Characteristics and clinical assessment of unexplained sudden cardiac arrest in the real-world setting: focus on idiopathic ventricular fibrillation

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Aims

Recent studies have shown that in more than half of apparently unexplained sudden cardiac arrests (SCA), a specific aetiology can be unmasked by a careful evaluation. The characteristics and the extent to which such cases undergo a systematic thorough investigation in real-life practice are unknown.

Methods and results

Data were analysed from an ongoing study, collecting all cases of out-of-hospital cardiac arrest in Paris area. Investigations performed during the index hospitalization or planned after discharge were gathered to evaluate the completeness of assessment of unexplained SCA. Between 2011 and 2016, among the 18622 out-of-hospital cardiac arrests, 717 survivors (at hospital discharge) fulfilled the definition of cardiac SCA. Of those, 88 (12.3%) remained unexplained after electrocardiogram, echocardiography, and coronary angiography. Cardiac magnetic resonance imaging yielded the diagnosis in 25 (3.5%) cases, other investigations accounted for 14 (2.4%) additional
Introduction

Sudden cardiac arrest (SCA), defined as a natural and unexpected collapse of presumed cardiac aetiology,1 is a major contributor to cardiovascular mortality (~ 50%), with an estimated number of 300,000 cases a year in Europe.2,3 While SCA is principally related to coronary artery disease (80%), other causes include cardiomyopathies and electrical disorders, which are of particular importance due to their often dominant inherited (or familial) pattern and the potential for preventive measures among relatives.5–11 The diagnosis of idiopathic ventricular fibrillation (IVF) is reserved for cases where there is no evidence of underlying structural or electrical heart disease.12,13 However, this requires a thorough and comprehensive evaluation and should be a diagnosis of exclusion. Studies have suggested that a definitive diagnosis could be unmasked in more than half of apparently unexplained SCA, through a complete systematic medical assessment.14–16 This is crucial from several perspectives including prognostication, implementation of specific therapy when possible, appropriate lifestyle counselling, and also optimization of screening and prevention among relatives.5,8,10,11,17,18 However, clinical characteristics of unexplained cardiac arrests and the extent to which such a comprehensive cardiac assessment is carried out in the real-life setting has not been investigated so far at the community level. Hence, we aimed to describe characteristics of relatives.20–22 Briefly, it is a prospective population-based registry comprising Paris and suburbs, encompassing a residential population of approximately 6.7 million and covering 762 km². Owing to a close collaboration with all the pre-hospital emergency medical services (EMS), every adult (≥18 years) case of out-of-hospital cardiac arrest occurring in the area of interest is systematically and prospectively enrolled in the Paris-SDEC registry since May 2011. In Paris, management of out-of-hospital cardiac arrest involves the firefighters and mobile emergency units, including at least one trained physician in emergency medicine. Patients in whom a return of spontaneous circulation is achieved are referred to a centre with an intensive care unit (ICU) and coronary intervention facilities. Patients aged less than 18 years and cardiac arrests occurring outside the geographical area of interest are excluded. Regular audits on the registry show that 99% of cardiac arrest cases admitted alive to the hospital are detected.20

Study setting

The methodology of this study is consistent with the STROBE checklist for observational studies.19 The Paris Sudden Death Expertise Center (Paris-SDEC) registry is an ongoing study and has been described previously.20–22 Briefly, it is a prospective population-based registry comprising Paris and suburbs, encompassing a residential population of approximately 6.7 million and covering 762 km². Owing to a close collaboration with all the pre-hospital emergency medical services (EMS), every adult (≥18 years) case of out-of-hospital cardiac arrest occurring in the area of interest is systematically and prospectively enrolled in the Paris-SDEC registry since May 2011. In Paris, management of out-of-hospital cardiac arrest involves the firefighters and mobile emergency units, including at least one trained physician in emergency medicine. Patients in whom a return of spontaneous circulation is achieved are referred to a centre with an intensive care unit (ICU) and coronary intervention facilities. Patients aged less than 18 years and cardiac arrests occurring outside the geographical area of interest are excluded. Regular audits on the registry show that 99% of cardiac arrest cases admitted alive to the hospital are detected.20

