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The Association between Early Repolarization Pattern and Coronary Artery Disease Based on Coronary Angiography

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ABSTRACT

Background and Objective: Coronary artery disease is considered as the most important disease among cardiovascular diseases. Recently, evidence has emerged suggesting an association between early repolarization and coronary artery disease. Therefore, the present study was conducted to investigate the association between electrocardiographic early repolarization pattern and coronary artery disease based on coronary angiography in patients who underwent angiography at Ayatollah Rouhani Hospital in Babol, northern Iran.

Methods: This cross-sectional study was conducted on all patients who underwent angiography in 2019 at Rouhani Hospital in Babol. The association between early repolarization and demographic variables as well as laboratory tests of the patients was evaluated. Subsequently, patients were divided into high-risk, moderate-risk, and low-risk groups based on the Framingham criteria, and the association between early repolarization and coronary artery disease was investigated and compared in each group.

Findings: 1,351 patients were evaluated in this study. Overall, the early repolarization pattern was observed to be more common in men (190 [23.5%] vs. 102 [18.8%]; $p<0.01$). According to the Framingham criteria, 648 patients had low risk, 386 had moderate risk, and 317 had high risk of coronary artery disease. Among patients with low or moderate risk according to the Framingham criteria, those with an early repolarization pattern were more likely to have >50% coronary artery stenosis.

Conclusion: The results of the study demonstrated that even among patients with low or moderate risk according to the Framingham criteria, the presence of early repolarization, in addition to traditional risk factors, predicts a higher rate of coronary artery disease. Furthermore, these patients are at a higher risk for multivessel involvement.

Keywords: *Electrocardiography, Angiography, Coronary Artery Disease, Early Repolarization*.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide (1). Approximately 80% of the global burden of CVD-related mortality occurs in low- and middle-income countries (2). Nearly 50% of all deaths in high-income countries and approximately 28% of deaths in low- and middle-income countries are attributable to cardiovascular disease, which has now become a major cause of death even in those regions (3). Ischemic heart disease (IHD) is the leading cause of death in developed countries and one of the main contributors to the disease burden in developing countries (4). The two main manifestations of IHD are angina pectoris and acute myocardial infarction; 75% of global deaths due to IHD occur in low- and middle-income countries (5, 6).

Acute myocardial infarction (AMI) is the complete occlusion of a major coronary artery with total deficiency of oxygen and nutrients, leading to necrosis of the cardiac muscle. AMI is typically diagnosed by electrocardiographic changes, elevation of serum enzymes such as creatine phosphokinase and troponin T or I, and angina-like pain (7, 8).

Mortality remains high 30 days after AMI. Even with optimal medical therapy, the rate remains approximately 33%, with half of all deaths occurring before the patient reaches the hospital (9, 10). Even in a hospital with a coronary care unit where advanced care options are available, mortality is still 7% (11). In a hospital where such facilities or treatments are not available, the mortality rate approaches 30% (12).

Identifying individuals at higher or lower risk of cardiovascular events is important to facilitate the effective use of resources and interventions and to reduce the disease burden at both the individual and community levels. Each of the known risk factors for cardiovascular disease - including age, gender, dyslipidemia, hypertension, diabetes mellitus, and smoking - has been appropriately highlighted for risk prediction (13). The integration of these factors into risk scores (e.g., the Framingham risk score) provides a quantitative prediction of the future risk of developing coronary artery disease (CAD), which, after calibration of absolute risks, is generalizable across different populations (14).

Electrocardiographic (ECG) early repolarization (ER) pattern is defined as a slurring or notching morphology with J-point elevation of ≥0.1 mV in two contiguous leads and has been considered a marker of health, as it is more common in athletes, younger individuals, and at slower heart rates (15, 16). Some recent reports have demonstrated an association between ER and an increased risk of arrhythmic death and idiopathic ventricular fibrillation (IVF) (17-20).

