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Electrocardiogram May Fail to Identify Proportion of High-Risk Individuals: Analysis of Series of 50 Sudden Death Cases

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Abstract: Background: An electrocardiogram (ECG) is an essential and easily available diagnostic test in the management of cardiomyopathies and channelopathies. Different strategies based on ECG have been recommended for general population and athlete screening. Objectives: The purpose of this study was to explore the value of the ECG for the diagnosis of sudden cardiac death (SCD) cases. Methods: ECGs from 50 (aged 37.6 ± 19.9 years, 37 men) resuscitated cardiac arrest (26, 52%) and SCD cases (24, 48%) were analyzed. Relevant medical history and results from clinical tests were reviewed. ECG findings were compared with the final diagnosis. Results: Final ECG classification was as follows: 9 (18%) normal, 15 (30%) unspecific, 14 (28%) suggestive, and 12 (24%) diagnostic. Amongst 13 hypertrophic cardiomyopathy patients, ECGs were diagnostic in 6 (46%) and suggestive in 1 (8%). Arrhythmogenic right ventricular cardiomyopathy was diagnosed in seven patients, two (28%) with suggestive ECG. Dilated cardiomyopathy was diagnosed in four patients, two (50%) with suggestive ECG. Six patients had Brugada syndrome: four (66%) had diagnostic ECGs, and two (33%) had suggestive ECG. Long QT syndrome was diagnosed in four cases; only one (25%) had a diagnostic ECG. Three patients had other cardiomyopathies. After the complete study, 13 (26%) patients remained with a non-conclusive diagnosis; their ECGs were unspecific or normal. Conclusion: ECG can be unspecific or normal in an important percentage of SCD cases (48%). Furthermore, a significant proportion of SCD cases after a comprehensive study remain without a definite diagnosis (26%). These findings should be considered when planning SCD preventive strategies.

Keywords: sudden cardiac death; electrocardiogram; inherited cardiomyopathy; channelopathy

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1. Introduction

Sudden cardiac death (SCD) is a devastating event at any age, particularly among the young. The annual incidence rate of SCD in individuals under 35 years of age ranges from 1 to 13 per a 100,000 population [1–4]. In adults, the most common cause of SCD is coronary artery disease, which is 10–15 times more prevalent than other cardiac conditions [2–4]. The second most frequent cause of death is unexplained. The term sudden adult death syndrome (SADS) has been used for cases with normal postmortem study. Genetics and family study leads to the identification of inherited arrhythmia syndromes or early

cardiomyopathic forms in up to 40% of SADS cases [5,6]. Cardiac non-ischemic conditions, such as cardiomyopathies and channelopathies, are common causes of SCD in individuals under 35 years and in athletes [7,8].

A twelve-lead electrocardiogram (ECG) is an important and easily available diagnostic test in cardiomyopathies and channelopathies. The ECG has been proposed as a useful tool to identify cardiac disease and hence individuals at risk for SCD. It is widely used in familial screening of cardiomyopathies and channelopathies, as well as in the pre-participation cardiovascular evaluation of competitive athletes [9,10].

The main aim of this study was to explore the value of the ECG for the retrospective diagnosis of non-ischemic SCD cases, and to compare ECG findings with the final clinical diagnosis in patients in whom the case of SCD or SCA was a suspected or confirmed cardiomyopathy or channelopathy.

2. Methods

2.1. Study Population

One hundred and twenty-two non-ischemic SCD or sudden cardiac arrest (SCA) cases consecutively referred to a cardiac screening clinic from January 2005 to January 2011 were retrospectively evaluated (Supplementary Figure S1). The study was approved by the ethical committee of our hospital.

Coronary artery disease was ruled out by means of coronary angiography in SCA patients, and by autopsy study in SCD cases. Patient clinical records were reviewed and previous ECGs were analyzed in SCD cases when available. ECGs performed later than 48 h after resuscitation were employed in survivors of a cardiac arrest. Finally, 50 cases (41%) were included in this study. The time delay between the date of the ECG and the date of death in the 24 SCD cases was 1008 ± 947 days.

A final diagnosis in SCD cases was achieved after postmortem study and clinical record review. The evaluation of SCA patients included the medical history, physical examination, 12-lead ECG, M mode, two-dimensional and Doppler echocardiography, and coronary angiography. Patients with unexplained SCA and no evident cardiac disease (with normal echocardiography, coronary arteries, and resting ECG) underwent an exercise test and pharmacological challenge with adrenaline and an antiarrhythmic-type Ic agent to unmask subclinical primary electrical disease. Familial study and a genetic test were offered in all cases.

