Cardiac arrest – unexplained or uninvestigated?

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Take Home Messages

- The cause of sudden cardiac arrest is usually identifiable following routine investigations in most cardiac arrest survivors. However, there is still a small but significant number of cases of unexplained cardiac arrest.
- Systematic investigation of unexplained cardiac arrest will yield a diagnosis in up to 50% of cases.
- A specific diagnosis might have implications on treatment, family screening, counselling, and research.
- If no specific diagnosis is found following currently available investigations, a diagnosis of idiopathic ventricular fibrillation is assigned.

Introduction

Sudden cardiac death (SCD) accounts for approximately 50% of deaths due to cardiovascular disease in developed countries.(1) Cardiac arrest survival rates are improving, providing an opportunity to thoroughly investigate for an underlying cause in the sudden cardiac arrest (SCA) survivor.(2) Coronary heart disease (CHD) is the cause in approximately 80% of survivors.(3) However, a cause may not be identified after initial assessment with an ECG, echocardiogram, and coronary assessment in a significant proportion of SCA survivors, leading to a diagnosis of unexplained cardiac arrest (UCA).(2,4)

This article will highlight the current available investigations for a SCA survivor with UCA.

Diagnosis

After exclusion of non-cardiac causes, cardiac causes of UCA fall into two broad categories, namely structural heart disease and electrical/conduction abnormalities. (Figure 1).

Structural heart disease

In the immediate period following a SCA, ST-segment changes and T-wave inversions are nonspecific. However, serial 12 lead electrocardiograms (ECG) should be performed for hints to an underlying cause. Similarly, a post-arrest transthoracic echocardiogram usually shows nonspecific impaired left ventricular (LV) function but may also reveal features suggestive of hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) or arrhythmogenic ventricular cardiomyopathy (AVC). Echocardiographic features in the Padua criteria for diagnosis of AVC include ventricular dilatation, RV/LV regional akinesia/dyskinesia, aneurysms and global RV/LV/biventricular systolic dysfunction. Cardiac MRI (CMR) can however show the characteristic fibro-fatty infiltration in AVC due to better tissue characterisation.(5) It can also highlight early-stage subtle structural disease and is therefore the imaging modality of choice for identifying structural heart disease in UCA.

With regards to CHD, an acute reversible myocardial lesion might be represented by oedema on T2-weighted CMR sequences, with a key differential being acute myocarditis. Repeat CMR in three months is often performed to confirm resolution or sequelae. On the other hand, chronic irreversible lesions (scars) on late gadolinium enhancement (LGE) sequences are a substrate for ventricular tachycardia and subsequent fibrillation, therefore provide Class I justification for a secondary prevention implantable cardioverter defibrillator (ICD). (6) When there's a high suspicion of coronary ischaemia in the absence of a significant coronary lesion and a negative CMR scan, provocative testing with intracoronary infusion of acetylcholine may be considered for a diagnosis of vasospastic coronary artery disease; another potential cause of SCA.(7,8)

CMR in DCM can identify two forms of fibrosis, with different prognostic implications. Mid-wall irreversible replacement fibrosis is associated with increased risk of an arrhythmic event and mortality compared to diffuse interstitial fibrosis. (9,10) In HCM, higher LV mass is associated with a worse prognosis. CMR measures LV mass more accurately than echocardiography with the added benefit of identifying and quantifying characteristic fibrosis pattens with LGE. Patients with HCM usually have higher LGE in the areas with greatest hypertrophy and RV septal insertion sites.(11) Like in DCM, the extent of LGE in HCM is associated with an increased risk of SCA and mortality.(12) ICD should therefore be considered in patients with a 5-year risk of ≥4 to 6% if there is significant (≥15% of LV mass) LGE at CMR. (8) On the contrary, the prognostic value of LGE burden in cardiac sarcoidosis

and amyloidosis is yet to be confirmed but there is mounting evidence to suggest that it confers a worse prognosis. (11,13)

In patients who have survived SCA with a diagnosis of the above cardiomyopathies, secondary prevention ICD is also a class I recommendation.(14) However, an accurate diagnosis will guide medical therapy to improve symptoms, LV function and potentially reduce the need for device therapy.

Electrical abnormalities

Electrical abnormalities can be classified into primary electrical conditions and conduction system abnormalities. Provocative testing can unveil transitory pathognomonic ECG changes in primary electrical conditions.

