International Journal of Cardiology 196 (2015) 7–13

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Early repolarization and positive T-wave alternans as risk markers for life-threatening arrhythmias in patients with vasospastic angina☆

Yukihiro Inamura [a,f,*], Mitsuhiro Nishizaki [a], Masato Shimizu [a], Hiroyuki Fujii [a], Noriyosi Yamawake [a], Makoto Suzuki [b], Harumizu Sakurada [c], Masayasu Hiraoka [d,e], Mitsuaki Isobe [f]

[a] Department of Cardiology, Yokohama Minami Kyosai Hospital, Yokohama, Japan
[b] Department of Cardiology, Kameda Medical Center, Chiba, Japan
[c] Division of Cardiology, Tokyo Metropolitan Health and Medical Treatment Corporation Ohkubo Hospital, Tokyo, Japan
[d] Department of Health Examination, Toride Kitasoma Medical Center Hospital, Ibaraki, Japan
[e] Tokyo Medical and Dental University, Tokyo, Japan
[f] Department of Cardiology, Tokyo Medical and Dental University, Tokyo, Japan

ARTICLE INFO

*Article history:*
Received 15 March 2015
Received in revised form 21 May 2015
Accepted 26 May 2015
Available online 29 May 2015

*Keywords:*
Vasospastic angina
J wave
T wave alternans
Multivessel vasospasm
Ventricular fibrillation

ABSTRACT

*Background:* Several arrhythmogenic markers have been suggested as predictors for risk of life-threatening arrhythmias during symptom-free periods in vasospastic angina (VSA), but no definite conclusion has been drawn.
*Objective:* To investigate prevalence of fatal ventricular tachyarrhythmia in VSA and its relation to appearance of early repolarization (ER) and positive T wave alternans (p-TWA) in patients with VSA during symptom-free periods.
*Methods:* We studied 116 consecutive patients with chest pain who underwent an acetylcholine provocation test for VSA diagnosis. Patients were divided into two groups with positive (VSA group; 66 cases) and negative (control group; 50 cases) provocation test results. The presence of ER on electrocardiogram and the modified moving average analysis of TWA during symptom-free periods were explored.
*Results:* The incidences of ER and p-TWA were higher in the VSA than in the control group ($P = 0.001$ and $P = 0.006$, respectively). Multivariate analysis revealed that ER and p-TWA were independent predictors of VSA (odds ratio, 5.65 and 4.94; 95% confidence interval: 1.11–28.9 and 1.22–19.9, respectively). The incidence of coexisting baseline ER and p-TWA was significantly higher in VSA patients with life-threatening arrhythmic events (3/3 vs. 6/38; $P < 0.001$) than in those without.
*Conclusions:* VSA patients with arrhythmic events showed a high incidence of ER and p-TWA during symptom-free periods. Therefore, baseline ER and p-TWA may help to identify VSA patients at high risk for life-threatening arrhythmias.



## 1. Introduction

Vasospastic angina (VSA) is caused by coronary artery vasospasm resulting in severe chest pain and transient ST-segment elevation on electrocardiogram (ECG). VSA episodes are generally not provoked by physical activity or emotional stress, but occur at rest without specific warning signs. VSA can be complicated by life-threatening ventricular arrhythmias and atrioventricular conduction block, or, if prolonged spastic events, by acute myocardial infarction. Life-threatening ventricular arrhythmia is a serious complication that can occur during attacks of VSA. While the incidence of life-threatening arrhythmias is not high (<10%), the events are nonetheless clinically important due to an increased risk for sudden cardiac death in subjects without significant coronary stenosis [1,2]. Our previous studies indicated that patients with VSA had potential substrates for malignant ventricular tachyarrhythmia with increased vulnerability and repolarization abnormalities [3,4]. Patients with VSA experienced frequent episodes of polymorphic ventricular tachycardia (PVT), which was inducible by programmed ventricular stimulation [3,4]. Even during asymptomatic periods, the patients showed increased QT dispersion, an indicator of inhomogeneous ventricular repolarization [5,6]. The modified moving average

