Sudden Cardiac Arrest in a Normal Heart- Approach to Evaluation

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Received: December 02, 2019; Published: December 23, 2019

Abstract

The true incidence of cardiac arrest in apparently normal heart is difficult to estimate. Historically 10 - 15% of all cardiac arrest are in apparently normal heart whereas, up to 40% cardiac arrest in young are in apparently normal hearts. Majority of the cardiac arrest in normal heart is due to recurrent ventricular arrhythmia caused by abnormalities in myocardial depolarization and repolarisation, usually due to inherited channelopathy, metabolic or drug induced. Any survivor of sudden cardiac arrest require a comprehensive clinical and in depth sequential testing such as resting and exercise ECG, echocardiography, angiography and various provocative test and genetic testing if needed. General and cardiological evaluation of family member of victim of sudden unexplained cardiac arrest may yield the presence of heritable condition in up to 40% of family members. All first and second degree relatives of sudden cardiac arrest victim in the absence of any overt heart disease should be informed regarding the potentially increased risk of cardiac events and counselled for assessment at a center with experience in the diagnosis and management of inherited cardiac conditions and genetic testing should be undertaken whenever any identifiable condition exist. This review focus on the common conditions leading to cardiac arrest in an individual with apparent normal heart and approach to evaluation and diagnosis of the victim and their close family members.

Keywords: Cardiac Arrest; Normal Heart

Introduction

Sudden cardiac arrest is abrupt loss of cardiac pumping function leading to haemodynamic collapse, resulting in loss of breathing and consciousness and if untreated ultimately death. The majority of sudden cardiac arrest are due to underlying pathological cardiac condition or secondary to some other systemic problems, minority of arrest are without any apparent abnormality.

The true incidence of cardiac arrest in apparently normal heart is difficult to estimate as majority of arrest are undiagnosed and not all cases post-mortem autopsy are performed. As previously reported, 10 - 15% of all cardiac arrest are in apparently normal heart whereas, up to 40% cardiac arrest in young are in apparently normal hearts [1-3]. However, not all patients without any identifiable pathological cardiac condition may not have absolutely normal heart, there might be some hidden undiagnosed cardiac conditions which may be undiagnosed because of limitation of the diagnostic test and are often labelled as unknown or idiopathic, many of which can be identifiable with complete evaluation. Most of these disorder fall under electrical disorder or channelopathies such as long QT syndrome, Brugada syndrome, Wolf-Parkinson-White (WPW), early repolarisation syndrome etc [4]. In addition, sudden cardiac arrest can be secondary to non-cardiac causes such as hypovolemia, electrolyte disturbances, hypothermia, pulmonary embolism, hypoxia etc. The term overt heart disease is controversial and have subjectivity bias. Conventionally it is defined as absence of identifiable structural abnormality on coronary angiography, echocardiography or electrical abnormality in electrocardiography.

By far majority of sudden cardiac arrest are caused by coronary artery disease or structural heart disease. Once the underlying cardiac condition has been excluded, the possible causes include latent or primary electrical disease, latent structural cause and secondary causes. Whatever the cause of cardiac arrest, majority of the cardiac arrest in normal heart is due to recurrent ventricular arrhythmia caused by abnormalities in myocardial depolarization and repolarisation, usually due to inherited channelopathy, metabolic or drug induced.

Another subgroup of patient exist which has apparent normal cardiac structure and function but has underlying sub-clinical or latent cardiac involvement such as viral myocarditis, sarcoidosis, arrhythmogenic right ventricular cardiomyopathy, coronary spasm. The structural or functional abnormality in such condition may be subtle or even undetectable with standard testing [4,5].

Evaluation of survivor

Any survivor of sudden cardiac arrest require a comprehensive clinical and in depth sequential testing. Clinical evaluation includes detailed presenting history, drug history, past medical conditions as well as family history of sudden cardiac death or accident like unexplained drawing, unexplained car accident, sudden infant death syndrome, frequent miscarriage etc.