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Data collection

Uttein23 templates for patient data collection were followed. General data included demographic characteristics and location of SCA (residential or public setting). Pre-hospital data recorded included SCA circumstances, preceding warning symptoms, presence of bystander, bystander cardiopulmonary resuscitation before EMS arrival, presence of shockable rhythm before advanced life support, and time intervals from collapse to basic life support and from basic life support to return of spontaneous circulation. Past medical history (cardiac disease, cardiovascular risk factors, comorbidities, treatment), final diagnosis and preventive measures implemented [implantable cardioverter defibrillator (ICD), family screening] were collected from both ICU and cardiology medical reports. The diagnostic process was undertaken by the local medical staff, but two investigators reviewed each medical report to ensure that appropriate diagnostic criteria were used, and provided final central adjudication. In cases of divergent opinion, a third expert was asked to arbitrate. The vital status and the neurological outcome at hospital discharge were assessed for all patients. Survival with favourable neurological prognosis was defined by a Cerebral Performance Category (CPC) score 1 or 2, with 1 representing full recovery or mild disability and 2, moderate disability but independent in activities of daily living.
Assessment of medical investigations

Medical investigations initiated and carried out among survivors were at the discretion of the managing medical team (real-world setting). Data regarding all investigations performed during the index hospitalization for SCA or planned subsequently after discharge were gathered to evaluate the completeness of initial assessment in cases labelled as IVF. The referring physician of each case was also contacted to collect all examinations performed and clinical events during the follow-up. In addition to 12-lead electrocardiogram (ECG), echocardiography and coronary angiography, cardiac magnetic resonance imaging (MRI) and provocative tests (ergonovine, ajmaline, and adrenaline) are those which have been demonstrated to have substantial yield in this clinical setting.18,15,24-34 Complete medical investigation was therefore defined as performance of cardiac MRI, ergonovine challenge, and pharmacological tests, besides the traditional tests. Diagnostic criteria were based on the latest international guidelines or major previous reports (see Supplementary material online, File S1).12,31,32,34,35 Data on performance of electrophysiological study,13,36 exercise testing,14 Holter-ECG,37 cardiac biopsy,38 signal averaged ECG,39 right ventricular angiography,40 Fourier phase analysis of gated blood pool single-photon emission computed tomography,41 myocardial voltage mapping,42 and genetic tests were also collected, as these tests can potentially reveal specific phenotypes in some cases of unexplained SCA.

We finally hypothesized that academic centres (with dedicated electrophysiology units), and specific patients’ characteristics, could be associated with more thorough investigations.

Statistical analysis

Continuous data were expressed as mean ± standard deviation. Categorical data were expressed as frequencies and percentages. Comparisons used the χ² or Fisher’s exact test for categorical variables and Student’s t-test or Mann–Whitney–Wilcoxon test, when appropriate, for continuous variables. Univariate logistic regressions were used to assess the association of completeness of investigations with patient characteristics such as age and sex, as well as treating centre. Missing data on study variables were no more than 1%, except for EMS call before SCA occurrence (15.6%), collapse to basic life support (9.2%) and basic life support to return of spontaneous circulation (14.1%) delays. Results were considered statistically significant at P-value < 0.05. All analyses were two-tailed. Statistical analysis was performed using R software, version 3.3.2 (R Project for Statistical Computing).

