Review

Noninvasive risk stratification of lethal ventricular arrhythmias and sudden cardiac death after myocardial infarction

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ABSTRACT

Prediction of lethal ventricular arrhythmias leading to sudden cardiac death is one of the most important and challenging problems after myocardial infarction (MI). Identification of MI patients who are prone to ventricular tachyarrhythmias allows for an indication of implantable cardioverter-defibrillator placement. To date, noninvasive techniques such as microvolt T-wave alternans (MTWA), signal-averaged electrocardiography (SAECG), heart rate variability (HRV), and heart rate turbulence (HRT) have been developed for this purpose. MTWA is an indicator of repolarization abnormality and is currently the most promising risk-stratification tool for predicting malignant ventricular arrhythmias. Similarly, late potentials detected by SAECG are indices of depolarization abnormality and are useful in risk stratification. However, the role of SAECG is limited because of its low predictive accuracy. Abnormal HRV and HRT patterns reflect autonomic disturbances, which may increase the risk of lethal ventricular arrhythmias, but the existing evidence is insufficient. Further studies of noninvasive assessment may provide a new insight into risk stratification in post-MI patients.

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1. Introduction

Ventricular tachycardia (VT) and ventricular fibrillation (VF) leading to sudden cardiac death (SCD) are responsible for significant morbidity and mortality in patients with myocardial infarction (MI). Identification of MI patients who are prone to VT/VF allows for an indication of implantable cardioverter-defibrillator (ICD) placement. For this purpose, there has been an increase in research on the noninvasive risk stratification of lethal ventricular arrhythmias and SCD. To date, various noninvasive methods such as signal-averaged electrocardiography (SAECG) [1–4], microvolt T-wave alternans (MTWA) [5–7], heart rate variability (HRV) [8–10], and heart rate turbulence (HRT) [11,12] have been developed, and currently, MTWA and SAECG are widely used for risk stratification in patients with prior MI.

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2. Microvolt T-wave alternans (MTWA)

T-wave alternans is a periodic beat-to-beat variation in the amplitude or morphology of the T wave on electrocardiography (ECG) (Fig. 1). Beat-to-beat T-wave alternans is considered to reflect increased dispersion of ventricular repolarization, and it is known to often precede the development of lethal ventricular arrhythmias [13,14]. A prior experimental study suggests that T-wave alternans observed at rapid rates under long-QT conditions is largely the result of alternation of the M-cell action potential duration, leading to exaggeration of transmural dispersion of repolarization during alternate beats [15]. MTWA testing is a noninvasive test, which can detect subtle beat-to-beat fluctuations in T-wave morphology and amplitude using fast Fourier transform (spectral method, Fig. 2) [16]. In general, MTWA measurement using the spectral method is commonly performed during bicycle or treadmill exercise at an optimum heart rate using dedicated noise-reducing electrodes, and the development of T-wave alternans at a heart rate < 110 bpm is defined as positive. MTWA testing has been found to be able to identify patients who will benefit from ICD therapy [17]. Recent clinical trials have shown that a positive MTWA result is associated with serious ventricular arrhythmic events and SCD [18–20]. The ALPHA (T-wave alternans in patients with heart failure) study demonstrated that patients who had heart failure due to idiopathic dilated cardiomyopathy and had abnormal MTWA test results had an adjusted hazard ratio of 3.2 for the combined primary endpoint of cardiac death and lethal arrhythmias, whereas patients with

