Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

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

Original article

The acetylcholine administration time plays the key role for provoked spasm in the spasm provocation test

Shozo Sueda (MD, FJCC)[a,*], Hiroaki Kohno (MD)[b]

[a] Department of Cardiology, Ehime Niihama Prefectural Hospital, Niihama City, Japan
[b] Department of Cardiology, Tsukazaki Hospital, Japan

ARTICLE INFO

Article history:
Received 26 August 2016
Received in revised form 22 October 2016
Accepted 25 October 2016
Available online xxx

Keywords:
Coronary artery spasm
Acetylcholine
20 s
3 min

ABSTRACT

Background: Acetylcholine (ACh) was administered for 3 min in the ENCORE study, while the Japanese Circulation Society guidelines recommended the 20 s ACh injection as an ACh test.
Objectives: We compared the ischemic findings between ACh administration for 3 min and ACh injection for 20 s in the same patients and in the same ACh doses without administration of nitrates in the left coronary artery.
Methods: We investigated 30 patients with ischemic heart disease (25 men, 67 ± 10 years, ACh 50 μg: 3, ACh 100 μg: 9, ACh 200 μg: 18) by the above two ACh injection procedures. Temporary pacemaker was inserted and set at the rate of 40/min. Positive provoked spasm was defined as transient ≥90% narrowing and typical chest symptoms or ischemic electrocardiographic (ECG) changes.
Results: Provoked spasm was observed in 22 patients with ACh 20 s injection, while 10 patients had provoked spasm by ACh 3 min administration (73.3% vs. 33.3%, $p < 0.05$). Ischemic ECG changes (50.0% vs. 23.3%, $p < 0.05$) and chest symptoms (73.3% vs. 43.3%, $p < 0.05$) were significantly higher with ACh 20 s injection than ACh 3 min administration. Pacemaker rhythm was recognized in 19 patients with ACh 20 s injection, whereas 7 patients with ACh 3 min administration had a pacemaker rhythm (63.3% vs. 23.3%, $p < 0.01$). Maximal ST elevation by ACh 20 s injection was significantly higher than that by ACh 3 min administration (0.47 ± 0.94 vs. 0.13 ± 0.51, $p < 0.05$), while maximal ST depression was not different between the two procedures. Coronary artery diameter after ACh 20 s injection was significantly lower than that after ACh 3 min administration in the left anterior descending artery.
Conclusions: ACh administration procedures (3 min or 20 s injection) may influence the ischemic findings in spasm provocation testing.

Introduction

Yasue and Okumura reported the usefulness of acetylcholine (ACh) spasm provocation testing approximately 30 years ago [1–3]. In 2008, the Japanese Circulation Society (JCS) established the guidelines for coronary spastic angina, which were the first in the world [4]. The ACh spasm provocation test procedure proposed by Yasue and Okumura was recommended in the JCS guidelines. ACh injection time is for 20 s under the insertion of temporary pacemaker, whereas in the ENCORE study, ACh administration time for 3 min was employed without temporary pacemaker insertion [5,6]. The ACh spasm provocation test procedure may become simpler and less costly in the cardiac catheterization laboratory, if we could perform ACh spasm provocation testing without temporary pacemaker insertion. On the other hand, we often encountered the back-up pacing rhythm in the right coronary artery (RCA) during ACh spasm provocation tests. In this study, we investigated the difference of coronary responses and the necessity of back-up pacing in the left coronary artery (LCA) when we performed the two ACh injection procedures, 20 s injection or 3 min administration, in the same patients to document coronary artery spasm as a spasm provocation test.

Methods

Study patients

From April 2015 to June 2016, we performed the ACh spasm provocation tests in 79 patients. We could perform the ACh 20 s injection and the ACh 3 min administration without injection of

* Corresponding author at: Department of Cardiology, Ehime Prefectual Niihama Hospital, Hongou 3 choume 1-1, Niihama City, Ehime Prefecture 792-0042, Japan. Fax: +81 897 41 2900.
E-mail address: EZF03146@nifty.com (S. Sueda).

http://dx.doi.org/10.1016/j.jjcc.2016.11.003
0914-5087/

Table 1
Patients' clinical characteristics.

Number	30
Rest angina	16 (53.3%)
Post PCI	10 (33.3%)
IHD suspected	4 (13.3%)
Male (%)	25 (83.3%)
Age (year)	67.1 ± 9.7
Organic stenosis	0
Smoking	23 (76.7%)
Hypertension	15 (50.0%)
Dyslipidemia	24 (80.0%)
Diabetes mellitus	12 (40.0%)
Total cholesterol (mg/dl)	195.6 ± 39.7
Triglyceride (mg/dl)	131.6 ± 57.6
Low-density-lipoprotein cholesterol (mg/dl)	120.3 ± 37.8
High-density-lipoprotein cholesterol (mg/dl)	50.2 ± 13.9
Fasting blood sugar (mg/dl)	117.2 ± 23.7
Glycohemoglobin (%)	6.2 ± 0.7

PCI, percutaneous coronary intervention; IHD, ischemic heart disease.

nitrates before completing the spasm provocation tests in 30 patients in the LCA. All 30 patients had ischemic heart disease consisting of 16 with rest angina pectoris, 10 after percutaneous coronary intervention, and 4 ischemic heart diseases suspected. A total of 25 patients were male. No significant organic stenosis was found. A history of smoking was observed in 23 patients (76.7%) and hypertension was recognized in 15 patients (50.0%). Dyslipidemia was also found in 24 patients (80.0%), while diabetes mellitus was observed in 12 patients (40.0%) as shown in Table 1.

