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How to diagnose the cause of sudden cardiac arrest

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Abstract

Sudden cardiac death or sudden cardiac arrest (SCA) is defined as natural death that occurs within an hour of the onset of acute symptoms or during sleep due to a primary cardiac cause. Most cases of SCA are attributable to coronary artery disease, with occult cardiomyopathy or inheritable arrhythmic syndromes accounting for a minority of SCA. Diagnosing the cause of SCA has potential implications for the patient and the family, and demands a comprehensive approach. This review summarizes the potential causes of SCA and outlines a systematic diagnostic approach to the SCA survivor. (Cardiol J 2011; 18, 2: 210–216)

Key words: cardiac arrest, genetics, diagnosis

Introduction

Sudden death is defined as natural (non-traumatic) death that occurs within an hour of the onset of acute symptoms or during sleep [1]. Although sudden non-traumatic deaths are frequently attributed to cardiac disease, autopsy studies in unselected subjects suggest that about one third of sudden deaths have non-cardiac causes (eg: intracranial bleed, pulmonary embolism, acute asthma) [2]. The sub-division of sudden death based on underlying cardiac causes is defined as sudden cardiac death or sudden cardiac arrest (SCA). There may or may not be a pre-existing diagnosis of heart disease, but the time and mode of death are unexpected.

The reported incidence rates of SCA are variable. This variability is related to the study population and the inherent vagaries of classifying the mode and time of death, particularly in the absence of post-mortem studies. The incidence of SCA increases from less than 10 per 100,000 person-years in young healthy individuals (age < 35 years) to over 50 per 10,000 person-years in patients with structural heart disease, and the incidence is greater in males compared to females [3].

Coronary artery disease (CAD) and the associated complications account for the majority of SCA [4], and arrhythmic syndromes are often regarded the prima facie cause of SCA in the absence of significant CAD. Avoiding the pitfalls of misdiagnosis, the potential implications for the patient and the family demands a comprehensive and systematic approach for the identification of reversible or attributable causes in the SCA survivor. This review will outline a diagnostic approach to the SCA survivor.

Diagnostic strategy

A systematic approach to the evaluation of survivors of SCA should identify potentially correctable or reversible causes, underlying structural heart disease and the less common inherited arrhythmia syndromes. An explanation for SCA can be identified in the majority of survivors from routine diagnostic investigations (including coronary

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angiography and cardiac imaging), as SCA occurs most commonly in the context of structural heart disease.

The remaining patients with unexplained cardiac arrest based on initial diagnostic evaluation should undergo further systematic and progressive clinical testing, including cardiac imaging and provocative pharmacological testing. A cause can be identified in more than half of the patients with apparently unexplained cardiac arrest with this strategy of systematic diagnostic testing (Figs. 1, 2) [5]. The minority of patients without an identifiable cause despite this strategy of rigorous testing are diagnosed with idiopathic ventricular fibrillation.

Routine assessment/investigations

Clinical history

The value of a detailed clinical history cannot be overstated. Details of the circumstances preceding the cardiac arrest are crucial and witnesses may need to be interviewed. Cardiac arrest associated with exertion is suggestive of CAD [6, 7], but is also a well-recognized trigger in the less common inherited arrhythmic syndromes (eg: long QT syndrome [LQTS] and catecholaminergic polymorphic ventricular tachycardia [CPVT]) [8] and some cardiomyo-

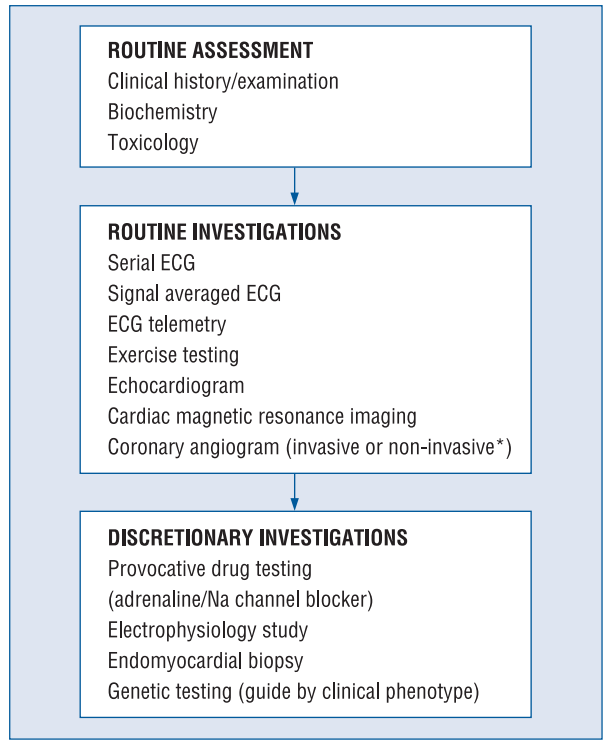

Figure 1. Progressive diagnostic evaluation of the sudden cardiac arrest survivor; *non-invasive assessment of coronary artery abnormalities by cardiac computed tomography or magnetic resonance imaging.