Repolarisation reserve can be assessed with an exercise test or epinephrine infusion. A normal QT interval is affected by autonomic changes e.g. sinus tachycardia shortening the interval. Patients with Long QT Syndrome (LQTS) lack this normal response. This is reflected on exercise testing (ET) where a recovery phase QTc duration ≥480ms after four minutes post-exercise is a diagnostic feature in LQTS scoring systems (see *Table 1).* ET is also useful in the diagnosis of catecholaminergic polymorphic ventricular tachycardia (CPVT) where polymorphic or bidirectional VT is usually seen during exercise. In both LQTS and CPVT, epinephrine infusion lacks specificity therefore ET is preferred. (2)

In suspected Brugada syndrome, e.g. nocturnal SCA/precipitated by fever, but with a normal baseline ECG, a modified ECG with high right ventricular leads in the second and third intercostal spaces can unmask the diagnostic ≥2mm coved ST-segment elevation with accompanying T-wave inversion characteristic of the type 1 Brugada pattern. Provocation testing with a short acting sodium channel blocker such as ajmaline may also be used to reveal a diagnostic type 1 morphology.(15) Of note, the saddleback shaped ST-segment elevation in type 2(>2mm) and type 3(<2mm) is not diagnostic.

Electrophysiology studies are not routinely recommended in investigation of UCA, however, can be considered on an individual basis, especially for suspected supraventricular and bundle branch re-entrant tachyarrhythmias. (2,16) Finally, endomyocardial biopsy is rarely needed, and although genetic testing is useful after diagnosis of an inherited condition, it is unclear what its role is in UCA with normal investigations. (2)

Conclusion

Identifying a specific diagnosis in UCA guides medical management, lifestyle changes, family screening and prevention strategies. A systematic approach to investigation is therefore recommended. (Figure 2) CMR is often performed prior to ICD implantation, however, subsequent provocation testing, electrophysiology studies and specialist cascade screening services might not always be readily available at every centre. Early referral to an inherited cardiac conditions clinic is appropriate, where non-diagnostic cases will also be followed up for evolving changes in phenotype and/or advances in diagnostic testing.

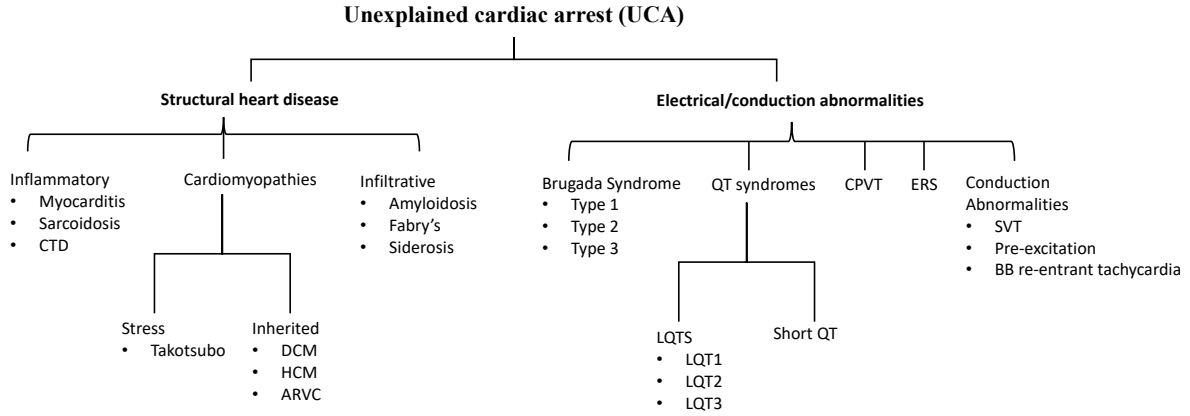

Figure 1. This figure shows the potential causes of unexplained cardiac arrest. CTD, connective tissue disease, DCM, dilated cardiomyopathy, HCM, hypertrophic cardiomyopathy, ARVC, arrhythmogenic right ventricular cardiomyopathy, LQTS, long QT syndrome, CPVT, catecholaminergic polymorphic ventricular tachycardia, ERS, early repolarization syndrome, SVT, supraventricular tachycardia, BB, bundle branch. (Adapted from Suna et al(2))

