The Prognostic Value of Early Repolarization Pattern for the Ventricular Tachyarrhythmias of Acute Myocardial Infarction Patients: A Meta-Analysis

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Keywords

Early repolarization · Acute myocardial infarction · Ventricular tachyarrhythmias · Prognosis

Abstract

Several studies have indicated that early repolarization (ER) is a risk factor for ventricular tachyarrhythmias (VTAs) in acute myocardial infarction (AMI) patients. The prognostic values of ER detail characteristics except J-point morphology, and inferior leads ER location for VTAs are still unclear. We searched PubMed, Embase, and the Cochrane Library for eligible studies up to March 4, 2019. Studies to investigate the relationship between ER and the incidence of VTAs in AMI patients were extracted. A total of 10 studies with 2,672 participants were included in the analysis. ER significantly predicted the incidence of VTAs (odds ratio [OR] 3.62, 95% confidence intervals [CI] 2.77–4.73), regardless of the type of AMI. The presence of ER before AMI (OR 5.58, 95% CI 3.41 to 9.12) and after AMI (OR 3.02, 95% CI 2.19–4.15) increased the risk of VTAs. The prognostic value of ER for VTAs in the long follow-up (≥ 30 days) (OR 2.39, 95% CI 1.59–3.59) fell by half compared to the short follow-up duration (< 30 days) (OR 4.97, 95% CI 3.48–7.09). Patients with ER displayed a higher

risk of developing ventricular fibrillation (VF) (OR 6.94, 95% CI 3.87–12.43) than those without ER. However, neither J-point elevation with OR = 2.48 nor lateral leads' ER location with OR = 3.83 remarkably increased the risk of VTAs in patients with AMI. ER is significantly associated with increasing risk of VTAs, particularly VF, in AMI patients. This relationship is weaker in the 30-day follow-up and is not reinforced by J-point elevation and lateral leads' ER location.

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Introduction

The early repolarization (ER) pattern is a common electrocardiogram (ECG) finding that historically has been regarded as a benign phenomenon [1]. However, recent studies have demonstrated that patients with ER are susceptible to ventricular tachyarrhythmias (VTAs) after the onset of acute myocardial infarction (AMI) [2–11]. A meta-analysis by Zhang et al. [12] in 2015 revealed that the ER pattern is significantly related to VTAs in patients with AMI, especially the notched ER pattern located in inferior leads. However, the authors did not analyze other specific ER characteristics except J-point morphol-

Fig. 1. Flow chart of the selection procedure.

ogy (notching or slurring) and inferior leads' ER location due to lack of available data. More importantly, 1 study was missed, and 3 new studies were reported. Therefore, we performed an updated systematic review and meta-analysis to assess whether ER and its detail characteristics were associated with increasing risk of VTAs in patients with AMI.

Methods

Owing to the inevitable biases of observational studies, we performed this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13].

Two investigators (S.X. and L.Y.) conducted a systematic search of PubMed, Embase, and the Cochrane Library for eligible studies up to March 4, 2019, using the following keywords: "Osborn wave," "Osborn waves," "J-wave," "J-waves," "J wave," "J waves," "early repolarization," "ST elevation myocardial infarction," "non-ST segment elevation myocardial infarction," "acute myocardial infarction," "STEMI," "NSTEMI," "AMI," and "MI."

We included observational studies to investigate the relationship between the ER pattern and the incidence of VTAs in patients with AMI. Two investigators (S.X. and L.Y.) independently screened titles and abstracts and determined eligible articles if they met the following criteria: (1) the study was written in English; (2) the study was a case-control or cohort design; (3) the endpoints were nonsustained ventricular tachycardia (VT), sustained VT, and ventricular fibrillation (VF); (4) the odd ratio (OR) or hazard ratio with 95% confidence interval (CI) was provided or the data was available to calculate these for evaluating ER in predicting the risk of VTAs in patients with AMI. Conference abstracts were excluded without available full text. Only the latest article was included when studies were carried out on the same population. The disagreements were resolved by discussion with a third investigator (X.W.).

Two investigators (S.X. and L.Y.) independently extracted the information of potentially relevant studies using a prepared checklist which contained the following information: details of the publications (first author's last name, year of publication), study design, study location, sample size, patients' age, follow-up duration, diagnosis of ER before or after AMI onset, endpoint events, number of ST segment elevation myocardial infarctions (STEMI), and number of percutaneous coronary interventions (PCI). Disagreements were resolved by consensus.

