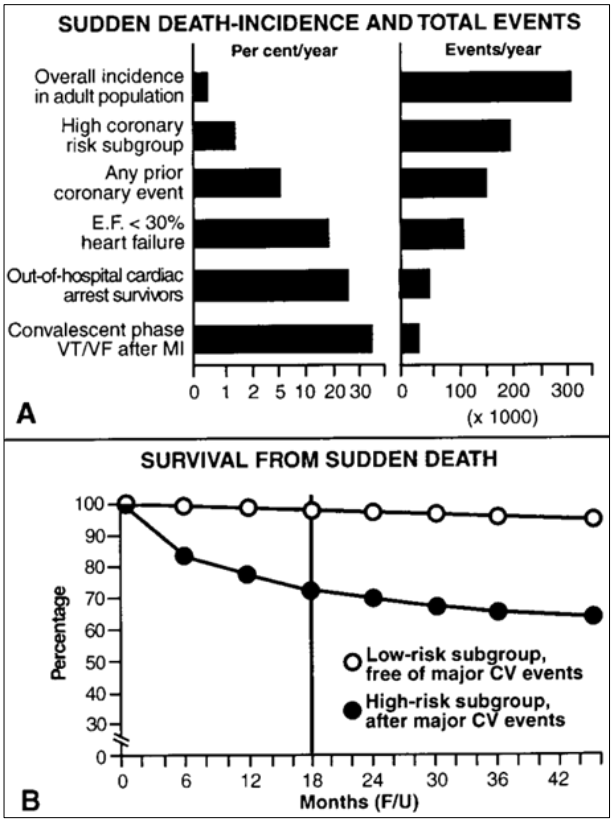

Fig 1: A, Sudden death incidence and total events for vari- ous population pools, showing inverse relationship between risk and total number of events. B, Attrition over a 6- to 18-month interval in a high-risk subgroup compared with a low-risk sub- group. After initial falloff, curves become parallel. Reproduced with permission from Reference 2, p 744.

heart disease increases with age (Figure 2). However, among patients with coronary heart disease, the proportion of coro- nary deaths that are sudden decreases with age. Sudden cardiac death has a much higher incidence in men than women, reflecting sex differences in the incidence of coro- nary heart disease as well. Thus, ≈75% of sudden cardiac deaths occur in men, with an annual incidence 3 to 4 times higher than in women. The peaks in incidence of sudden cardiac death occur between birth and 6 months of age because of the sudden infant death syndrome, and then again between 45 and 75 years of age as a result of coronary artery disease. Sudden cardiac death accounts for 19% of sudden deaths in children between 1 and 13 years of age and 30% between 14 and 21 years of age [5].

Activity

The impact of physical activity on sudden cardiac death is somewhat controversial. Although vigorous exercise can trigger sudden cardiac death and acute myocardial infarction [6], in part possibly by increasing platelet adhesiveness and aggregability, moderate physical activity may be beneficial by decreasing platelet adhesiveness and aggregability [7]. Incardiac rehabilitation programs, cardiac arrests occur at a rateof 1 in 12 000 to 15 000, and during stress testing, cardiac arrest occurs at a rate of 1 per 2000, at least 6 times greater than the general incidence of sudden cardiac death for

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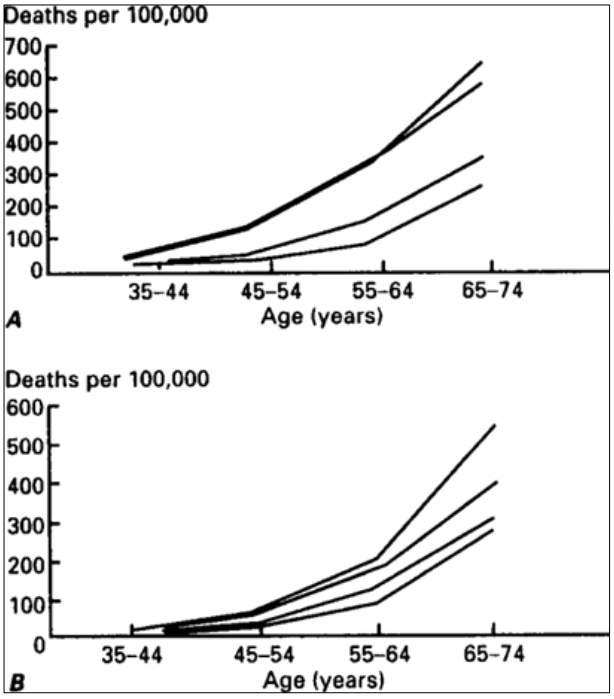

Fig 2: Mortality rates in deaths per 100 000 for patients with ischemic heart disease occurring out of hospital or in emergency room (estimate for sudden cardiac death rate) (A) and occurring in hospital, according to age, sex, and race in India, 1985 (B). Reproduced with permission from Reference 7

patients known to have heart disease. Experimentally, it appears that regular exercise in dogs prevents ischemia- induced ventricular fibrillation and death by increasing vagal activity [8]. Thus, it may be that regular exercise decreases cardiovascular morbidity and mortality, whereas vigorous exercise, particularly in untrained individuals, may have an adverse effect. The annual incidence of sudden cardiac death during exercise is 1 per 200 000 to 250 000 healthy young people [1], whereas in competitive athletes, sudden cardiac death is very rare, despite the publicity, with only 20 to 25 sports- related sudden cardiac deaths from cardiac causes annually in the India [9]. In young athletes (Figure 3), sudden cardiac death most often occurs from hypertrophic cardiomyopathy, and in older athletes, from coronary heart disease [10]. Interestingly, in Europe, particularly in northern Italy, arrhythmogenic right ventricular dysplasia, possiblycongenital, is the predominant anatomic finding in athletes with sudden cardiac death [10]. Commotio cordis, that is, con- cussion of the heart from nonpenetrating blunt trauma to the anterior chest, can lead to fatal cardiac arrest, due to either myocardial trauma or the mechanoelectrical triggering of a ventricular tachyarrhythmia during the vulnerable period of the T wave [12]. As with some other risk factors, the overall impact of activity on sudden cardiac death may be small. In the Maastricht Sudden Death study, 67% of the sudden death victims were physically inactive at the time of the event [3].

Anatomy

Anatomic findings at autopsy include acute changes in coronary plaque morphology, such as thrombus, plaque disruption, or both, in >50% of cases of sudden coronary death, whereas in hearts with myocardial scars and no acute infarction, active coronary lesions are identified in 46% of

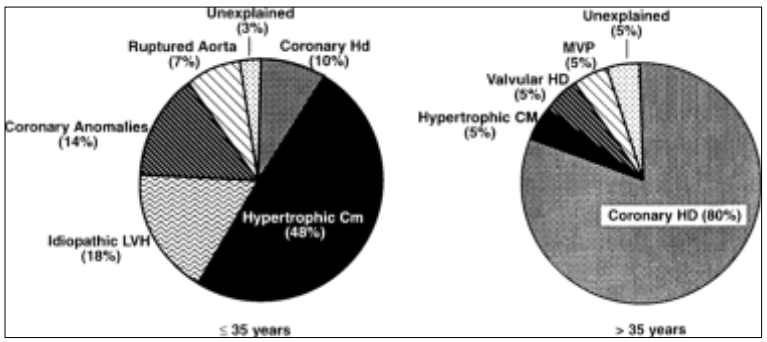

Fig 3: Causes of sudden cardiac death in competitive athletes. CM incidates cardiomyopathy; HD, heart disease; MVP, mitral valve prolapse; and LVH, left ventricular hypertrophy. Reproduced with permission from Maron BJ, Epstein SE, Roberts WC. Causes of sud- den death in competitive athletes. *J Am Coll Cardiol*. 1989;7:204 –214

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cases. Erosion of proteoglycan-rich and smooth muscle cell– rich plaques lacking a superficial lipid core, or plaque rupture, is a frequent pathological finding [13]. Plaque rupture appears to be more common in older women [14]. Apoptosis may participate in the genesis and pathophysiology of some cardiac arrhythmias or conduction disturbances responsible for sudden cardiac death [15]. However, these anatomic abnor- malities are not represented by specific clinical risk factors different from those that identify patients with coronary heart disease in general. In addition, because mechanisms respon- sible for sudden cardiac death depend in part on anatomic substrate, which naturally varies from one individual to another, the usefulness of risk assessment modalities varies from one patient and particular type of anatomic substrate to another. Furthermore, in addition to inter patient variations, there may be intrapatient variation due to temporal changes in specific diseases (Figure 1).

