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Early repolarization and markers of ventricular arrhythmogenesis in patients referred to ambulatory 24-hour ECG recording

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ABSTRACT

Background: Recent reports suggest that early repolarization, a common electrocardiographic (ECG) pattern that has been always considered benign, could be a substrate for ventricular arrhythmias and sudden cardiac arrest.
Methods: We examined the associations between early repolarization and markers of ventricular arrhythmogenesis as defined by presence of ventricular late potentials (LPs) in the Signal Averaged ECG (SA-ECG), depressed heart rate variability (HRV) and/or presence of ventricular ectopy in patients referred to ambulatory 24-hour ECG recording (Holter).
Results: This study included 687 patients (57% females) who were 51.2 ± 5.1 years. In unadjusted and multivariable adjusted analyses, early repolarization was not significantly associated with any of the measures of SA-ECG, HRV or ventricular ectopy. The lack of significant associations persisted in all subgroup analyses where different definitions of early repolarization in different groups of ECG leads were tested.
Conclusions: Early repolarization has no significant association with markers of ventricular arrhythmogenesis as detected by SA-ECG, HRV and ventricular ectopy. These findings suggest that the mechanisms of arrhythmic events in early repolarization (if they truly exist), are not likely to be through pathological pathways that could be detected by these markers.

1. Introduction

Early repolarization is a common ECG finding present in 1 to 5% of the general population with a greater prevalence in young men and athletes, yet it is not rare in women or in older or inactive people [1–3]. Since it was first reported almost 65 years ago, early repolarization has been considered benign [4]. However, recent reports suggest that early repolarization may be part of a spectrum of cardiovascular abnormalities related to non-ischemic ST elevation, including Brugada syndrome, and subsequently can become a substrate for ventricular arrhythmias and sudden cardiac arrest in some individuals [5,6]. This suggestion has been supported by recent reports of adverse outcomes in individuals with early repolarization [7–9]. Examining associations between early repolarization and markers/substrates of ventricular arrhythmogenesis will enhance our understanding of the potential mechanisms by which early repolarization can cause arrhythmic events. This may subsequently help in risk stratification of arrhythmic events in this group of people. Previous reports examined HRV [10–13] and ventricular LPs [14–19] in patients with Brugada syndrome (which is also an ECG phenotype characterized by elevated ST segment), but limited data exist on the association between early repolarization and these markers of arrhythmogenesis.

In this study we examined associations between early repolarization and markers of ventricular arrhythmogenesis as defined by presence of ventricular late potentials (LPs) in the Signal Averaged ECG (SA-ECG), depressed heart rate variability (HRV) and presence of ventricular ectopy (premature ventricular complexes (PVCs) and ventricular tachycardia) in a large sample of patients referred to ambulatory 24-hour ECG recording (Holter).

2. Methods

2.1. Study population

The description of the study population has been previously described [20]. In summary, this study included all patients (N = 1007) who were referred to the National

Abbreviation: LPs, Ventricular late potentials; ECG, Electrocardiogram; SA-ECG, Signal Averaged ECG; HRV, Heart rate variability; PVCs, Premature ventricular complexes; SDNN, The standard deviation of all filtered RR intervals over the length of the recording; SDNNi, Mean of the standard deviations of all filtered RR intervals for all 5-minute segments of the recording; SDANNi, The standard deviation of the means of all filtered RR intervals for all 5 minutes segments of all recording; RMSSD, The root mean square of the difference of successive RRs; PNN50, Percentage of RR intervals that are greater than adjacent RR by 50 ms; QRSd, Filtered QRS duration; RMS-40, Root-mean-square voltage of the last 40 ms of the QRS complex; LAS, Duration of low amplitude signal of the terminal portion of the QRS; NSVT, Non-sustained ventricular tachycardia.

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Heart Institute, Egypt for 24-hour ambulatory ECG recording (Holter) in the period from 1998 to 2000. Patients were referred to Holter for evaluation of symptomatic palpitations (48%), unexplained dizziness/fainting (21%), chest pain with normal resting and exercise ECG (17%), assessment of the function of implanted pacemaker or effectiveness of antiarrhythmic (7%), or "others" such as risk stratification (7%). For the purpose of this analysis, we excluded 320 patients with poor quality resting 12-lead ECG, with Holter recording less than 20 h, or with complete left or right bundle branch block, Wolff–Parkinson–White syndrome, pacemaker or had myocardial infarction, unstable angina or heart failure admission within the past 6 months.

