Sudden unexpected cardiac death generally occurs in persons with known or previously unrecognized heart disease. However, it has become evident that it occurs often enough in patients without any identifiable structural abnormality to warrant the cardiologist's attention. Mostly, it concerns young, active, and otherwise healthy individuals. This paper focuses on various categories of patients with life-threatening events considered to have occurred on a solely "electrical" basis. Currently, several entities are recognized with distinct electrophysiological abnormalities, including Wolf-Parkinson-White syndrome, long QT syndrome, the Brugada syndrome, short-coupled torsade de pointes, and catecholamine-induced polymorphic ventricular tachyarrhythmia. The remaining patients without such distinct abnormalities are categorized as having idiopathic ventricular fibrillation. Although mechanical cardiac function may seem normal, such patients might have certain discrete anatomic abnormalities, unidentifiable with current investigational tools. Possibly in the future, with development of newer and more sophisticated tools (magnetic resonance imaging, positron emission tomography, genetic testing), some or all cases of idiopathic ventricular fibrillation must be redefined as having specific genetic and/or anatomic bases. All patients successfully resuscitated from cardiac arrest due to ventricular tachyarrhythmia without clear precipitating factors (acute myocardial infarction, severe electrolyte or metabolic disturbances) are at high risk of recurrences. Long-term prophylactic therapy is indicated. Contrasting with older belief, survivors of idiopathic ventricular fibrillation are now also considered high-risk patients. The implantable cardioverter-defibrillator appears to be the safest and most effective therapy. (J Am Coll Cardiol 2004;43:1137–44) © 2004 by the American College of Cardiology Foundation

Sudden cardiac death (SCD) is defined as unexpected natural death from a cardiac cause occurring within a short time (generally within 1 h of onset of symptoms) in persons without prior conditions that would appear fatal (1,2). Most victims (>90%) have previously known or unrecognized cardiac abnormality (1–5). At autopsy, coronary artery disease, hypertrophic cardiomyopathy (with or without obstruction), and valvular aortic stenosis are the most common causes. Small percentages show no structural abnormalities. Evidently, however, SCD occurs often enough in patients with apparently normal hearts to warrant cardiologic attention. Sudden cardiac death has a bimodal incidence peaking between birth and six months (sudden infant death syndrome), and between 45 and 75 years of age, due to development of coronary artery disease. Patients without underlying disease, however, are usually strikingly younger (<40 years old) (1). Despite better pathophysiologic understanding and development of refined diagnostics and treatment modes, SCD remains a major issue. Annual numbers are 300,000 to 400,000 (U.S.) (2) and 30,000 to 40,000 (the Netherlands). Sudden cardiac death is mostly (80%) due to ventricular fibrillation (VF) or rapid ventricular tachycardia (VT) (1). The chance of reaching the hospital after successful resuscitation is small (<30%); the chance of leaving the hospital alive even smaller (6). Epidemiologic studies revealed that the overall group of cardiac arrest (VT/VF) survivors are at major risk of recurrent life-threatening events (25% to 40% within two years) if no or only empiric treatment is offered (7). Current agreement is that such patients should be analyzed in-hospital with extensive (non)invasive procedures to detect causes and mechanisms of death and to assess proper treatment. In patients without demonstrable underlying disease, certain electrical conditions are assumed to have led at some point to electrical derangement. In some patients, these are attributable to distinct primary electrophysiologic entities; in others, they remain unidentified. It should be realized that, although mechanical cardiac function may be (grossly) normal, patients might have discrete abnormalities, which are currently unidentifiable. This paper focuses on categories of patients suffering a life-threatening event (especially VF), in whom the cause is considered to have a solely "electrical" basis. As idiopathic VF can generally be diagnosed only after a battery of investigations, we will start with a survey of etiologies that should be considered first.
ASSOCIATED ABNORMALITIES

Conditions that may be associated with or may mimic SCD are summarized in Table 1 (8–22). Most VT/VF patients (80%) have atherosclerotic coronary artery disease; ≥50% have remote myocardial infarction. Ventricular tachycardia/ventricular fibrillation may also develop during acute coronary syndromes and coronary artery spasm (23). Cardiomyopathies form the second largest group of etiologies. Other conditions are rare. Genetic screening may be necessary for