The relatively high prevalence of the ER pattern in the general population (3-5%), compared with the incidence of IVF (approximately 10 cases per 100,000 persons), means that the ER pattern will almost always be an incidental ECG finding without clinical consequences (21). However, a primary arrhythmic disorder such as IVF due to ER becomes much more likely when it is associated with syncope or resuscitated sudden cardiac death in the absence of other causes (22).

The ER pattern may be sporadic or hereditary, although first-degree relatives of an individual with an ER pattern appear to be two to three times more likely to have the ER pattern on ECG (23). While the vast majority of ER is probably sporadic, hereditary ER appears to be transmitted in an autosomal dominant manner (24).

The ER pattern is not always visualized on a standard electrocardiogram (ECG) due to its intermittent nature. In a study by Krishnamurthy et al., among 542 individuals with a baseline ER pattern who underwent follow-up ECG five years later, ER (≥0.1 mV) was not observed in approximately 20% of cases (25). No systematic evaluation has been conducted regarding the reported prevalence of concealed ER in the general population, and the clinical significance, if any, of concealed ER remains unclear.

As noted, ER is an ECG finding and may, in rare cases, be associated with a primary arrhythmic disorder of idiopathic ventricular fibrillation (IVF) in the absence of structural heart disease. Given the high prevalence of the ER pattern in the general population and the very low incidence of IVF, the diagnosis of IVF secondary to malignant ER is a diagnosis of exclusion, made after ruling out other etiologies (26). In the absence of syncope or sudden cardiac arrest, no further testing is warranted in individuals displaying an ER pattern (27). Having patients perform the Valsalva maneuver may reveal or accentuate the ER pattern. While this maneuver aids in identifying the high-risk hereditary ER pattern, this finding has not been validated, and its utility has not been assessed in large, asymptomatic populations (28). Therefore, the present study was conducted to investigate the association between early repolarization pattern and coronary artery disease in patients who underwent angiography at Ayatollah Rouhani Hospital in Babol.

Methods

After approval by the Ethics Committee of Babol University of Medical Sciences (code: IR.MUBABOL.HRI.REC.1400.182), this cross-sectional study was conducted on all patients who underwent elective angiography at Ayatollah Rouhani Hospital in Babol in 2019. Patients with a pacemaker, those who had experienced an acute myocardial infarction (MI), those with atrial fibrillation (AF), bundle branch block (BBB), or Wolff-Parkinson-White (WPW) syndrome on their initial ECG, as well as patients whose angiography data were not recorded in their medical records or whose initial ECG was not available in the records, were excluded from the study. The sample size was estimated to be 1500 patients using the sample size formula (α=0.05, p=0.2, d=0.02) (29). After applying the exclusion criteria, 1351 patients were ultimately analyzed.

To record patient data, the necessary information was collected from their medical records, including ECG findings, angiography reports, age, gender, smoking or alcohol consumption history, history of chronic diseases such as diabetes mellitus (DM) and hypertension (HTN), blood pressure at admission, body mass index (BMI), fasting blood glucose (FBG), and lipid profile. Since the data were collected from medical records, obtaining informed consent was not required. Echocardiographic data available in the hospitalization records were used to differentiate between prior myocardial infarction or prolonged ischemia and classic ER with ST-segment elevation. To confirm the presence of an ER pattern on patients' ECGs, the new 2015 American Heart Association (AHA) criteria were applied, along with the opinion of a cardiologist who was a faculty member; in equivocal cases, a second specialist's opinion was sought. Patients were categorized into low, moderate, and high-risk groups based on the Framingham Risk Score (FRS). According to the Framingham criteria, patients were first stratified by gender (male vs. female). Different points were assigned based on each of the following variables: age, high-density lipoprotein (HDL) cholesterol, total cholesterol, systolic blood pressure (SBP), history of hypertension, smoking status, and history of diabetes mellitus. In the second step, the sum of these points was entered into the 10-year cardiovascular disease risk assessment table, and the risk level was calculated. Patients with a risk of less than 10% were classified as the low-risk group, those with a risk of 10-20% as the moderate-risk group, and those with a risk greater than 20% as the high-risk group (14, 30, 31).