Other Risk Factors

Age, hypertension, left ventricular hypertrophy, intraventric- ular conduction block, elevated serum cholesterol, glucose intolerance, decreased vital capacity, smoking, relativeweight, and heart rate identify individuals at risk for sudden cardiac death (Figure 4). Smoking is an important risk factor. In the Framingham study, the annual incidence of sudden cardiac deaths increased from 13 per 1000 in nonsmokers to almost 2.5 times that for people who smoked >20 cigarettes per day. Stopping smoking promptly reduced this risk, whichmay be mediated by an increase in platelet adhesiveness, release of catecholamines, and other mechanisms. Elevated serum cholesterol appears to predispose patients to rupture of vulnerable plaques, whereas cigarette smoking predisposes patients to acute thrombosis [16]. Female survivors of cardiac arrest are less likely to have underlying coronary artery disease, even though coronary artery disease status is the most important predictor of cardiac arrest in women; im- paired left ventricular function appears to be the most important predictor in men [17]. In patients with severe heart failure, nonsustained ventricular tachycardia may be an inde- pendent marker of increased mortality due to sudden cardiac death [18]. According to one study [19], sudden coronary deaths are less likely to occur at home than nonsudden coronary deaths, whereas individuals who die of sudden coronary death are more likely to have been current cigarette smokers. However, in the Maastricht study [3], 80% of sudden cardiac deaths occurred at home. Emotional stress can be an important trigger for sudden cardiac death, as shown by the Northridge earthquake that struck the Los Angeles area at 4:31 AM January 17, 1994 [20]. Depression in a patient in the hospital after myocardial infarction is a significant predictor of the 18-month post–myocardial infarction cardiac mortality, and

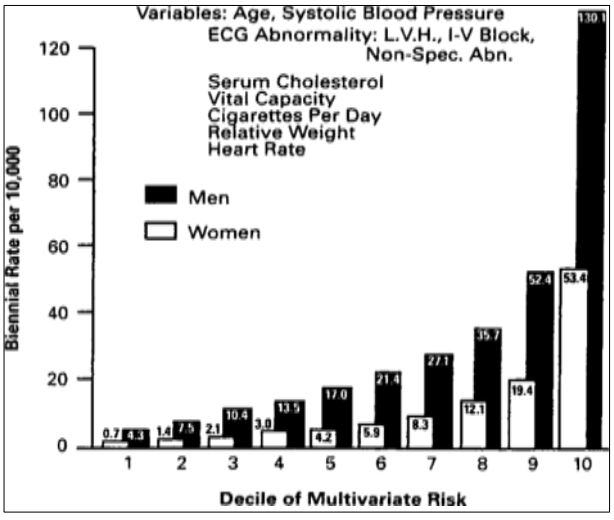

Fig 4: Risk of sudden cardiac death by decile of multivariate risk: 26-year follow-up, Framingham Study. L.V.H. indicates left ventricular hypertrophy; I-V, intraventricular; and Non-Spec. Abn, nonspecific abnormality. Reprinted with permission from Kannel WB, Schatzkin A. Sudden death: lessons from subsets in popula- tion studies. *J Am Coll Cardiol*. 1985:5(suppl):141B–149B

the risk associated with depression was greatest among patients with frequent premature ventricular complexes. So- cioeconomic factors are also important; sudden cardiac death after myocardial infarction increases 3-fold in men with low levels of education and complex ventricular ectopy compared with better educated men who have the same arrhythmias.

History can provide clues to the high-risk patient. For exam- ple, in patients with ventricular tachycardia after myocardial infarction, on the basis of clinical history, the following 4 variables identify patients at increased risk of sudden cardiac death: (1) syncope at the time of the first documented episode of arrhythmia, (2) NYHA class III or IV, (3) ventricular tachycardia/fibrillation occurring early after myocardial in- farction (3 days to 2 months), and (4) history of previous myocardial infarctions [21]. In some patients, family history can be important [22].

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Left ventricular dysfunction is a major independent predic- tor of total and sudden cardiac mortality in patients with ischemic and nonischemic cardiomyopathy [23]. For example, in survivors of cardiac arrest who have a left ventricular ejection fraction <30%, the risk of sudden cardiac death exceeds 30% over 1 to 3 years if the patients do not have inducible ventricular tachycardia, whereas it ranges between 15% and 50% in those who have inducible ventricular tachyarrhythmias despite therapy with drugs that suppress the inducible arrhythmias or with empirical amiodarone [24, 25]. Whether an ICD will reduce total mortality in patients with severe left ventricular dysfunction alone is the subject of several prospective trials, including the Multicenter Auto- matic Defibrillator Implantation Trial (MADIT II) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [26]. These patients have competing causes of death, and unless death is caused primarily by a ventricular tachyarrhythmia that can be terminated by prompt defibrillation, the ICD may not have an important impact. Although prompt defibrillation generally restores sinus rhythm with a very high success rate, it may not be as successful in patients with very advanced ventricular dysfunction.

Certain ECG abnormalities can help identify patients at increased risk for sudden cardiac death. These include the presence of AV block or intraventricular conduction defects and QT prolongation, an increase in resting heart rate to >90 bpm, and increased QT dispersion in survivors of out-of- hospital cardiac arrest. A recent study failed to support the usefulness of QT dispersion in predicting risk in patients after myocardial infarction [27]. The presence of complex ventricular arrhythmias, such as non-sustained ventricular tachycardia, is also a marker [1] (Figure 5).

Transient Risk Factors

Unfortunately, most of these more stable risk factors lack sufficient sensitivity, specificity, and predictive accuracy to pinpoint the patient at risk with a degree of accuracy that would permit using a specific therapeutic intervention before an actual event. This probably relates, at least in part, to the transient nature of many risk factors, such as myocardial ischemia and reperfusion; hemodynamic dysfunction; abnormalities in electrolytes, such as hypokalemia and hypomagnesemia, often due to diuretics; changes in pH or PO2; the

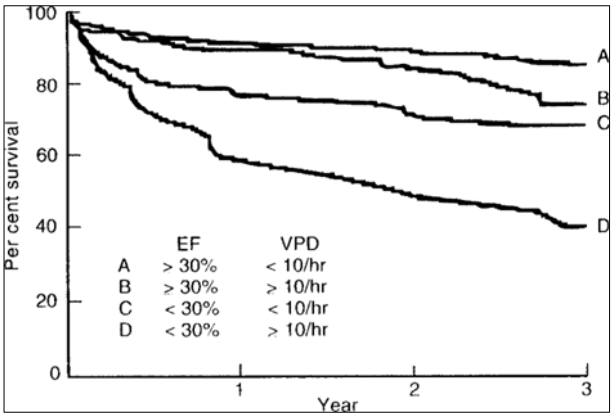

Fig 5: Relationship between left ventricular ejection fraction (EF) and ventricular premature depolarizations (VPD) and sur- vival during 3 years of follow-up after myocardial infarction. Reproduced with permission from Bigger JT. Relation between left ventricular dysfunction and ventricular arrhythmias after myocardial infarction. *Am J Cardiol*. 1986;57:8B

influence of central and peripheral neurophysiological actions; and the transient effects of toxins such as drugs [28] or alcohol [1, 2]. Structural cardiac abnormalities of the myocardium, coronary arteries, or cardiac nerves provide the substrate on which a transient risk factor operates. Although it is possible that intense functional changes alone may create electrical instability of the normal heart to the degree that a ventricular tachyarrhythmia can be provoked, the vast majority of cardiac arrests occur in patients with hearts that have structural abnormalities. One group that was identified before a cardiac arrest with sufficient accuracy to warrant ICD placement was the MADIT population [29], who were post myocardial infarction and had spontaneous nonsustained ventricular tachycardia, inducible sustained ventricular tachycardia not suppressed by intravenous procainamide, and an injection fraction <35%.

As noted earlier, the most common structural abnormality is coronary atherosclerosis and its consequences, such as myocardial infarction. Interestingly, only ≈20% of patients who survive cardiac arrest develop features of a transmural myocardial infarction, and it is assumed that transient myo- cardial ischemia, perhaps caused by coronary spasm or unstable platelet thrombi [13, 30], plays an important role in precipitating a lethal ventricular tachyarrhythmia. Myocardial hypertrophy, congestive heart failure, and cardiac dilation [31, 32], as well as regional autonomic dysfunction [33, 34], all may be important. Although almost 50% of deaths in heart failure patients are sudden, among patients with cardiomyopathies, those with better-preserved functional capacity (NYHA func- tional classes I and II)

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have lower total death rates, but the fraction of all deaths that are sudden and unexpected is higher; among class IV patients, total death rates are higher, but the fraction of sudden deaths is lower; thus, the impact ofreducing sudden cardiac death in this population will be influenced by competing causes of other mechanisms of death [1, 2]. Time of day is also important, with more sudden cardiac deaths, strokes, and myocardial infarctions occurring in the morning on arising from bed, perhaps related to increased sympathetic discharge in response to venous pooling that then triggers increased blood viscosity and platelet aggregation [35]. The lack of association between the times of day in almost 600 patients who had at least 2 separate cardiac arrests supports the hypothesis that a person's activity may also play a role in triggering the cardiac arrest [36].