Electrocardiography (ECG)

Resting 12 lead ECG and old ECG (if available) should be reviewed ASAP after return of spontaneous circulation (ROSC) and repeated as required to look for coronary ischaemia, repolarization abnormalities, ventricular pre-excitation or ectopics. Immediate pot ROSC ECG can have some repolarisation and depolarisation abnormalities and should be interpreted very cautiously. Moreover, many patients are put on targeted temperature management which may itself manifest as transient ECG changes (Osborne J wave, transient QT prolongation), hypothermia indirectly affect the electrolyte balance which can also manifest as ECG changes. Many patients after ROSC required inotropic and vasopressor support that can also affect repolarisation process. The ECG changes in these metabolically deranged states should be interpreted cautiously and should only be used to guide further investigation or diagnosis once the normal physiology is restored [5].

Coronary angiography

Routine coronary angiography is required to rule out coronary artery disease specially in patients with history of chest pain or risk factors for ischaemic heart. Angiography also help to exclude abnormal or congenital anomaly of coronary arteries. Distal coronary spasm during the catheter placement is significant whereas proximal spasm may be due to reflex action to catheter position.

Echocardiography

Routine echocardiographic (transthoracic or transesophageal) evaluation of heart should be done even when ventriculography has been done in cath lab. Detail echocardiographic evaluation focusing on chamber size, Apical hypertrophy, septal thickness, regional wall motion abnormality, presence of valvular dysfunction, compliance of ventricles and systolic function should be performed as soon as feasible.

Provocative test

Physical or pharmacological provocative test to unmask a primary cause should only be performed when the above mentioned test are negative to identify a clear pathology. The choice of testing depend on the patients general and functional condition and available facilities. Physical exercise testing in the form of Treadmill testing is a standard test which serve as a provocative test for some idiopathic ventricular arrhythmias including catecholaminergic polymorphic ventricular tachycardia (CPVT) and often uncover some rare conditions like inadequate QT shortening, Postural or exercised change in T wave. Signal-averaged ECG finding is used to screen evidence of subclinical arrhythmogenic right ventricle, latent cardiomyopathies and Brugada syndrome.
Sudden Cardiac Arrest in a Normal Heart- Approach to Evaluation

Various pharmacological provocation test include injection of sodium channel blocker or sympathomimetic drugs to unmasked the arrhythmogenic conditions like long QT syndrome, Catecholaminergic polymorphic ventricular tachycardia and Brugada Syndrome. These tests are usually performed under intensive monitoring in coronary care unit or electrophysiologic laboratory.

When diagnosis remain unclear, advanced radiological imaging can be utilised such as high resolution computed tomography or gated cardiac magnetic resonance imaging to detect any subclinical arrhythmogenic right ventricle, myocarditis, myocardial injury secondary to coronary spasm and sarcoidosis.

Genetic testing

All victim of cardiac arrest without any appreciable cause should undergo genetic testing, ideally prior to declaration of death but it can also be done as part of autopsy if resuscitation is futile. The number of genes and the mutations in each gene with their variable expression and penetration are continued to develop, but till date we don't have clear gene pool database. Genetic screening in specialised centres provided diagnosis in up to one-third victim of sudden cardiac arrest without overt heart disease [8-10].

In a recent publication by Lahrouchi N., et al. who conducted a post mortem molecular autopsy genetic testing in cases of sudden cardiac arrest with negative autopsy and toxicologic evaluation, a total of 302 cases were analysed with sequencing for a panel of 77 genes associated with arrhythmias and cardiomyopathies [11]. The study identified pathogenic or likely pathogenic genetic mutation in 13% of the victims, most frequent variants encountered were catecholaminergic associated ventricular tachycardia and congenital long QT syndrome.

When we combined the genetic testing with clinical evaluation of surviving family member, the accuracy of making clinical diagnosis increased from 26 - 39 percent.