To investigate the association between ER pattern and coronary artery disease, patients were divided into two groups based on the presence or absence of ER pattern on their initial ECG. In each group, the percentage frequency of stenosis >50% reported on angiography for each major epicardial coronary artery was calculated. The overall percentage of patients with >50% obstruction in major coronary arteries, with and without ER, was determined for each low-risk, moderate-risk, and high-risk subgroup according to the Framingham criteria.

Data were analyzed using SPSS software (version 26) and T-test, Mann-Whitney U test, Chi-squared test, and Fisher's exact test. A p-value<0.05 was considered statistically significant.

Results

After applying the exclusion criteria, 1351 patients remained and were analyzed from an initial cohort of 1500 patients who underwent angiography. Of these, 292 patients (21.6%) exhibited an early repolarization (ER) pattern.

Of the total 1351 patients, 809 (59.9%) were male and 542 (40.1%) were female. Among these, 190 males (23.5%) and 102 females (18.8%) exhibited an ER pattern ($p < 0.01$). The mean age of the participants was 63.1±11.5 years. The mean age of patients with an ER pattern was 63.0±12.4 years, while those without an ER pattern had a mean age of 63.1±11.3 years. A total of 903 patients (66.9%) had hypertension. Among these, 713 (67.3%) were without an ER pattern, and 190 (65.1%) exhibited an ER pattern (Table 1).

The mean heart rate is all patients was 71±14 bpm. This value was 69.4±14.2 bpm in patients with an ER pattern and 71.5±13.9 bpm in patients without an ER pattern. No statistically significant difference was observed between the two groups (Table 2).

Table 1. The association between the presence of ER pattern and medical history risk factors

Study Group	Total Number	Early Repolarization Pattern Yes Number(%)	Early Repolarization Pattern No Number(%)	p-value
All patients	1351	292(21.6)	1059(78.4)	-
Hypertension	903	190(21.0)	713(79.0)	0.23
Hyperlipidemia	968	148(15.2)	820(84.8)	<0.01*
Diabetes Mellitus	440	86(19.5)	354(80.5)	0.27
Smoking	230	54(23.4)	176(76.6)	0.04*

***Statistically significant (p<0.05)**

Table 2. The association between ER pattern and CAD in Framingham risk groups

Risk Group	Total number	CAD (>50% Stenosis) Number(%)	CAD (<50% Stenosis) Number(%)	p-value
Low				
Without ER pattern	498	295(59.3)	203(40.7)	<0.01*
With ER pattern	150	50(33.3)	100(66.7)	
Moderate				
Without ER pattern	282	145(51.4)	137(48.6)	0.02*
With ER pattern	104	36(34.6)	68(65.4)	
High				
Without ER pattern	279	100(35.8)	179(64.2)	0.78
With ER pattern	38	13(34.2)	25(65.8)	
Total				
Without ER pattern	1059	540(51.0)	519(49.0)	0.02*
With ER pattern	292	99(33.9)	193(66.1)	

In the assessment of patients' blood pressure at admission, the mean systolic blood pressure for all patients was 137.4±24.8 mmHg, and the mean diastolic blood pressure was 79.6±15.2 mmHg. Patients with an ER pattern had a mean systolic blood pressure of 135.0±19.9 mmHg and a mean diastolic blood pressure of 77.7±12.2 mmHg. Patients without an ER pattern had a mean systolic blood pressure of 138.0±25.9 mmHg and a mean diastolic blood pressure of 80.1±15.9 mmHg. It was observed that patients with an ER pattern had significantly lower systolic and diastolic blood pressures compared to those without an ER pattern, and this difference was statistically significant ($p<0.01$).