negative MTWA results had a good prognosis and were unlikely to benefit from ICD therapy [18]. The Risk Estimation Following Infarction, Noninvasive Evaluation (REFINE) study showed that combined assessment of HRT, MTWA, and left ventricular ejection fraction (LVEF) $< 50\%$ beyond 8 weeks after MI reliably identified patients at risk of cardiac death or resuscitated cardiac arrest, whereas that at 2–4 weeks after MI did not predict the risk of serious cardiac events [19]. In contrast, the MATER (Microvolt T-Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) trial and a prospective substudy of the Sudden Cardiac Death Heart Failure Trial (SCD-HeFT) found that MTWA testing did not predict arrhythmic events or mortality among patients with left ventricular systolic dysfunction [20,21]. A recent meta-analysis including 15 studies (5681 patients) reported that the positive predictive value (PPV) of MTWA testing during the mean 26-month follow-up period was 14%, negative predictive value (NPV) was 95%, and univariate risk ratio was 2.35 [22]. According to the literature, a positive MTWA result indicated an approximately 2.5-fold higher risk of cardiac death and life-threatening arrhythmia, and MTWA testing showed a very high NPV both in ischemic and nonischemic patients. It is notable that MTWA has been reported to have a high NPV for malignant ventricular arrhythmias after MI. Ikeda et al. reported that the sensitivity and NPV of MTWA in predicting arrhythmic events were very high (93% and 98%, respectively) [23]. The Alternans Before Cardioverter Defibrillator (ABCD) trial was conducted to test the hypothesis that MTWA testing as well as invasive electrophysiological study (EPS) should be performed to determine ICD indication for primary prevention of SCD [24]. The trial was a multicenter prospective study that enrolled patients with ischemic cardiomyopathy and nonsustained VT. All patients underwent MTWA testing and EPS, and an ICD was implanted if either test result was positive. The event rates at the mean follow-up period of 1.9 years were significantly higher in patients with either a positive MTWA (hazard ratio, 2.1; $p=0.03$) or a positive EPS (hazard ratio, 2.4; $p=0.007$) than in those with both tests negative/indeterminate. The PPV and NPV of the MTWA test for predicting appropriate ICD discharge or SCD were 9% and 95%, respectively, which were comparable to the PPV and NPV of the EPS (11% and 95%, respectively).
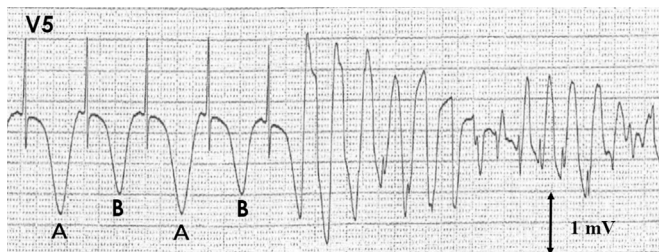

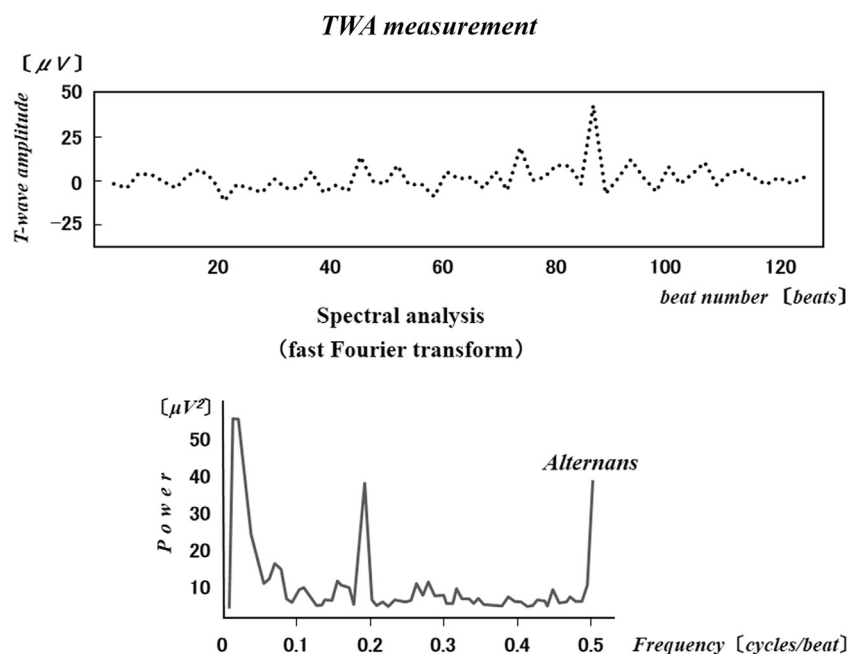**Fig. 1.** T-wave alternans (ABAB oscillation) leads to ventricular fibrillation (VF).

Fig. 2. Algorithm for evaluating T-wave alternans based on the spectral method. The amplitudes of the T wave are measured for 128 beats, and the power spectrum of this time series is described using fast Fourier transform methods. Microvolt TWA represents a peak at one-half of the beat frequency (0.5 cycles per beat).