Evaluation of family members

Genetic inheritance may be an important factors in some cases of premature heart disease including sudden cardiac arrest particularly young victims and the risk appears higher in 1st and 2nd degree relative of the victim of sudden cardiac death. In a nationwide prospective cohort study in Denmark from 2000 to 2006, identified 470 victims of sudden cardiac death who were 35 years age or younger. The first and second degree relatives (3073 in total) of cardiac arrest victim were followed for up to 11 years, there was significantly higher incidence of cardiovascular disease in those family member than in the general population [12].

General and cardiological evaluation of family member of victim of sudden unexplained cardiac arrest may yield the presence of heritable condition in up to 40% of family member as demonstrated by some clinical studies [13-15]. Behr E., et al. conducted a study involving 32 families of victim of unexplained cardiac death, they evaluated family member by routine electrocardiogram (ECG), holter monitor and stress induced ECG. A total of 107 family members were evaluated, seven families (22%) demonstrated some heritable patterns commonly the long QT syndrome, cardiomyopathies, myotonic dystrophy [13].

In another study by Tan HL., et al. evaluated 43 families involving 183 relatives of young (less than 40 years) victim of cardiac arrest. After identifying the clinical predisposition as evident on history, ECG, echocardiography, exercise tolerance and by provocative tests, genetic testing for the suspected member was performed. Additional 15 family members were screened after the reports of confirmed genetic testing. 17 families (40%) were identified with a heritable pattern- 5 catecholaminergic associated ventricular tachycardia, 4 with long QT syndrome, 3 with arrhythmogenic right ventricle, 2 with Brugada, 1 with hypertrophic cardiomyopathy [11]. Asymptomatic carrier rate of 8.9 carrier per family was identified, many through the genetic analysis. chances of identification of specific cardiac disease increases when 2 or more family members suffer unexplained cardiac arrest and if more members underwent evaluation [14].

Sudden Cardiac Arrest in a Normal Heart- Approach to Evaluation

Keeping in view of these studies, the general recommendation is that all first and second degree relatives of sudden cardiac arrest victim in the absence of any overt heart disease should be informed regarding the potentially increased risk of cardiac events and counselled for assessment at a centre with experience in the diagnosis and management of inherited cardiac conditions and genetic testing should be undertaken whenever any identifiable condition exist [16].

Common causes of unexplained sudden cardiac arrest

The commonly encountered causes of sudden cardiac arrest are as follows. Many of these conditions are familial and are associated with an increased risk of sudden cardiac death in the in close relatives.

Long or prolonged QT syndrome

There are different subtypes of QT syndrome, 95% of cases are due to abnormalities in the rectifier potassium or inward sodium channel. It may be secondary to drugs or electrolytes abnormalities. Many patients of inherited or congenital QT syndrome 30 - 50% are symptomatic at some point of time, mostly presenting as syncope. The lifetime risk of cardiac arrest is 3 - 5% and may be the initial manifestation in some patient [17,18]. The arrhythmias associated with long QT syndrome is polymorphic ventricular tachycardia called torsades de pointes, it’s a pause-dependent, specific form of polymorphic ventricular tachycardia in which rapid irregular QRS complex appear to be oscillating or twisting around the base line ECG. Presentation may be at any age, but often present in teen age group often induced my provocative events like exercise (in type 1), auditory or strong emotional trigger (in type 2) and rest or sleep related events (in type 3). sometime, the arrhythmias in long QT may not be detectable as victim may present as unexplained accident like drowning, single vehicle accident, sudden infant death syndrome or epilepsy. QT may also manifest n early post partum period in female which is also considered as high risk period [18-21].

Diagnosis of long QT syndrome is based on 12 lead ECG, absolute QT interval ideally should be measured from the start of the QRS to the end of T wave. The absolute values to label as prolonged QT is an open debate. Instead of absolute QT duration, corrected QT interval (> 440 msec in men and > 460 msec in women) is suggested as measure of prolonged QT. Bazett’s formula (QTc = QT/√R-R [seconds]) is widely used to calculate the corrected QT interval, but it is less accurate at extreme of heart rate.