All the potential references were imported into the EndNote software. We analyzed data with Review Manager (RevMan version 5.3; Cochrane Collaboration, Oxford, UK). The summary OR and the corresponding 95% CI were calculated for the value of ER to predict the incidence of VTAs in the patients suffering from AMI (two-tailed $p < 0.05$ was considered statistically significant). Relative risk and hazard ratio values in the primary study were considered as OR in all studies, and adjusted OR is prior to unadjusted OR. Heterogeneity in our analysis was evaluated by using I^2 [14]. If the I^2 was $< 50\%$, which means low heterogeneity existed, a fixed-effects model was used in the meta-analysis for pooling effect sizes. Otherwise a random-effects model was used. A funnel plot was used to assess the publication bias. Sensitivity analyses were conducted by omitting the study if its sample size was less than 100. We systematically evaluated study quality with the Newcastle-Ottawa Scale (NOS) [15].

Results

The flow of the selection is shown in Figure 1. The search strategy yielded 476 potentially relevant studies, of which 154 studies were excluded for duplication. Then, 295 out of the remaining 322 studies were subsequently excluded for not meeting eligibility criteria. At the same time, 13 conference abstracts were excluded. After detailed evaluation, 1 study [16] was excluded because its

Table 1. Summary of the characteristics of the 10 studies

Author, year	Study design	Study location	Sample size	Mean age, years	Follow-up	Diagnosis of ER before or after AMI	Endpoint events	STEMI, n (%)	PCI, n (%)	Covariate adjustment
Ali Diab et al. [9], 2015	Case-control	Egypt	102	48.4	48 h	Before	Sustained VT/VF	72 (70.6)	102 (100)	LVEF QTc and QTd
Kim et al. [5], 2014	Cohort	Korea	296	61.23±13.41	48 h	Before	VF	193 (65.2)	296 (100)	Unadjusted
Naruse et al. [8], 2015	Cohort	Japan	281	69±12	48 h	Before	Sustained VF	227 (81)	281 (100)	Unadjusted
Patel et al. [2], 2012	Case-control	America	100	65.5	72 h	Before	VTAs	100 (100)	100 (100)	peak creatine kinase MB level or LVEF
Chen et al. [11], 2017	Cohort	China	654	58.4	30 days	After	Sustained VT/VF	654 (100)	304 (46.48)	ACEI, male, LVEF, cTnT, NT-proBNP, acute PCI, QTc, HR
Endo et al. [4], 2014	Cohort	Japan	184	64.5	30 days	After	Sustained VT/VF	NA	184 (100)	Killip grade II–IV
Ozcan et al. [6], 2014	Cohort	Turkey	521	57.2	30 days	After	Sustained VT/VF	521 (100)	269 (51.6)	Unadjusted
Park et al. [7], 2014	Cohort	Korea	266	61.6±12.7	6.7±4.5 days	After	VTAs	266 (100)	266 (100)	Inferior myocardial infarction E/E' LVEF (<45%)
Rudic et al. [3], 2012	Case-control	Germany	60	61.8±13.1	During hospitalization	After	VF	33 (55)	60 (100)	LVEF and QTc
Wu et al. [10], 2019	Case-control	Taiwan China	208	68.9±15.4	During hospitalization	After	VTAs	71 (34.1)	NA	Chronic kidney disease

ER, early repolarization; AMI, acute myocardial infarction; STEMI, ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; VTAs, ventricular tachyarrhythmias; VT, ventricular tachyarrhythmia; VF, ventricular fibrillation; LVEF, left ventricular ejection fraction; QTc, corrected QT interval; QTd, QT dispersion; ACEI, angiotensin-converting enzyme inhibitors; cTnT, cardiac troponin; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; HR, heart rate; E/E', peak early diastolic mitral flow and lateral annular velocities; NA, no information available.

Table 2. Detail quality assessment of case-control studies

Case-control	Adequate definition of cases	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis ¹	Ascertainment of exposure	Same method of ascertainment	Non-response rate	Total
Patel et al. [2], 2012	☆	☆		☆	☆☆	☆	☆	☆	8
Wu et al. [10], 2019	☆	☆		☆	☆☆	☆	☆	☆	8
Ali Diab et al. [9], 2015	☆			☆	☆☆	☆	☆		6
Rudic et al. [3], 2012	☆	☆		☆	☆☆	☆	☆	☆	8

¹ A maximum of two stars can be allotted in this category. Studies that controlled for age received one star, whereas studies with adjusted analyses received one additional star.

endpoints consisted of VT/VF and sudden death, which would lead to significant contamination of data. Another study [17] was not selected because some patients with VT/VF were calculated repeatedly. Meanwhile, the article by Naruse et al. [18] in 2012 was excluded because it was carried out on the same population as the article published in 2015 [8]. Therefore, 10 studies [2–11] with a total of 2,672 participants were included in the final analysis.