Patients were diagnosed with hypertrophic cardiomyopathy (HCM), idiopathic dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), Brugada syndrome (BS), long QT syndrome (LQTS), or short QT syndrome (SQTS) so long as they fulfilled current diagnostic criteria [11–18]. If a certain diagnosis could not be established after complete study, patients were classified as SADS.

Reasons for exclusion from the study were lack of a postmortem examination, a drug/toxic cause, a non-cardiac cause of cardiac arrest, no ECG available, or paced ECG. A flowchart detailing excluded subjects is provided in Supplementary Figure S1.

2.2. ECG Analysis

Standard 12-lead ECG tracing at a 25 mm/s paper speed and 10 mm/mV amplitude was used. Two cardiologists, blind to the final diagnosis, performed the ECG reading, using a manual caliper as the only aid. Bazett's formula was used to correct the QT interval (QTc) for heart rate. Therefore, ECGs were classified as normal, unspecific–abnormal, suggestive, or diagnostic, according to the following criteria:

- Normal ECG: This included a sinus rhythm, a rate of 50–100 beats per minute, normal intervals and frontal axis (-30° to 110°), and normal transition and amplitudes.

- Unspecific–abnormal: This included ECGs not fulfilling neither normality criteria nor any of the following categories. Abnormalities considered in this category were atrial fibrillation, a right bundle branch block, frontal axis deviation, a short PR interval, the presence of a delta wave, an early repolarization pattern defined as an elevation in the J-point more than 0.1 mV from baseline presented in two or more of the inferior (II, III, and aVF) or lateral (I, aVL, V5 to V6) leads [19], and fragmented QRS that includes the presence of an additional R wave (R′) or notching in the nadir of the R wave or the S wave, or the presence of >1 R′ (fragmentation) in 2 contiguous leads in narrow QRS complexes, or more than 2 R′ or S waves in wide QRS complexes [20].
- Suggestive: This included CG characteristics suggesting a cardiomyopathy or channelopathy as the cause of SCD or SCA, not meeting diagnostic criteria. The following ECG patterns were classified in this group:
    - Left ventricular hypertrophy not fulfilling Romhilt–Estes criteria [21] (Supplementary Table S1).
    - Type 2 or 3 Brugada patterns [16] (type 2, "saddleback" significant ST-segment elevation, and type 3, "coved" or "saddleback" mild ST-segment elevation in right precordial leads).
    - A moderately prolonged QTc interval (less than 480 ms and more than 450 ms in men or 460 ms in women).
    - A moderately shortened QTc interval (less than 380 ms and more than 360 ms).
    - Epsilon waves or negative T waves in V1–V4 leads in the absence of a right bundle branch block.
    - A left bundle branch block (LBBB) as suggestive of DCM.
- Diagnostic: The ECG is unmistakably diagnostic of a condition potentially causing SCD/SCA, such as a spontaneous type 1 Brugada pattern defined by coved ST-segment elevation $\geq$ 2 mm (0.2 mV) followed by a negative T wave in at least one right precordial lead (V1 to V3) positioned in the 2nd, 3rd, or 4th intercostal space; this includes a prolonged QT interval (QTc $\geq$ 480 ms), or a short QTc interval less than 360 ms [18]. For the diagnosis of HCM, the Romhilt–Estes ECG score was applied, and a definitive diagnosis was achieved if 5 or more points were obtained.

2.3. Statistical Analysis

Continuous variables are presented as the mean $\pm$ standard deviation. Qualitative variables are presented as percentages. The SPSS for PC statistical software (SPSS, Chicago, IL, USA, version 17.0) was used for the analysis.

3. Results

Population clinical characteristics: A total of 50 consecutive patients were included; 26 (52%) of them were SCA patients and 24 (48%) were SCD victims. Mean age at the time of sudden death was 37.6 $\pm$ 19.9 years old; 37 (74%) patients were men. After a comprehensive study, a definitive diagnosis was achieved in 37 (74%) patients, whereas 13 (26%) patients remained undiagnosed; percentages of patients in each group are presented in Table 1 and Figure 1. In 20 (40%) cases, the event occurred during daily normal activities, 10 (20%) during exercise, 11 (22%) at rest, and 4 (8%) during sleep, and 1 (2%) was related to emotional stress; in 4 (8%) cases, the context was unknown (Table 1). Causative mutations related to specific conditions were found in 17 patients (46%) from 37 cases with complete genetic study (Supplementary Table S2), and familial disease was demonstrated in 15 (35%) cases from 43 cases with family study.

Table 1. Summary of final clinical diagnoses, sudden death context, genetic findings, and familial disease.