QT prolongation may not be apparent on resting ECG in long QT syndrome and the relationship between symptoms, genotype and QT interval is often discrete [22]. Various provocative test involved exercise protocol, sympathomimetic drug, intravenous erythromycin, adenosine boluses, facial immersion and combination of exercise and postural related QT changes.

Prevention of torsade in long QT syndrome involved avoidance of triggering agents and drugs. Pharmacological therapy involved either betablocker or sodium channel blocker, advanced therapy like permanent sympathetic denervation and implantable cardiac defibrillator is reserved for drug resistance long QT syndrome.

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Polymorphic ventricular tachycardia with normal QT interval is either caused by cardiac ischaemia or CPVT. In those patients without evidence of cardiac ischemia, CPVT remain the most suspicious cause for the VT. CPVT is an inherited channelopathy caused by mutation in the cardiac ryanodine receptor which failed to re-uptake calcium into the cardiac sarcoplasm resulting in excessive intracellular calcium. Affected individual typically present in late childhood and early adolescent with cardiac arrest or syncopal attack occurring during intense emotional or physical stress [23,24].

Resting ECG in CPVT is essentially normal, recently it has been suggested to have tall U wave and secondary T waves as markers of delay after depolarization [25]. Resting bradycardia has been linked the CPVT genotype. Provocative test with exercise or sympathomimetic drugs induced significant ventricular ectopy or polymorphic ventricular tachycardia or bidirectional ventricular tachycardia is highly

Sudden Cardiac Arrest in a Normal Heart- Approach to Evaluation

suggestive of CPVT. Apart from cardiac ryanodine receptor mutation, cardiac calsequestrin gene or other unknown gene. One report suggested that CPVT may account for at least one in seven cases of sudden unexplained death [26]. Untreated CPVT has poor prognosis with cardiac arrest in 1/3 by the age of 30 years. Beta blockers are the mainstay of therapy, resistance to beta blocker require other invasive therapy like cardiac sympathectomy or implantable cardiac defibrillator. Cardiac defibrillator may be ineffective because shock therapy itself is associated with adrenergic effects leading to early arrhythmia recurrence. Selective left cardiac sympathectomy can be an attractive options.

Brugada syndrome

Brugada syndrome named after brugada brother who described the syndrome as persistent ST segment elevation and right bundle branch block pattern in a case series of survivor of cardiac arrest victim with normal heart [27]. Initially it was believed to be a very common cause of sudden cardiac arrest, recent data suggest that overall prevalence of Brugada syndrome is no more than 5% of sudden cardiac arrest without overt heart disease [28]. Brugada syndrome is basically a repolarisation abnormality due to sodium channel encoded by SCN5A gene and there may be some overlap with an early manifestation of arrhythmogenic right ventricular syndrome (ARVC). More than 293 mutations linked with Brugada have been documented. However, only 21% of patients there is identifiable genetic mutation, some of these mutations are asymptomatic even with provocative test. Recent evidence suggests that there might be calcium channel also involved in some form of Brugada syndrome with short QT interval. There are many triggering factors for ECG changes and or arrhythmias, common triggering factors includes fever, full stomach, autonomic activation, sodium channel blocking drugs etc. Brugada has also been linked with atrial fibrillation, SVT and bradyarrhythmia’s [29,30].

ECG is the cornerstone of diagnosis. Three types of Brugada syndrome has been reported, right bundle branch pattern is common to all three types. Type 1- is characterised by ST elevation >2 mV coved with T wave inversion in 2 consecutive precordial leads, in type 2 and 3 pattern have a saddle back appearance. Latent Brugada can be diagnosed after provocative test with sodium channel blocking drugs like flecainide, ajmaline and procainamide. Treatment is generally implantable cardiac defibrillator [31].