*Abbreviations:* Ach, acetylcholine; CI, confidence interval; ECG, electrocardiography; ER, early repolarization; LAD, left anterior descending artery; LCX, left circumflex artery; MMA-TWA, modified moving average analysis of T-wave alternans; OR, odds ratio; p-TWA, positive T wave alternans; PVT, polymorphic ventricular tachycardia; RCA, right coronary artery; TWA, T wave alternans; VF, ventricular fibrillation; VT, ventricular tachycardia; VSA, vasospastic angina.

☆ This paper was presented at the 78th Annual Scientific Meeting of the Japanese Circulation Society.

* Corresponding author at: Yokohama Minami Kyosai Hospital, 1-21-1 Mutsuura-higashi, Kanazawa-ku, Yokohama 236-0037, Japan.
*E-mail address:* janes.ina929@gmail.com (Y. Inamura).

http://dx.doi.org/10.1016/j.ijcard.2015.05.147
0167-5273/

analysis of T-wave alternans (MMA-TWA) was shown to be superior to the measurement of QT dispersion for assessing the inhomogeneity of ventricular repolarization and predicting risk for life-threatening tachyarrhythmia and sudden cardiac death [7–10]. Our studies using the MMA-TWA also indicated that patients with VSA had high T wave alternans (TWA) values during event-free periods [11,12].

Early repolarization (ER) had been regarded as a benign ECG sign for many years because of its frequent association with healthy, young individuals and athletes without overt heart disease [13]. Recent clinical reports, however, have indicated that an ER pattern in the inferolateral leads is associated with the development of ventricular fibrillation (VF) in patients with idiopathic VF [14–17], and similar ER patterns with horizontal/descending ST segment have been associated with increased cardiac mortality in general populations [18,19]. Further, the presence of an ER pattern has also been shown to indicate a high risk for fatal ventricular arrhythmias in patients with Brugada syndrome [20], acute myocardial infarction [21,22], and Takotsubo cardiomyopathy [23]. Therefore, ER plays a critical role in the pathogenesis of malignant ventricular arrhythmias in certain clinical settings, while the genesis of the ER is controversial as to whether it is caused by repolarization or by depolarization abnormality [24–26].

Oh et al. reported that ER could predict cardiac death and fatal arrhythmias in patients with VSA [27]. It was not known, however, whether the presence of ER could predict life-threatening arrhythmic risk due to repolarization or depolarization abnormalities. The aim of the present study was to investigate prevalence of fatal ventricular tachyarrhythmia in VSA and its relation to appearance of early repolarization (ER) and positive T wave alternans (p-TWA) as a measure of inhomogeneous repolarization, in VSA patients during the asymptomatic period.

## 2. Methods

### 2.1. Patient population

The study included 116 consecutive patients who had chest pain at rest and underwent coronary angiography with an acetylcholine (ACh) provocation test for the diagnosis of VSA between July 2010 and April 2014 at the Yokohama Minami Kyosai Hospital (71 men and 45 women; mean age, 63.1 ± 11.2 years). Patients were divided into two groups according to the results of the Ach provocation test: the VSA group (n = 66) with ACh-induced vasospasm and the control group (n = 50) without ACh-induced vasospasm. All patients in the VSA group were given vasodilator drugs and/or calcium antagonists after the coronary angiography and followed at our outpatient clinic until October 2014 or their last visit. Patients with bundle branch block, intra-ventricular conduction disturbances, or Wolff–Parkinson–White syndrome were excluded from analysis. In this study, patients taking calcium channel blockers during Holter monitoring were included.

The study protocol was approved by the ethics committee of Yokohama Minami Kyosai Hospital. Written informed consent was obtained from all subjects before enrollment in the study.