	HCM	DCM	ARVC	BS	LQTS	Others	SADS
Number of patients	13	4	7	6	4	3	13
Age (mean)	43.2 ± 15.9	57.5 ± 10.7	36.9 ± 11.1	47.2 ± 18.0	31.7 ± 26.9	25.3 ± 11.0	27.1 ± 23.7
Male gender	10 (77%)	3 (75%)	5 (78%)	6 (100%)	2 (50%)	2 (67%)	7 (54%)
Clinical presentation							
Sudden cardiac death	7 (53.8%)	2 (50%)	4 (57.1%)	1 (16.7%)	1 (25%)	2 (66.7%) †, ‡	7 (53.8%)
Aborted cardiac arrest	6 (46.2%)	2 (50%)	3 (42.9%)	5 (83.3%)	3 (75%)	1 (33.3%) §	6 (46.2%)
Sudden death context							
Daily activities	5 (38.5%)	4 (100%)	3 (42.9%)	2 (33.3%)	1 (25%)	1 (33.3%) §	4 (30.8%)
Exercise	1 (7.7%)	-	2 (28.6%)	-	2 (50%)	1 (33.3%) †	4 (30.8%)
Rest	5 (38.5%)	-	-	3 (50.0%)	-	-	3 (23.1%)
Sleep	-	-	-	1 (16.7%)	1 (25%)	-	2 (15.4%)
Emotional stress	-	-	-	-	-	1 (33.3%) ‡	-
Unknown	2 (15.4%)	-	2 (28.6%)	-	-	-	-
Positive genetics	5 (13.5%)	3 (8.10%)	4 (10.8%)	0	4 (10.8%)	1 (2.7%) ‡	0
Familial disease	5 (11.6%)	4 (9.3%)	4 (9.3%)	2 (4.6%)	0	0	0

§ Endomyocardial fibroelastosis, † Chagas cardiomyopathy, ‡ Catecholaminergic ventricular tachycardia.

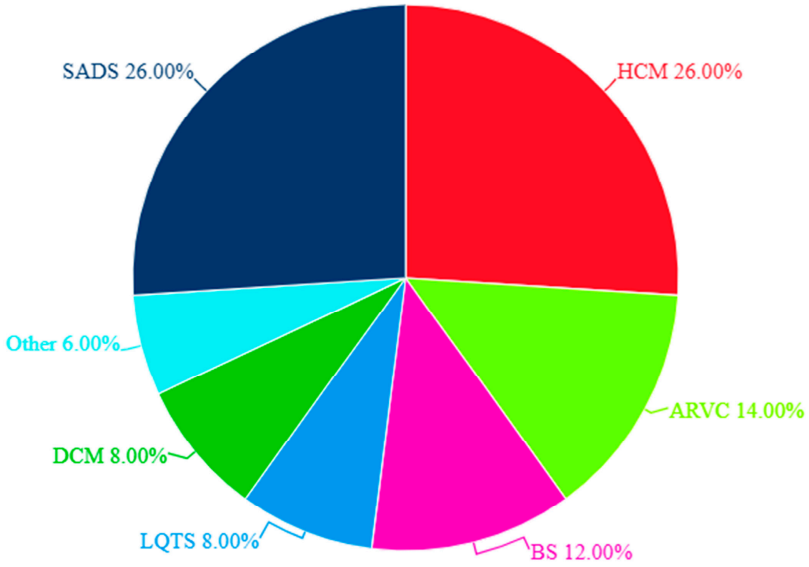

Figure 1. Final clinical diagnoses.

ECG findings: Forty-six ECGs (92%) presented a sinus rhythm, while three patients showed atrial fibrillation and one a low atrial rhythm. The PR interval was 157.8 ± 35.0 ms. QRS duration was 101.5 ± 21.3 ms. QT and QTc intervals were 376.7 ± 47.3 ms and 430.2 ± 39.9 ms, respectively.

Out of 50 ECGs, 9 (18%) met normality criteria, 15 (30%) were considered non-specific abnormal ECGs, 14 (28%) were suggestive of specific disease, and 12 ECGs (24%) met diagnostic criteria (Figure 2; Figure 3, Supplementary Table S3).

Among 12 diagnostic ECGs, 6 were diagnostic of HCM, with five or more points for the Romhilt–Estes score (1 scored five points, 2 ECGs scored six points, 2 ECGs scored seven points, and the remaining ECGs scored eight points). Four showed a type 1 Brugada ECG pattern, and the other two ECGs were considered as diagnostic of long QT syndrome, as QTc was 500 and 550 ms, respectively. Final diagnoses agreed with ECG classification in all patients. The patient diagnosed with endomyocardial fibroelastosis fulfilled ECG criteria for HCM.