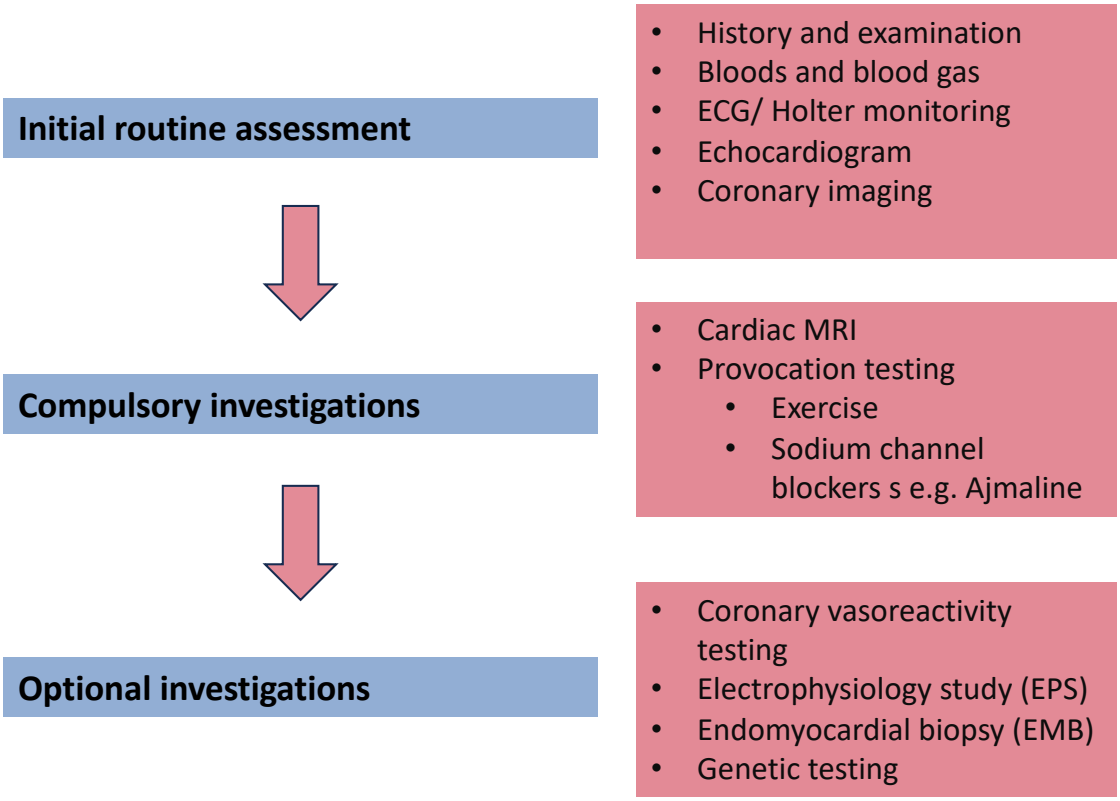

Figure 2. This figure shows the investigations to be performed/considered following a sudden cardiac arrest (SCA). (Adapted from Suna et al(2))

Findings			Points
EKG [1]	QTc [2]	≥480 ms	3.5
		=460-479 ms	2
		=450-459 ms (in males)	1
		≥480 ms during 4th minute of recovery from exercise stress test	1
	Torsade de pointes [3]		2
	T wave alternans		1
	Notched T wave in 3 leads		1
	Low heart rate for age [4]		0.5
Clinical history	Syncope [3]	With stress	2
		Without stress	1
Family history	Family member(s) with definite LQTS [5]		1
	Unexplained sudden cardiac death at age <30 yrs in immediate family [5]		0.5
Genetic finding	Pathogenic mutation		3.5

Adapted from Schwartz & Crotti 2011 and ESC 2022
Scoring: ≤1.0 point = low probability of LQTS; 1.5-3.0 points = intermediate probability of LQTS; Diagnosis of LQTS with a score >3
1.In the absence of medications or disorders known to affect these electrocardiographic features
2.QTc (corrected QT) calculated by Bazett's formula where QTc = QT/√RR
3.Mutually exclusive
4.Resting heart rate <2nd %ile for age
5.The same family member cannot be counted for both criteria.

Table 1. Table showing the modified scoring system for diagnosis of Long QT syndrome. (Adapted from Schwartz & Crotti and ESC 2022 (8,17))

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