Table 1. Abnormalities Associated With Sudden Death

<table>
<thead>
<tr>
<th>Coronary artery abnormalities</th>
<th>Atherosclerotic</th>
</tr>
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<tbody>
<tr>
<td>Nonatherosclerotic (arteritis, embolism, dissection, congenital malformations, anomalous origin of left coronary artery from pulmonary artery or right or noncoronary aortic sinus of Valsalva [artery passing between the aortic and pulmonary artery roots])</td>
<td>(8)</td>
</tr>
<tr>
<td>Myocardial abnormalities</td>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>(11)</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular dysplasia (congenital right ventricular cardiomyopathy)</td>
<td>(12,13)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>(14)</td>
</tr>
<tr>
<td>Sarcoïdosis or other infiltrative diseases</td>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td>Valvular and congenital heart disease</td>
<td></td>
</tr>
<tr>
<td>Other conditions</td>
<td>Aortic dissection</td>
</tr>
<tr>
<td>Acute cardiac tamponade</td>
<td>Rapid exsanguination</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Café coronary (15) (acute glottis obstruction by food)</td>
<td>Holiday heart syndrome (16)</td>
</tr>
<tr>
<td>Acute alcoholic states</td>
<td>Massive pulmonary embolism</td>
</tr>
<tr>
<td>Severe asthmatic attacks</td>
<td>Peripartum air or amniotic fluid embolism</td>
</tr>
<tr>
<td>Proarrhythmic effects*</td>
<td>Antiarrhythmic drugs (20,21)</td>
</tr>
<tr>
<td>Psychotropic agents, phenothiazines, antihistamines, antibiotics, gastrointestinal drugs</td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>Toxic substances</td>
<td>Electrolyte abnormalities (22)</td>
</tr>
</tbody>
</table>

Abbreviations and Acronyms

- AV = atrioventricular
- EPS = electrophysiologic study
- ICD = implanted cardioverter-defibrillator
- IVF-US = Idiopathic Ventricular Fibrillation Registry of the United States of America
- LQTS = long QT syndrome(s)
- SCD = sudden cardiac death
- U-CARE = Unexplained Cardiac Arrest Registry Europe
- VF = ventricular fibrillation
- VT = ventricular tachycardia
- WPW = Wolff-Parkinson-White

*Often (but not always) associated with QT prolongation (acquired long QT). Classic proarrhythmia usually occurs within days after initiation of treatment but may extend over one year of exposure (21).
Treatment. For symptomatic patients, catheter ablation is now first-choice therapy with >95% effectiveness. If ineffective, antiarrhythmic drugs prolonging the anterograde effective refractory period of the accessory pathway or cardiac surgery are alternatives. Consensus remains that in asymptomatic patients catheter ablation is not indicated (29). As SCD may be the first manifestation (28), and in view of current high success rates of catheter ablation, this opinion might need reconsideration.

CONGENITAL LONG QT SYNDROMES (LQTS)

Congenital LQTS (25,30) have long been considered idiopathic. At present, LQTS have been identified as genetically determined heterogeneous diseases affecting the potassium or sodium channels, and causing abnormally prolonged repolarization. This leads to QT prolongation on the ECG; the traditional criterion being a QT corrected for heart rate >0.44 s for men and >0.46 s for women (3,30).

Other ECG criteria are dispersion of (corrected) QT, abnormal STT wave contours, (macroscopic) T wave alternans, lower than normal heart rates, and the occurrence of sinus node pauses (30,31). When marked QT prolongation is present, the diagnosis is straightforward. For less clear cases, a scoring system has been introduced in which other characteristics (T-wave alterations, clinical phenotype, and family history) are taken into account (30). In the future, genetic screening will undoubtedly allow for more accurate establishment of the diagnosis.