### 2.2. Coronary angiography and acetylcholine provocation test

All vasodilator drugs and calcium antagonists were discontinued at least 3 days before coronary angiography. The coronary angiography began around 9 am on the morning of the study day. After confirming no significant stenotic lesions in both right and left coronary arteries, a bipolar electrode catheter was inserted into the right ventricular apex through the right femoral vein and connected to a temporary pacemaker. The pacing rate was set at 50 bpm. Incremental doses of acetylcholine were injected into the left coronary artery (20, 50, and 100 μg) and the right coronary artery (20, 50, and 70 μg) until acetylcholine-induced coronary vasospasm was detected angiographically or until the maximum dose was given. Coronary vasospasm was defined as total or subtotal occlusion of single or multiple coronary arteries with delayed filling of their distal segments and was associated with chest pain and/or ischemic ST-T changes on ECG [28]. If coronary vasospasm was induced in the left coronary artery, we waited until coronary vasospasm recovered spontaneously and then performed the ACh provocation test for the right coronary artery as well as for the diagnosis of multi-vessel vasospasm.

### 2.3. ECG analysis

ER was defined as a J point elevation ≥1 mm above baseline and slurring or notching of the terminal portion of QRS at ≥2 inferior (II, III, aVF) and/or lateral (I, aVL, V5–6) leads [15,24]. We analyzed ECG records obtained before and during the ACh provocation test for VSA. The presence and lead locations of ER as well as the amplitude of the J wave were evaluated. ER during the ACh provocation test was defined as positive if ER became apparent when coronary vasospasm was induced by coronary angiography regardless of the presence or absence of ST-T wave changes, and defined as negative if there was no ER 60 s after ACh provocation test. New ER was defined as an ER which newly appeared during the ACh provocation test.

We categorized ST segment patterns after ER as either the horizontal/descending or the concave/rapidly ascending type. The horizontal/descending type was defined as descending or ≤0.1 mV elevation of the ST segment at 100 ms after the J point. The concave/rapidly ascending ST segment type was defined as >0.1 mV elevation of the ST segment at 100 ms after the J point or a persistently elevated ST segment of >0.1 mV through the ST segment [19].

The QT interval and QRS duration were measured in all 12-leads of ECG recorded at a speed of 50 mm/s for 2 consecutive cycles. The QT interval was measured from the beginning of the QRS complex to the end of the T wave, which was defined as the return to the TP baseline (between the end of the T wave and the following P wave). And QT interval was rate-corrected with a modification of Bazett's formula as follow: QTc interval = QT / square root of the QT interval [5,29].

### 2.4. MMA-TWA analysis

The MMA-TWA was analyzed from two channel records (NASA and CM5) by ambulatory Holter monitoring using MARS PC version 7.03 (GE Healthcare, Milwaukee, WI) and identified periods of possible TWA by applying an MMA in 68 patients (41 in the VSA group and 27 in the control group). MMA is a time-domain-based method that bifurcates the beat stream and generates a separate moving average template (ABABABA) [8–10] Average values were updated by a weighting factor one-eighth of the difference between the ongoing average and the current pair of beats. A noise level of 20 μV was adopted in the system configuration. Manual editing was performed if the data were not eligible for analysis because of artifacts or noise. The maximum TWA value was defined as the highest value in either channel. Positive TWA (p-TWA) was defined as a TWA value >65 μV, in accordance with previous reports [30,31].

### 2.5. Definition of arrhythmic events

We defined arrhythmic events as spontaneous PVT/VF documented before the ACh provocation test and during follow-up period of 26.1 ± 14.0 months. We excluded syncope without documentation of PVT/VF from arrhythmic events, even if syncope occurred with chest pain. Syncope without documentation of PVT/VF might be caused by other conditions such as hemodynamic deterioration, complete atrioventricular-block, or sinus arrest due to ischemic events. None of the VSA group in this study developed complete atrioventricular block or acute myocardial infarction throughout the follow-up period.