

May 30 2016

Fang-Fang Ji, Science Editor, Editorial Office

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Editor-in-Chief

World Journal of Cardiology

Dear Editor,

Please find enclosed the edited manuscript in Word format (file-name: text 26883)

Title: 12-LEAD ECG FEATURES OF ARRHYTHMIC RISK: A FOCUS ON EARLY
REPOLARIZATION

Runtile: ECG features of Early Repolarization

Authors: Caterina Rizzo, MD, Francesco Monitillo, MD, Massimo Iacoviello, MD, PhD.

Name of journal: World Journal of Cardiology

ESPS Manuscript NO: 26883

Manuscript Type: MINIREVIEW

- We thank the editor and the reviewers for the constructive comments on the manuscript; the manuscript has been improved according to the suggestions of reviewers.
The manuscript has been edited for English language by one native English-speaking editor.
We performed a check of the revisited manuscript using CrossCheck iThenticate; the similarity index was 22%

Answers to reviewer

Reviewer 00503274:

This is an interesting and well written paper on ECG features of arrhythmic risk, focusing mainly on early repolarization. Given that clinical role of dispersal parameters is questioned I feel that this section should be omitted or shortened.

- We thank the reviewer for his/her helpful suggestions.
We removed the section about QT dispersion.

Reviewer 02794723:

The manuscript is well written gives an interesting and complete overview of early repolarisation. But some shortening is needed and some tables will be helpful to improve readability. Furthermore add page numbers.

- We thank the reviewer for his/her helpful suggestions. We shortened the text by removing the sections regarding long QT syndrome, short QT syndrome, Brugada syndrome and QT dispersion.
We added a new table that summarizes the main studies evaluating the relationship between ER pattern and death due to arrhythmia in order to improve readability.

Ref.	N. patients	Study population	ER pattern	Results
Tikkanen JT et al. [36], 2009	10.864	community-based general population of middle-aged subjects	elevation of at least 2 mm of the J point-ST segment flat, horizontal or descending-inferior leads	relationship between mortality and ER
Überoi et al. [42], 2011	29 281	resting ambulatory ECGs	J-point elevation ≥ 0.1 mV-notching and slurring type- in at least 2 lateral or inferior-lateral leads	no significant association between any components of early repolarization and cardiac mortality
Haissaguerre et al. [10], 2008	206	Patients who were resuscitated after cardiac arrest due to IVF	elevation of the QRS-ST junction of at least 0.1 mm-inferior or lateral lead-QRS slurring or notching	correlation between ER and sudden cardiac arrest
Nam GB et al. [40], 2008	1410	1595 controls and 15 patients with IVF	J-point elevation ≥ 0.1 mV-notching and slurring type- in at least 2 lateral or inferior leads	arly-repolarization pattern is indicative of a highly arrhythmogenic substrate
Rosso R et al. [41], 2008	290	45 patients with idiopathic VF were compared with 124 age- and gender-matched control subjects and with 121 young athletes	J-point elevation ≥ 0.1 mV-notching and slurring type- in at least 2 lateral or inferior-lateral leads	J-point elevation is found more frequently among patients with idiopathic VF than among healthy control subjects. The frequency of J-point elevation among young athletes is intermediate
Rosso R et al. [29], 2011	8980	331 patients with IVF and 8.649 controls	J waves >2 mm	the presence of J waves >2 mm in amplitude in asymptomatic adults is associated with a threefold increased of arrhythmic death
Aizawa Y et al. [44], 2012	116	Forty patients with J-wave-associated idiopathic VF compared with 76 non-VF patients	J-wave amplitude was measured in the beat immediately after a pause and compared with the mean J-wave measured in almost three beats before the pause. J waves were defined as those ≥ 0.1 mV above the isoelectric line.	Pause-dependent augmentation of J waves was confirmed in about one-half of the patients with idiopathic VF after sudden R-R prolongation. Such dynamicity of J waves was specific to idiopathic VF and may be used for risk stratification
Tikkanen JT et al. [35], 2011	321	21 athletes with a history of previous cardiac arrest of unknown etiology compared with more than 300 healthy athletes	ER pattern with horizontal/descending or rapidly ascending/upslowing	athletes with a horizontal pattern of ER and ST were 11 times more at risk of cardiac arrest
Naruse Y et al. [37], 2012	220	patients with AMI	elevation of the QRS-ST junction of ≥ 0.1 mV - 2 inferior or lateral leads- QRS slurring or notching	The presence of ER increased the risk of VF occurrences within 48 hours after the AMI onset
Rudic B et al. [39], 2012	60	Patients with AMI	J-point elevation ≥ 0.1 mV-notching and slurring type- in at least 2 lateral or inferior leads	Early repolarization pattern seems to be associated with ventricular tachyarrhythmias in the setting of acute myocardial infarction
Tikkanen JT et al. [38], 2012	964	432 consecutive victims of SCD because of acute coronary event and 532 survivors of such an event	elevation of the QRS-ST junction of ≥ 0.1 mV - 2 inferior or lateral leads- QRS slurring or notching	the presence of ER increases the vulnerability to fatal arrhythmia during acute myocardial ischemia
Su-Hua W et al. [43], 2013		meta-analysis		correlation of ER with a higher risk of arrhythmic death but not of cardiac death or death from other causes

