

Who is at high-risk in J wave syndromes?

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Early repolarization (ER) and J wave have long been thought to be innocent signs that usually appear in young healthy people and athletes. However, not all J waves are innocent: Haissaguerre et al. reported that patients with idiopathic ventricular fibrillation (VF) more frequently had ER than did control subjects (Haissaguerre et al., 2008). After that index study, it has been gradually revealed that ER is associated with malignant ventricular arrhythmias in patients with various heart diseases (Antzelevitch et al., 2016; Tikkanen et al., 2012). Brugada syndrome (BrS) is characterized by a specific J-point elevation in right precordial leads, and this ECG pattern was initially thought to be ER of the right ventricle. Antzelevitch et al. proposed that BrS and idiopathic VF with ER (ER syndrome: ERS) were in the same category of J-wave syndromes (Antzelevitch and Yan, 2010).

Leads of J point elevation are different in BrS and ERS: J point elevation appears in the right precordial leads in BrS, whereas ERS has significant J waves in the inferior or lateral leads. The diagnostic criteria for these two syndromes are therefore different. Diagnosis of BrS is very simple: if a patient has a type 1 ECG (coved-type ST elevation), a diagnosis of BrS can be made regardless of the presence or absence of symptoms, family history and VF (Priori et al., 2013). In 2016, Antzelevitch et al. proposed a new diagnostic criterion for BrS based on a point score system (Shanghai Score System for diagnosis of BrS). Patients are divided into 3 categories by this score system: probable/definite BrS, possible BrS and nondiagnostic. Using this score system, patients can be diagnosed as having probable/definite BrS if they only have a spontaneous type 1 ECG. Thus, detection of a type 1 ECG is very important for diagnosis of BrS.

Diagnosis of ERS is also based on ECG findings, however, the diagnosis has a limitation. According to the Expert Consensus Statement published in 2013, ERS can be

diagnosed if patients have a J wave (≥ 1 mm and ≥ 2 contiguous leads) and suffer from VF or sudden cardiac death (Priori et al., 2013). Asymptomatic subjects with a J wave are considered as having an ER pattern. Antzelevitch et al. proposed the Shanghai Score System for diagnosis of ERS (Antzelevitch et al., 2016). The point score system divides patients with ERS into 3 categories, possible/definite, probable and non-diagnostic, according to the points. If a patient has VF and a tall J wave (≥ 2 mm), the patient can be diagnosed as having ERS. If a patient has a tall J wave but does not have symptoms, PVCs, or family history, the patient is categorized as non-diagnostic.

Since asymptomatic patients with type 1 ECG can be diagnosed as having BrS, why cannot asymptomatic patients with a tall J wave be diagnosed as having ERS? One answer to the question is the difference in incidences of Brugada ECG and J wave. The incidence of Brugada ECG has been reported to be $\approx 0.3\%$ in the general population (Antzelevitch et al., 2016) but the incidence of ER has been reported to be up to 20–30% in the general population. Thus, there would be many patients with ERS if diagnosis is made only from an ECG. The second answer to the question is the incidences of new onset of VF in asymptomatic patients. The development of the VF in asymptomatic patients with BrS has been reported to be 0.5%/year (Antzelevitch et al., 2016); however, the frequency is very low in individuals with ER: Rosso et al. estimated that the risk for developing idiopathic VF in general population with ER is 1:10,000 (Rosso et al., 2011). If diagnosis of ERS is made only by an ECG, a huge number of subjects should be screened, and we could detect only few high-risk patients with ERS.

Various risk markers for detecting high-risk asymptomatic patients have been reported. In BrS, various ECG markers including spontaneous type 1 ECG, fragmented

QRS, and long interval of the peak to the end of T wave (TpTe), VF inducibility by programmed electrical stimulation (PES) are useful for identifying patients at high risk. The predictability of VF by each factor is relatively weak, but the combination of several risk factors could improve the risk prediction. High-risk patients could be identified according to the score of the Shanghai Score System for BrS (Kawada et al., 2018). Sieira et al. reported a point score system for risk stratification of BrS that includes spontaneous type 1 ECG, family history, inducible VF by PES, syncope, sinus node dysfunction and sudden cardiac death (Sieira et al., 2017). Asada et al. reported that the combination of two ECG markers (fragmented QRS and long TpTe interval) and inducible VF by PES is useful for identifying high-risk asymptomatic patients (Asada et al., 2020). They showed that the incidence of new onset of VF in asymptomatic patients with two ECG markers and inducible VF was 4.4%/year. Although it has not been determined which risk markers should be used in the risk stratification, we have many tools to evaluate the risk for asymptomatic patients with BrS.

It has also been reported that malignant ER signs indicate a high-risk for VF. Most of the markers are based on ECG findings, but inducibility of VF by PES could not predict prognosis. A long TpTe interval, horizontal or down-sloping ST segment, high amplitude of the J wave (≥ 0.2 mV) and dynamic change of the J wave are malignant ERs (Antzelevitch et al., 2016). However, there are no reliable methods for risk stratification in asymptomatic individuals with ER because of incidence of ER and new onset of VF in asymptomatic individuals.

The diagnosis of ERS in the following patient was difficult. A 24-year-old man was referred to our hospital since a tall J wave was found in a routine medical examination. He did not have any symptoms or family history of sudden death. An ECG showed tall J

wave (0.45 mV) in inferolateral leads, and exercise decreased J wave amplitude. An ambulatory ECG only showed Wenckebach type 2nd degree AV block when he was sleeping at night. We recommended him to receive a routine medical check every year. One year later, he experienced syncope when he was having blood taken for a routine medical examination. Before the syncope episode, he felt sick and had sweating and blurred vision, then he lost conscious for several seconds. An ambulatory ECG did not show any arrhythmic events. From the typical prodrome and situation, we diagnosed his syncope as reflex syncope. One year after that episode, he died suddenly at home. A diagnosis of ERS could be finally made after his sudden death.

Diagnosis and risk stratification in asymptomatic subjects with ER are difficult. ER can include innocent ER to malignant ER, whereas it is difficult to distinguish true malignant ER. ER is a phenomenon at the end of the QRS complex and it can include the end of depolarization and the early phase of repolarization. Antzelevitch et al. explained the mechanism of J wave by the repolarization or depolarization abnormalities (Antzelevitch and Diego, 2021). From observations of epicardial mapping in patients with ERS represented both two mechanisms could produce J wave and VF (Nademanee et al., 2019). Since there is currently no reliable method for distinguishing a depolarization J wave and a repolarization J wave, it is difficult to identify high-risk patients among subjects with a mixture of repolarization and depolarization J waves. The next issue for the risk stratification in subjects with ER should be differentiation of depolarization and repolarization J waves.

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