Long QT syndrome patients carry a relatively high risk of development of polymorphic VTs called “torsades de pointes.” These are typical, rapid, polymorphic, but still organized VTs with progressive changes in morphology, amplitude, and polarity of the QRS complexes twisting around the isoelectric line. The long coupling interval (600 to 800 ms) of the initial complex is typical (32). Torsades de pointes are triggered by early afterdepolarizations, often (but not always) occurring in the setting of high adrenergic activity (physical or emotional stress, sudden arousal) (33). Although frequently causing loss of consciousness, they are often self-terminating, but sometimes deteriorate into VF. The clinical picture is sometimes mistaken for epileptic seizures.

Two major clinical LQTS have been characterized based on genetic transmission pattern: the more common autosomal dominant form with a pure cardiac phenotype, Romano-Ward syndrome (34,35), and the rare autosomal recessive form with coexisting congenital deafness, Jervell-Lange-Nielsen syndrome (36).

Genetic background. Genetic research has recently identified six loci and five genes associated with Romano-Ward syndrome. They are located on chromosomes 3, 4, 7, 11, and 21 (37). KvLQT1 (LQT1, chromosome 11), HERG (LQT2, chromosome 7), KCNE1 and KCNE2 (LQT5 and LQT6 respectively, chromosome 21) encode potassium-channel subunits, while SCN5A (LQT3, chromosome 3) encodes the cardiac sodium-channel. Homozygous mutations in KvLQT1 and KCNE1 are associated with the Jervell-Lange-Nielsen syndrome (37). For LQT4, the gene at chromosome 4 has not yet been identified. There are families with LQTS not linked to any of these five loci. So there must be other genes encoding LQTS. LQT1 and LQT3 are the most frequently encountered forms; LQT3, LQT4, and LQT5 are rare.

The incidence of cardiac events is higher in LQT1 and LQT2 than in LQT3 patients; however, the lethality of cardiac events is higher for LQT3 than for LQT1 and LQT2 patients (38). In LQT1 patients, torsades de pointes are especially triggered by physical stress, particularly swimming and diving; in LQT2 patients, by sudden arousal (33). In LQT3 patients, arrhythmias predominantly occur at rest or during sleep (38,39).

Sudden infant death syndrome. This is a leading cause of death in the first year of life. The incidence peaks between 5 and 12 weeks of age. The etiology is still unknown, although recent data suggest that it may be due to a subtype of LQT3 with low penetrance (40). Indeed, these entities have certain clinical features in common, such as the occurrence of SCD at rest or during sleep.

Treatment. For most patients with LQTS (LQT1, LQT2, LQT3, LQT4, and the Jervell-Lange-Nielsen syndrome), beta-blocker therapy is the first option with an often satisfactory response. In some cases, beta-blockers should be combined with high thoracic left sympathectomy (39). When still ineffective, pacemaker implantation to ensure stable heart rates may be necessary. If risk remains, implantation of an implantable cardioverter-defibrillator (ICD) is warranted. This should always be combined with beta-blockers, as shock delivery is associated with a strong adrenergic stimulus. For LQT3 patients, ICD implantation combined with beta-blockers would be first-choice therapy (38,39).

THE BRUGADA SYNDROME

In 1992, Brugada et al. (41) described eight cases of aborted SCD in patients without demonstrable structural cardiac disease and a peculiar ECG pattern consisting of (in)complete right bundle branch block or elevated J point in association with ST-segment elevation in leads V1 to V3, and a normal QT interval. The ST segments in the right precordial leads may either show an upward convex or a so-called saddle-back–shaped contour. Often, left axis deviation is also present (42). Since the first publication (41), more reports emerged, suggesting a disorder more common than previously assumed (42–45). At present, the diagnostic criteria for the Brugada syndrome are not unequivocal. The prerequisite is ST-segment elevation in the right precordial leads, but no consensus exists about the required amount of elevation (≥1 mm or ≥2 mm). Furthermore, the ST-segment abnormalities may have a dynamic character. They may be transient, at times even absent, or have a changing...
expression. The J-point elevation on the ECG may be exaggerated, but is sometimes only discernible after administration of a sodium-channel blocking agent (gilurysthal, flecainide, procainamide) (45). The J-point elevation may be due to a more prominent epicardial manifestation of the spike-and-dome action potential morphology, mediated by a transient outward potassium current (Ito) (45). Conditions that enhance Ito predispose the epicardium to regional all-or-none repolarization, resulting in dispersion of repolarization, which may lead to arrhythmias based on phase-2 re-entry. This phenomenon is most pronounced in the right ventricular free wall and outflow tract, which, therefore, have been suggested as the site of arrhythmia origin (41–45). Symptomatic patients either present with VF (73%) or syncope (27%) (44). However, individuals with a “Brugada” ECG may remain asymptomatic. Syncope and (aborted) SCD are specifically ascribed to the occurrence of rapid polymorphic VT/VF. In some cases, conduction defects such as atrial standstill have been described (46). During EPS, a prolonged HV-interval is often found. In about 75% of patients with the Brugada syndrome, polymorphic VT/VF is inducible (44). Monomorphic VTs (with left bundle branch morphology that seemed to originate in the right ventricle) occurring spontaneously and being inducible at EPS are quite unusual (47).