Figure 1 The main studies evaluating the relationship between ER pattern and death due to arrhythmia.

ER: Early repolarization. **IVF:** idiopathic ventricular fibrillation **AMI:** acute myocardial infarction

- We added page numbers.

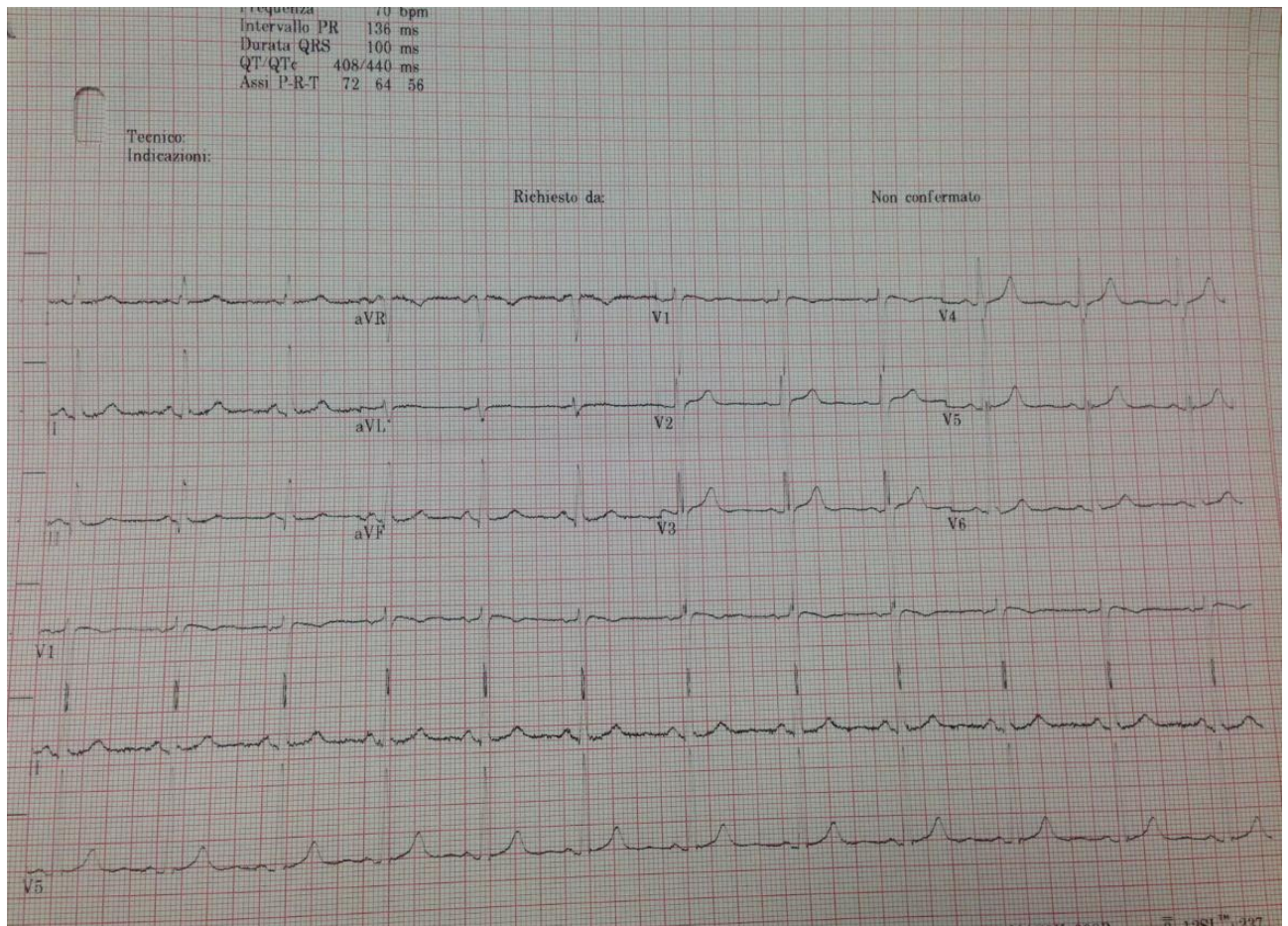
Reviewer 00236103:

