Early Repolarization: When Is It a Normal Pattern?

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11.1 Case 1

A 38-year-old man was referred to an emergency room for a chest pain that started 2 days before and worsened with a deep breath. He also complained of dizziness. He was recently discharged from the neurology clinic where a diagnosis of migraine, nystagmus and ataxia was made. In the past he was admitted once to an emergency room for agitation and alcohol abuse. The cardiologic past medical history was unremarkable.

The initial 12-lead ECG revealed:

Sinus rhythm, heart rate of 60 bpm, normal atrioventricular conduction (PQ 160 ms), electrical axis 0° and normal interventricular conduction (QRS width 80 ms).

An end-QRS notch in inferior (II, III and aVF) and anterolateral (I and V2–V6) leads is present, with an elevation of J point ≥0.1 mV in lateral and anterior precordial leads (I, aVL and V2–V4) and a rapidly upsloping ST segment and tall T waves. QTc 400 ms (Fig. 11.1).

At hospital admission baseline parameters were normal and stable: blood pressure 125/75 mmHg, arterial blood saturation of 98% without oxygen supplementation and body temperature 36.4 °C.

The preliminary diagnosis was ST-elevation myocardial infarction. Therefore, the patient went to coronary angiography, which revealed normal coronary arteries.

At echocardiography only a mild concentric hypertrophy of the left ventricle with normal wall motion was recorded, without any pericardial effusion or valve abnormalities. The patient was transferred to our clinic for further evaluation.

The laboratory tests showed normal values of blood count, haemoglobin, troponin, creatinine, electrolytes and negative C-reactive protein.

Hyperkalaemia and hypothermia as possible causes of the ECG abnormalities were excluded. Subacute pericarditis was also an unlikely hypothesis because of the absence of pericardial effusion and of the normal inflammatory markers. Moreover, the ST elevation was not associated to a PR depression that is usually present during the acute phase of a pericarditis. We could reasonably exclude also a myocarditis, considering the normal troponin in three consecutive blood samples, the normal left ventricle ejection fraction and the absence of history of recent fever, flu or gastroenteritis.

A treadmill stress test was performed in order to investigate possible repolarization changes during physical activity. During the exercise ST segments normalized and returned to baseline during recovery. Any arrhythmias or symptoms