The Brugada syndrome may be a heritable disease, involving the SCN5A gene encoding the cardiac sodium-channel (43). Of interest, defects of the SCN5A gene are associated with both LQT3, Brugada syndrome, and familial conduction defects (familial Lenègre’s disease) (48). Also, the typical manifestations of LQT3 (QT prolongation) and Brugada syndrome (ST elevation in leads V1 to V3) may coexist in the same patients. Moreover, both diseases have the following clinical features in common: 1) suspected or certain lack of efficacy of beta-blockers; 2) high lethality during cardiac events; and 3) arrhythmias occurring at rest or sleep. These observations raise questions about the actual differences between LQT3 and the Brugada syndrome (40,46).

**Sudden unexpected nocturnal death syndrome.** Sudden unexplained death, occurring at night (usually during sleep), has been observed in apparently healthy Southeast Asian subjects (49–51). It is known under different names: bangungut (rising and moaning during sleep), Philippines; pokkuri (sudden unexpected death), Japan; and laitai (sleep death), Laos. Annual prevalences of 1:2,500 inhabitants (Thailand) and 1:1,000 (Laos) have been reported (51). Events are accompanied by night terrors and nocturnal vocalizations. Debate exists concerning possible cause(s) (2,3). A toxic cause has been suspected. Some pathologic examinations reported cardiomegaly and abnormalities of the specialized conduction tissue. Recent evidence suggests that the syndrome may, in fact, be an expression of the Brugada syndrome (51).

**Treatment.** Consensus exists that symptomatic patients fulfilling the criteria of the Brugada syndrome should receive an ICD (41–45). The same may apply to asymptomatic individuals who fulfill the ECG criteria of the syndrome and have a (malignant) family history of SCD.

**SHORT-COUPLED TORSADE DE POINTES**

In 1994, Leenhardt et al. (32) first described an entity of torsades de pointes in patients without demonstrable structural heart disease and without QT prolongation on the ECG. In contrast with LQTS patients, torsades de pointes were initiated by extremely short-coupled ventricular extra-systoles. A family history of SCD may be present in up to 30%. The arrhythmia is observed in the context of a particular profile of the autonomic nervous system with low heart rate variability and high sympathetic to parasympathetic ratio.

**Treatment.** Class I antiarrhythmic drugs, beta-blockers, and amiadarone appeared ineffective. Verapamil seemed to diminish the occurrence of torsades de pointes, but not the occurrence of SCD. Implantable cardioverter-defibrillator implantation seems the safest therapy.

**CATECHOLAMINE-INDUCED POLYMORPHIC VENTRICULAR TACHYARRHYTHMIA IN CHILDREN**

Serious ventricular tachyarrhythmia occurs rarely in children. A clearly defined entity, apart from LQTS, the Brugada syndrome, and the short-coupled torsades de pointes, is that of the so-called catecholaminergic polymorphic VT in childhood and adolescence. In 1975, Coumel et al. (52) first described four cases of severe ventricular arrhythmias in children with normal QT intervals. Ventricular tachycardia/ventricular fibrillation are reproducibly provoked by any form of sympathetic stimulation. Very recently, it was demonstrated that mutations in the cardiac ryanodine receptor gene (hRyR2) are responsible (53).