The mean total cholesterol level among all patients was 187.9±51.3 mg/dL. This value was 190.6±52.4 mg/dL for patients without an ER pattern, but 178.2±46.0 mg/dL for patients with an ER pattern ($p<0.01$). The mean low-density lipoprotein (LDL) level among all patients was 118.1±40.5 mg/dL. This value was 120.3±40.8 mg/dL in patients without an ER pattern and 110.1±38.2 mg/dL in patients with an ER pattern ($p=0.01$). The mean high-density lipoprotein (HDL) level among all patients was 40.8±10.2 mg/dL. This value was 40.8±10.2 mg/dL for patients without an ER pattern and 40.8±10.1 mg/dL for patients with an ER pattern. The mean triglyceride level among all patients was 161.2±152.2 mg/dL. This value was 164.7±159.3 mg/dL for patients without an ER pattern, but 148.3±121.6 mg/dL for patients with an ER pattern ($p<0.01$).

According to the Framingham criteria, of the 1351 patients studied, the largest group consisted of 648 patients classified as low risk for coronary artery disease. Moreover, 386 patients were classified as moderate risk and 317 patients as high risk. On assessment of patients' angiography reports, >50% coronary artery stenosis was reported in 712 patients (52.7%). Of these, 193 patients (27.1%) exhibited an ER pattern, while 519 patients (72.9%) did not. On more detailed analysis using the Framingham criteria, the results were as follows: of the 648 low-risk patients, 303 had >50% stenosis, of whom 100 exhibited an ER pattern and 203 did not. Among patients classified as low risk according to the Framingham criteria, those who exhibited an ER pattern on ECG were significantly more likely to have >50% coronary artery stenosis. This difference was statistically significant ($p<0.01$).

Of the 386 patients with moderate risk, 205 had >50% coronary artery stenosis. Of these, 68 exhibited an ER pattern and 137 did not. It was observed that among moderate-risk patients according to the Framingham criteria, those with an ER pattern were significantly more likely to have >50% coronary artery stenosis. This difference was statistically significant ($p<0.02$). Among the 317 high-risk patients, 204 had >50% stenosis, of whom 25 exhibited an ER pattern and 179 did not (Table 2). Of the total 712 patients with >50% stenosis, 293 (41.2%) had single-vessel disease (SVD), 213 (29.9%) had two-vessel disease (2VD), and 206 (28.9%) had three-vessel disease (3VD). Regarding the association between ER pattern and the extent of coronary artery involvement, among patients with SVD, 74 exhibited an ER pattern and 219 did not; this difference was not statistically significant. Among patients with 2VD, 64 exhibited an ER pattern and 149 did not; this difference was statistically significant ($p<0.02$). Among patients with 3VD, 55 exhibited an ER pattern and 151 did not ($p=0.04$). Patients with an ER pattern were more likely to have multivessel involvement (2VD or 3VD) (Table 3).

Table 3. The association between ER pattern and the number of vessels with >50% stenosis

Group	Total Number	ER pattern		p-value
		Yes Number(%)	No Number(%)	
SVD (Single-Vessel Disease)	293	74(25.2)	219(74.8)	0.58
2VD (Two-Vessel Disease)	213	64(30.0)	149(70.0)	0.02
3VD (Three-Vessel Disease)	206	55(26.7)	151(73.3)	0.04
Total	712	193(27.1)	519(72.9)	-

ER pattern was significantly associated with stenosis of the right coronary artery, left anterior descending artery, and left circumflex coronary artery. Coronary artery stenosis in patients with an ER pattern was observed in association with ER pattern localized to the inferior leads or the lateral leads, and this association was statistically significant ($p < 0.05$). However, no significant association was observed in individuals with an ER pattern present in both the inferior and lateral leads simultaneously (Table 4).