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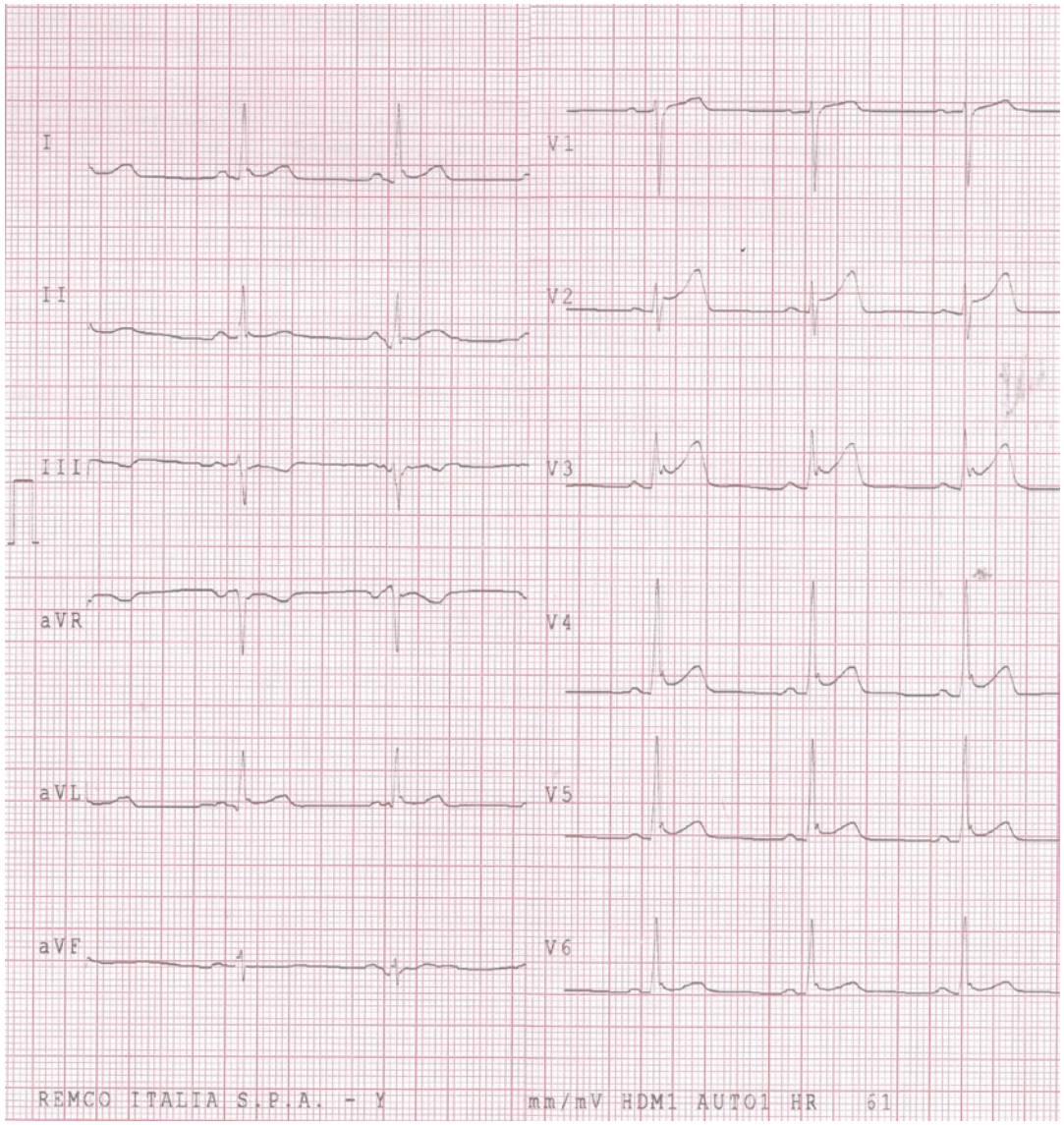

Fig. 11.1 12-lead ECG

occurred. Thus, we were left with an early repolarization likely diagnosis (Fig. 11.2).

The patient was then dismissed with the diagnosis of nonspecific chest pain and early repolarization ECG pattern.

11.1.1 Definition

Early repolarization is usually defined by the presence of three electrocardiographic features: J wave, concave ST-segment elevation and tall symmetrical T wave in two contiguous leads.

More recently, a consensus paper focused on the terminology of early repolarization proposed a new definition including some new measurements and parameters.

Early repolarization is identified by presence of an end-QRS notch or slur with an elevation of the QRS-ST-segment junction (J point) ≥0.1 mV above the isoelectric baseline, in at least two contiguous leads (e.g., inferior or lateral leads;