**Treatment.** Crucial is that these patients comply with beta-blockers. Analogies may exist between catecholamine-induced polymorphic ventricular tachycardias and LQTS. Genetic research may be required for further clarification. Implantable cardioverter-defibrillator treatment may become part of the therapy, although special attention should be given to the catecholaminergic influence of ICD shock delivery. As in LQTS, ICDs should never be implanted without concomitant beta-blockers.

**IDIOPATHIC VF**

**Terminology.** The remaining group of VF patients without identifiable structural heart disease is classified as having idiopathic VF. The syndrome has also been referred to as primary electrical disease (1), primary VF, or arrhythmic death without identifiable heart disease (3). These terms may be too broad or misleading. Therefore, idiopathic VF is presently considered the best terminology to acknowledge the current inability to identify a specific cause. This does not imply that a patient’s heart is completely free of any
structural or functional abnormality, but merely that if an abnormal finding (e.g., first-degree AV block or atrial fibrillation) is present, it is not considered responsible for the VF episode (3). Because idiopathic VF may not represent a homogeneous disease, future research may identify specific causes in certain subsets, as was the case for LQTS. Minor abnormalities. Current consensus is that some minor abnormalities, unknown to be associated with the occurrence of VF, do not rule out the diagnosis. A combined Task Force of the Unexplained Cardiac Arrest Registry of Europe (UCARE) and Idiopathic Ventricular Fibrillation Registry of the United States of America (IVF-US) (3) recently summarized a variety of minor abnormalities that may be compatible with a diagnosis of idiopathic VF. These include nonspecific biopsy findings, minor hemodynamic abnormalities, such as borderline right and left ventricular indexes, subtle wall motion abnormalities, and isolated mitral valve prolapse without valve redundancy, thickening, regurgitation, left ventricular dysfunction, QT prolongation or ST-T changes. There is general agreement that paroxysmal and chronic atrial fibrillation, per se, have no specific relation to SCD in the absence of WPW or hyperthyroidism or in persons <70 years old. Other findings not associated with SCD are first-degree AV block and temporary second-degree AV block (Wenckebach type) not associated with marked bradycardia, hypertension without left ventricular hypertrophy, isolated modest thickening of the interventricular septum or left ventricular free wall (<10% of normal), and isolated bundle branch block.

Incidence. Sudden cardiac death in patients without major underlying disease occurs infrequently although, in larger referral centers, percentages varying from 1% to 14% were reported (1); UCARE (3) reported a prevalence of about 5%. These estimates indicate that VF with absent organic heart disease may be more common than previously recognized.

Recurrence risk. Previously, prognosis was considered excellent (1,54). There appeared to be agreement that only symptomatic patients with recurrent arrhythmia should be treated. No particular efforts were directed toward identification of high-risk subgroups or SCD prevention. Data from several recent studies, however, suggest recurrence rates of VF, syncope, or cardiac arrest varying from 25% to 43% over longer follow-up (1,3).

In the early 1990s, our center was the first to report results of a prospective study of patients with primary electrical disease who survived a VF episode (1). The major finding of this study was the high recurrence rate of life-threatening events during long-term follow-up, in often young (<40 years) patients.

Until 1999, 37 survivors of out-of-hospital cardiac arrest due to idiopathic VF were referred to our institute. Mean age was 35 (range, 13 to 73) years. There were 26 males and 11 females. Mean follow-up was 77 ± 41 months. Total mortality was 3 of 37 patients (8%); 16 of the 37 patients (43%) had recurrent episodes of syncope, documented ventricular tachyarrhythmia, or SCD during follow-up. Figure 1 shows the Kaplan–Meier curve for survival free of these events. One patient died from a noncardiac cause after a 30-month follow-up. Previously, he had received shocks for documented VT/VF.

In our series, patients with (possible) ECG signs indicative of the Brugada syndrome were not excluded. Retrospective analysis showed that nine of 37 patients (24%) could have been classified as having Brugada syndrome based on the presence of (in)complete right bundle branch block and ≥1 mm ST elevation in the precordial leads V1 to V3. If the prerequisite amount of elevation would be ≥2 mm in leads V1 to V3, 3 of the 37 patients (8%) would have been classified as having Brugada syndrome. Recurrence rate was 3 of 9 (33%) in the patients with ≥1 mm ST–segment elevation, 2 of 3 in the patients with ≥2 mm ST–segment elevation, and 13 of 28 (46%) in the remaining patients.