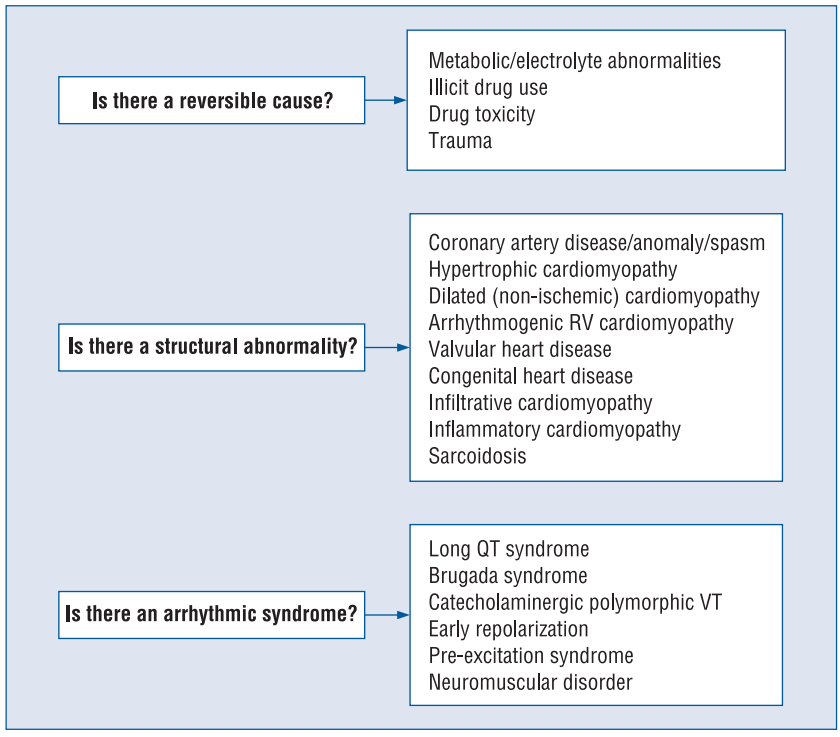

Figure 2. Causes of sudden cardiac death (idiopathic ventricular fibrillation is diagnosed in the absence of an identifiable cause from these investigations); RV — right ventricular; VT — ventricular tachycardia.

pathies. Febrile illness should raise suspicion of myocarditis, particularly if associated with features of heart failure. Ventricular arrhythmias may also be precipitated by febrile illness in patients with Brugada syndrome [9].

The family history is vital in the diagnostic evaluation of possible heritable arrhythmic syndromes. A simple inquiry restricted to premature deaths in first-degree relatives risks missing all but the most conspicuous patterns of phenotypic transmission of heritable conditions. A detailed inquiry should ideally include a three-generation pedigree of not only premature deaths, but also individuals with syncope, neuromuscular disorders, learning difficulties, unexplained single vehicle accidents, sudden infant deaths and even sensorineural deafness (Jervell Lange-Nielsen syndrome [10]). Multidisciplinary team support from clinical geneticists and genetic counselors is invaluable in the diagnosis of potential heritable arrhythmic syndromes, particularly if genetic assessment is considered.

The association between drugs and fatal ventricular arrhythmias is well documented. The use of QT prolonging drugs in susceptible individuals, or pharmacokinetic and pharmacodynamic drug interactions can increase the risk of ventricular arrhythmia. A detailed drug history should include the use of all drugs, whether prescribed, over the counter or recreational/illicit and supplements. A history suggestive of drug use should prompt toxicology screening in addition to routine biochemistry.