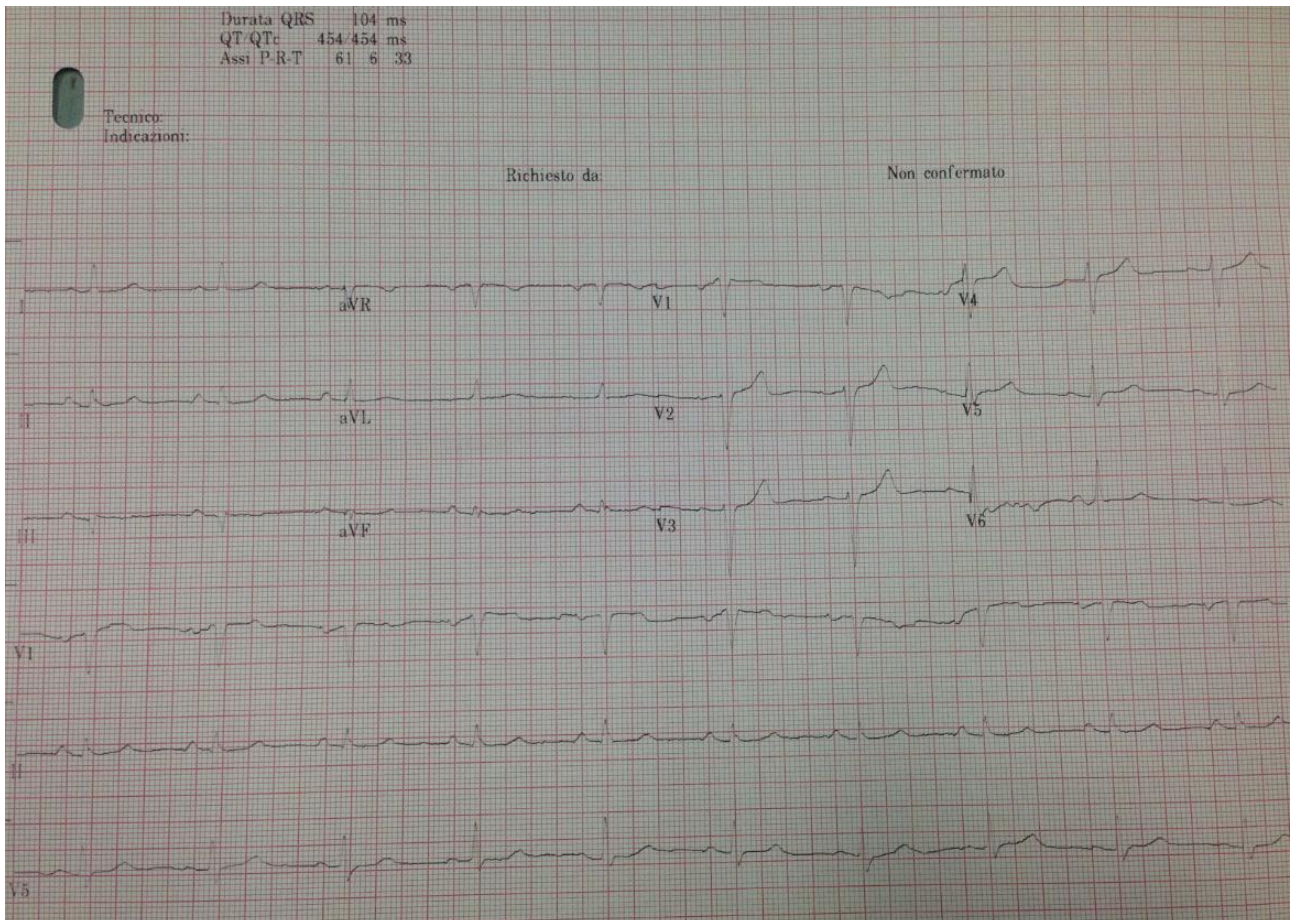
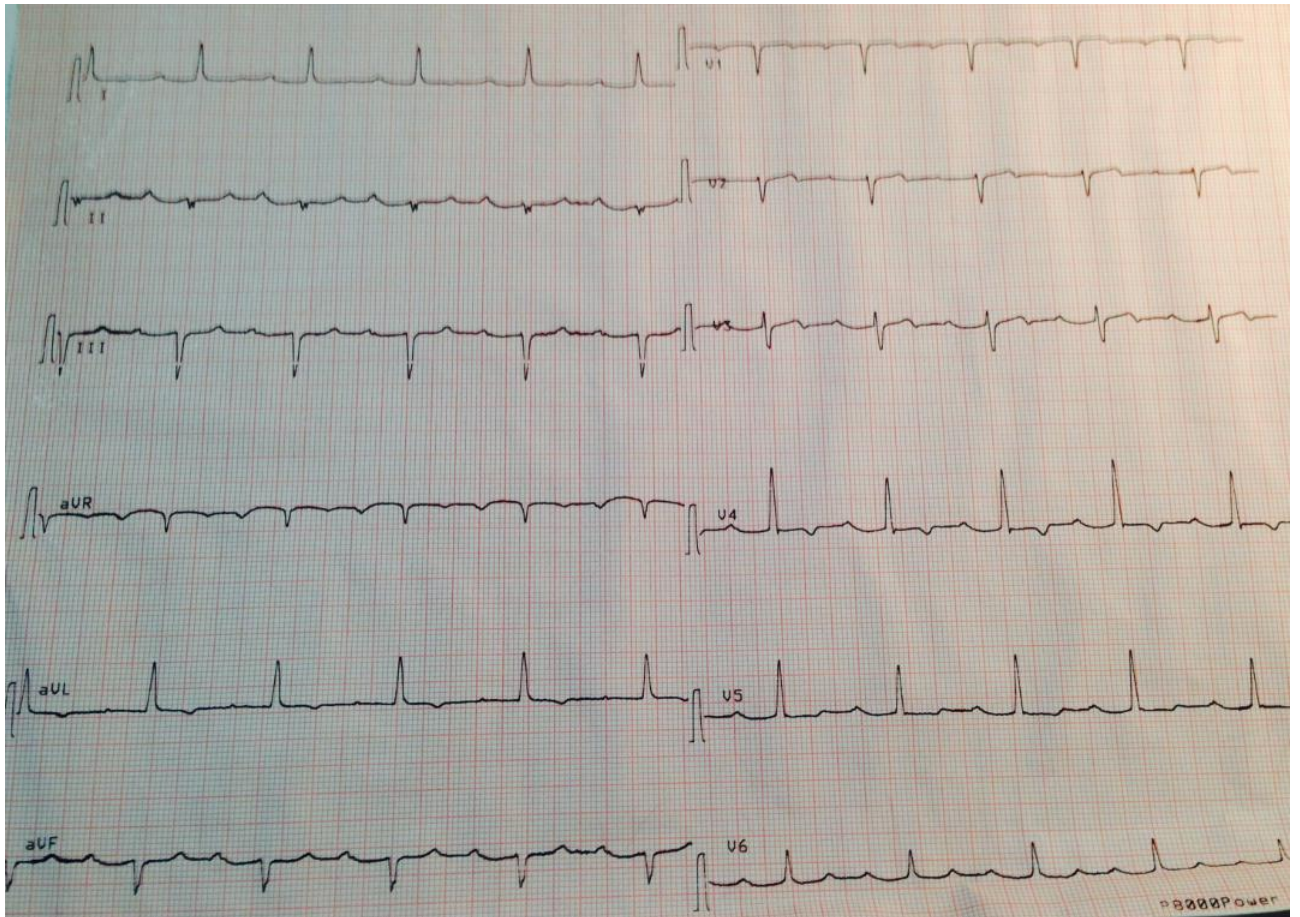
1. The text should be shortened and focus on EP (keep out long QT Syndrome, Brugada etc)