Ergonovine testing was not performed routinely during baseline analysis before 1992 (1,23). However, in 11 patients included before 1992 who had received an ICD, ergonovine testing was done later, resulting in only one positive reaction. All together, positive ergonovine testing with completely normal coronary anatomy in our experience is very rare in this patient subset (1,55).

Treatment. In this subgroup, prognosis is mainly related to the ability to control the electrophysiologic derangements. Additional risk due to advanced myocardial disease is absent. Therefore, if the arrhythmic risk is controlled, prognosis of these patients may be similar to that of matched controls from the general population. Some authors have reported favorable results with class I antiarrhythmic agents guided by serial drug testing (56). However, in addition to uncertainties about long-term efficacy, patient compliance to antiarrhythmic drugs remains a major concern. Even if an antiarrhythmic drug regimen would be effective, it is well known that many patients (25%) discontinue their drugs over time, either because of adverse effects or due to negligence during event-free periods. Currently, there is consensus that, in these patients, preventive therapy with antiarrhythmic drugs, including beta-blockers, is in-

Figure 1. Kaplan–Meier curve showing survival free of major events (sudden death, recurrent episode of syncope, or documented ventricular tachyarrhythmia) of 37 consecutive patients with idiopathic ventricular fibrillation admitted to our center between 1985 and 1999.
sufficient and that ICD implantation is the safest and most effective secondary prevention therapy.

**DIAGNOSTIC EVALUATION**

**Noninvasive evaluation.** Idiopathic VF is a diagnosis by exclusion. Therefore, this diagnosis can only be made when thorough clinical evaluation does not provide evidence for structural heart disease or other known causes of VT/VF. It is recommended to perform an extensive evaluation using a predefined protocol. Acute myocardial infarction must be excluded, as well as transient and correctable causes of VT/VF (acute myocardial ischemia, metabolic or electrolyte disturbances, drug toxicity). After prolonged resuscitation (>15 min), a transient period of ventricular dysfunction may ensue, lasting for 48 h or longer. Therefore, ventricular function assessment should not be performed too soon after the index episode.

Baseline evaluation starts with a careful analysis of the patient's history, family history, use of drugs, complete routine physical examination, laboratory testing, and chest roentgenograms.

Laboratory testing should include serum measurement of electrolytes (potassium, calcium, magnesium), and thyroid function. Furthermore, analysis of possible drugs in the serum should be performed. It may be worthwhile to save some serum for later investigations. Urine testing may include vanilyl mandelic acid measurement and analysis of drug toxicity (3).

Electrocardiographic analysis includes (repeated) 12-lead ECGs, 24- to 48-h Holter monitoring, exercise testing, analysis of the response to the Valsalva maneuver (57), and arousal. Preexcitation and long QT interval patterns, either persistent or transient, must be excluded. To enable thorough analysis, it is mandatory that patients stay on telemetry monitoring during hospitalization. Further analysis may include signal-averaged ECG and measurement of heart rate variability and baroreflex sensitivity.

**Imaging techniques.** Echocardiography and Doppler screening must be performed to analyze ventricular wall motion and valvular function at appropriate timing after the index event. Contrast echocardiography may additionally be performed. Nuclear scintigraphic evaluation comprises assessment of left and right ventricular ejection fraction, and analysis of myocardial perfusion. Magnetic resonance imaging or positron emission tomography scanning may be of help to establish the diagnosis in patients with otherwise non-overt right ventricular cardiomyopathy or other congenital abnormality.

**Invasive evaluation.** Left and right heart catheterization must be performed including measurement of pressures and oxygen saturations (in the superior and inferior caval veins, right atrium, both ventricles, pulmonary artery and pulmonary wedge position, and thoracic aorta). Catheterization must include cineangiography of both ventricles and coronary angiography. Testing for coronary artery spasm should particularly be considered in the presence of hemodynamically insignificant coronary artery lesions (23). Myocardial bridging would lead to exclusion of the diagnosis of idiopathic VF only when accompanied by evidence of myocardial ischemia. Although not considered mandatory, multiple biopsies may be taken from the right ventricular endomycocardium.