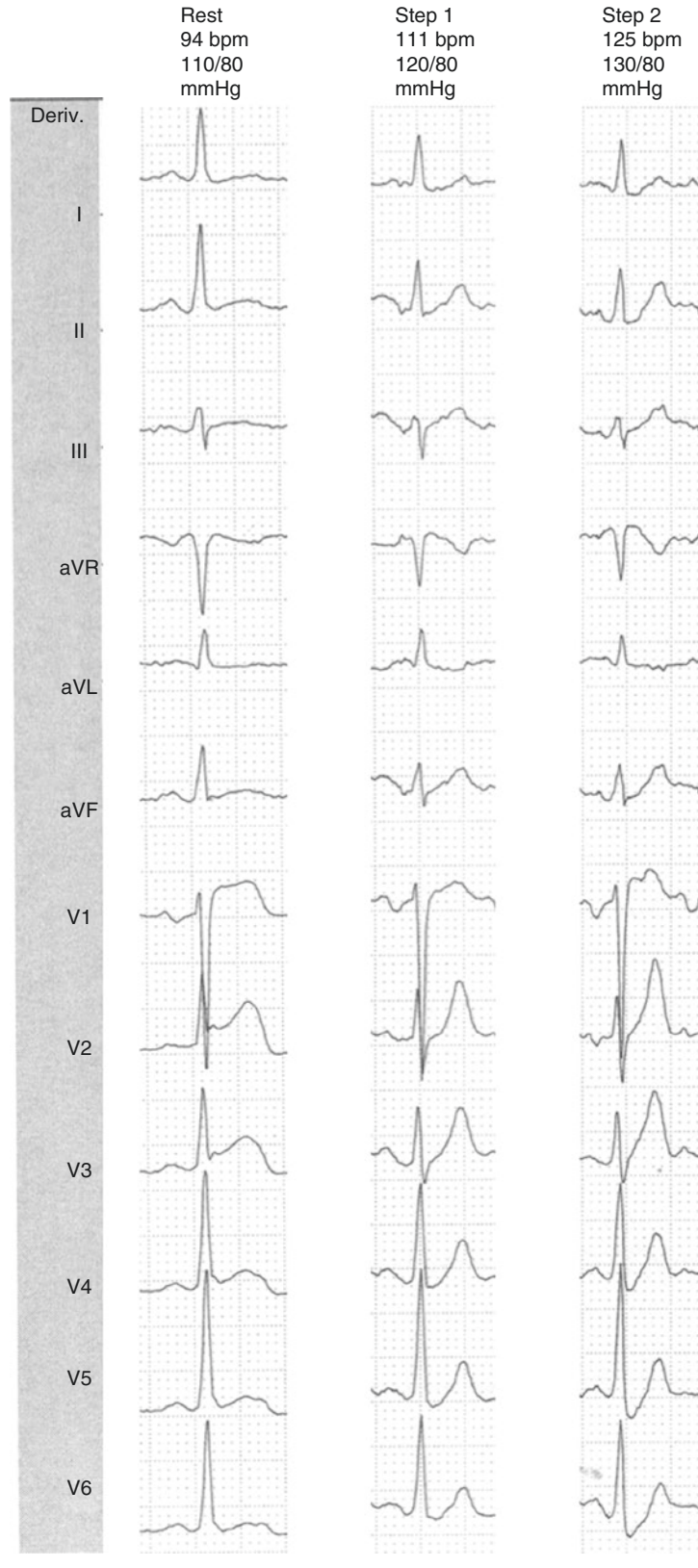

Fig. 11.2 ECG treadmill stress test

excluding leads V1–V3), accompanied by a narrow QRS (duration <120 ms).

End-QRS notch is a positive deflection with a dome morphology occurring on the final 50% of the downslope of R wave, whereas the end-QRS slur is an abrupt slowing of the end of QRS complex.

The J point is the site where the QRS ends and the ST segment begins. The correct way to define J-point elevation is to measure the amplitude of the peak of the notch or the onset of a slur, named J peak (Jp) (Fig. 11.3).

ST-segment slope should be distinguished in three different morphologies: ascending/upsloping, horizontal or descending/downsloping. The amplitude of the ST segment should be measured 100 ms (interval M) after the J termination (Jt), defined as the end of slur or notch (Fig. 11.4).

If the amplitude of the ST segment is inferior to the amplitude of Jt, the ST segment is defined as descending, if it is equal as horizontal and if it is superior as ascending.

QRS duration should be measured on leads where slur or notch is not present [1].

When an early repolarization pattern is associated with aborted cardiac arrest, documented ventricular fibrillation (VF) or polymorphic VT, in absence of any structural heart disease, we can diagnose an early repolarization syndrome (ERS) [2].

11.1.2 Epidemiology

Prevalence of early repolarization pattern in normal population ranges from 2 to 31% [1].

This wide variability could reflect differences in the criteria used for its definition, the demographic features of the population and dynamicity of this pattern with the time along.

Early repolarization pattern is more frequent in young men, African ethnicity people and athletes [3].