- We thank the reviewer for his/her helpful suggestions.
We shortened the text by eliminating the part regarding long QT, short QT, Brugada syndrome and QT dispersion.
2. with regard to the EP story the authors outline a very long description on special ECG patterns and the underlying transmembrane electrolyte patterns, but ending in their short conclusions on the very last page of the review that the clinical significance of all these observations is highly disputed and even may be of clinical irrelevance. It is strongly recommended to start with the clinical problems and the actual discussion on the clinical relevance of the various sorts of EPs before going into detail
 3. There must be (at the end of the paper) a clear message with respect to the clinical relevance, and under which situations the clinical cardiologists have to care on EPs or not
- We thank the reviewer for his/her helpful suggestions,
 - About points 2 and 3, we tried, as suggested, to improve the conclusions on the very last page of the review, highlighting the clinical relevance of the ER patterns and their role as predictors of arrhythmic risk and we attempted to give a clearest message about the importance of recognizing the "malignant ER pattern" in clinical practice.
4. The authors say that older patients with structural heart disease or myocardial infarction in history do have a higher risk. This message simply is banal, as ischemia may alter cell membranes and their currents in a large number of ways, and in the clinical situation we finally deal with the sum of numerous changes at the molecular and cellular level.
- We recognize the relevance of reviewer's comment and we are aware that this message may seem trivial, but literature brings to our attention a large number of studies that analyze the relationship between ER pattern and the onset of ventricular arrhythmias in this particular patient population. What we essentially do, is a study of the literature, reporting the most relevant data, which in large part involve patients with a history of myocardial infarction or structural heart diseases.
5. are there any data available on the clinical false positive or false negative detections of EPs in clinical practice. The authors must be aware that the detection of EPs in clinical practice may be difficult. Therefore it should be stated more clearly and also be demonstrated by