Early repolarisation syndrome

Early repolarisation syndrome (ERS) is relatively common entity in survivor of sudden cardiac arrest, recently reported data suggest ERS in up to 31% of patients with idiopathic ventricular fibrillation. The survivors with ERS had tendency for recurrent ventricular fibrillation compared with those cardiac arrest survivors without early re-polarisation abnormality [22]. As per the Cardiac Arrest Survivors with Preserved Ejection Fraction registry (CASPER), the estimated prevalence of ERS in cardiac arrest without overt heart disease was 8% [33].

Exact mechanism of ERS is incompletely understood, various debate and controversies exist, one theory suggests regional phase 1 potential differences due to localised early repolarisation pattern cause current flow in region to region and ST -segment shift [34]. The prevalence of ERS in normal population is believes to be around 5% but it is more common in young men, athletic and black population. The diagnosis of ERS is based on ECG, ST segment elevation with notchting or slurring of the QRS-ST junction (J point) of at least 0.1 mV in the inferior-lateral chest leads [35]. Currently there is no provocative test or confirmed genetic association of ERS, although there are some progress and genetic study is under way. There is no recommended pharmacological therapy at present as most antiarrhythmic therapy are unhelpful, for recurrent VF -Preventive use of intracardiac defibrillator is recommended.

Short QT syndrome

Short QT syndrome (corrected QT interval < 360 ms) is a rare inherited channelopathy first reported in 2003 as familial cause of sudden death. Affected individual exhibit a markedly shortened QT interval. In contrast to long QT syndrome, short QT syndrome is related to shortening of refractory period predisposing individual to a risk of atrial and ventricular arrhythmias [33]. No standard test exist

apart from ECG and electrophysiologic testing to document extremely short atrial and ventricular refractory period [36,37]. Currently no therapy is proven to be effective except for intracardiac defibrillator for prevention of ventricular fibrillation.

**Arrhythmogenic right ventricular cardiomyopathy (ARVC)**

ARVC is a primary disease of heart muscle where fibrofatty tissue replaces the myocytes. Although it was originally described to affect the right ventricle only, recent findings suggest that it can affect both ventricles [38,39]. Exact etiology of ARVC is not yet known clearly, it may be an inflammatory process modulated by genetic influences in desmosome-related proteins. Generally, ARVC affects young male below 40 years but it has been described even in 9th decade [40]. Clinical manifestation may vary from asymptomatic to conduction abnormalities and arrhythmias to sudden cardiac arrest. Many cases are diagnosed only at autopsy. The symptoms, haemodynamic and ECG finding are nonspecific. Magnetic resonance imaging (MRI) is diagnostic. Electroanatomic voltage mapping of the ventricles in electrophysiology laboratory can be considered to detect the latent ARVC [41]. Genetic testing has high diagnostic yield of 40 - 50% in suspected cases [42].

**Idiopathic ventricular fibrillation**

The diagnosis of idiopathic ventricular fibrillation is made only when no other structural or electrical cause of fibrillation is found. It is estimated that 5% of all sudden cardiac death is attributed to idiopathic ventricular fibrillation [43]. A recent meta-analysis of 639 patients from 23 studies with idiopathic ventricular fibrillation, among whom 80% patients had an implantable cardiac defibrillator for secondary prevention, 31% patients had recurrent rate of VF with a pooled mortality rate of 3.1% during an average 5 years follow up. The results of baseline electrophysiological studies are not predictive of future VF [44].

**Commotio cordis**

Commotio Cordis a Latin word translate literally as agitation of heart is defined as sudden cardiac arrest secondary to relatively innocent chest wall impact leading to VF. It is one of the common cause of sudden death in young athletes. Affected victims have no structural heart disease nor any significant damage to the heart, chest wall or thoracic cavity. More than 200 cases of commotio cordis has been published since the establishment of national commotio cordis registry in united state in 1990. The exact mechanism remain unknown but appear to be electrical event rather than mechanical impact. Several factors appear to influence the likelihood of commotio cordis including the timing of impact during cardiac cycle, location, velocity of impact, hardness and shape of impact. The exact incidence still remain unknown. Diagnosis is presumptively made based on clinical scenario and ECG finding of VF and absence of structural or electrical heart damage [45,46].

