Circ J 2009; **73:** 767–769

Importance of Dual Induction Tests for Coronary Vasospasm and Ventricular Fibrillation in Patients Surviving Out-of-Hospital Cardiac Arrest

Yusuke Takagi, MD; Satoshi Yasuda, MD; Jun Takahashi, MD; Morihiko Takeda, MD; Masaharu Nakayama, MD; Kenta Ito, MD; Masanori Hirose, MD; Yuji Wakayama, MD; Koji Fukuda, MD; Hiroaki Shimokawa, MD

Background: The pathogenesis of out-of-hospital cardiac arrest (OHCA) without organic heart disease has not been fully investigated.

Methods and Results: Induction tests were performed in 12 consecutive patients with OHCA for both coronary vasospasm with intracoronary acetylcholine and ventricular fibrillation (VF) with programmed stimulation at 1 month after the event. All patients were positive for 1 of the tests: coronary vasospasm alone in 3, VF alone in 2, and both in 7. All patients underwent implantable cardioverter defibrillator (ICD) implantation and appropriate ICD shock was documented in 1 patient.

Conclusions: OHCA has a heterogeneous pathogenesis and so dual induction tests are necessary. (*Circ J* 2009; **73:** 767–769)

Key Words: Coronary vasospasm; Electrophysiology; Sudden cardiac death

The widespread implementation of defibrillation programs has saved many patients with out-of-hospital cardiac arrest (OHCA), making subsequent care of these patients more important than ever[1]. Although structural heart diseases (eg, acute myocardial infarction) are the major underlying causes of OHCA[2], accumulating evidence indicates that cardiac arrest in the absence of structural heart disease is more common than previously expected[3]. Sudden death in the absence of organic heart disease is termed "Pokkuri disease" in Japan, where both coronary vasospasm and ventricular fibrillation (VF) may play an important role in pathogenesis, although this has not yet been fully investigated. In the present study, we examined the prevalence of these 2 factors in OHCA survivors by performing induction tests for both coronary vasospasm and VF.

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Methods

The present study was approved by the Ethical Committee of Tohoku University, and informed consent was given by each patient.

Study Patients

We examined 12 consecutive patients without organic heart disease who had survived an OHCA (M/F, 11/1; age, 44±12 [SD] years) between December 2004 and December 2008 (**Table**). The diagnosis of organic heart disease was made by physical examination, laboratory tests, 12-lead ECG, chest X-ray, 2-dimensional and color-flow-Doppler echocardiography, left ventriculography and coronary angiography. The induction tests for coronary vasospasm with intracoronary acetylcholine (ACh) and VF with programmed stimulation were performed after full recovery from the OHCA event (15–58 days, mean 31 days).

Acetylcholine Provocation Test for Coronary Vasospasm

The protocol has been described previously[4] Briefly, following control coronary angiography, ACh was administrated into the coronary artery (12.5, 25, 50, and 100 μg). A positive response was defined as the development of >90% stenosis accompanied by chest pain and/or ischemic ECG changes. The type of coronary spasm was classified as focal or diffuse[5]

Electrophysiological Study for VF

We performed the electrophysiological study (EPS) after the ACh provocation test (0–19 days, mean 9 days). All patients with a positive response to the ACh provocation test were treated with a calcium-channel blocker (CCB) when undergoing the EPS. The programmed stimulation protocol included a minimum of 2 basic pacing cycle lengths (600 and 400 ms) with single, double or triple extra-stimuli at the right ventricular apex. If VF was not induced, the same protocol was repeated under isoproterenol stimulation and/or pacing in the right ventricular outflow. Drug challenge test using intravenous flecainide (2 mg/kg) or pilsicainide (1 mg/kg) was also performed to diagnose Brugada syndrome[6]

(Received January 21, 2009; accepted February 1, 2009; released online March 3, 2009)

Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

The Guest Edittor for this article was Hisao Ogawa, MD.