Thus, if structural factors for the most part only create a substrate on which the transient factors operate to initiate a ventricular tachyarrhythmia, risk identification requires finding those subjects whose inherent physiological characteristics make the initiation of electrophysiological instability more likely when these conditions are met. This requires clinically identifiable, genetically based or acquired, individual differences in the responses of membrane channels, receptors, exchangers, and pumps in the susceptible individual [2], a formidable challenge at present. Patients with the congenital long-QT syndrome (see below) serve as the prototypic example of the interaction between a molecular myocardial abnormality, an "ionopathy," and an inciting event, eg, exercise in LQT1 and sleep/rest in LQT3 [37]. Some patients may have a non– clinically manifest abnormality in repolarization, a latent form of long-QT syndrome, that becomes provoked only by exposure to certain drugs.[37] Thus, molecular abnormalities in the long-QT syndrome, as well as in conditions such as hypertrophic cardiomyopathy [38], help provide genetic markers of patients at increased risk.

An antiarrhythmic drug can create the abnormality on which a transient risk event, such as ischemia, interacts to provoke a lethal arrhythmia [39]. For example, in the CAST experience, despite the increased risk of sudden cardiac death established by the presence of complex forms of ventricular ectopy, particularly in older age groups and in patients post myocardial infarction, suppression of those ventricular ar- rhythmias with encainide and flecainide conferred an in- creased risk of death and/or no improvement in survival with moricizine [40]. Death among those treated with an antiarrhyth- mic drug may have resulted from an interaction between the substrate of coronary artery disease, the transient risk factor of acute myocardial ischemia, and the exacerbation of ische- mia-induced conduction slowing produced by drugs with negative dromotropic actions, such as encainide or flecain- ide [41]. The results of CAST taught us at least 3 important lessons: (1) that mechanisms responsible for premature ven- tricular complexes, which were suppressed, were different from mechanisms that caused sudden cardiac death, presum- ably from a ventricular tachyarrhythmia, which was in- creased; (2) that proarrhythmia from an antiarrhythmic agent could occur months after drug initiation and was not always an early event; and (3) that antiarrhythmic drugs could become a risk factor when the myocardial substrate changed, presumably when ischemia developed.

Electrophysiological End Points

Two tests that reflect autonomic actions on the sinus node can also be useful risk stratifiers. Baroreflex sensitivity, reflecting a vagal response to acute blood pressure elevation, is reduced in patients at risk of sudden cardiac death [42], and heart rate variability, a measure of beat-to-beat variations of sinus- initiated RR intervals, with its Fourier-derived parameters, is also blunted in these patients [43]. It is important to stress that both of these parameters judge autonomic modulation at the sinus node, which is taken as a surrogate for autonomicactions at the ventricular level. Autonomic effects at the sinusnode and ventricle can easily be dissociated experimentally [44] and may possibly be a cause of false-positive or false-negative test results.

According to chaos theory, apparently irregularly irregular events, such as ventricular ectopy, are nonrandomly distrib- uted in time, and their clustering can be quantified by fractal geometric analysis, which may help identify patients at risk for sudden cardiac death [45]. Late potentials, which are electrical activity in the microvolt range extending the duration of a filtered QRS complex and detected by signal-averaged ECG, has good negative predictive value but low positive predictive value in patients after myocardial infarction [1]. More recently, late potentials were not found to be useful in identifying patients who might benefit from ICD implantation and who were undergoing coronary artery bypass surgery [46].

T-wave alternans, that is, T-wave changes in alternate beats, can at times be visible in the scalar ECG and, when present, denote patients with an electrically unstable ventricle. Recently, T- wave alternans detectable only by computer averaging techniques has been used to identify patients at risk for subsequent ventricular arrhythmias [47]. Finally, electrophysio- logical studies to induce sustained ventricular arrhythmias can be useful to help select appropriate therapy, including drug therapy, catheter ablation, surgery, or ICD implantation, and in identifying high-risk patients such as those suitable for treatment with an ICD [29].

Disease States

Coronary Artery Disease

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As indicated earlier, at least 80% of patients who experience sudden cardiac death have coronary artery disease as the underlying anatomic substrate due to atherosclerotic changes of the coronary arteries. Nonatherosclerotic coronary artery abnormalities are important in only a very small number of sudden cardiac deaths and include problems such as coronary arteritis, embolism, dissection, and congenital malformations of anomalous origin of a left coronary artery from the pulmonary artery or of a left coronary artery from the right or noncoronary aortic sinus of Valsalva, passing between the aortic and pulmonary artery roots [1, 2].

In survivors of cardiac arrest, coronary heart disease with vessels exhibiting more than 75% cross-sectional stenosis are found in ≈40% to 86% of patients, depending on age and sex of the population studied. Although <50% of the patients resuscitated from ventricular fibrillation evolve evidence of myocardial infarction by elevated cardiac enzymes and <25% have Q-wave myocardial infarction, autopsy studies have reported that a recent occlusive coronary thrombus was found in 15% to 64% of victims of sudden cardiac death, caused by ischemic heart disease, with many hearts showing plaque fissuring, hemorrhage, and thrombosis [48]. There ap- pears to be no specific pattern of distribution of coronary artery lesions that favors the development of sudden cardiac death. Abrupt changes in regional myocardial blood flow due to alterations in coronary artery structure and/or function, such as spasm, platelet thrombi, dissection, plaque rupture, or other vasoactive events can provoke acute ischemia [13, 30]. Transition of stable atherosclerotic plaques by fissuring that leads to platelet activation and aggregation followed by thrombosis formation, as well as other biochemical events that can have a direct effect on electrophysiological proper- ties of the heart, may be important in provoking ventricular arrhythmias [13, 30]. Healed infarctions are present in ≥50% of hearts of sudden cardiac death victims at autopsy and in those of survivors of cardiac arrest. Interestingly, chronic ischemia may exert a protective effect by causing the development of coronary collaterals that can help mitigate the extent of ischemia produced by sudden coronary occlusion. Therefore, an acute occlusion of a minimally stenosed coronary artery can result in a more disastrous outcome than occlusion of a severely stenosed coronary artery with the jeopardized myo- cardium protected by collaterals.

Cardiomyopathy

Cardiomyopathies represent the second largest group of patients who experience sudden cardiac death. Hypertrophic cardiomyopathy has a prevalence of ≈2 in 1000 young adults and an incidence of sudden cardiac death of 2% to 4% per year in adults and 4% to 6% per year in children and adolescents [49] (Figure 3). In patients with hypertrophic cardio-myopathy, a history of sudden cardiac death or sustained ventricular tachycardia, family history of sudden cardiac death, a diverse genotype, recurrent syncope, multiple epi- sodes of nonsustained ventricular tachycardia, and massive left ventricular hypertrophy are the strongest risk factors for sudden cardiac death [38, 49]. Multiple mechanisms may be re- sponsible, including arrhythmias, abrupt hemodynamic dete- rioration, and/or ischemia. Hemodynamic and echocardio- graphic variables are generally not useful in identifying patients at high risk for sudden cardiac death, and the results of ambulatory ECG monitoring and invasive electrophysio- logical study are controversial [49]. The presence of mutations in the α-tropomyosin as well as in the β-myosin heavy chain gene has been associated with sudden cardiac death [38, 49].

Idiopathic dilated cardiomyopathy is a substrate for ≈10% of sudden cardiac deaths in the adult population. Mortality in patients with idiopathic dilated cardiomyopathy ranges from 10% to 50% annually, depending on the severity of the disease. In a compilation of 14 studies including 1432 patients, mean mortality rate after a follow-up of 4 years was 42%, with 28% of deaths classified as sudden [50]. The presence of nonsustained ventricular tachycardia in this group identi- fies a population at high risk of sudden death, presumably on the basis of a ventricular tachyarrhythmia [18]. Bundle-branch reentry can be an important cause of ventricular tachycardia in patients with dilated cardiomyopathy.[51] The terminal eventcan also be asystole or electromechanical dissociation, par- ticularly in patients with advanced left ventricular dysfunc- tion [23]. Multiple triggering events in heart failure patients include myocardial stretch, neuroendocrine factors, electro- lyte abnormalities, proarrhythmic effects of antiarrhythmic drugs, and excessive activation of the sympathetic and renin- angiotensin systems [31]. Syncope in heart failure patients appears to be an important clinical variable that also identifies patients with a higher risk of sudden cardiac death [50].