2.2. Electrocardiography

2.2.1. Standard 12-lead resting ECG

Early repolarization was determined from a 12-lead resting ECG that was recorded just before the Holter recording. Early repolarization was diagnosed using a definition developed by the Epidemiological Cardiology Research Center (EPICARE), Winston Salem, NC which is based on application of strict criteria selected from previous publications as follows: a) *Definite early repolarization*: STJ elevation >1 mm in ≥50% of beats, T wave amplitude ≥5 mm, prominent J point, upward concavity of the ST, and a distinct notch or slur on the downstroke of the R wave in any of V3-V6; *or* STJ elevation >2 mm in ≥50% of beats, T wave amplitude ≥5 mm, prominent J point and upward concavity of the ST segment in any of V3-V6- ; b) *Probable early repolarization*: STJ elevation >1 mm in ≥50% of beats, prominent J point, and upward concavity of the ST segment in any of V3–V6 and T wave amplitude ≥8 mm in any of the chest leads; and *c) Possible early repolarization*: presence of Minnesota code 9–2 [ST segment elevation >=1.0 mm in any of leads I, II, III, aVL, aVF, V5 and V6 OR ST segment elevation >=2.0 mm in any of leads V1–V4] or Minnesota code 9–5 [T-wave amplitude >12 mm in any of leads I, II, III, aVL, aVF, V1, V2, V3, V4, V5, V6] [21]. All ECGs were read for early repolarization by a single reader. To validate the repeatability of reading, a random sample of 50 ECGs was reread blindly by the same reader. There was very high repeatability; Kappa statistic and 95% confidence interval: 0.93 (0.84, 1.00). We also validated the comparability of detecting early repolarization using this method with the clinical diagnosis by a trained cardiologist in 60 randomly selected ECGs. For this purpose, possible and probable in our results were collapsed into one group (possible/probable) and the cardiologist (who was blinded to the results) was asked to classify the ECGs as definite, possible/probable, or no early repolarization. As reflected by the high Kappa statistic (kappa statistic (95% confidence interval): 0.84 (0.70, 0.98)), detection of early repolarization using the strict criteria that we used in this analysis reflected the clinical diagnosis of early repolarization.

2.3. Twenty four-hour ambulatory ECG recording (Holter)

Twenty-four-hour ambulatory ECG recording (Holter) was obtained using Oxford Medilog Prima Holter management system (Oxford Medical Instruments, Old Woking, Surrey, UK) which included a three-channel recorder and a prima Holter analysis software version 7.1 running under Microsoft Windows. The system has capabilities for arrhythmia, SA-ECG and HRV analyses. All recordings were analyzed by a trained cardiologist.

2.3.1. Heart rate variability (HRV)

HRV indices were obtained from the 24-hour ambulatory ECG recordings (Holter). Non-sinus-originated beats (supraventricular and ventricular ectopic beats, AV blocks, atrial fibrillation attacks) and artifacts were initially detected by the software and then checked and confirmed by a trained cardiologist. Patients with insufficient recordings (record duration <20 h and/or sinus beats <50%)-were excluded. Five HRV indices were calculated [22]: The standard deviation of all filtered RR intervals over the length of the recording (SDNN); mean of the standard deviations of all filtered RR intervals for all 5-minute segments of the recording (SDNNi); the standard deviation of the means of all filtered RR intervals for all 5-minute segments of all recording (SDANNi); the root mean square of the difference of successive RRs (RMSSD); and the percentage of RR interval that are greater than adjacent RR by 50 ms (PNN50).

2.3.2. Signal Averaged ECG (SA-ECG)

Time domain SA-ECG was used to detect ventricular late potentials (LPs). QRS complexes were recorded and analyzed by an Oxford Medilog system (Oxford Medical Instruments, Old Woking, Surrey, UK). The system is designed to acquire electrocardiographic data from the 24-hour ECG recording. QRS complexes in each of the three-channel in a predetermined period were averaged and filtered. The 40 Hz high pass filter was used in this study. This filter can attenuate only the low frequency component of the sine wave lower than 40 Hz, while higher frequencies are passed. The maximum noise level allowed was 0.7 μV. Ventricular LPs were considered present (Positive LPs) if any two of three criteria were met [23]: 1) filtered QRS duration (QRSd) >114 ms, 2) root-mean-square voltage of the last 40 ms of the QRS complex (RMS-40) <20 micro volt (μV), and 3) duration of low amplitude (<40 μV) signal of the terminal portion of the QRS (LAS) >38 ms.