Results

Between May 2011 and 2016, among the 18 622 out-of-hospital cardiac arrests, 717 survivors at hospital discharge from 48 different hospitals fulfilled the definition of cardiac SCA. Coronary artery disease was the main underlying aetiology (525 patients, 73.2%), followed by cardiomyopathies (88 patients, 12.3%) (Figure 1, flow chart). Among the 717 SCA survivors, ECG, coronary angiogram as well as echocardiography established the diagnosis in 629 (87.7%) cases. Cardiac MRI yielded the diagnosis in another 25 (3.5%) cases. Other investigations accounted for 14 (2.4%) additional diagnoses (Figure 2). Among the 88 patients without a diagnosis after the initial evaluation (ECG, echocardiogram, and coronary angiography), the proportion of unexplained SCA decreased from 100% to 55.7% after performance of subsequent examinations (cardiac MRI, ergonovine test, and pharmacological tests, Figure 3). In this group (unexplained SCA after initial evaluation), cardiac MRI revealed the diagnosis in 34.7%, ergonovine test in 30.8%, catecholamine test in 7.7%, and ajmaline challenge in 4.2% of investigated cases (diagnostic yield, Figure 2). Finally, a diagnosis of IVF was considered in 49 patients managed in 13 different hospitals, with no evidence of underlying structural or electrical heart disease discovered within the ambit of the performed investigations.

Characteristics of IVF cases compared with other SCA are summarized in Table 1. Idiopathic ventricular fibrillation patients were younger (48.7 ± 14.8 vs. 57.3 ± 14.2 years, P < 0.001), had fewer traditional cardiovascular risk factors, and greater likelihood of family history of SCA (18.4% vs. 3.9%, P < 0.001). Emergency medical services were less frequently called prior to SCA in the IVF group (0% vs. 18.1%, P = 0.001), mostly related to a lower proportion of warning cardiac symptoms reported (defined as chest pain, dyspnoea, palpitations or faintness/syncope in the 4 weeks before SCA, 16.3% vs. 44.9%, P < 0.001). Average collapse to basic life support time was longer (5.2 ± 4.9 vs. 3.0 ± 4.1 min, P < 0.001) in IVF patients. The observed differences in sex distribution (69.4% vs. 80.8% of male, P = 0.080) and proportion of cases occurring during sport activity (16.7% vs. 9.6%, P = 0.132) were not statistically significant.

In the IVF group, investigations were more comprehensive, but inconsistently performed (Table 2). In addition to the almost universally performed ECG, echocardiogram, and coronary angiography (47 of 49 cases), the most frequent other examinations conducted were cardiac MRI in 40 (81.6%) patients, ajmaline challenge in 21 (42.9%), provocative testing with ergonovine in 19 (38.8%), and electrophysiological study in 12 (24.5%), most often with isoprenaline infusion during the study [10 (20.4%) patients]. Genetic testing was initiated in only 9 (18.4%) patients during the index hospital stay, while other investigations such as 24 h Holter-ECG (6, 12.2%), right ventricular angiography (5, 10.2%), exercise testing (4, 8.2%), signal averaged ECG (2, 4.1%), and cardiac scintigraphy (1, 2.0%) were performed in a very low proportion of cases. Cardiac biopsy, adrenaline challenge and voltage mapping were not performed. Only 8 (16.3%) patients benefited from all three examinations shown to have the highest diagnostic yield (cardiac MRI, ergonovine, and pharmacological testing, Figure 2). Younger patients [odds ratio (OR) 6.00, 95% confidence interval (CI) 1.80–22.26, P = 0.005 for patients < 45 vs. > 45 years] and those admitted to university centres with dedicated electrophysiology units as compared with non-academic hospitals (OR 3.60, 95% CI 1.12–12.45, P = 0.035) were more thoroughly investigated. There was no significant difference according to sex (P = 0.371). No complication was reported during the investigations, and there was no correlation between the length of hospital stay after ICU discharge and the number of investigations performed (average of 11.5 ± 5.3 days, r = 0.25, P = 0.087).