Arrhythmogenic right ventricular dysplasia is a particular kind of cardiomyopathy responsible for sudden death in young individuals and adults, with a gene defect recently localized to chromosomes 1 and 14 q23-q24 [11, 52]. It occurs asa familial disorder in ≈30% of cases, with autosomal domi- nant inheritance. Exercise can precipitate ventricular tachycardia in these patients, with an annual incidence of sudden death estimated to be ≈2%. Two pathological pat- terns, fatty and fibrofatty myocardial infiltration, have been identified. In the fibrofatty variety, myocardial atrophy ap- pears to be the consequence of acquired injury and myocyte death and repair by fibrofatty replacement, mediated by patchy myocarditis. Apoptosis may be important. The left ventricle and ventricular septum can be involved in 50% to 67% of cases, often later in the disease, confirming a poor prognosis [52]. ECG during sinus rhythm often exhibits T-wave inversion in V1 to V3 or complete or incomplete right bundle-branch block, and the ventricular

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tachycardia has a left bundle-branch block contour, with the frontal-plane axis reflecting the site of origin in 1 of 3 predilection sites for ventricular fatty degeneration: right ventricular inflow and outflow tracts and apex, the so-called "triangle of dysplasia. "During sinus rhythm, intraventricular conduction may be sufficiently slow as to produce a terminal notch on the QRS complex that Fontaine called an epsilon wave (Figure 6).

Left Ventricular Hypertrophy

Left ventricular hypertrophy, whether established by ECG or by cardiac echo, is a strong independent risk factor for cardiovascular deaths and, in particular, sudden cardiac death in patients who also had a history of hypertension. Multiple disease states can result in hypertrophy, including valvular heart disease, obstructive and non-obstructive hypertrophic cardiomyopathy, primary pulmonary hypertension with right ventricular hypertrophy, and various congenital heart disorders. Although ventricular repolarization (QT interval) is prolonged in hypertensive hearts, potentially setting the stage for triggered activity (see below), myocardial ischemia, interstitial fibrosis, and electrolyte disturbances can all contribute to the genesis of ventricular tachyarrhythmias [1].

Valvular Disease

The risk of sudden death in asymptomatic patients with aortic valve disease appears to be low. After prosthetic or hetero- graft aortic valve replacements, patients remain at some risk for sudden cardiac death caused by arrhythmias, prosthetic valve dysfunction, or coexistent coronary artery disease. Hence, sudden cardiac death has been reported to be the second most common mode of death after valve replacement surgery, with an incidence of ≈2% to 4% over a follow-up of 7 years, accounting for ≈20% of the postoperative deaths [1].

Whether mitral valve prolapse causes sudden cardiac death is unresolved. Its prevalence is so high that its presence may be just a coincidental finding in victims of sudden cardiac death and not causally related [1]. However, patients with mitral valve prolapse who have mitral regurgitation and left ventric- ular dysfunction or myxomatous degeneration of the valve

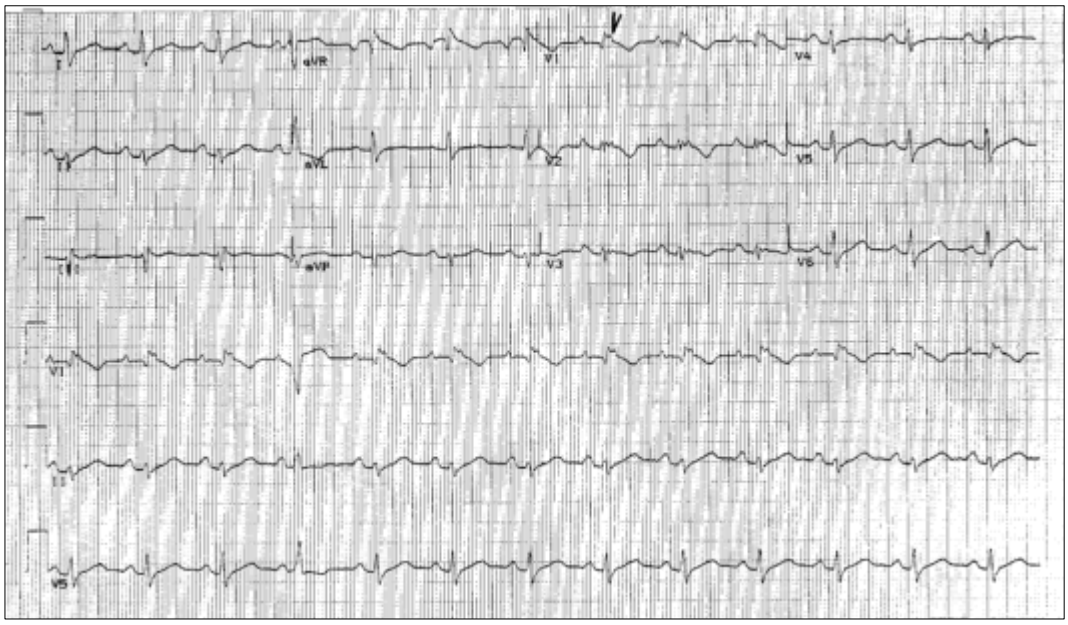

Fig 6: Epsilon wave (arrowhead) in a patient with arrhythmogenic right ventricular dysplasia

are clearly at higher risk for complications, such as infective endocarditis, cerebroembolic events, and sudden cardiac death.

Congenital Heart Disease

An increased risk of sudden cardiac death due to arrhythmias has been found predominantly in 4 congenital conditions, including tetralogy of Fallot, transposition of the great arter- ies, aortic stenosis, and pulmonary vascular obstruction. Sudden cardiac death has also been described as a late complication after surgical repair of complex congenital cardiac lesions, such as tetralogy of Fallot and transposition of the great arteries, and in patients with primary or secondary pulmonary hypertension. In tetralogy of Fallot, QRS prolon- gation relates to right ventricular size and predicts patients at risk for sudden cardiac death [53].

Primary Electrophysiological Abnormalities

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Patients with primary electrophysiological abnormalities rep- resent a group in whom mechanical function of the myocar- dium is normal and an electrophysiological derangement represents the primary cardiac problem. This includes pa- tients with the congenital long-QT syndrome, Wolff- Parkinson-White syndrome, several types of distinctive ven- tricular tachycardias, idiopathic ventricular fibrillation [54] (including a newly described entity characterized by right bundle-branch block and ST-segment elevation, Brugada's syndrome) [55], congenital complete AV block, and a variety of acquired abnormalities, such as the acquired long-QT syn- drome and acquired diseases of the sinus node, AV node, and His-Purkinje system, such as Lenegre's disease or Lev's disease [2]. Isolated cardiac conduction disturbances can be due to an autosomal dominant defect that includes various com- binations of bundle-branch or fascicular blocks [56]. It is impor- tant to remember that the absence of structural abnormalities is established by relatively gross tests, such as cardiac catheterization and echocardiography. Other imaging tech- niques, for example, those that evaluate sympathetic neural function, are often abnormal in these patients. [57] With the development and validation of new diagnostic tools, includ- ing autonomic imaging by positron emission tomography, genetic testing [58], and magnetic resonance imaging, many forms of "idiopathic" sudden cardiac death in patients with apparently structurally normal hearts may have to be reclas- sified, because these patients may become identified as having a specific structural and/or genetic abnormality. A fascinating recent discovery is that the gene responsible for the Brugada syndrome, the cardiac sodium channel gene *SCN5A* on chromosome 3 [58], is the same gene, with different defects, that causes LQT3 syndrome [37] (Table 1).

The idiopathic (congenital) long-QT syndrome is caused by prolongation of repolarization due to abnormal movementof sodium ions into or potassium ions out of the cardiac myocyte, creating prolonged periods of intracellular positiv- ity [37]. Such prolongation of repolarization can lead to thedevelopment of early afterdepolarizations (Figure 7). A specific kind of ventricular tachycardia called torsade de pointes occurs in patients with the long-QT syndrome, whether congenital or acquired (Figure 8). In addition toprolonged repolarization, ECG characteristics of this congen- ital disorder include abnormal T-wave contours, T-wave alternans, a relative sinus bradycardia, and torsade de pointesthat can produce syncope and sudden cardiac death. Genetic heterogeneity (Table 1) may make therapies specifically targeted for the electrophysiological abnormality somewhat difficult. Syndromes LQT1 through LQT5 are inherited as

Table 1: Genetics of the Long-QT Syndrome

	LQT1	**LQT2**	**LQT3**	**LQT4**	**LQT5**
Chromosome locus	11p15.5	7q35-36	3p21-24	4q25-27	21q22.1
Gene mutation/protein	KvLQT1	HERG	SCN5A	?	KCNE1*
Current/channel (subunit)	IKs (α)†	IKr	INa	?	IKs (β)†
Channel function	Reduced function	Reduced function	Gain of function	?	Reduced function
Action potential	Delayed phase 3	Delayed phase 3	Prolonged phase 2	?	Delayed phase 3
Clinical syndrome					
Heterozygous mutation	R-W	R-W	R-W	R-W	R-W
Homozygous mutation	J-L-N	NR	NR	NR	J-L-N

R-W indicates Romano-Ward syndrome; J-L-N, Jervell and Lange-Nielsen syndrome with deafness; and NR, not reported.