Electrocardiogram (ECG), telemetry and signal-averaged ECG

Serial ECGs are mandatory in SCA survivors for the diagnosis of acute myocardial ischemia/infarction, conduction abnormalities, and depolarization and repolarization abnormalities. Additional right-sided, lateral and posterior leads may be helpful if acute myocardial ischemia/infarction is suspected from adjacent standard leads or elevated markers of myocardial damage. Continuous ECG telemetry (> 72 h) can identify recurrent myocardial ischemia and sustained or non-sustained arrhythmias, and should be routine during hospitalization.

Bradyarrhythmias account for about 1 in 5 of all SCA based on recordings from ambulatory ECGs [11]. Myocarditis, infiltrative cardiomyopathies and neuromuscular disorders may be associated with significant conduction abnormalities. Paroxysmal atrio-ventricular block as a result of disease in the His-Purkinje system is characterized by an abrupt change from 1:1 conduction to complete heart block, which can lead to prolonged ventricular asystole or torsades de pointes [12]. A preceding history of syncope is common and normal 1:1 conduction on resting ECG does not exclude this condition. Diagnosis requires clinical vigilance, continuous ECG telemetry and serial ECGs. A prolonged PR interval (> 210 ms) may also identify patients with Brugada syndrome with SCN5A mutation [13].

Areas of myocardial necrosis, scar or ischemia result in inhomogenous ventricular depolarization and present a substrate for reentrant ventricular arrhythmias. This may manifest as additional notching (R' or S') or fragmentation of the QRS complexes on surface ECG. Quantitatively defined fragmentation of the QRS complexes based on specific scoring algorithms is associated with increased mortality [14] and arrhythmic events in patients with implantable defibrillators [15]. Areas of slow conduction due to myocardial scarring can also be detected as late potentials at the terminal portion of the QRS on signal-averaged ECG (SAECG). The latter is a useful tool to assess for a potential latent myopathic process such as arrhythmogenic right ventricular cardiomyopathy (ARVC), sarcoidosis, or myocarditis. A filtered QRS duration longer than 114 ms is the most sensitive parameter on SAECG at predicting the risk of sudden cardiac death [16]. Other parameters that are considered abnormal are low-amplitude signal duration ≥ 38 ms and a root mean square voltage of the terminal 40 ms of the QRS complex less than 20 μV at 40-Hz filter settings. These parameters in the SAECG have recently been included as minor criteria in the 2010 Task Force Criteria for the diagnosis of ARVC [17].

Sudden cardiac death related to abnormalities of ventricular repolarization (eg: long QT, Brugada and early repolarization syndromes) is well recognized. The T wave morphology and QT interval should be measured and adjusted for heart rate. Linear regression functions have been recommended for the adjustment of the QT interval for heart rate [18], but the Bazett formula (measured QT divided by the square root of the RR interval) [19] remains widely used. The method of QT adjustment for heart rate should be specified. Transient repolarization changes and QT prolongation related to acute myocardial infarction [20], anoxic brain injury [21] and induced hypothermia [22] is common. Conversely, repolarization changes may be absent on the resting ECGs in patients with congenital repolarization abnormalities. In this regard, serial ECGs and provocation testing are helpful (see below).

Coronary angiography

Coronary angiography is indicated in most cardiac arrest survivors. Conventional invasive coronary angiography is preferred in patients with clinical suspicion of CAD or evidence of myocardial infarction (eg: elevated cardiac enzymes or abnormalities on cardiac imaging). However, coronary angiography by computed tomography now offers a non-invasive alternative for the assessment of coronary artery anatomy, particularly in patients with low clinical suspicion of CAD (eg: young patients with no cardiovascular risk factors and normal left ventricular dysfunction).

Coronary spasm and consequent myocardial ischemia may precipitate ventricular arrhythmias [23]. Minor, non-obstructive coronary stenoses are typical in patients with coronary spasm, and a completely normal coronary angiogram is unusual [24]. Provocation testing with ergonovine or acetylcholine is generally limited to selected cases in view of the small risk of precipitating potentially fatal myocardial infarction and arrhythmias. Magnetic resonance imaging (MRI) detection of late gadolinium enhancement may be useful for detecting occult infarction that warrants consideration of a careful search for coronary spasm.

Cardiac imaging

Cardiac imaging in the SCA survivor aims to (i) assess cardiac morphology and function, (ii) characterize the cardiomyopathy, and (iii) stratify risk of adverse clinical outcomes and guide therapeutic interventions. This process often requires different imaging modalities. Echocardiography and cardiac MRI represent the dominant imaging modalities in clinical practice.