The higher prevalence in males could be due to testosterone, which physiologically increases

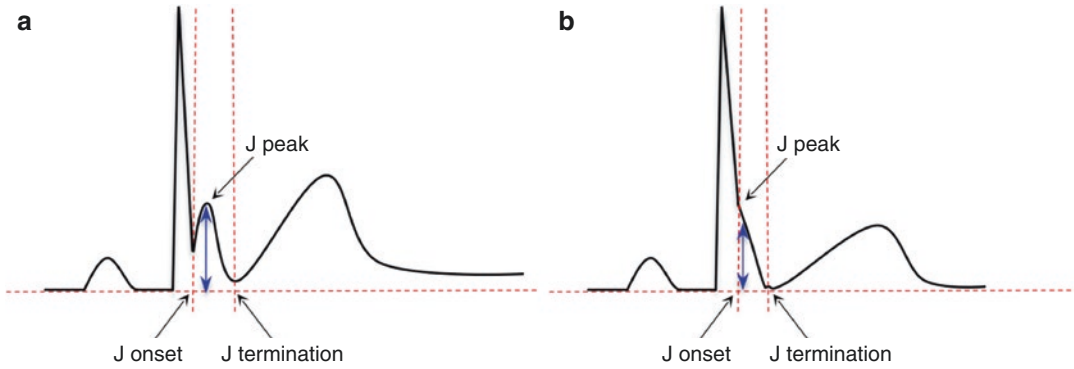

Fig. 11.3 End-QRS notch and slur terminology: end-QRS notch (**a**); end-QRS slur (**b**)

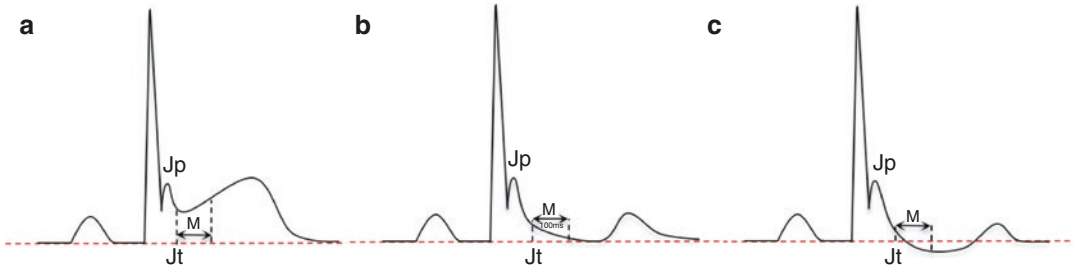

Fig. 11.4 ST-segment slope: ascending/upsloping (**a**); horizontal (**b**); descending/downsloping (**c**)

the outward repolarizing currents of cardiac action potential (AP). Moreover, in males the prevalence of this pattern decreases with age [4].

Also the association between ER and physical activities is largely mentioned. This correlation may be explained by high prevalence of males and black individuals among athletes and by the lower heart rate and pronounced vagal tone typical of sportsmen [3].

This electrocardiographic finding is located preferentially in the inferior and lateral leads, ranging from 0.6 to 7.6% and from 0.4% to 9%, respectively [3].

Early repolarization features in inferior and/or lateral leads together with a rapidly ascending/upsloping ST segment are the most common pattern in healthy and young people practicing physical activity, leading to the conviction that this aspect might be related to athlete-type ECG changes such as a physiological left ventricular hypertrophy. On the other hand, horizontal/descending ST-segment morphology is usually seen in middle-aged population [5].

ER has a heritable basis and it is more prevalent in siblings and offspring of ERP-positive individuals [3].

11.1.3 Pathophysiology

The electrophysiological basis of early repolarization pattern is not completely clear, and it is still a matter of debate.

Experimental evidence indicates that the J wave ECG inscription is a manifestation of a transmural voltage gradient from the epicardium to endocardium, occurring in the early phases of action potential (AP).

During AP phase 1 (early repolarization), the membrane repolarizes rapidly through a progressive attenuation of sodium inward current (I*Na-late*) and simultaneous activation of outward currents (current I*to and* I*Cl*).

In the human heart, both density and properties of recovery of transient outward K+ current (I*to*) vary between epicardium and endocardium. These differences create a physiologic transmural voltage gradient.

However, an imbalance between outward and inward repolarizing currents may result in a prominent I*to* current capable of developing a further faster repolarization in the epicardial cells. As opposed, the action potential is maintained normal in endocardial cells, with a consequent increase of transmural repolarization heterogeneity [6].

These regional differences might increase dispersion of repolarization, thereby facilitating a local re-excitation (phase 2 re-entry). This, in turn, may develop closely coupled premature beats, sometimes degenerating in ventricular arrhythmias.