*KCNE1 is also referred to as minK.

†The KvLQT1 gene encodes the α-subunit protein of the IKs channel, with the KCNE1 gene encoding the β-subunit protein of this same channel. The α- and β-subunit proteins combine together to form a cardiac potassium channel expressing the I Ks current. Reproduced with permission from Reference 37.

autosomal dominants, whereas the Jervell-Lange-Nielsen syndrome, dominant for the long-QT manifestation, is reces- sive for the associated deafness and appears to be due to the presence of both alleles responsible for LQT1. The incidence of cardiac events is higher in LQT1 and LQT2 than in LQT3, whereas the lethality of cardiac events is higher in LQT3 than in LQT1 and LQT2 patients.[37] Interestingly, atrial tachyarrhythmias, induced in an animal model by mecha- nisms similar to those that cause torsade de pointes in the

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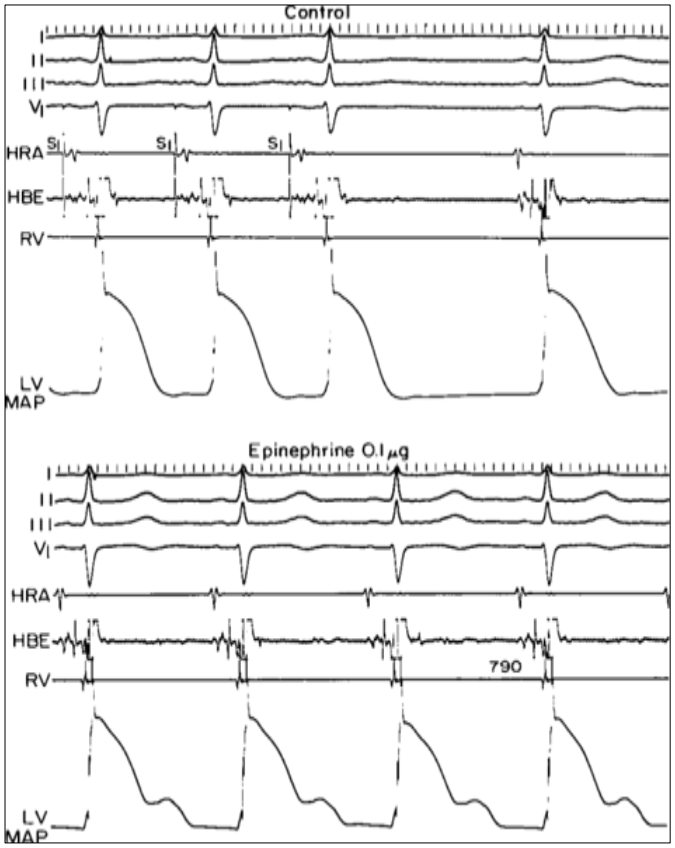

Fig 7: Early afterdepolarizations induced after epinephrine infusion shown in monophasic action potential recording from left ventricle from patient with congenital long-QT syndrome (ge- notyped not to be LQT1, LQT2, or LQT3).

Ventricles [59], do not seem to be important clinically, even though the same ionopathy affecting the ventricles should be present in the atria.

Patients with the Wolff-Parkinson-White syndrome have a risk of sudden cardiac death <1 per 1000 patient-years of follow-up. Almost all survivors of sudden cardiac death with Wolff-Parkinson-White syndrome have had symptomatic ar- rhythmias before the event, but up to 10% experience sudden cardiac death as their first manifestation of the disease [60]. The responsible mechanism most probably is the development of atrial fibrillation, with rapid conduction to the ventricles over the accessory pathway that produces ventricular rates so rapid that the rhythm degenerates to ventricular fibrillation (Figure 9). The best predictor for development of ventricular fibril- lation is a rapid ventricular response over the accessory pathway during atrial fibrillation, with the shortest interval between ventricular beats conducted over the accessory pathway ≤250 ms. Although this response identifies virtually 100% of patients at risk for developing ventricular fibrilla-tion, its specificity is low, because it may be found in 20% of asymptomatic patients with Wolff-Parkinson-White conduc- tion and 50% of those with mild to moderate symptoms due to atrioventricular reentrant tachycardia.

Idiopathic ventricular tachycardias with monomorphic contours that occur in patients with apparently structurally normal hearts include paroxysmal and repetitive forms that originate from the region of the right ventricular outflow tract. This ventricular tachyarrhythmia characteristically has a left bundle-branch block contour and inferior axis and pos- sesses the unique quality of termination with vagal maneu- vers such as adenosine infusion [61]. Far less common is a ventricular tachycardia from the left ventricular outflow tract. A left septal ventricular tachycardia arises in the left posterior septum and is sometimes called a fascicular tachycardia because it is often preceded by a fascicular potential. It has a right bundle-branch block, left-axis-deviation contour. Cal- cium channel blockers characteristically suppress this ar- rhythmia. Sudden cardiac death rarely occurs in this population.

Several types of idiopathic polymorphic ventricular tachycardias have been described and are associated with a

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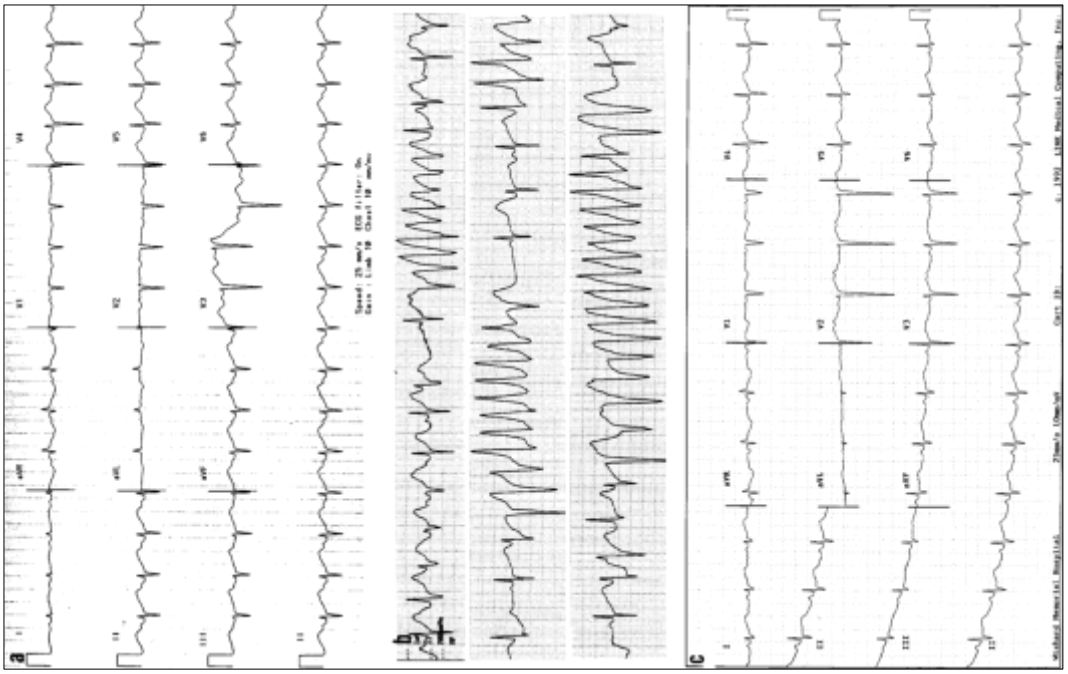

Fig 8: Torsade de pointes. Note typical "twisting about on its points" that is characteristic of this ventricular tachycardia associated with long-QT syndrome, in this instance in a patient who developed a prolonged QT interval (a) and torsade de pointes (b) after just 50 mg hismanol. c, Reversion of QT interval to normal after drug cessation.