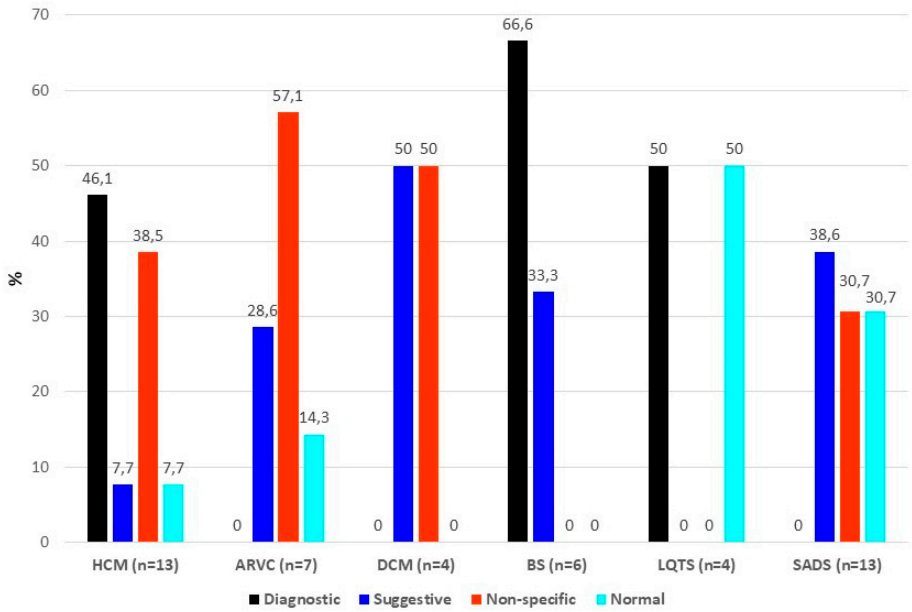

Figure 2. Final clinical diagnoses and ECG findings. Chagas cardiomyopathy, catecholaminergic ventricular tachycardia, and endomyocardial fibroelastosis are excluded from this analysis. HCM: hypertrophic cardiomyopathy; ARVC: arrhythmogenic right ventricular cardiomyopathy; BS: Brugada syndrome; LQTS: long QT syndrome; DCM: dilated cardiomyopathy; SADS: sudden adult death syndrome.