Mailing address: Hiroaki Shimokawa, MD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: shimo@cardio.med.tohoku.ac.jp

Table. Patient Characteristics and Results of Dual Induction Tests

Patient no.	Age (years)/ sex	Coronary risk factors	Rhythm at cardiac arrest	Bystnder CPR	Therapeutic hypothermia	LVEF (%)	Acetylcholine provocation	VF induction	Drug challenge test	Late potential	CCB (daily dose)	ICD implantation	Follow-up (months)	ICD shocks
1	54/M	S, HL	VF	+	–	60	+ (F)	–	NA	–	Amlodipine/5 mg	+	48	0
2	32/M	–	VF	+	–	72	+ (D)	+	–	–	Benidipine/2 mg	+	28	0
3	57/M	S	VF	+	–	59	+ (D)	+	+	+	Benidipine/2 mg	+	25	3
4	41/M	S	VF	+	+	70	+ (D)	–	–	–	Benidipine/8 mg, Diltiazem/200 mg	+	21	0
5	60/M	S	VF	+	+	78	+ (F)	–	–	–	Benidipine/4 mg	+	21	0
6	41/M	S	VF	+	–	61	–	+	+	+	–	+	20	0
7	22/M	S	VF	–	+	64	+ (D)	+	–	–	Benidipine/8 mg, Diltiazem/200 mg	+	18	0
8	47/F	–	VF	+	–	74	+ (D)	+	–	–	Benidipine/4 mg	+	18	0
9	31/M	S	VF	+	–	55	–	+	–	–	–	+	15	0
10	39/M	S	VF	+	+	75	+ (D)	+	+	+	Diltiazem/200 mg	+	7	0
11	59/M	–	VF	+	+	72	+ (D)	+	–	+	Benidipine/8 mg	+	7	0
12	56/M	S	VF	–	+	56	+ (D)	+	–	–	Benidipine/8 mg	+	1	0

CPR, cardiopulmonary resuscitation; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; CCB, calcium-channel blocker; ICD, implantable cardioverter defibrillator; S, smoking; HL, hyperlipidemia; F, focal vasospasm; D, diffuse vasospasm; NA, not available.

Results

OHCA had occurred between midnight and early morning in 10 patients (83%) and VF had been documented as the initial rhythm at cardiac arrest in all patients (**Table**). The prevalence of coronary risk factors was relatively low, except for smoking habit (**Table**). Bystander cardiopulmonary resuscitation had been performed in 10 patients and therapeutic mild hypothermia in 6 (**Table**). The left ventricular ejection fraction was fairly well preserved (66±7%).

All patients were positive for 1 of the 2 tests: coronary spasm alone in 3, VF alone in 2, and both in 7 (**Table**). ECG changes typical of Brugada syndrome was induced by pilsicainide in 1 patient with VF alone and in 2 patients with both coronary spasm and VF (**Table**). Importantly, 7 of the 10 patients with coronary spasm also had inducible VF, even under intensive medical therapy with CCBs, and all of them had the diffuse type of spasm (**Table**).

All patients subsequently underwent ICD implantation. During the follow-up period (1–48 months, mean 19 months), none had chest pain or syncope. However, appropriate ICD shock for VF was documented in 1 patient with both coronary spasm and Brugada syndrome (**Figure**).

Discussion

The major finding of the present study is that the patients surviving an OHCA without organic heart diseases were positive for either coronary vasospasm or VF, suggesting heterogeneity of the pathogenesis of OHCA and the importance of performing the induction tests for both of the disorders that could cause OHCA.

The survival rate of OHCA, especially in witnessed cases of VF or pulseless VT, is increasing in association with the decrease in the time interval from ambulance call to electrical shock[1] Among OHCA survivors, a number of patients have not had apparent structural cardiac abnormalities, indicating a potential role of functional cardiac impairment in the pathogenesis of OHCA[3] In the present study, all the OHCA survivors were positive for either coronary spasm or VF, and 50% were positive for both tests, indicating the importance of performing both inductions and subsequent medical therapy based on the results of the provocation tests. It remains to be examined in future studies whether coronary microvascular impairment is also involved in patients with both coronary spasm and VF[5]

ICD implantation is a useful therapy for OHCA survivors with induced VF and/or Brugada syndrome diagnosed by EPS[7] but it is still controversial whether ICD is also effective for secondary prevention of sudden cardiac death caused by coronary spasm. Meisel et al previously reported both the efficacy and limitation of ICD therapy in patients with refractory variant angina[8] In their 7 patients with variant angina complicated by VF, appropriate ICD shocks were documented in 4 patients, but 1 patient died of electromechanical dissociation even under intensive medical treatment with CCBs[8] In clinical practice, the efficacy of medication for preventing coronary vasospasm is assessed on the basis of symptoms; however, it is also known that silent myocardial ischemia because of coronary vasospasm can initiate fatal arrhythmias[9] and that coronary vasospasm could be induced despite a fair clinical course with CCBs[10] Therefore, it remains to be examined in a future multicenter study whether ICD therapy can improve the prognosis of OHCA survivors with coronary vasospasm.