original ECGs, which of the possible EP patterns potentially are of interest with a good or bad prognosis.

- We thank the reviewer for his/her helpful suggestions. We could not find in the literature available data on the clinical false positive or false negative detection of EPs in clinical practice. We are aware that the detection of EPs in clinical practice may be difficult. However, as suggested, we proposed original ECGs that show the early repolarization pattern in order to make a real impact with the clinical reality. We also added the description of the pattern based on its location and J wave width.





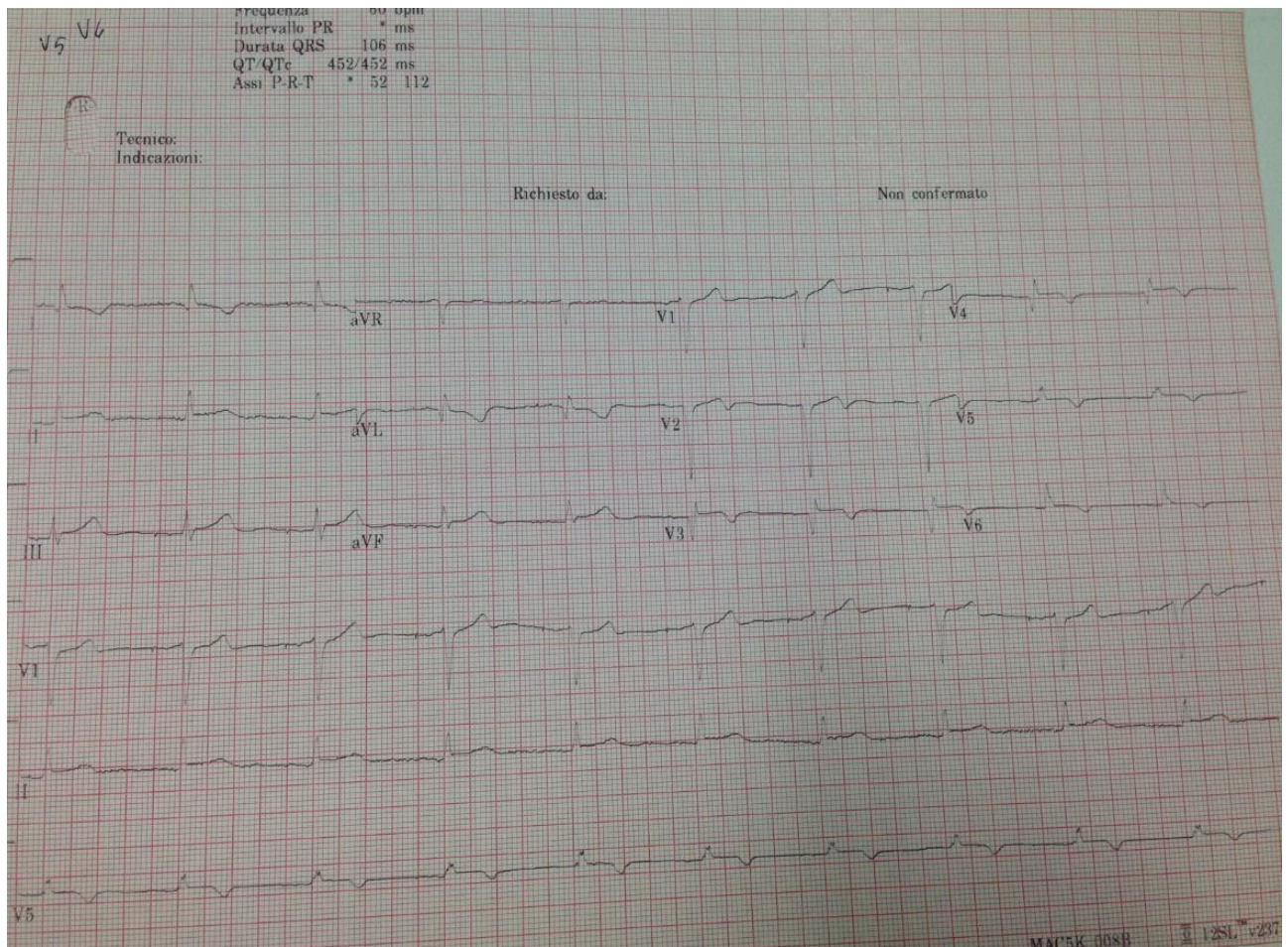


Figure 6 (a-b-c-d) Early Repolarization in clinical practice.