**Summary of conditions causing sudden cardiac arrest**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Clinician feature</th>
<th>Diagnosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long QT syndrome</td>
<td>Abnormally long and/or morphologically abnormal QT/T wave (&gt; 440 ms male, &gt; 460 ms female)</td>
<td>History, ECGs, exercise, and adrenaline provocation and genetic testing</td>
<td>Preventable with Beta blocker, ICD</td>
</tr>
<tr>
<td>Catecholaminergic polymorphic ventricular tachycardia</td>
<td>Normal resting ECG but exercise/sympathetic stimulation induced ectopy and ventricular polymorphic tachycardia</td>
<td>History, exercise, and adrenaline provocation and genetic testing</td>
<td>Genetic testing may be useful</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>Abnormal ST elevation in precordial leads (V1-V3) with RBBB pattern</td>
<td>History, ECGs, and sodium channel blockers provocation testing</td>
<td>Genetic testing low yield</td>
</tr>
</tbody>
</table>

### Sudden Cardiac Arrest in a Normal Heart- Approach to Evaluation

<table>
<thead>
<tr>
<th>Early repolarization syndrome</th>
<th>ST elevation or J-point slurring in inferolateral leads</th>
<th>12 lead ECG</th>
<th>No provocative test, therapy only ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-QT syndrome</td>
<td>Shortened QT interval with peaked T wave; consider if QTc &lt;360 ms</td>
<td>QT on ECG, peaked T wave</td>
<td>Usually QTc &lt;320 ms</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>Features of right ventricular dilatation, thinning, fibrosis, and aneurysm formation, often not seen on echocardiogram; epsilon waves, right bundle branch block; may have ventricular tachycardia originating in the right ventricle</td>
<td>ECGs, imaging especially MRI, genetic testing, electroanatomic voltage map, biopsy in select cases</td>
<td>Often has structural change evident on MRI/Autopsy</td>
</tr>
<tr>
<td>Commotio cordis</td>
<td>sudden cardiac arrest secondary to relatively innocent chest wall impact leading to VF</td>
<td>ECG during arrest and absence of structural or electrical heart damage</td>
<td>Unknown mechanism</td>
</tr>
<tr>
<td>Idiopathic Ventricular fibrillation</td>
<td>It is estimated that 5% of all sudden cardiac death is attributed to idiopathic ventricular fibrillation.</td>
<td>Diagnosis of exclusion, when no other structural or electrical cause of fibrillation is found.</td>
<td>Most cases may be undiagnosed occult cardiac conditions</td>
</tr>
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</table>

### Conclusion

Although the risk of sudden cardiac arrest and death is higher in individuals with structural heart disease, however as many as 10-5% of sudden cardiac arrest occur in individuals with apparently normal hearts.

Common causes of sudden cardiac arrest in absence of overt heart disease prolonged QT interval, Catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, early repolarisation syndrome, short QT syndrome, Arrhythmogenic right ventricular cardiomyopathy, Idiopathic ventricular fibrillation and commotio cordis.

A strong family history of sudden cardiac death in absence of overt heart disease is associated with higher risk of primary sudden cardiac arrest.

Victim of sudden cardiac death, particularly young one should undergo an autopsy and genetic testing if needed.

Survivors of sudden cardiac arrest should undergone extensive testing including provocative and genetic testing and should be put on secondary preventive therapy including implantable defibrillator.

Close Family member of victim of unexplained cardiac arrest should routinely undergone periodic general cardiology evaluation and on strong clinician suspicious may undergo provocative, electrophysiology or even genetic testing to diagnosed any heritable cardiac condition.

### Bibliography

Sudden Cardiac Arrest in a Normal Heart- Approach to Evaluation


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