Echocardiography in the presence of good acoustic windows is a reliable imaging modality for the assessment of cardiac size/function and valvular abnormalities, but may be inadequate for the phenotypic characterization of the cardiomyopathy. In contrast to echocardiography, cardiac MRI has unrestricted range of tomographic planes and high spatial resolution, allowing excellent delineation of endocardial and epicardial borders and more reproducible data. As a result, cardiac MRI is now considered the 'gold standard' for the assessment of cardiac anatomy, chamber volumes and ventricular function. Angiography by cardiac MRI can also be used to assess coronary artery anomalies.

Cardiac MRI can identify and quantify myocardial scar/fibrosis by using specific inversion recovery gradient echo sequences at least 10 min after the intravenous injection of gadolinium-chelated contrast agents (late gadolinium enhancement). The pattern/distribution of late gadolinium enhancement can distinguish ischemic (typically sub-endocardial or transmural) from non-ischemic cardiomyopathy (mid-myocardial or epicardial). In addition, T2--weighted imaging, which highlights unbound water in the myocardium, can identify areas of edema associated with inflammation (such as myocarditis and sarcoidosis) or acute ischemia [25]. Myocardial fibrosis detected by late gadolinium enhancement on cardiac MRI is associated with increased frequency of ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy and hypertrophic cardiomyopathy [26–28].

T1-weighted images (with and without fat suppression) on cardiac MRI have been used to identify areas of fatty infiltration in the right ventricular wall, but this parameter has poor sensitivity and specificity for the diagnosis of ARVC [29]. In contrast, global or regional right ventricular wall motion abnormalities are specific (in experienced hands) and recognized as a criterion for the diagnosis of ARVC [17].

Exercise test

Exercise testing is used routinely for the assessment of CAD and often overlooked following coronary angiography. Exercise testing should be performed in patients with unexplained cardiac arrest to unmask phenotypic evidence of inherited arrhythmic syndrome or exercise-induced arrhythmia such as polymorphic ventricular tachycardia in CPVT, sustained ventricular tachycardia in ARVC and QT prolongation/T wave changes in LQTS. Type 1 LQTS (LQT1) is associated with marked prolongation of QTc interval at peak exercise [30, 31]. Exercise testing may also induce ECG changes in Brugada syndrome [32].

Exercise testing should be accompanied by continuous ECG monitoring with measurement of the ST segment, QT interval and blood pressure measurements. Intravenous beta-blocking agents and resuscitation equipment should be available in the event of exercise-induced ventricular arrhythmia. The failure of blood pressure to increase or a drop in blood pressure in response to upright exercise testing can identify patients with hypertrophic cardiomyopathy at increased risk of sudden death [33].

Discretionary investigations

Pharmacological challenge

The diagnostic features of arrhythmic syndromes are often intermittent, subtle or absent on

the resting ECG. Challenging or 'stressing' the dominant ion channel abnormality or the specific mechanism of the arrhythmia with pharmacologic agents can unmask the latent ECG abnormalities.

Epinephrine infusion has been used in the clinical evaluation of LQTS. Two infusion protocols have been developed — the epinephrine bolus followed by infusion [34] and the graded epinephrine infusion [35]. The latter is better tolerated and may be associated with lower incidence of false-positive responses. The graded epinephrine infusion is commenced at 0.05 μg//kg/min, doubling every 5 min to 0.2 μg/kg/min, and the QT interval is measured at each increment and at 5 and 10 min following the infusion. An absolute increase in QT interval of at least 30 ms at low dose epinephrine infusion ($\leq$ 0.1 μg/kg/min) is considered abnormal and provides a presumptive diagnosis of LQT1 [36]. Of note, the result of epinephrine challenge should not be inferred from exercise testing and vice versa, as epinephrine infusion results in greater QT shortening for a given increase in heart rate compared to exercise testing [37]. Epinephrine infusion can also been used to unmask catecholaminergic polymorphic ventricular tachycardia [38].

Epinephrine infusion should be stopped in the event of raised systolic blood pressure over 200 mm Hg, non-sustained ventricular tachycardia or polymorphic ventricular tachycardia, frequent (> 10) premature ventricular contractions/minute, T-wave alternans, or patient intolerance. Appropriate resuscitation equipment (and intravenous metoprolol) should be available despite the reported safety of epinephrine challenge.