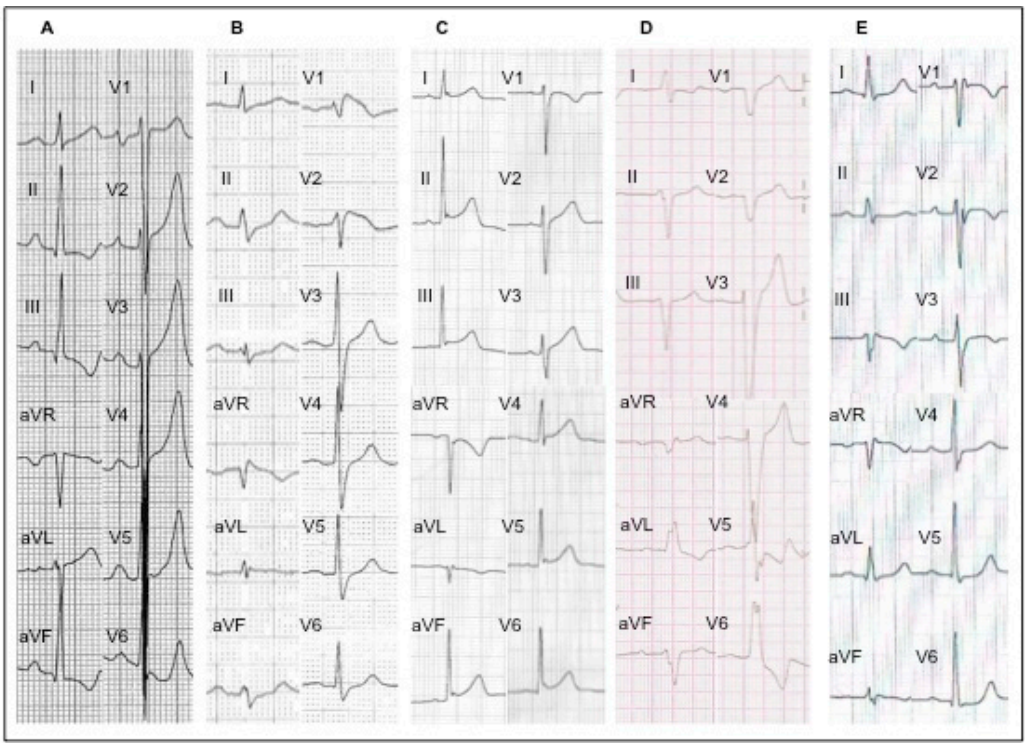

Figure 3. Some electrocardiograms from sudden cardiac death cases. (**A**): ECG fulfilling Romhilt–Estes criteria for left ventricular hypertrophy in patient diagnosed with hypertrophic cardiomyopathy and positive genetic test. (**B**): Type 1 Brugada pattern. (**C**): Early "notched" repolarization in inferior and lateral leads in sudden adult death syndrome case. (**D**): Left bundle branch block and long PR interval in patient diagnosed with dilated cardiomyopathy. (**E**): Presence of epsilon waves in V1 and V2 leads, and negative T waves in right precordial leads; this patient was diagnosed with arrhythmogenic right ventricular cardiomyopathy.

In the suggestive ECG group, cardiac diseases suspected by the ECG were two cases of ARVC, four of BS, two of DCM, and two of HCM with 4 points for the Romhilt–Estes score, and three cases of long QT syndrome, as QTc was 465, 480, and 475 ms, respectively. Both ECGs suggestive of ARVC belonged to two patients with this final diagnosis. Among the four ECGs with suspected BS, two corresponded to patients with this condition and the other two to HCM and SADS cases. Two patients with LBBB were diagnosed with DCM. Of the two patients with ECG suggestive of HCM, the disease was diagnosed in one of them, the other ECG corresponding to a SADS case. The ECGs that were suggestive of LQTS corresponded to two patients with SADS, and a patient with ARVC. This patient showed a markedly prolonged QTc interval (480 ms) and slightly negative T waves in right precordial leads; therefore, this ECG was classified as suggestive of LQTS but the echocardiogram was suggestive of ARVC and the genetic study showed a causative mutation in Plakophilin-2. In our series, two patients had a QTc interval between 350 and 370 ms, although these ECGs were not classified as suggestive of SQTS as suggestive findings of HCM and BS were present, respectively.

Final clinical diagnoses in the non-specific ECG group were four cases of HCM, two of DCM, three of ARVC, one of LQTS, one of Chagas cardiomyopathy, and four of SADS. The most common abnormality was a right bundle branch block in four patients (27%). Two patients in this group presented "notched" early repolarization in inferolateral leads (Figure 3), and after a detailed study, they remained without a diagnosis. One patient diagnosed with ARVC showed fragmented QRS complexes on the ECG.

Final clinical diagnoses in the patients with normal ECGs were catecholaminergic ventricular tachycardia, and two cases of LQTS, one of ARVC, one of HCM, and four of SADS.

4. Discussion

This is the first publication to our knowledge that has compared ECG findings with the postmortem (in SCD cases) or post-resuscitation (in SCA cases) final diagnosis in non-ischemic cardiac conditions. This investigation sought to determine the accuracy of the ECG for the diagnosis of SCD cases in a selected SCD/SCA cohort. The main finding of the present study was that a high proportion of SCD/SCA patients have ECG abnormalities (82%): 30% of patients had unspecific–abnormal ECG; 28% of them had an ECG suggestive of specific disease, and 24% had a diagnostic ECG.

The identification of a false negative ECG (unspecific or normal) in cardiomyopathies and channelopathies is not novel. Although the proportion of each condition with non-diagnostic ECGs is not well established, it has been estimated between 5 and 20% of cardiomyopathies [8,13]. In channelopathies, ECG findings are typically variable both in the BS and in LQTS. The proportion of non-diagnostic ECGs in SCD/SCA cases has not been reported.

Theoretically, patients with the more severe phenotypes (ECG and morpho-functional) are usually at higher risk of developing ventricular arrhythmias and sudden cardiac death. As examples, QRS duration has been associated with severity of left ventricular systolic function in DCM, some repolarization abnormalities (ST elevation) have been associated with event rates in HCM, and an extreme QT interval is considered a high-risk feature in LQTS. The results from our retrospective analysis of a small cohort do not seem to confirm the assumption that the severity of ECG findings is associated with SCD/SCA.

In our series, there were disorders in which ECGs showed unspecific abnormalities or were normal in a large number of patients, being the conditions ARVC (57%) and LQTS (65%). In contrast, HCM and BS were associated with a high proportion of diagnostic or suggestive ECGs (54% and 100%, respectively). Although DCM does not have specific ECG findings, LBBB has been associated with LV dilatation and dysfunction. In total, 25–28%

of DCM patients have LBBB and an increased proportion of 45% in cases with arrhythmic events [22–25]. As most other causes of LBBB like ischemic and valvular disease were ruled out during postmortem examination and the prevalence of hypertension was low (10%), we decided to consider LBBB as a suggestive finding of DCM. In keeping with Grimm et al.'s findings [25], 50% of patients from our series with DCM had LBBB on the ECG.