All 49 patients with a diagnosis of IVF had a favourable neurological outcome (CPC Score 1 or 2), and were implanted with an ICD for secondary prevention. Family screening was initiated during initial hospitalization in only 12 (24.5%) patients. The median follow-up was 48.7 months (range 11.7–71.2), with comprehensive data available in 46 (93.9%) patients. Aetiological investigations performed during follow-up after the initial evaluation were exercise testing in six patients, Holter-ECG in four, genetic testing in four, ergonovine challenge in three, and cardiac scintigraphy in two patients. These additional examinations eventually revealed two coronary vasospasms and one long QT syndrome (unmasked by exercise testing, Figure 3). Regarding genetic findings, one variant of unknown significance was found in the KCNQ1 gene in the patient with long QT...
syndrome diagnosed by exercise testing. During the follow-up, 10 (21.7%) IVF patients had a recurrence of ventricular arrhythmia (ventricular fibrillation or sustained ventricular tachycardia), after a median time of 281 days (range 64–1088 days), with an annual incidence rate of 5.7% (95% CI 2.8–10.3%). These patients also experienced a significant burden of inappropriate shocks [8 (17.4%) patients].

**Discussion**

To the best of our knowledge, this is the first study evaluating the completeness of medical assessment among survivors of unexplained SCA in the community. Our findings suggest that in a real-life setting, there is a significant lack of comprehensive cardiac investigation, leading to an overuse of the diagnosis of IVF. These findings call for the implementation of a standardized, systematic diagnostic approach in such cases.

Maximizing the ability to establish a diagnosis in ‘unexplained’ SCA has several implications. Firstly, it allows for provision of specific medical therapies, which might otherwise not be considered in a particular case. Although ICD implantation is almost universally done after SCA without acute or reversible cause, targeted pharmacological treatment can reduce ventricular arrhythmias and device therapies, as can implementation of essential lifestyle changes (avoiding high-risk drugs in long QT and Brugada syndromes, limiting excessive alcohol intake and immediate treatment of fever with antipyretic drugs in
to have inherited cardiac disorders, obtaining a diagnosis is crucial to perform targeted screening of family members, allowing early diagnosis and implementation of primary prevention for these patients, before the potential occurrence of a life-threatening event as first presentation. It has been tested and demonstrated that in the absence of a clear aetiology after ECG, echocardiography, and coronary angiography, a global workup strategy using a systematic algorithm including in particular pharmacological, exercise, and genetic testing, may allow the identification of cardiac abnormalities in more than half of apparently unexplained SCA. In our population, less than 20% of the cases labelled IVF received a comprehensive investigation. In particular, while cardiac MRI was performed in the majority of cases (80%), coronary vasospasm provocative testing and ajmaline tests were clearly underused. Also, the very low rate of exercise testing and Holter-ECG recording could have led to missed opportunities to diagnose catecholaminergic polymorphic ventricular tachycardia cases or unmask some long QT syndromes. Concerning adrenaline challenge and QT analysis, its predictive value and interpretation remains debated and often challenging, whereas it is much more useful and simple to perform both an exercise test and a 12-lead 24 h Holter recording to observe specific changes in repolarization during the recovery phase or night-time. These striking findings illustrate the gap between results reported by highly specialized electrophysiology teams working in tertiary centres, and our real-world approach involving numerous unselected hospitals. Moreover, our results emphasize that very few investigations are performed during follow-up subsequent to the initial evaluation during index hospitalization. The

Brugada syndrome, and limiting or avoiding sports activities in exercise-related rhythm disorders.12,43 Secondly, because patients with SCA and no structural heart disease most of the time turn out

Figure 2 Yield of different aetiological examinations. ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; SCA, sudden cardiac arrest; TTE, transthoracic echocardiography.

Figure 3 Unexplained sudden cardiac arrest (‘idiopathic ventricular fibrillation’) rate by number of additional examinations after the initial workup (electrocardiogram, echocardiography, and coronary angiography) and during follow-up. Cardiac MRI, ergonovine challenge, and pharmacological tests (ajmaline or catecholamine) were considered for the initial evaluation. The three additional diagnoses made during the follow-up were revealed by two ergonovine challenges (coronary vasospasms) and one exercise testing (long QT syndrome). IVF, idiopathic ventricular fibrillation.