A summary of the characteristics of the 10 studies is presented in Table 1. All of the studies, except the study by

Rudic et al. [3], involved a sample size which was equal to or greater than 100. The mean age of the participants in the 10 studies ranged from 48.4 to 69 years; 4 studies only recruited the patients after the onset of STEMI, and 7 studies included the patients who absolutely underwent PCI. The adjustments for covariates differed across studies.

Tables 2 and 3 show detail quality assessment of the included studies according to NOS. 9 studies were considered as high quality, and only 1 study with a score of 6 was considered as moderate quality.

Table 3. Detail quality assessment of cohort studies

Cohort	Representa- tiveness of the exposed cohort	Selection of the non- exposed cohort	Ascertain- ment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis ¹	Assess- ment of outcome	Was follow- up long enough for outcomes to occur ²	Adequacy of follow- up of cohorts	Total
Naruse et al. [8], 2015	☆	☆	☆	☆	☆	☆		☆	8
Park et al. [7], 2014	☆	☆	☆	☆	☆☆	☆		☆	8
Chen et al. [11], 2017	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Endo et al. [4], 2014	☆	☆	☆	☆	☆	☆	☆	☆	9
Ozcan et al. [6], 2014	☆	☆	☆	☆	☆	☆	☆	☆	8
Kim et al. [5], 2014	☆	☆	☆	☆	☆	☆		☆	7

¹ A maximum of two stars can be allotted in this category. Studies that controlled for age received one star, whereas studies with adjusted analyses received one additional star. ² Studies with a follow-up time of 30 days were awarded one star.

Fig. 2. Forest plot for the association between early repolarization and the risk of ventricular tachyarrhythmias in patients after the onset of acute myocardial infarction.

All studies agreed unanimously with the conclusion that ER increases the risk of VTAs in patients after the onset of AMI. The I^2 for testing heterogeneity among the individual studies was 27%; therefore, the fixed-effects model was used. The pooled OR of the 10 studies was 3.62 (95% CI 2.77–4.73; $p < 0.00001$), which revealed that the risk of VTA was significantly greater in AMI patients with ER compared to controls (Fig. 2).

For minimizing potential heterogeneity, we performed subgroup analyses according to the time of diagnosis of ER (before vs. after infarction), follow-up duration (<30 vs. ≥ 30 days), type of AMI (All patients with STEMI), endpoint events (only VF), J-point elevation, and lateral leads' ER location. Table 4 shows the final results of subgroup analyses. The I^2 of all the subgroup analyses were

less than 25%, except J-point elevation analysis ($I^2 = 42\%$). We found that the presence of ER before AMI (OR 5.58, 95% CI 3.41–9.12) [2, 5, 8, 9] and after AMI (OR 3.02, 95% CI 2.19–4.15) [3, 4, 6, 7, 10, 11] both significantly increased 6- and 3-fold the risk of VTAs, respectively. Overall, 3 studies reported the risk of VTAs in long follow-up duration (≥ 30 days) [4, 6, 11]; the pooled analysis of these studies (OR 2.39, 95% CI 1.59–3.59) indicated that the risk of VTAs in the long follow-up duration (≥ 30 days) fell by half compared to that in the short follow-up duration (<30 days) (OR 4.97, 95% CI 3.48–7.09) [2, 3, 5, 7–10]. A total of 4 studies only recruited patients suffering from STEMI [2, 6, 7, 11]; the meta-analysis of these studies revealed that patients with ER also had an increased risk of VTAs (OR 2.67, 95% CI 1.80–3.97) com-

Table 4. The final results of subgroup analysis

Subgroup	Studies, <i>n</i>	Meta-analysis			Heterogeneity	
		OR	95% CI	<i>p</i> value	<i>I</i> ²	<i>p</i> value
Time of diagnosis of ER						
Before infarction	4	5.58	3.41–9.12	<0.00001	0%	0.54
After infarction	6	3.02	2.19–4.15	<0.00001	15%	0.32
Follow-up duration						
≥30 days	3	2.39	1.59–3.59	<0.00001	0%	0.73
<30 days	7	4.97	3.48–7.09	<0.00001	0%	0.6
All patients with STEMI						
Yes	4	2.67	1.80–3.97	<0.00001	0%	0.65
No	6	4.66	3.24–6.69	<0.00001	24%	0.26
Endpoint events						
VF	3	6.94	3.87–12.43	<0.00001	0%	0.82
J-point elevation	6	3.51	1.69–7.26	0.0007	42%	0.13
Lateral leads' ER location	4	3.83	1.65–8.89	0.002	0%	0.74

ER, early repolarization; STEMI, ST segment elevation myocardial infarction; VF, ventricular fibrillation; OR, odds ratio; CI, confidence interval.

pared to those without ER. Overall, 3 studies examined the relationship between ER and the occurrence of VF [3, 5, 8]; our meta-analysis showed that the risk of developing VF was nearly 7 times that without ER (OR 6.94, 95% CI 3.87–12.43). A total of 6 studies reported the data about J-point elevation [2, 3, 5, 6, 9, 11]; we found that J-point elevation was associated with an increased risk of VTAs compared to no J-point elevation (OR 2.48, 95% CI 1.26–4.86). Finally, 4 studies reported the relationship between lateral leads' ER location and the risk of VTAs [3, 8–10]; we also found that lateral leads' ER location was associated with an increased risk of VTAs (OR 3.83, 95% CI 1.65–8.89).