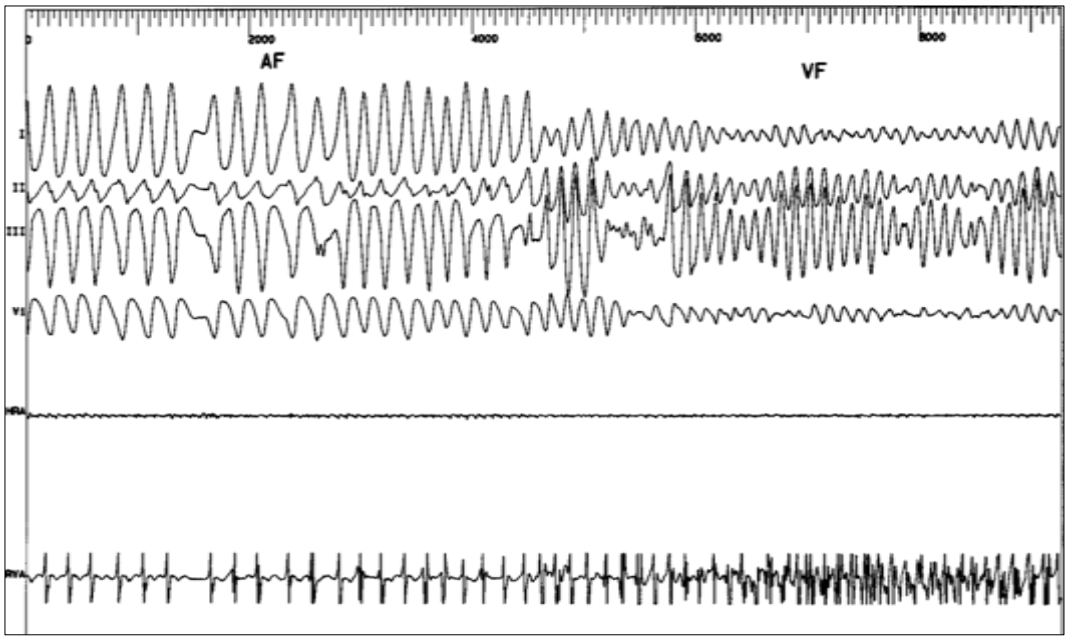

Fig 9: Atrial fibrillation with rapid ventricular response due to conduction over an accessory pathway degenerating into ventricular fibrillation. Reproduced with permission from Zipes DP. Specific arrhythmias: diagnosis and treatment. In: Braunwald E, ed. *Heart Dis- ease: A Textbook of Cardiovascular Medicine*. Philadelphia, Pa: WB Saunders; 1997:674.

less favorable outcome than the idiopathic monomorphic ventricular tachycardias noted above. They may occur as sporadic or familial forms, frequently precipitated by cate- cholamine release during physical or emotional stress. Pa- tients with catecholaminergic polymorphic ventricular tachycardia apparently have a favorable response to β-blockade therapy, whereas those with idiopathic ventricular fibrillation or short coupled torsade de pointes may not.

Sudden cardiac death can occur in patients with poly- morphous ventricular tachycardia who have normal QT intervals and normal systolic cardiac function; closely cou- pled premature complexes can initiate the spontaneous epi- sodes [62]. Perhaps related is a similar ventricular tachyarrhythmia characterized by a torsade de pointes con- tour and normal QT interval and initiated by premature ventricular complexes with extremely short coupling intervals [63].

Sudden cardiac death due to primary ventricular fibrilla- tion, ie, without apparent evidence of structural

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heart disease (see above) [54], occurs in ≈5% of victims of sudden cardiac death. Preliminary data suggest that these patients have a 30% recurrence rate of ventricular fibrillation, syncope, and car- diac arrest, and it is important to stress that their survival is largely related to potentially controllable or reversible elec- trophysiological disturbances rather than death due to ad- vanced heart disease. ICDs should be particularly useful in these patients [64].

Sudden unexplained nocturnal death can occur in young, apparently healthy, males of Southeast Asian origin and has several names, such as lai-tai (sleep death, Laos), pokkuri

Table 2: Secondary Causes of Acquired QT Prolongation

Antiarrhythmic agents
Class IA: quinidine, procainamide, *N*-acetylprocainamide, disopyramide
Class III: amiodarone, low risk of torsade de pointes
Class IV: bepridil, mibefradil
Antihistamines
Terfenadine
Astemizole
Antimicrobials
Erythromycin
Trimethoprim-sulfamethoxazole
Claritromycin
Cotzimoxazole
Azithromycin
Ketoconazole
Pentamidine
Chloroquine
Gastrointestinal
Cisapride
Liquid protein diets
Anorexia nervosa
Lipid lowering
Probucol
Psychotropic agents
Tricyclic and tetracycline antidepressants
Haloperidol
Phenothiazines
Risperidone
Selective serotonin reuptake inhibitors
Other agents
Organophosphates
Diuretics (reduced K^+, Mg^{2+})
Vasopressin (severe bradycardia)
Chloral hydrate amantadine
Electrolyte abnormalities
Hypokalemia
Hypomagnesemia
Hypocalcemia

Autonomic Nervous System

Abnormalities of the autonomic nervous system appear to be involved in the genesis of sudden cardiac death.[8] Myocardial infarction, for example, produces regional cardiac sympa- thetic and parasympathetic dysfunction not only in the in- farcted area but also in regions apical to the infarct, presum- ably because of interruption of afferent and efferent nerve fibers traversing the infarct (Figure 10). Similar changes have been found in patients after myocardial infarction [8]. Dener- vated regions show supersensitivity to catecholamine infu- sion, with disproportionate shortening of refractoriness that creates autonomic heterogeneity, resulting in dispersion of refractoriness and/or conduction, which can be conducive to development of ventricular arrhythmias [8]. Similar increased dispersion of refractoriness can occur after ventricular dila- tion and heart failure. Any process that creates electrical heterogeneity favors the development of ventricular fibrilla- tion. Recent data indicate that sympathetically denervated ventricular myocardium demonstrates abnormal oxygen uti- lization, which could also affect arrhythmogenesis

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(G.D. Hutchins, PhD, unpublished observations, 1998).

Most data suggest that vagal stimulation, profibrillatory for the atria, mitigates the development of ventricular arrhyth- mias in a variety of experimental situations. Whether para- sympathetic stimulation is protective because of a direct electrophysiological effect on ventricular myocardium, by opposing sympathetic actions, or by albeit minimally pro- longing refractoriness [8] is not known. Because it is difficult to study the effects of vagal activity on ventricular electrophys- iological properties noninvasively in humans, the behavior of the sinus node has been used as a surrogate for ventricular actions by measurement of indices of heart rate variability (reflecting primarily tonic vagal action) and evaluation of baroreflex sensitivity (as a measure of reflex vagal activity). Responses can be misleading because vagal actions at the sinus node and ventricles can easily be dissociated [44], as mentioned earlier. Reductions in heart rate variability [43], as well as baroreflex sensitivity [42], identify patients at risk for a subsequent cardiac event. An increase in vagal tone in animals [66] and patients [67] has been achieved by scopolamine patches, without a clear benefit on preventing ventricular arrhythmias. In contrast, exercise conditioning in animals, demonstrated to increase vagal "tone," has been shown to have a protective effect on preventing ventricular fibrillation in dogs with coronary occlusion [8]. Naturally, exercise conditioning does many things that may be unrelated to neural function. Vagal stimulation can terminate a specific type of ventricular tachycardia originating in the right ventricular outflow tract [61], but neural innervation at that site may be unique [8].

Mechanisms

In one sense, sudden cardiac death can be considered an electrical accident because, although many individuals have anatomic and functional substrates conducive to developing a life-threatening ventricular tachyarrhythmia and many pa- tients have transient events that could predispose to the initiation of ventricular tachycardia or ventricular fibrillation, only a relatively small number of patients actually do develop sudden cardiac death. It is this interplay between the anatomic and functional substrates, modulated by the transient events that perturb the balance, and the impact of all 3 on the underlying potential arrhythmia mechanisms possessed by all hearts that precipitates sudden cardiac death [, 2, 35] (Figure 11). Understanding this is critical to understanding the pathophys- iology of sudden cardiac death.

The figure also indicates the complexity as well as the potential variations in the inciting factors, because each category in the Venn diagram can interact with the others in almost endless permutations and combinations. Most often, interaction of a single item in each circle with a single item in the other circle (points at which only 2 circles overlap) may normally be insufficient to produce sudden cardiac death, unless the single abnormality is extremely severe. For exam- ple, mild electrolyte abnormalities, such as a potassium concentration of 2.7 mEq/L, alone are usually insufficient to cause a problem. Even in a patient with stable coronary artery disease, that combination may not necessarily be lethal. However, if the patient had preexisting reentry pathways in the ventricular myocardium, perhaps due to an old infarction, then the combination of the 3, ie, coronary artery disease,

Fig 10: Autonomic denervation after myo- cardial infarction. Extent of cardiac hydroxyephedrine (^{11}C-HED, sympathetic neu- rotransmitter taken up by prejunctional sympa- thetic nerve endings) defect exceeds reduction in myocardial blood flow (imaged by [^{13}N] am- monia, ^{13}N-NH3), consistent with regional sym- pathetic denervation after myocardial infarction. Image obtained with help of Gary Hutchins, PhD, and Erica D. Engelstein, MD.