The ERP response to pharmacologic therapy could confirm the central role of I*to* current. In this regard, studies have reported that quinidine, the only agent with significant I*to*-blocking properties available around the world, is useful to suppress both the J wave and arrhythmic manifestations of ERS. Similarly, beta-adrenergic agonist (isoproterenol) and some phosphodiesterase III inhibitors (milrinone, cilostazol) have been shown to act in reversing the repolarization abnormalities by suppressing the I*to*, augmenting the I*ca* or both [7].

However, discrepant response to I*Na* blockade, in particular ajmaline, pointed out that the mechanism underlying early repolarization still remains to be completely clarified [6].

The response to an increase in heart rate can differentiate a repolarization defect from a conduction defect. At faster rates, as during premature beats, J waves usually are reduced whereas are accentuated by bradycardia or long pauses.

11.1.4 A New Marker of Arrhythmic Risk

Sudden cardiac death prevention has always been one of the main goals of the cardiologists.

For decades the early repolarization was considered a normal variant with a benign outcome.

However, recently case-control and large population studies revealed an association between early repolarization and an increased risk of arrhythmic death, mostly due to idiopathic ventricular fibrillation (IVF) [8, 9].

Some clinical and electrocardiographic characteristics have been evaluated with the aim to improve our ability to distinguish "benign" from "malignant early repolarization".

In multiple studies, the J wave amplitude, distribution and dynamicity as well as the ST-segment morphology have been reported to reflect a different arrhythmic risk.

The observation that a J-point elevation >0.1 mV is increasingly associated with idiopathic ventricular fibrillation (IVF) in patients without structural heart disease has focused on the height of J-point elevation, rather than on its mere presence, as increased arrhythmic risk. In these subjects, early repolarization pattern occurred mainly in the inferior leads and less commonly in lateral leads [10]. It is noteworthy though that a lateral J wave position heralds the lowest risk; the risk progressively increases when early repolarization manifests itself in inferior or even widespread in all the leads [8, 11].

While early repolarization pattern with horizontal or descending ST segment has been linked to an increased risk of arrhythmic death, a rapidly ascending ST-segment morphology has not yet been associated with adverse outcomes, and it is considered generally benign, with few exception [5, 12].

Several studies showed that the presence of high J wave amplitude (>0.2 mV) in the inferior leads together with a horizontal or descending ST segment is a strong predictor of death for arrhythmic causes that is the same percent of other well-known electrocardiographic risk markers, such as long QTc interval and left ventricular hypertrophy [11].

In consideration of ER pathophysiological background, the J wave accentuation during bradycardia or after long pauses could be explained by the pause-dependent augmentation in transient outward current I*to*. Since this behaviour has been noticed only in patients with idiopathic ventricular fibrillation, J wave dynamicity is considered an important predictor of arrhythmic risk in the setting of ER [13–15].

It is also easily understandable how patients with frequent and short-coupled ventricular premature beats (VPBs) have a significant increased risk of arrhythmic deaths [8, 14].

Syncope is also common in early repolarization population. It may occur at rest or during sleep, and it may suggest an early repolarization-related arrhythmic event.

However, syncope has a low specificity in predicting future events in these early repolarization patients, where sudden death is rare compared to a high syncope frequency [14].

A positive family history of sudden cardiac death may be a good sign of a higher arrhythmic risk.

Finally, it is important to point out that in patients with other arrhythmic syndromes, such as short QT and Brugada syndromes, the simultaneous presence of early repolarization pattern does correlate with a worse outcome [16, 17].

None of these clinical or electrocardiographic findings per se has a valid stratification risk tool [18].

Currently, in early repolarization setting, provocative pharmacological and functional tests do not improve accuracy in arrhythmic risk stratification [14]. However, persistence of ERP during exercise and/or ajmaline testing seems to identify patients at higher risk of arrhythmic events, but further prospective evaluation is required to confirm their positive predictive value [19].

Also, ventricular fibrillation inducibility during electrophysiology study (EPS) does not predict risk for future arrhythmias. Moreover, a positive EPS doesn't correlate with the presence of more "malignant" ECG variant of the early repolarization pattern [20].

In conclusion, to date we have difficulties to distinguish the very common "benign early repolarization" from the truly rare malignant form. That is anyway a rare complication.

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