Despite SCD/SCA having a relatively low incidence in the general population, its effects are devastating. There is an increasing recognition of the role of inherited cardiac conditions in SCD/SCA in young individuals and in SADS cases. A correct diagnosis is of paramount importance for first-degree relatives at risk of having a cardiac condition. An early diagnosis, risk stratification, appropriate treatment, and genetic counseling are essential to avoid complications.

In the last decade, digital ECG machines have become available in most health care systems. ECG devices include automatic measurement of the heart rate, duration of the P wave, PR, QRS, QT intervals, QRS voltages, repolarization abnormalities, and sophisticated algorithms that help physicians with the interpretation of diagnostic findings.

Moreover, digital ECG allows the incorporation of artificial intelligence that might in the future increase our capability to identify individuals at risk of having an underlying cardiac condition [26,27]. In the meantime, it should be acknowledged on the basis of the results presented here that ECG might not capture a proportion of cases with an inherited cardiomyopathy or channelopathy.

Screening programs in the general population and particularly in athletes have been implemented worldwide. There is controversy on whether the protocol should include an interview on symptoms of heart disease, family history of premature cardiac disease, or sudden death and physical examination [28]. Resting ECG is recommended in most pre-participation strategies. Exercise ECG is routine for pre-participation programs in Italy and imaging tests are usually saved for symptomatic individuals or abnormal ECGs [9,29].

Based on the findings of our series, careful review of ECG for the identification not only of characteristic findings but also of suggestive features is needed for the identification of patients at risk. Further investigation on larger series is needed in order to evaluate the threshold for additional tests. Cardiac imaging tests, exercise tests, and/or pharmacological tests might increase diagnostic yield in this scenario.

5. Limitations

The main limitation of our study is the small number of patients included, the retrospective nature, and the delay of time between the date of the ECG and the date of death. Only 41% of SCD/SCA cases of this prospective series had available ECGs for evaluation. Despite that cardiomyopathies and channelopathies are genetic conditions, disease expression could have occurred after the ECG was recorded.

6. Conclusions

Despite the ECG being a useful tool in the assessment of patients or relatives with suspected cardiomyopathies or channelopathies, the results from the present study support the importance of a complete cardiovascular screening that includes detailed family history, cardiac imaging, and stress or pharmacological tests in order to avoid misdiagnosing patients with cardiomyopathies and channelopathies, particularly in patients with baseline abnormal ECG.

7. Future Perspectives

Inherited cardiac conditions are major causes of fatal arrhythmias and sudden cardiac death (SCD). In one in two SCD cases with an underlying inherited cardiac disease, the ECG is unremarkable. This finding might have an impact in the design of future SCD preventive strategies.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cardiogenetics15010005/s1, Figure S1: Flow chart for study inclusion of cases; Table S1: Romhilt-Estes score for left ventricular hypertrophy (LVH) based on ECG findings; Table S2: Genetic results identified in the study cohort; Table S3: ECG classification and relationship with the final clinical diagnosis.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committeeof CEI Hospital Universitario Virgen Arrixaca (protocol code 2023-5-11-HCUVA and date of approval 27th June 2023).

Informed Consent Statement: Informed consent was obtained from all resuscitated cardiac arrest subjects involved in the study. Patient consent was waived due to death in patients with sudden cardiac death.

Data Availability Statement: Data are available upon request to the authors. It is not publicly available due to privacy or ethical restrictions.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

ARVC	arrhythmogenic right ventricular cardiomyopathy
BS	Brugada syndrome
DCM	idiopathic dilated cardiomyopathy
ECG	electrocardiogram
HCM	hypertrophic cardiomyopathy
LBBB	left bundle branch block
LQTS	long QT syndrome
QTc	heart rate-corrected QT interval
SADS	sudden adult death syndrome
SCA	sudden cardiac arrest
SCD	sudden cardiac death