Baseline EPS should be performed off antiarrhythmic drugs including analysis of sinus node recovery time and AV conduction parameters (1). Programmed electrical stimulation should be performed according to standard techniques and protocols, including burst pacing and—if necessary—isoproterenol infusion (1,58). End points of the procedure are completion of programmed electrical stimulation protocols or reproducible induction of VT/VF associated with hemodynamic collapse.

**Pharmacologic testing.** Ergonovine testing is advocated either during catheterization or at another stage under ECG monitoring, once the coronary anatomy is known. Administration of gilurythmal, flecainide, or procainamide (45) may be done during EPS or at another stage under careful ECG monitoring. Of note is that administration of these drugs in the presence of concealed Brugada syndrome may also provoke VT/VF.

**Genetic evaluation.** Advances in molecular genetics have shed new light on the mechanism of many disease states, including arrhythmias. Further progress may ultimately break down the enigma of idiopathic VF, much as it did so in the LQTS. At present, however, genetic analysis is time-consuming, costly, and not widely available. It is, therefore, not considered part of the routine diagnostic protocol. Moreover, other important questions need to be dealt with: 1) which patients should undergo genetic evaluation; 2) is genetic evaluation of the patient’s relatives indicated; 3) what are the consequences of such investigations for the patients and their relatives; and 4) genetic counseling. Elaboration of these questions is beyond the scope of this paper.

**Minimally required diagnostic tests.** For exclusion of underlying structural heart disease, the Joint Steering Committees of UCARE and IVF-US have advocated the following minimally required diagnostic tests: clinical history, physical examination, blood chemistry, ECG, exercise stress test, 24-h Holter recording, echocardiography, coronary angiography, right and left ventricular cineangiography, and EPS (3). Other investigations are strongly recommended but not mandatory.

**Evaluation during follow-up.** A disease is called idiopathic if present knowledge and investigational tools have not (yet) identified an underlying etiology. However, an index episode with electrical instability may be the first expression of structural cardiac disease not yet detectable at present. Currently, the absence of structural abnormalities is usually concluded from findings of relatively gross tests (cardiac catheterization, echocardiography). Possibly, development of newer and more refined diagnostic techniques
may change the situation. During follow-up, clinical reevaluation using noninvasive tests, such as ECG, Holter recording, echocardiography, and, eventually, magnetic resonance imaging must be repeated at certain intervals (e.g., once a year) to assess whether abnormalities develop over time.

**Summary.** Sudden cardiac death occurs in >90% of cases in persons with known or previously unrecognized structural or functional cardiac abnormalities. Coronary artery disease and cardiomyopathies are the predominant underlying abnormalities. A minority of patients does not show any abnormality. Currently, several entities are recognized without structural heart disease but with distinct electrophysiological abnormalities, including WPW syndrome, long QT syndrome, Brugada syndrome, short-coupled torsade de pointes, and catecholamine-induced polymorphic ventricular tachycardia (in children). In the remainder, some 5%, no such abnormalities are identifiable. Such patients are categorized as having idiopathic VF. Mostly, this concerns patients at a younger age (<40 years). Possibly in the future, with development of newer diagnostic tools (magnetic resonance imaging, positron emission tomography, genetic testing), some or all cases of idiopathic SCD may have to be redefined as having a specific genetic and/or anatomic basis.

All patients successfully resuscitated from VT/VF without clear precipitating factors (acute myocardial infarction or severe electrolyte or metabolic disturbances) are at high risk of recurrent events. Long-term preventive therapy is indicated. In contrast with earlier beliefs, survivors of idiopathic VF are now considered at high risk. In our experience, the recurrence rate of life-threatening episodes was as high as 43% after lengthy follow-up (77 ± 41 months). Preliminary data of U-CARE suggest a 30% recurrence rate. The ICD is the safest and most effective therapy.

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