Investigation of unexplained SCA in real life
last consensus document defining the minimal requirements for the diagnosis of IVF was published more than two decades ago in 1997, and clearly needs updating in the light of recent advances in imaging, genetic and molecular testing. While recent European guidelines have underlined the crucial role of family screening, stating a clear diagnostic approach with ECG, echocardiography (and/or MRI), Holter-ECG, exercise testing, signal averaged ECG, and provocative test with ajmaline (when Brugada syndrome is suspected), the need for further thorough investigations in the index case is left to the treating specialist’s discretion. The value of genetic tests has also been emphasized in case of clinical suspicion of a specific phenotype with an inherited cardiac disorder. Although targeted genetic testing has been reported to find causative mutations in up to almost 50% of cases of apparently unexplained SCA, genetic screening for a large panel of genes in IVF patients is not currently recommended, due to its low yield in the absence of a specific clinical suspicion to guide testing, where multiple rare variants of unknown significance cannot formally be considered as causal in the absence of informative familial analyses. Nevertheless, being initiated in only 9 (18.4%) patients in the present study, there is a clear, present scope to enhance the role of genetic testing in the diagnostic armamentarium, particularly in the light of promising results from recent studies.

Screening of first-degree relatives of an unexplained SCA is essential, and several studies have shown its clinical relevance. Krahn and colleagues reported cardiac abnormalities in 17–30% (depending on levels of diagnostic strength) of a large population of 398 first-degree family members of unexplained SCA. In addition to enabling early, specific management in case of identification of a clear

Table 1  Characteristics of patients labelled idiopathic ventricular fibrillation compared with other sudden cardiac arrests

|                      | IVFs (n = 49), n (%) | Other SCAs (n = 668), n (%) | P-value |
|----------------------|----------------------|-----------------------------|---------|
| Age (years), mean ± SD | 48.7 ± 14.8          | 57.8 ± 14.2                 | <0.001  |
| Male sex             | 34 (69.4)            | 540 (80.8)                  | 0.080   |
| Cardiovascular risk factors |                 |                             |         |
| Current/ex-smoking    | 19/7 (38.8/14.3)     | 292/121 (43.8/18.2)         | 0.449   |
| Hypertension          | 8 (16.3)             | 241 (36.2)                  | 0.005   |
| Dyslipidaemia         | 8 (16.3)             | 204 (30.6)                  | 0.035   |
| Overweight (BMI >25 kg/m²) | 16 (32.7)   | 274 (41.1)                  | 0.309   |
| Coronary heredity     | 8 (16.3)             | 80 (12.0)                   | 0.508   |
| Diabetes mellitus     | 5 (10.2)             | 86 (12.9)                   | 0.744   |
| Family history of SCA | 9 (18.4)             | 26 (3.9)                    | <0.001  |
| Cardiac warning symptoms | 8 (16.3)         | 300 (44.9)                  | <0.001  |
| Public location       | 30 (61.2)            | 398 (59.6)                  | 0.940   |
| EMS call prior to SCA onset | 0 (0)            | 102 (18.1)                  | 0.001   |
| Bystander             | 48 (98.0)            | 645 (96.6)                  | 1.000   |
| Bystander CPR         | 38 (77.6)            | 527 (79.6)                  | 0.872   |
| Collapse to basic life support (min), mean ± SD | 5.2 ± 4.9         | 3.0 ± 4.1                    | <0.001  |
| Basic life support to ROSC (min), mean ± SD | 19.8 ± 13.8        | 19.1 ± 18.4                  | 0.758   |
| Sport-related SCA     | 8 (16.7)             | 64 (9.6)                    | 0.132   |

BMI, body mass index; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; IVF, idiopathic ventricular fibrillation; ROSC, return of spontaneous circulation; SCA, sudden cardiac arrest; SD, standard deviation.