References

1. Risgaard, B.; Winkel, B.G.; Jabbari, R.; Behr, E.R.; Ingemann-Hansen, O.; Thomsen, J.L.; Ottesen, G.L.; Gislason, G.H.; Bundgaard, H.; Haunsø, S.; et al. Burden of sudden cardiac death in persons aged 1 to 49 years: Nationwide study in Denmark. *Circ. Arrhythm. Electrophysiol.* **2014**, *7*, 205–211. [CrossRef] [PubMed]
2. Priori, S.; Aliot, E.; Blomstrom-Lundqvist, C.; Bossaert, L.; Breithardt, G.; Brugada, P.; Camm, A.; Cappato, R.; Cobbe, S.; Di Mario, C.; et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur. Heart J.* **2001**, *22*, 1374–1450. [CrossRef] [PubMed]
3. Zheng, Z.-J.; Croft, J.B.; Giles, W.H.; Mensah, G.A. Sudden Cardiac Death in the United States, 1989 to 1998. *Circulation* **2001**, *104*, 2158–2163. [CrossRef]
4. Straus, S.; Bleumink, G.; Dieleman, J.; Stricker, B.; Sturkenboom, M. The incidence of sudden cardiac death in the general population. *J. Clin. Epidemiol.* **2004**, *57*, 98–102. [CrossRef] [PubMed]
5. Behr, E.; Wood, D.A.; Wright, M.; Syrris, P.; Sheppard, M.N.; Casey, A.; Davies, M.J.; McKenna, W. Sudden Arrhythmic Death Syndrome Steering Group: Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome. *Lancet* **2003**, *362*, 1457–1459. [CrossRef]
6. Tan, H.; Hofman, N.; van Langen, I.; van der Wal, A.; Wilde, A. Sudden Unexplained Death. Heritability and Diagnostic Yield of Cardiological and Genetic Examination in Surviving Relatives. *ACC Curr. J. Rev.* **2005**, *14*, 62. [CrossRef]
7. Bowker, T.; Wood, D.; Davies, M.; Sheppard, M.; Cary, N.; Burton, J.; Chambers, D.; Dawling, S.; Hobson, H.; Pyke, S.; et al. Sudden, unexpected cardiac or unexplained death in England: A national survey. *Qjm* **2003**, *96*, 269–279. [CrossRef]
8. Behr, E.R.; Dalageorgou, C.; Christiansen, M.; Syrris, P.; Hughes, S.; Esteban, M.T.T.; Rowland, E.; Jeffery, S.; McKenna, W.J. Sudden arrhythmic death syndrome: Familial evaluation identifies inheritable heart disease in the majority of families. *Eur. Heart J.* **2008**, *29*, 1670–1680. [CrossRef] [PubMed]
9. Corrado, D.; Pelliccia, A.; Bjørnstad, H.H.; Vanhees, L.; Biffi, A.; Borjesson, M.; Panhuyzen-Goedkoop, N.; Deligiannis, A.; Solberg, E.; Dugmore, D.; et al. Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: Proposal for a common European protocol. Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur. Heart J.* **2005**, *26*, 516–524.
10. Thiene, G.; Corrado, D.; Basso, C. Revisiting definition and classification of cardiomyopathies in the era of molecular medicine. *Eur. Heart J.* **2008**, *29*, 144–146. [CrossRef] [PubMed]
11. Lehnart, S.E.; Ackerman, M.J.; Benson, D.W., Jr.; Brugada, R.; Clancy, C.E.; Donahue, J.K.; George, A.L., Jr.; Grant, A.O.; Groft, S.C.; January, C.T.; et al. Inherited arrhythmias: A National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation* **2007**, *116*, 2325–2345.
12. Gersh, B.J.; Maron, B.J.; Bonow, R.O.; Dearani, J.A.; Fifer, M.A.; Link, M.S.; Naidu, S.S.; Nishimura, R.A.; Ommen, S.R.; Rakowski, H.; et al. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J. Am. Coll. Cardiol.* **2011**, *58*, 212–260.
13. Marcus, F.I.; McKenna, W.J.; Sherrill, D.; Basso, C.; Bauce, B.; Bluemke, D.A.; Calkins, H.; Corrado, D.; Cox, M.G.; Daubert, J.P.; et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: Proposed Modification of the Task Force Criteria. *Eur. Heart J.* **2010**, *121*, 1533–1541. [CrossRef]
14. Fatkin, D.; CSANZ Cardiac Genetic Diseases Council Writing Group. Guidelines for the diagnosis and management of familial dilated cardiomyopathy. *Heart Lung. Circ.* **2011**, *20*, 691–693. [CrossRef]
15. Schwartz, P.J.; Moss, A.J.; Vincent, G.M.; Crampton, R.S. Diagnostic criteria for the long QT syndrome. An update. *Circulation* **1993**, *88*, 782–784. [CrossRef]
16. Antzelevitch, C.; Brugada, P.; Borggrefe, M.; Brugada, J.; Brugada, R.; Corrado, D.; Gussak, I.; LeMarec, H.; Nademanee, K.; Perez Riera, A.R.; et al. Brugada syndrome: Report of the second consensus conference: Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* **2005**, *111*, 659–670. [CrossRef]
17. Priori, S.G.; Wilde, A.A.; Horie, M.; Cho, Y.; Behr, E.R.; Berul, C.; Blom, N.; Brugada, J.; Chiang, C.E.; Huikuri, H.; et al. Executive summary: RS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Europace* **2013**, *15*, 1389–1406. [CrossRef] [PubMed]