The definition of positive spasm

Positive spasm was defined as ≥90% transient stenosis and typical chest symptoms or ischemic ECG changes. We considered ECG changes to be positive when ST-segment elevation of ≥0.1 mV and/or ST-segment depression of 0.1 mV were evident 80 ms after the J point in at least two contiguous leads during and/or after the ACh test. We also considered a negative U wave as an ischemic ECG change and positive test result.

ACh spasm provocation test

All drugs except for nitroglycerine were discontinued for ≥24 h before the study and nitroglycerine was also discontinued ≥4 h before the study. Cardiac catheterization was performed between 9:00 am and 4:00 pm in the fasting state, as previously reported [7–9]. We attempted to perform the pharmacological spasm provocation tests in the morning as often as possible. Before testing, baseline coronary arteriograms were obtained of the LCA in the right anterior oblique with caudal projection and of the RCA in the left anterior oblique view with cranial projection by injection of 8–10 mL of contrast medium. A bipolar electrode catheter was inserted into the right ventricular apex through the antecubital vein and was connected to a temporary pacemaker set at the rate of 40 beats/min.

Provocation of coronary artery spasm was performed with an intracoronary injection of ACh, as previously reported [10–12]. ACh chloride (Neucholin-A, 30 mg/2 mL; Zeria Seiyaku, Tokyo, Japan) was injected in incremental doses of 20, 50, 100, and 200 μg into the LCA and of 20, 50, and 80 μg into the RCA over 20 s with at least a 3-minute interval between each injection. After the spontaneous relief of vasoconstriction to control state without use of nitrates, we again administered the same maximal ACh dose into the LCA over 3 min in the 30 patients apart from at least 12 min after the ACh 20 s injection into the LCA, as shown in Fig. 1. Coronary arteriography was performed when ST-segment changes and/or chest pain occurred or after 1–2 min of the completion of each injection. When an induced coronary spasm did not resolve spontaneously within 3 min after the completion of the ACh injections or when hemodynamic instability occurred as the result of coronary spasm, 2.5–5.0 mg of nitrate was injected into the involved vessel. A standard 12-lead electrocardiogram (ECG) was recorded every 30 s.

During the study, arterial blood pressure and ECG were continuously monitored on an oscilloscope with Nihon-Kohden polygraphy. In the present study, coronary arteriograms were analyzed separately by 2 independent observers. The percent luminal diameter narrowing of coronary arteries was measured by an automatic edge-counter detection computer analysis system (Q AngioXA 7.3, Medis Medical Imaging Systems, Leiden, the Netherlands). The size of the coronary catheter was used to calibrate the images in millimeters, with the measurement performed in the same projection of coronary angiography at each stage. Focal spasm was defined as a discrete transient vessel narrowing of 90% or more localized in the major coronary artery, whereas diffuse spasm was diagnosed when transient vessel narrowing of 90% or more, compared with baseline coronary angiography, was observed from the proximal to distal segment in the 3 major coronary arteries. Patients with catheter-induced spasms were excluded from this study. Significant organic stenosis was defined as ≥50% luminal narrowing according to the American College of Cardiology/American Heart Association classification [13]. Systolic/diastolic blood pressure, pacing rhythm time, and maximal ST elevation/depression were also compared between the two ACh procedures in the LCA.

The study protocol complied with the Declaration of Helsinki. Written informed consent was obtained from all patients before the study, and the study protocol complied with the guidelines of the ethical committee at our institution.

Statistical analysis

All data were presented as the mean ± 1 SD. Ischemic findings between the ACh 20 s injection and the ACh 3 min administration were analyzed by the χ^2 test with correction. Several parameters between the two ACh procedures, such as systolic/diastolic blood pressure, maximal ST level shifts, change of coronary artery diameter in the LCA, and the duration of pacing time, were compared by the paired-*t* test. Values of $p < 0.05$ were considered significant.

Results

Comparisons of chest symptoms, ischemic ECG changes, and provoked spasm between the two procedures in all 30 patients

Maximal ACh dose of 50 μg, 100 μg, and 200 μg was observed in 3 patients, 9 patients, and 18 patients, respectively. As shown in Table 2, chest symptoms and ischemic ECG changes during ACh

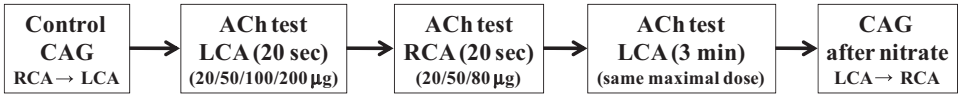

Fig. 1. Procedure schema of the coronary angiography and acetylcholine spasm provocation test. CAG, coronary angiography; RCA, right coronary artery; LCA, left coronary artery; Ach, acetylcholine; Sec, second; Min, minute.

Please cite this article in press as: Sueda S, Kohno H. The acetylcholine administration time plays the key role for provoked spasm in the spasm provocation test. J Cardiol (2016), http://dx.doi.org/10.1016/j.jjcc.2016.11.003