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scarred myocardium, and hypokalemia, might now be suffi- cient to provoke a ventricular tachyarrhythmia, causing sud- den cardiac death. Changes in the anatomic substrate can alter the susceptibility of the myocardium to the effects of the transient initiating events. For example, experimental studies indicate that hypertrophied myocardium, as well as myocar- dium after a healed myocardial infarction, exhibits a greater arrhythmogenic response than normal tissue to the same

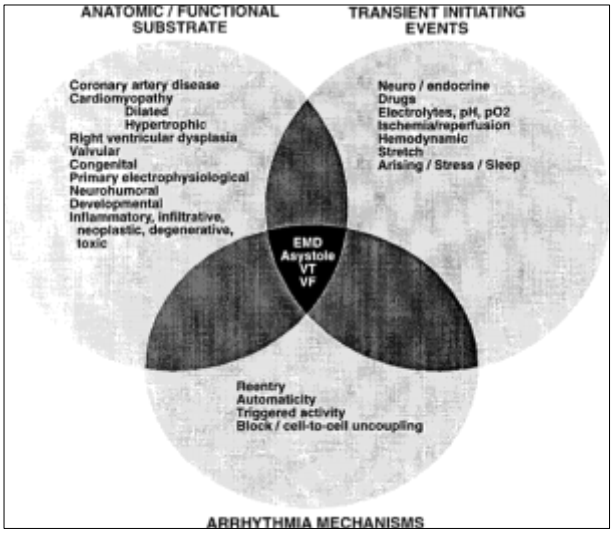

Fig 11: Venn diagram showing interaction of various anatomic/functional and transient factors that modulate potential arrhythmogenic mechanisms capable of causing sudden car- diac death

extent of acute ischemia [2]. Catecholamine release can modu- late some of the effects of acute coronary occlusion and reperfusion, and reduction in sympathetic action with drugs introduced to the pericardial sac to superfuse sympathetic nerves [68] can prevent ventricular arrhythmias. Conversely, acute ischemia alone, involving a sufficiently large area of myocardium in an otherwise normal ventricle, can precipitate ventricular fibrillation without interplay with other factors, although it is interesting to consider the many balloon angioplasties performed and the infrequent occurrence of ventricular fibrillation during that procedure. Perhaps the duration of the ischemia is too short to initiate ventricular fibrillation. Although unquestionably the above logic repre- sents a very simplistic synthesis (Figure 11) and actual mechanisms are more complex, nevertheless it offers a conceptual framework to understand the interactive forces precipitating sudden cardiac death.

In the experimental animal, a very definite set of arrhyth- mogenic intervals has been described after acute coronary occlusion, including an arrhythmogenic interval within the first few minutes after coronary occlusion that begins to abate after 30 minutes and reappears after several hours. In addi- tion, the initial 30 minutes of arrhythmias can be divided into the first 10 minutes, presumably directly related to the initial ischemic injury, and the second 20 to 30 minutes, related to either reperfusion or the evolution of different injury patterns in the epicardial and endocardial muscles and Purkinje fibers [1, 2]. In the ischemic myocardium, a dramatic reduction in tissue pH to <6.0, an increase in interstitial potassium levels to values >15 mmol/L, increases in intracellular calcium concentration, and neurohumoral changes all contribute to creating electrophysiological changes characterized by slowed conduction, reduced excitability and prolonged re- fractoriness, cell-to-cell uncoupling, and the generation of spontaneous electrical activity [69]. Other metabolic changes, such as accumulation of free fatty acids and their metabolites, formation of lysophosphoglycerides, and impaired myocar- dial glycolysis, may contribute to the development of elec trical instability leading to cardiac arrhythmiasv [1, 2]. Although reentry is considered to be a dominant mechanism responsi- ble for ventricular fibrillation, regional changes in automatic- ity, as well as triggered activity due to afterdepolarizations, are probably important as well. Reperfusion can also be arrhythmogenic, although the seriousness of this problem appears to be greater in the experimental animal than clinically.

Cardiac arrest due to severe bradycardia, asystole, or pulseless electrical activity (electromechanical dissociation) appears to be more common in severely diseased hearts, probably representing more global myocardial dysfunction [23]. The outlook for patients exhibiting these disturbances at the time of attempted resuscitation is worse than for patients who exhibit ventricular fibrillation at that time.

A major, if not the major, electrophysiological feature responsible for the initiation of ventricular fibrillation appears to be electrical heterogeneity. A heart that is totally homoge- neous electrically, that is, all cells are at the same stages of depolarization and repolarization and conduct normally with- out delay or block, very probably cannot develop ventricular fibrillation. However, even in the normal state, these condi- tions do not exist, because various cell types, eg, ventricular muscle versus Purkinje fibers, exhibit different action poten- tial characteristics, refractoriness, and conduction velocities. However,

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when heterogeneity becomes extreme, for instance, if one region of the myocardium exhibits ischemia-induced conduction delay and/or block that is different from neigh- boring regions, or when there is regional sympathetic dys- function[8] or unequal stretch [70] that can produce regional electrophysiological alterations, the stage becomes set for development of ventricular fibrillation. Such alterations can be provoked by anatomic/functional substrates and by tran- sient initiating events and can modulate basic arrhythmia mechanisms of reentry, automaticity, and triggered activity to provoke ventricular arrhythmias (Figure 11). Reentry appears to be the major mechanism responsible for ventricular ar- rhythmias due to acute and chronic coronary disease and must be dependent on heterogeneity. While we know a great deal about the electrophysiological alterations that accompany acute and chronic ischemia in a variety of experimental preparations, the events surrounding the onset of ventricular fibrillation in humans, even after 50 years of study, remain fairly opaque. The "holy grail" of the electrophysiologist to match a particular antiarrhythmic drug that has a specific mechanism of action to an arrhythmia caused by a unique set of electrophysiological alterations has, to date, still proved elusive. In fact, the only drugs shown to reduce mortality from sudden cardiac death are β-blockers and amiodarone (by meta-analysis) [71]. Neither drug has specific and single ion channel actions. The reason ICDs are so successful is that a "dose of electricity" is generic; ie, the mechanism causing the ventricular tachyarrhythmia and the nature of the underlying heart disease, both critical for antiarrhythmic drug effective- ness, are largely irrelevant.

Treatment

Because different electrophysiological mechanisms in the presence of different types of cardiac disease can cause sudden cardiac death and because many of the victims do not have symptoms or signs identifying them as being at high risk before the event, a preventive approach to the problem becomes complicated. Furthermore, to test the value of primary preventive measures such as abstinence from smoking, exercise, weight reduction, control of high blood pressure, and lipid abnormalities in patients without a history of cardiac disease, studies have to be performed in communitiesin which it is possible not only to randomize to preventive versus no preventive measures but also to register all cases of sudden deaths accurately, including the unwitnessed ones. Naturally, this is difficult, if not impossible. However, be- cause most cases of sudden cardiac death occur in the population with coronary artery disease, it is logical that in recent years most attention has been given to secondary preventive therapy in patients with proven coronary artery disease and especially to survivors of a myocardial infarction.

Risk Stratification for Treatment

During the past 2 decades, a number of tests have been developed to stratify cardiac patients as to their risk of dying

Table 3: Test Used for Risk Stratification for Sudden Death

Coronary perfusion
Coronary angiography
Exercise testing (including imaging)
ST-segment changes using ambulatory recordings
Pump function
NYHA functional class
Left ventricular ejection fraction
Exercise duration
Arrhythmias
Long-term ambulatory recordings
Signal-averaged ECG
QT-interval duration, dispersion, and dynamic changeT-wave alternans
Exercise testing
Programmed electrical stimulation
Neurohumoral
Heart rate variability
Baroreflex sensitivity
Psychosocial
Depression

suddenly. As shown in Table 3, these tests address different cardiac and noncardiac factors that have been shown to affect mortality. The relatively low positive predictive accuracy of these tests adversely

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affects their usefulness. At best, alone or in combination, the tests reach a positive predictive accuracy of 30%, indicating that if adequate protective treatment were available, 10 patients would have to be treated to save 3. Although this may not be a problem when low-cost, effective therapy free of adverse effects is possible, unfortunately, this is not the case.