18. Gollob, M.H.; Redpath, C.J.; Roberts, J.D. The Short QT Syndrome: Proposed Diagnostic Criteria. *J. Am. Coll. Cardiol.* **2011**, *57*, 802–812. [CrossRef]
19. Tikkanen, J.T.; Anttonen, O.; Junttila, M.J.; Aro, A.L.; Kerola, T.; Rissanen, H.A.; Reunanen, A.; Huikuri, H.V. Long-Term Outcome Associated with Early Repolarization on Electrocardiography. *N. Engl. J. Med.* **2009**, *361*, 2529–2537. [CrossRef]
20. Das, M.K.; Zipes, D.P. Fragmented QRS: A predictor of mortality and sudden cardiac death. *Heart Rhythm.* **2009**, *6*, S8–S14. [CrossRef]
21. Romhilt, D.W.; Estes, E.H., Jr. A point-score system for the ECG diagnosis of left ventricular hypertrophy. *Am. Heart J.* **1968**, *75*, 752–758. [CrossRef] [PubMed]
22. Brembilla-Perrot, B.; Alla, F.; Suty-Selton, C.; Huttin, O.; Blangy, H.; Sadoul, N.; Chometon, F.; Groben, L.; Luporsi, J.D.; Zannad, N.; et al. Nonischemic Dilated Cardiomyopathy: Results of Noninvasive and Invasive Evaluation in 310 Patients and Clinical Significance of Bundle Branch Block. *Pacing Clin. Electrophysiol.* **2008**, *31*, 1383–1390. [CrossRef] [PubMed]
23. Gulati, A.; Ismail, T.F.; Jabbour, A.; Ismail, N.A.; Morarji, K.; Ali, A.; Raza, S.; Khwaja, J.; Brown, T.D.; Liodakis, E.; et al. Clinical utility and prognostic value of left atrial volume assessment by cardiovascular magnetic resonance in non-ischaemic dilated cardiomyopathy. *Eur. J. Heart Fail.* **2013**, *15*, 660–670. [CrossRef] [PubMed]
24. Merlo, M.; Pivetta, A.; Pinamonti, B.; Stolfo, D.; Zecchin, M.; Barbati, G.; Di Lenarda, A.; Sinagra, G. Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: Changing mortality over the last 30 years. *Eur. J. Heart Fail.* **2014**, *16*, 317–324. [CrossRef]
25. Grimm, W.; Christ, M.; Bach, J.; Muller, H.; Maisch, B. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: Results of the Marburg Cardiomyopathy Study. *Circulation* **2003**, *108*, 2883–2891. [CrossRef] [PubMed]
26. Bleijendaal, H.; Ramos, L.A.; Lopes, R.R.; Verstraelen, T.E.; Baalman, S.W.E.; Oudkerk Pool, M.D.; Tjong, F.V.Y.; Melgarejo-Meseguer, F.M.; Gimeno-Blanes, F.J.; Gimeno-Blanes, J.R.; et al. Computer versus cardiologist: Is a machine learning algorithm able to outperform an expert in diagnosing a phospholamban p.Arg14del mutation on the electrocardiogram? *Heart Rhythm.* **2021**, *18*, 79–87. [CrossRef]
27. Burattini, L.; Zareba, W.; Burattini, R. Assessment of physiological amplitude, duration, and magnitude of ECG T-wave alternans. *Ann. Noninvasive Electrocardiol.* **2009**, *14*, 366–374. [CrossRef]
28. Maron, B.J.; Thompson, P.D.; Ackerman, M.J.; Balady, G.; Berger, S.; Cohen, D.; Dimeff, R.; Douglas, P.S.; Glover, D.W.; Hutter, A.M., Jr.; et al. Recommendations and considerations related to pre-participation screening for cardiovascular abnormalities in competitive athletes: 2007 update: A scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: Endorsed by the American College of Cardiology Foundation. *Circulation* **2007**, *115*, 1643–1655. [PubMed]
29. Corrado, D.; Basso, C.; Schiavon, M.; Pelliccia, A.; Thiene, G. Pre-participation screening of young competitive athletes for pre-vention of sudden cardiac death. *J. Am. Coll. Cardiol.* **2008**, *52*, 1981–1989. [CrossRef] [PubMed]