- a) Example of ER pattern “notching tipe” in Inferior-lateral leads (D2,D3, aVF, V5,V6). Width: 1mm;**
- b) Example of ER pattern “slurring tipe” in lateral leads (D1,aVL, V5,V6). Width: 1mm;**
- c) Example of ER pattern “notching tipe” in Inferior leads (D2,D3, aVF). Width: 1,5mm;**
- d) Example of ER pattern “notching tipe” in lateral leads (V5,V6). Width: 1,8mm.**

6. Figure 4: x- any y-axes should clearly be assigned including voltage numbers (y) and seconds (x)for each single current.The meaning of the dotted lines is unclear
 - We thank the reviewer for his/her helpful suggestions. We improved Figure 4 as suggested

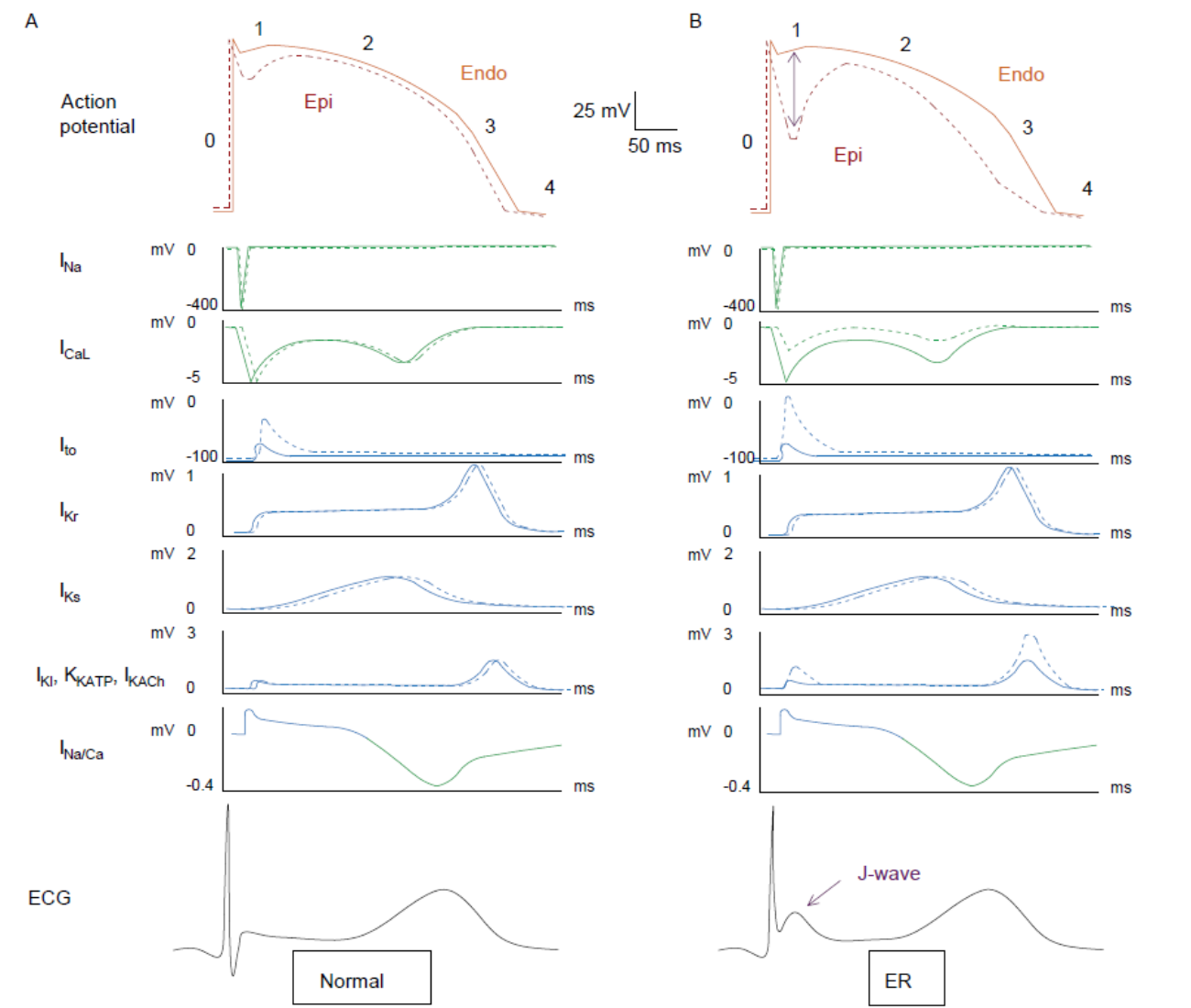


Figure 2 The pathophysiological background of J wave.

I_{Na} = Inward sodium current, I_{CaL} = Inward calcium currents, $I_{Na/Ca}$ = Sodium calcium exchange, I_{to} = Transient outward current, I_{Ks} = Slow delayed rectifier current, I_{Kr} = Rapid delayed rectifier current, I_{K1} = Inward rectifier current, I_{KATP} = Adenosine triphosphate-sensitive current, I_{KACH} = Acetylcholine-activated current.

A: The normal action potential, underlying currents and corresponding ECGs. Epicardial (Epi) action potential and current are shown by dotted lines and endocardial (Endo) by solid lines. Depolarizing currents are depicted downward in green and repolarizing currents upward in blue. The Epi action potential has a characteristic notch caused by larger phase -1 I_{to} compared with Endo.

B: Exaggeration of the Epi notch results from enhancement of net outward current. Phase-1 current flow from Endo to Epi produces the J-wave. The various ionic mechanisms that are believed to produce ER are shown with purple stars.

- are there any animal experiments or animal models for EP-generation that could help to understand the generation, development and consequences of EPs?

- We have not found any animal experiments or animal models for EP-generation that could help to understand the generation, development and consequences of EPs.

Reviewer 02445850:

The authors reported a review on arrhythmic risk focused on early repolarization. According to the manuscript title, we suggest to omit the description of arrhythmic risk associated to long and short QT syndrome, QT dispersion and Brugada syndrome. These chapters could be part of a general review on primary electrical disorders. In general, the topic of early repolarization is well analysed, but we suggest to shorten the individual paragraphs in order to achieve a more succinct description.

- We thank the reviewer for his/her helpful suggestions. We shortened the text by eliminating the part regarding long QT syndrome, short QT syndrome, Brugada syndrome and QT dispersion.

Reviewer 00227344:

1. ERP is a ECG phenotype and every ERP: notch or slur at the terminal part of QRS complexes, can't be really "early repolarization", but it may represent conduction delay: depolarization abnormality, and the discrimination is very important. For the discussion on the characteristic features of so-called two "ERPs", the following references would be of use: 1) J Am Coll Cardiol. 2012;59:1948-1953 and 2) Heart Rhythm. 2015;12:376-383. The second article will be of use in discussing the etiology of so-called J waves observed in patients with ischemic heart disease.
- We thank the reviewer for his/her helpful suggestions.
We used the two articles proposed in order to enrich the discussion on the characteristic features of so-called two "ERPs", and to clarify whether it is really "early repolarization" or rather depolarization abnormality.
2. As to the history of so-called J waves in idiopathic VF, the first report appeared in Am Heart J (1993;126:1473-4) may be of help. The article was cited in the experimental study of Antzelevitch and Yan (Circulation. 1996;9:372-379), and clinically by Haissaguerre. (N Engl J Med 2008; 358: 2016-23). Discussion on mechanisms of "ERP" and history would be appreciated to complete the review.
- We thank the reviewer for his/her helpful suggestions. We considered the article proposed and evaluated the citations in Antzelevitch and Haissaguerre works, already included in the part "definition and family form of early repolarization, a new electrocardiographic markers

of arrhythmic risk” and we expanded the part relating to the history and clinical evidence of J wave.

Best regards

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