Provocative pharmacological testing with intravenous class IC sodium channel blockers (ajmaline 1 mg/kg; flecainide 2 mg/kg, maximum 150 mg or procainamide 15 mg/kg, maximum 1 g depending on availability) is used to unmask or amplify the ST changes in patients with Brugada syndrome. The development of typical type 1 Brugada ECG pattern ($\geq$ 2-mm J-point elevation and coved type ST-T segment elevation in leads V1 and V2) is considered positive [39]. Monitoring should be continued until normalization of the ECG. Placing the precordial leads at higher intercostal space increases the sensitivity of detecting typical Brugada ECG pattern compared to conventional 12-lead ECG (Fig. 3) [40]. Isoproterenol may be used to suppress ventricular arrhythmias in patients with Brugada syndrome [41].

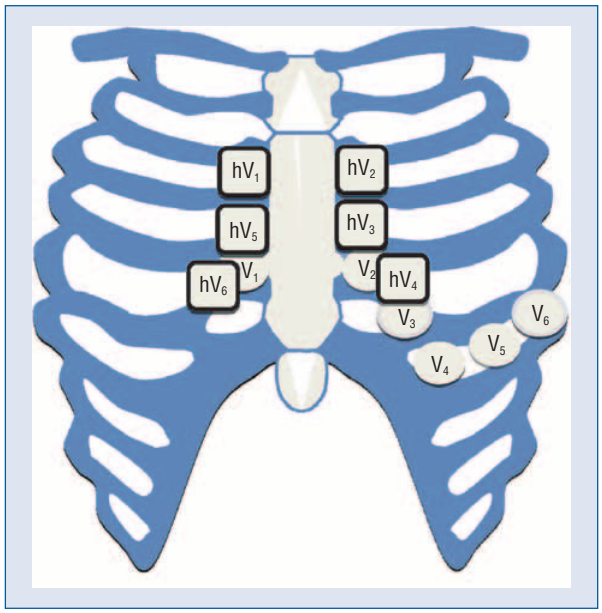

Figure 3. Positioning of high precordial leads (hV1 to hV6) for procainamide challenge to increase sensitivity of detecting Brugada pattern.

Electrophysiological study (EPS)

Electrophysiological testing has been used to identify patients with a substrate for ventricular arrhythmias and at high risk of SCA, though it has a limited role in general and is not routinely performed. In the presence of structural heart disease, inducible sustained monomorphic ventricular tachycardia with up to 3 ventricular extrastimuli at 2 drive cycle lengths is considered abnormal and associated with high risk of sudden cardiac death [42]. However, a low risk of SCA cannot be inferred by the absence of inducible ventricular tachycardia. EPS also provides little prognostic data in patients with non-ischemic cardiomyopathy [43]. Indeed, EPS has limited value in guiding therapeutic interventions in SCA survivors, as implantable cardioverter-defibrillator is indicated in all survivors in the absence of specific contraindications [44].

Similarly, the failure to induce ventricular tachycardia does not obviate the need for implantable cardioverter-defibrillator in patients with ARVC and prior cardiac arrest [45]. However, EPS in conjunction with voltage mapping can corroborate evidence of scar from imaging studies to support the diagnosis in ARVC [46] and may identify patients at high risk of recurrent arrhythmia [47]. EPS and ablation is indicated in patients with SCA and ventricular pre-excitation.

Other considerations

In rare cases, endomyocardial biopsy guided by the results of other diagnostic modalities may be

helpful in the diagnosis of myocarditis, ARVC or cardiac masses.

The discovery of mutations in genes associated with specific cardiac ion channels or cardiomyopathies has spurred interest in genetic testing to diagnose, risk stratify and guide the management of SCA survivors and their families. However, there are major caveats to the use of genetic testing, not least is the poor negative predictive value (a negative test does not exclude the presence of an inheritable arrhythmic syndrome) and the low yield (and unfavorable cost-effectiveness) of routine indiscriminate genetic testing without a defined clinical phenotype [48]. Hence, genetic testing can only be recommended as an adjunct to phenotypic testing in SCA survivors. The result of the genetic testing (guided by the clinical phenotype) can be used to identify other family members who have inherited that particular mutation and at risk of developing the disease (cascade screening) [49]. This is the primary purpose of conducting targeted genetic testing.

Conclusions

An underlying structural heart disease can be uncovered in the majority of SCA survivors from routine diagnostic testing. For the minority of patients without evident structural heart disease, a systematic use of invasive and non-invasive clinical testing, in particular provocative drug testing and advanced cardiac imaging can uncover a diagnosis and direct genetic testing to identify genetically-mediated arrhythmia syndromes.

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