Table 2  Medical investigations of cases labelled idiopathic ventricular fibrillation (performed during the index hospitalization following the sudden cardiac arrest or planned subsequently after discharge)

|                      | IVFs (n = 49), n (%) |
|----------------------|----------------------|
| Coronary angiography | 47 (95.9)            |
| Cardiac MRI          | 40 (81.6)            |
| Provocative testing  |                      |
| Ergonovine           | 19 (38.8)            |
| Ajmaline             | 21 (42.9)            |
| Isoprenaline         | 10 (20.4)            |
| Adenosine            | 2 (4.1)              |
| Adrenaline           | 0 (0)                |
| Electrophysiological study | 12 (24.5)  |
| Genetic testing      | 9 (18.4)             |
| Holter-ECG           | 6 (12.2)             |
| Right ventricular angiography | 5 (10.2)   |
| Exercise testing     | 4 (8.2)              |
| Signal averaged ECG  | 2 (4.1)              |
| Coronary CT          | 1 (2.0)              |
| Cardiac scintigraphy (for ARVC) | 1 (2.0) |
| Cardiac biopsy       | 0 (0)                |

ARVC, arrhythmogenic right ventricular cardiomyopathy; ECG, electrocardiogram; MRI, magnetic resonance imaging.
phenotype in relatives, family screening also has the potential to improve rates of aetiological diagnosis among index cases. As demonstrated by Jiménez-Jaímez et al.,15 when no cause of SCA is identified after conventional testing, family screening can sometimes establish the diagnosis retrospectively in the index case, because penetrance and expressivity among gene carriers in the same family is variable.

Our study highlights that a diagnosis of IVF is made in a significant minority of SCA cases (6.8%). Although its exact incidence is unknown and will probably decline with advancements in diagnostic testing and the discovery of new primary arrhythmia syndromes, similar rates from 5 to 10% have been reported in the literature.37,48 It represents, for example, a higher proportion of SCA than identified electrical primary disorders in our study [15 (2.1%) patients], although, as discussed above, inadequate medical investigations probably underestimate the true proportion of channelopathies. We also identified several clinical characteristics of cases labelled IVF. Patients were younger, with a distinct and lower cardiovascular risk factors profile, and a relatively good proportion of them had a family history of SCA (18.4%). Although circumstances of occurrence were similar to other SCAs, relatively fewer of them had specific cardiac symptoms during the weeks prior to the event, with resultant less pre-SCA EMS call and thus longer collapse to basic life support duration. These findings fit particularly with a primary electrical cardiac disorder, characterized by propensity toward ventricular fibrillation in an otherwise normal heart, and emphasize the challenge represented by the prediction of such cases, where SCA may be the inaugural event and alternative preventive strategies have to be sought.49–51

Study limitations

The present study has certain limitations. Firstly, our hospital data are extracted from medical records. While a central committee performed adjudication, this process was based on medical files provided by the different hospitals. Furthermore, we collected the performance of specialized key cardiac investigations, which are unlikely to be underreported in medical reports. We also contacted the referral physician of each IVF case to ensure that all examinations performed were collected. However, family screening, often implemented after completion of all clinical testing can be significantly delayed or initiated by other practitioners, and might be missed in some instances. Secondly, our data are based on a large population with numerous centres involved, but due to the limited number of cases as well as the relatively short study period, we were not able to adequately assess temporal trends in investigation of SCA over the years. Thirdly, disparities in the extent of SCA investigation may exist both regionally and in different Health systems and caution has to be exercised in generalizing these results. Finally, our main result focuses on investigations performed during hospitalization or planned at discharge, because our objective was to assess the comprehensiveness of the initial workup by the different teams in current practice before labelling SCA as IVF, but diagnoses could emerge remotely, especially in this population where a close follow-up has been shown to be essential.16,52,53 However, our data on follow-up emphasize that very few investigations are performed after the initial evaluation.

Conclusion

Our findings from a real-life setting emphasize the extent to which unexplained SCAs are insufficiently investigated and the diagnosis of IVF is probably overused, despite evidence supporting the yield of exhaustive medical investigations in this specific setting. Less than 20% of patients eventually benefit from a complete workup in this context, underlining the importance of referring these patients to expert centres. Guidelines have to be framed, promoting a standardized and systematic diagnostic strategy to improve the proportion of definite diagnosis in apparently unexplained SCA and allow optimized management and better preventive strategies, including among family members.

Supplementary material

Supplementary material is available at European Heart Journal online.

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