Table 4. The association between the leads with ER pattern and coronary artery with >50% stenosis

	Right Coronary Artery (RCA)		Left Anterior Descending (LAD)		Left Circumflex (LCX)	
	N	**p-value**	**N**	**p-value**	**N**	**p-value**
Without ER pattern	291	-	449	-	231	-
Any ER pattern	111	<0.01	170	<0.01	89	0.03
ER pattern in inferior leads	64	0.03	98	0.02	54	0.02
ER pattern in lateral leads	32	0.04	47	0.04	27	0.03
ER pattern in both inferior and lateral leads	15	0.13	25	0.09	8	0.34

Discussion

In the present study, of 1351 patients who underwent angiography, 292 exhibited an ER pattern on their ECG. A significantly increased risk of obstructive CAD was observed in individuals with ER pattern compared to those without ER pattern, even after adjustment for several risk factors. Among low-risk and moderate-risk patients, the presence of ER pattern, in addition to traditional risk factors, predicted a higher rate of obstructive CAD. Furthermore, ER pattern was associated with a higher risk of multivessel involvement. In this study, 190 males (23.5%) and 102 females (18.8%) exhibited an ER pattern. Overall, the ER pattern was more common in males. A large cohort study demonstrated that Black race and male sex are factors influencing the prevalence of ER (32). The association of ER pattern with male sex across studies may suggest a hormonal effect, although the reason for this higher prevalence in males has not been clearly identified (33). The role of male sex hormones in the manifestation of the ER pattern may be similar to that observed in Brugada syndrome; however, anabolic-androgenic steroids shorten the QT interval, making it difficult to explain this phenomenon (34). Consistent with the findings of previous studies, ER pattern was associated with several other characteristics, including smoking and blood pressure (35, 36). Moreover, TC, LDL-C, and TG levels were lower in individuals with ER pattern compared to those without this abnormality. However, mean resting heart rate and age did not differ between individuals with and without ER pattern. Previous studies have reported that the prevalence of ER pattern in the general population varies between 2% and 31%, depending on the definition of ER (29, 37). In our study, 21.6% of patients undergoing coronary angiography exhibited notching or slurring of the terminal QRS complex.

ER was traditionally considered a benign ECG finding. While the ER pattern is associated with certain adverse effects, it does not significantly influence mortality when compared to other coronary risk factors. A case-control study involving 90 patients demonstrated an association between the presence of an ER pattern and the severity of atherosclerosis (35). Conversely, a large meta-analysis that reported an increased risk of cardiovascular events in relation to ER morphology failed to confirm an association between J-point elevation and sudden cardiac death (SCD) or mortality due to coronary heart disease (CHD) (38).

Lee et al. showed that ER may be associated with cardiovascular events and that CAD patients with ER may experience more cardiac complications compared to CAD patients without ER (36). Other studies have demonstrated a relationship between ER and the risk of cardiac death (39). The presence of ER morphology is strongly associated with the development of IVF, particularly in patients with coronary artery disease, as well as with the occurrence of arrhythmias following myocardial infarction (MI) (40).

The majority of studies reporting an association between ER and adverse cardiovascular outcomes are case-control studies. In contrast, negative findings have largely come from longitudinal registry-based studies (41, 42). Differences in study populations and demographic characteristics are additional factors contributing to these conflicting results. Moreover, variability in the diagnostic criteria used to define ER and J-waves on the electrocardiogram creates substantial discrepancies across study findings.

This study is among the few to report an association between ER pattern and coronary artery stenosis as diagnosed by coronary angiography. In real-world clinical settings, low- and moderate-risk patients with CAD may be more prone to misdiagnosis than their high-risk counterparts. The findings of the present study suggest that when an ER pattern is detected on a patient's ECG, clinicians should exercise greater vigilance and consider further evaluation for obstructive coronary artery disease. Moreover, patients with multivessel CAD have a higher likelihood of acute myocardial infarction and sudden cardiac death (SCD) than those with single-vessel CAD, underscoring the importance of early identification in this subgroup. Consequently, our study may offer a potentially valuable clinical implication for stratifying low- or moderate-risk patients to determine which individuals would benefit from coronary angiography.

The fundamental mechanisms involved in the association between ER pattern and obstructive CAD remain unclear. Myocardial ischemia may reduce inward currents (primarily INa and ICa), which enhances outward potassium currents mediated by Ito, IK-ATP, and IK-Ach channels, particularly in the epicardium. This leads to a disproportionate augmentation of repolarization current in the epicardial myocardium, resulting in transmural differences during the early phases (phases 1 and 2) of the cardiac action potential. These differences may be responsible for the J-wave on the electrocardiogram. Another possible interpretation for this association is that an elevated J-point on the ECG may represent a peri-infarction block, which typically indicates underlying CAD. This hypothesis was supported by the augmentation of the J-wave with rapid pacing in a patient with vasospastic angina (43).