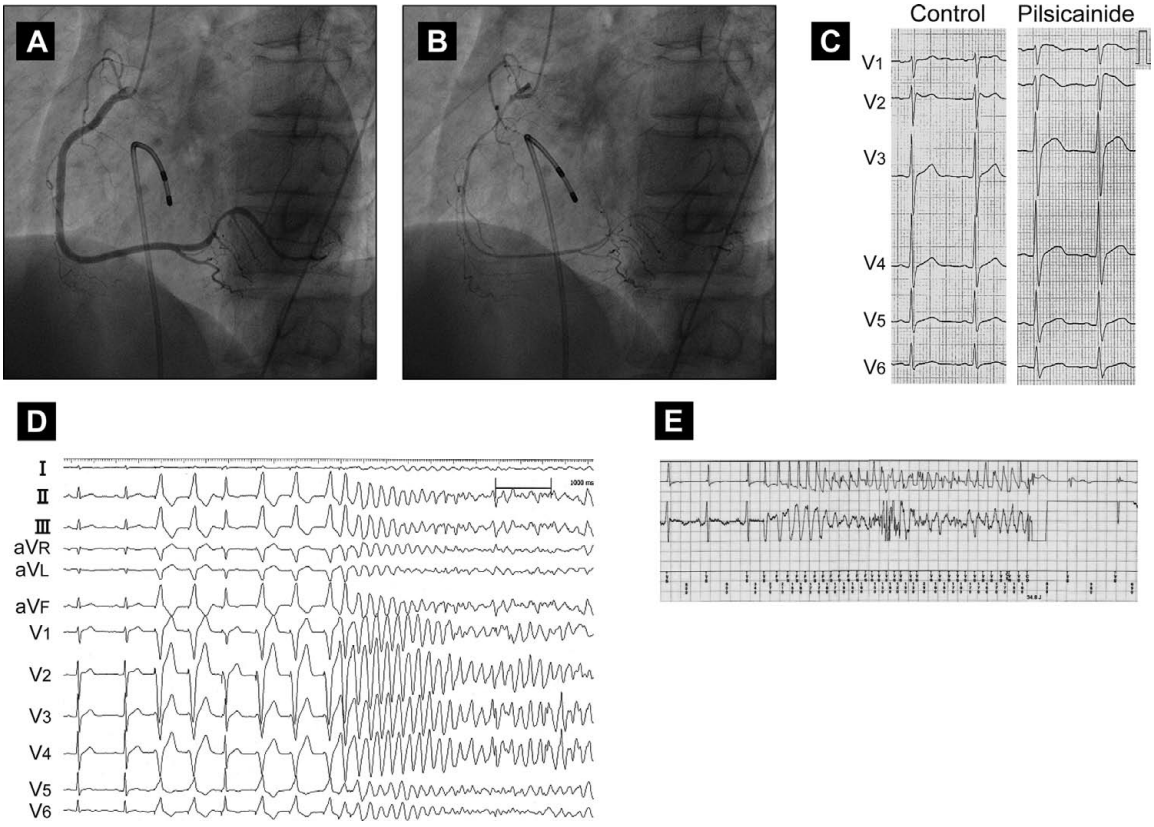

Figure. Representative case of out-of-hospital cardiac arrest (OHCA) with both coronary spasm and ventricular fibrillation (VF). In this 57 year-old male patient, coronary angiography (CAG) was performed 19 days after the onset of an OHCA. Although no significant coronary stenosis was found in control CAG (**A**), severe and diffuse coronary spasm was induced by intracoronary acetylcholine (**B**). Drug challenge test with 1 mg/kg pilsicainide demonstrated ECG changes typical for Brugada syndrome (**C**), and in the electrophysiological study performed under medication with calcium-channel blocker (CCB) 10 days after the CAG study, VF was induced by programmed stimulation (**D**). At 593 days after the onset of the OHCA, despite treatment with CCBs, recurrent VF (without proceeding ST-T changes) and an appropriate ICD shock was documented (**E**).

In conclusion, it is important that the induction tests for both coronary vasospasm and VF are performed in patients surviving a OHCA without organic heart disease.

Acknowledgments

The present study was supported in part by grants-in-aid from the Japanese Ministry of Education, Culture, Sports, Science and Technology, Tokyo, Japan.

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