Pharmacological Treatment

Of the different drugs that have been evaluated, only β- blockers and amiodarone have reduced sudden death in the myocardial infarction survivor [40]. Class I drugs (mexiletine, encainide, flecainide, moricizine), calcium antagonists, and class III drugs (*d*-sotalol, dofetilide) all failed to reduce or even increased the incidence of sudden cardiac death after a myocardial infarction [40, 41, 71, 72]. A major problem in drug treat- ment, as shown by the ESVEM study [73], is that noninvasive (Holter) and invasive (programmed stimulation of the heart) tests allow identification of an effective antiarrhythmic drug regimen in only a minority of patients with documented life- threatening ventricular arrhythmias. In a study from South America that included patients with different causes ofcardiac disease and diminished left ventricular function (ejec- tion fraction, <35%), empirical amiodarone was shown to beneficially affect mortality [18]. This was not confirmed in a multicenter VA trial, CHF-STAT [74]. Two recent studies using amiodarone in patients with reduced left ventricular function after a myocardial infarction showed a reduction in sudden (presumably arrhythmic) deaths but not in total number of deaths [75, 76]. Importantly, these studies showed no increase in mortality compared with placebo for patients treated with

Table 4: Measures to Reduce Sudden Death in Patients Known to Have Cardiac Disease

Correcting ischemia
Revascularization
β-Blocking agent
Preventing plaque rupture
Statin
ACE inhibitor
Aspirin
Stabilizing autonomic balance
β-Blocking agents
ACE inhibitor
Improving pump function
ACE inhibitor
β-Blocking agent
Prevention of arrhythmias
β-Blocking agent
Amiodarone

amiodarone, whereas a meta-analysis from 13 trials of 6500 patients treated with amiodarone after myocardial infarction or with heart failure showed a reduction in all-cause mortal- ity, death from arrhythmia, or sudden death [71]. Some data suggest that amiodarone may be more effective when used for patients with high (>90 bpm) resting heart rates. Preliminary data also suggest increased effectiveness when amiodarone is combined with a β-blocker. Both of these observations need further testing before adoption. The BHAT study showed that β-blockade with propranolol reduced all-cause mortality by 25% and that the drug was especially useful in patients with diminished left ventricular function and/or ventricular ar- rhythmias. No evidence indicates that selective β-blockers are better than nonselective ones. Although β-blocker therapy has been shown to be advantageous and should be prescribed for most patients after a myocardial infarction unless contra-indicated, in most countries a fraction of all patients who should receive a β-blocker after a myocardial infarction actually do so. This is especially true for women, diabetics, and the elderly [77].

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In view of the complexity of the mechanisms involved in sudden cardiac death, there has been growing interest in the use of measures that may halt or delay progress of cardiac disease or prevent disturbances in the autonomic balance of the heart, such as the administration of anti-ischemic drugs, drugs to prevent plaque rupture or thrombus formation, and drugs that stabilize the autonomic balance or improve pump function (Table 4). With this number and diversity of drugs, it has become increasingly difficult, if not impossible, to evaluate the individual contribution of each drug to the reduction in sudden cardiac death. Aggressive therapy using thrombolysis in acute ischemic syndromes or intracoronary interventions resulting in reduction of myocardial damage and scar formation and prevention of ventricular remodeling [13, 30] will diminish the occurrence of some of the mechanisms that play a role in a fatal arrhythmia. The role of specific potassium channel blockers like dofetilide and azi- milide needs to be established in the future.

Implantable Cardioverter-Defibrillator

For many patients who die suddenly, ventricular fibrillation is the culprit arrhythmia. Superiority of an ICD over antiar- rhythmic drug therapy (predominantly amiodarone) has been shown recently in the AVID trial [64] in this patient population. Results consistent with the AVID study were also reported from the CIDS [78] and the CASH [79] studies. At present, it is quite clear that an ICD is the initial treatment of choice for patients resuscitated from documented ventricular fibrillation not related to a reversible or transient cause such as an acute myocardial infarction, in patients with hemodynamically poorly tolerated VT, and probably in patients with a history of unexplained syncope in the presence of impaired ventricular function in whom a sustained ventricular arrhythmia can be induced during electrophysiological testing (Figure 12). The MADIT study included patients after a myocardial infarction

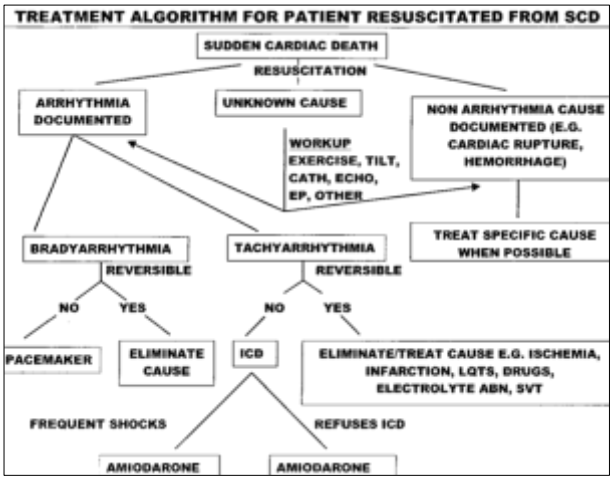

Fig 12: Treatment algorithm for patient resuscitated from cardiac arrest. Cath indicates catheterization; echo, echocardiography; EP, electrophysiological study; ABN, abnormality; and SVT, supraventricular tachycardia

The value of the ICD in patients with markedly diminished ventricular function in the absence of ventricular fibrillation, VT, or syncope, with or without a previous myocardial infarction, and with or without ambient ventricular ectopy is currently being evaluated. Trials like MUSST, MADIT-2, DEFINITE (Danish Investigations on Arrhythmias and Mor- tality on Dofetilide), ALIVE (azimilide postinfarct survival evaluation), and SCD-HeFT[26] all address patients with a 10% to 30% chance of dying within 2 years [80].

Again, we should realize that patients included in these trials represent a minority of the total number of patients who die suddenly out-of-hospital (Figure 1). Protection against sudden cardiac death by ICD implantation is expensive, as shown in the MADIT study ($27 000 per life year saved) [81], in which 100 devices had to be implanted to prevent 10 patients from dying suddenly, and therefore selection of the high-risk population must have very high predictive accuracy.

Out-of-Hospital Resuscitation

The majority of sudden cardiac death victims have no symptoms and are not identified as being at high risk before the event [82]. This stresses the enormous importance of improv- ing the outcome of resuscitation attempts outside the hospital (Figure 13). There is growing awareness that major changes are necessary to reach that goal. The short time frame after cardiac arrest during which circulation has to be restored to prevent death or irreversible cerebral damage is essential [83]. In the so-called chain of survival, several steps are crucial. The first step is to identify and locate the sudden cardiac arrest victim. In the Maastricht study, 80% of cardiac arrests occurred at home, and 40% were unwitnessed [3]. Therefore, we must have warning systems able to recognize cardiac arrest, to raise an alarm, and to

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transmit the exact location of the victim to providers of basic and advanced life support. Much attention has recently been given to public access defibrilla- tion, allowing nonphysicians to use widely distributed auto- mated external defibrillators to defibrillate [84]. In fact, it was

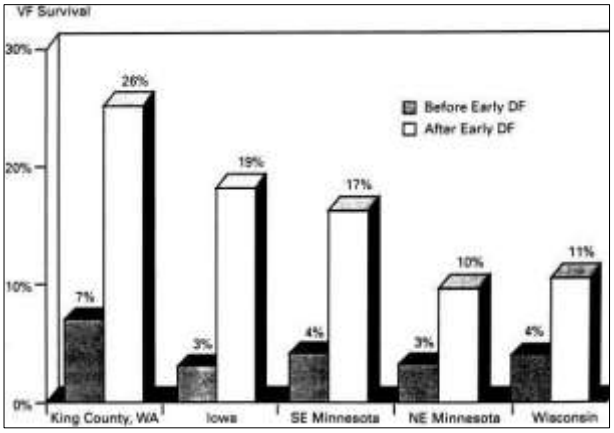

Fig 13: Survival before (open bars) and after (shaded bars) beginning early defibrillation pro- grams by emergency medical technicians. Repro- duced with permission from Ornato JP, Om A. Community experience in treating out-of-hospital cardiac arrest. In: Akhtar M, Myerburg RJ, Ruskin JN, eds. *Sudden Cardiac Death*. Baltimore, Md: Williams & Wilkins; 1994:450 – 462

suggested several years ago that external defibrillators be made "as common as fire extinguishers [85]," and they may have to be, to cover all the places a cardiac arrest can occur [86]. This idea has aroused a groundswell of enthusiasm but will obviously have the greatest impact when the sudden cardiac arrest victim is identified and located as soon as possible. The approach must be coupled with education, perhaps during the 4 years of high school [85], as well as legislative changes. When they function properly, devices that document cardiac arrest and locate the victim might be distributed initially to cohorts with known cardiac disease and then among asymptomatic people with risk factors for the development of cardiac disease. It will be more expensive for standard emergency medical systems to carry a defibrillator, but the potential impact on survival should warrant this approach.

Conclusions

Sudden cardiac death continues to be a major health issue. At present, although insight into mechanisms and circumstances of sudden cardiac death is increasing, our methods for identifying the high-risk candidate and predicting efficacy of measures to prevent sudden cardiac death are still inadequate. Because many victims are not known to suffer from heart disease and/or are considered to be at low risk for dying suddenly, more efforts are needed to improve out-of-hospital resuscitation by better warning systems and widespread availability of automated defibrillation devices. It is likely that these measures could increase the number of survivors of cardiac arrest. Implantation of the ICD, in many instances probably combined with an antiarrhythmic drug like amiod- arone, would then be used to maintain survival. Until we have better risk stratifiers and better methods of preventing ven- tricular tachyarrhythmias, the 2 major goals of the cardiolo- gist/electrophysiologist, that approach should still receive a major emphasis.

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