2.3.3. Ventricular ectopy

PVCs were visually confirmed and counted per 24-hour recording. Fusion beats were counted as PVCs. Non-sustained ventricular tachycardia (NSVT) was defined as three or more consecutive PVCs that last no more than 30 s and terminate spontaneously. The number of PVCs in each of the NSVT episodes was counted toward the total number of PVCs. None of the patients had sustained ventricular tachycardia. To have a uniform comparison of the number of PVCs between groups with different ECG recording durations, we used the PVCs/24-hour for comparison. This was obtained by using the formula: [(number of PVCs/duration of recording) × 24].

2.4. Other variables

Demographics and medical history including history of hypertension, diabetes, CHD, heart failure, use of antiarrhythmic drugs, left ventricular ejection fraction (LVEF), body mass index (BMI) and smoking status were obtained from the patients' health records.

2.5. Statistical analysis

Descriptive statistics are presented as means with standard deviations (SD) for continuous variables and as proportions (%) for categorical variables in all of the study population stratified by the early repolarization status. For the purpose of this analysis, probable and possible early repolarization were merged into one group named "possible early repolarization". We used linear regression analysis (for continuous outcomes) and logistic regression analysis (for categorical outcomes) to estimate the unadjusted and multivariable adjusted associations between different levels of early repolarization (compared to "no early repolarization") with SA-ECG, HRV, and PVCs/24-hour. The number of PVCs/24-hour, PNN50, and rMSSD were logarithmically transformed since they showed skewed distribution. However, in the descriptive statistics table we presented the mean and standard deviation of these values to allow for realistic presentation and comparison with other studies. The first set of the multivariable models was adjusted for demographic variables (age and sex). The final models included the demographic variables in the first set of models plus history of hypertension, diabetes, hypercholesterolemia, ejection fraction, smoking, heart rate, use of antiarrhythmic drugs, and BMI.

As secondary analyses, we reran all the models using different classifications of early repolarization as follows: We used early repolarization as "Yes" versus "No" where: 1) "Yes" included only definite early repolarization while "No" included possible, probable and no early repolarization; 2) "Yes" included definite and probable early repolarization while "No" included possible and no early repolarization; and 3) "Yes" included definite, probable and possible early repolarization while "No" included only no early repolarization. We also classified early repolarization as anterior, inferior, lateral or global early repolarization (using clinical review). Finally, we stratified early repolarization according to the degree of J-point elevation (≥0.1 mV or ≥0.2 mV) in either inferior or lateral leads as described by Tikkanen et al. [9]. The aim of these secondary analyses was to examine the consistency of the results.

3. Results

This analysis included 687 patients aged 51.2 (±5.1) years of whom 57% were females. All patients had 24-hour ambulatory ECG recording (Holter) with an average recording duration of 21.9 (±1.3) h. Table 1 shows the characteristics of the study population at the time of 24-hour ambulatory ECG recording (Holter) stratified by early repolarization status. As shown, patients with definite or possible early repolarization (compared to no early repolarization) tend to be younger, males, and have lower BMI and slower heart rate ($p<0.05$). No significant differences were observed in HRV, SA-ECG, and ventricular ectopy between different early repolarization strata.

In unadjusted and multivariable adjusted linear regression model, definite early repolarization and possible early repolarization (compared to no early repolarization) did not have significant associations with any of the HRV and SA-ECG measures nor the number of PVCs/24-hour (Table 2). Also, no significant association was observed between definite early repolarization and possible early repolarization (compared to no early repolarization) with positive late potential in logistic regression analysis (odds ratio (95% CI): 0.98 (0.44, 2.15); and 1.10 (0.37, 3.21) for definite and possible early repolarization respectively) (Fig. 1). These non-significant results persisted after adjusting for demographics and after further adjusting for history of hypertension, diabetes, CHD, heart failure, antiarrhythmic drugs use, smoking, heart rate, ejection fraction, and BMI. The same conclusions were also reached with using different combinations of definite/possible/probable/no early repolarization, looking at different lead groups separately, or stratifying the results by the level of STJ elevation. We also reran the analyses after including those with recent (within 6 months) myocardial infarction, angina or heart failure. Still, there were no significant associations between early repolarization and markers of arrhythmogenesis in any of the subgroup analyses (data not shown).