On visual inspection of the funnel plot (Fig. 3), the association between ER and VTAs in the patient setting of AMI was asymmetrical at its left middle portion either because of publication bias or a true inexistence of negative studies. We performed sensitivity analysis by removing the study by Rudic et al. [3], because its sample size was less than 100, and the primary result was not influenced (OR 3.56, 95% CI 2.71–4.67; $I^2 = 33\%$; $p = 0.16$).

Discussion

This meta-analysis identified 10 studies (2,672 participants) in diverse populations and demonstrated that ER on ECG predicts VTAs in patients after the onset of AMI,

Fig. 3. Funnel plot for the association between early repolarization and ventricular tachyarrhythmias in a patient setting of acute myocardial infarction.

regardless of the type of AMI. Although the ER pattern could be affected by the ongoing AMI, the presence of ER before and after AMI were both significantly associated with increasing risks of VTAs, and the risk of developing VF was more remarkable than in those without ER. However, neither J-point elevation nor lateral leads' ER location with OR = 3.83 remarkably increased the risk of VTAs in patients with AMI.

The ER pattern on ECG signals that a distinct action potential notch mediated by transient outward potassium current produces transmural electrical heterogeneity be-

tween the endocardium and epicardium during early ventricular repolarization. The repolarization dispersion enlarged by this heterogeneity leads to phase 2 reentry capable of initiating VF [19–21]. The prognostic significance of inferior ER location is nearly 3 times greater than the overall result, due to the greater predominance of outward potassium current in the right ventricular epicardium [12]. Our meta-analysis showed that the added risk of lateral leads' ER location was not evident, although the individual leads which constituted lateral leads were slightly different. In other words, inferior ER location has further value in predicting VTAs than lateral leads' ER location.

Similarly, we indicated that J-point elevation did not remarkably increase the risk of VTAs in patients with AMI. However, the amplitudes of J-point elevation were divergent, and ranged from 0.5 to 2.0 mV. Up to now, there is still no cut-off amplitude for J-point elevation that could accurately ascertain all patients at risk [22].

Finally, we confirmed that positive predictive values of ER pattern in the long follow-up duration (≥ 30 days) fell by half compared to those in the short follow-up duration (< 30 days). A cohort study by Park et al. [7] noticed that ER may sequentially appear and disappear during clinical follow-up. We suppose that the significant differences among different detection window are related to alteration of ER during clinical follow-up. Unfortunately, there is no available study with a little longer detection window (> 30 days).

Study Limitations

Our meta-analysis has several potential limitations. First, we did not extract other factors such as anti-arrhythmic drug use, door-to-balloon, and other underlying diseases which are related with VTAs in the setting of AMI from all of the studies. Second, Adler et al. [23] indicated that J waves followed by a horizontal or descending ST segment, rather than an ascending ST segment, were associated with increased arrhythmic risk. However, on account of the limited available data, we did not analyze ST segment morphology. Third, 3 studies without adjusted analyses were included in this meta-analysis, and the adjustments for covariates differed across studies. Fourth, several studies did not provide detailed and credible data about revascularization strategies such as PCI, thrombolysis, and surgical revascularization. Finally, our present findings are significantly limited by the inevitable selection bias of observational studies, although most studies were considered as high quality.

Conclusion

Our meta-analysis added ER as a potential prognostic marker for predicting VTAs, especially VF, in patients with AMI. The relationship between ER and the risk of VTAs in patients with AMI was weaker in the long detection window. J-point elevation and lateral leads' ER location did not remarkably increase the risk of VTAs. These may have some applicability in helping to further risk stratify patients that may be candidates for a wearable defibrillator [24]. More studies are required to provide evidence about the prognostic significance of ER detail characteristics in patients with AMI.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

Conceptualization and supervision: Danhua Hong and Xin Wang. Data curation, formal analysis, investigation, and methodology: Shangbo Xu and Lihua Yang. Project administration: Shangbo Xu and Xin Wang. Software: Shangbo Xu. Writing – original draft: Shangbo Xu. Writing – review and editing: Lan Chen and Xin Wang.

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