Given that ER pattern may increase the risk of sudden cardiac death and that CAD is associated with ER pattern, it is plausible that ER pattern lies on the causal pathway between obstructive CAD and SCD in some patients. The results of this study underscore the necessity of screening programs and the implementation of preventive care measures in the setting of ER morphology.

This study demonstrated a higher prevalence of ER in males, with a statistically significant association between gender and ER. As the underlying mechanism for this association remains unknown, further investigations are warranted to determine the prognostic significance of this relationship. Both abnormal coronary angiography findings and the severity of atherosclerosis were significantly greater in patients with ER compared to those without ER, and a statistically significant association was observed between ER prevalence and atherosclerotic burden. Given the paucity of similar studies examining the relationship between ER and the severity of atherosclerosis, large-scale prospective studies are needed to investigate patients with established atherosclerosis and to assess long-term outcomes and related events. Should this association be confirmed, the presence of ER could serve as an indication for diagnostic angiography independent of other risk factors. Timely diagnosis, improved management of atherosclerosis, and prevention of complications such as arrhythmias and cardiomyopathy represent key future objectives.

It is worth noting that the hospitalization period for the patients in this study extended from March 2019 to March 2020. Considering that the COVID-19 pandemic began in Iran and reached the city of Babol (where the study was conducted) in March 2020, this effectively means that COVID-19 was eliminated as a confounding factor in our study. While the potential ECG manifestations of COVID-19 have been reported in several studies, the long-term and delayed manifestations of the disease remain incompletely elucidated and are currently limited to a few case reports (44, 45). In fact, there have been published reports of early repolarization syndrome and subsequent ventricular fibrillation occurring as late as several months after recovery in these patients (45).

The findings of this study underscore that screening programs and the implementation of preventive care measures are essential in the presence of early repolarization, even among patients deemed low risk based on conventional risk factors. Timely diagnosis, improved management of atherosclerosis, and prevention of complications including arrhythmia and cardiomyopathy become achievable when both the risk factors examined in this study and the presence of an ER pattern are taken into account. Moreover, the results of this study may serve as a foundation for resource allocation and for the design of future prospective studies with larger sample sizes aimed at investigating the outcomes associated with the early repolarization pattern, with particular emphasis on its coronary sequelae.

Several limitations of the present study should be acknowledged. First, we selected patients who had undergone coronary angiography for various indications, including chest pain, preoperative assessment, or malignant ventricular arrhythmias. This may have introduced selection bias, as some patients with obstructive CAD may remain asymptomatic. Furthermore, several important confounders potentially associated with obstructive CAD—such as dietary habits, physical activity levels, and socioeconomic status—were not evaluated. The study population predominantly consisted of middle-aged and elderly patients referred for coronary angiography; consequently, we cannot comment on the implications of ER pattern for younger individuals. Additionally, the retrospective nature of the study precludes determination of the temporal relationship between ER pattern and CAD. That is, we cannot establish whether ER pattern precedes the development of CAD or, conversely, whether CAD induces ER pattern through myocardial ischemia. Nonetheless, it remains feasible to assess the association between these two entities. Finally, the epidemiological design of this study does not permit causal inference regarding the association between ER pattern and CAD or their underlying pathogenesis.

Given the retrospective nature of the present study, which precludes the ability to assess outcomes associated with ER pattern, we recommend that prospective studies be designed and implemented to investigate ER pattern outcomes, with a particular focus on its coronary sequelae. In future investigations, all participants should be assessed for lifestyle factors, family history, and other potential confounders. Additionally, the incidence and progression of coronary artery disease should be evaluated at both baseline and study completion, preferably utilizing less invasive modalities such as computed tomography angiography (CTA).

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