Safety and usefulness of acetylcholine provocation test in patients with no culprit lesion on emergency coronary angiography

（緊急冠動脈造影検査において責任病変が存在しない患者におけるアセチルコリン負荷試験の安全性と有効性）

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Abstract

Background: Vasospastic angina (VSA), which often causes acute coronary syndrome (ACS), can be diagnosed by intracoronary acetylcholine (ACh) provocation test. However, the safety and usefulness of ACh provocation test in ACS patients on emergency coronary angiography (CAG) compared to non-emergency settings is unclear.

Methods: A total of 529 patients undergoing ACh provocation test during emergency or non-emergency CAG were included. Patients with resuscitated cardiac arrest were excluded. The primary endpoint was adverse events defined as a composite of death, ventricular fibrillation or sustained ventricular tachycardia, myocardial infarction, cardiogenic shock, cardiac tamponade, and stroke within 24 hours after ACh provocation test.

Results: There were no significant differences of the clinical characteristics between the groups of emergency (n=84) and non-emergency (n=445) ACh provocation test. The rate of positive ACh provocation test was similar between the 2 groups (50% vs. 49%, p=0.81). Similarly, the incidence of adverse events in patients with emergency and non-emergency ACh provocation test did not significantly differ (1.2% vs. 1.3%, p=1.00).

Conclusion: ACh provocation test can be safely performed in ACS patients with no obstructive culprit lesions on emergency CAG, and may be useful to diagnose VSA in those patients.

1. Introduction

Vasospastic angina (VSA) is an important disorder which can cause acute coronary syndrome (ACS) and sudden cardiac death [1]. Recent guidelines across the world recommend intracoronary provocative test with acetylcholine (ACh) or ergonovine (ER) in suspected VSA patients (class I, IIa, or IIb) [2-4]. It is well-known that 8% to 12% of patients with ACS are found to have absent or only angiographically mild coronary lesions [5,6]. This phenomenon is recognized as myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA), in which VSA is a common etiology [5]. Although a recent study indicated the feasibility of intracoronary provocative test on emergency coronary angiography (CAG) [5,7], the safety of intracoronary provocative test for ACS patients on emergency CAG have not been fully understood, especially compared to those with non-emergency settings. The aim of this study was to evaluate the safety and usefulness of ACh provocation test in ACS patients with no culprit lesions on emergency CAG compared to those with the elective tests.

2. Methods

2.1. Study Population

From June 2012 to June 2017, a total of 546 patients underwent intracoronary ACh provocation test at Chiba University Hospital. Patients with resuscitated cardiac arrest (n=17) were excluded. Thus, 529 patients were included in the present study and divided into 2 groups: emergency and non-emergency ACh provocation test. Emergency ACh test was defined as the intracoronary provocative test during the same angiographic session

of emergency CAG performed within 24 hours after hospital admission due to ACS. Written informed consent for examination was obtained from all patients, and the ethical committee of Chiba University approved this study.

2.2 Intracoronary Acetylcholine Provocation Test

Intracoronary ACh provocation tests were performed according to the guidelines for diagnosis and treatment of patients with VSA by Japanese Circulation Society [2], as previous reported [8]. In brief, all vasodilators were discontinued at least 48 hours before the examination in non-emergency ACh test. After insertion of a temporary pacing electrode in the right ventricle via basilic, cephalic or internal jugular vein, ACh was injected in incremental doses of 20, 50 and 100 μg into the left coronary artery (LCA), and 20 and 50 μg into the right coronary artery (RCA) over a period of 20 seconds. In Chiba University Hospital, ACh provocation test was performed the same angiographic session of emergency CAG when there were no obstructive culprit lesions in ACS cases without other causes than suspected coronary vasomotor abnormalities such as myocarditis, Takotsubo cardiomyopathy, and severe renal dysfunction.

2.3. Definitions

Angiographic coronary artery spasm was defined as total or subtotal occlusion induced by ACh provocation test. It was evaluated by 2 experienced cardiologists who were blinded to patients' clinical characteristics. The positive diagnosis of intracoronary ACh provocation test was defined as angiographic coronary artery spasm accompanied by chest pain and/or ischemic electrocardiographic changes. Multivessel spasm was defined as ACh-induced coronary artery spasm of ≥2 major epicardial arteries.

ACS was defined as unstable angina or acute MI. The diagnosis of acute MI was based on the third universal definition of myocardial infarction [9]. The diagnosis of MINOCA was made based on the following criteria: 1) universal acute MI criteria, 2) non-obstructive coronary arteries on CAG, defined as no coronary stenosis ≥ 50%, 3) no clinically overt specific causes for the acute presentation [10]. Unstable angina was diagnosed using Braunwald's criteria [11].

The primary endpoint of the present study was major adverse events defined as a composite of death, ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) requiring electrical cardioversion, MI, cardiogenic shock, cardiac tamponade, and stroke within 24 hours after ACh provocation test. Non-sustained VT and paroxysmal atrial fibrillation (AF) during the procedures were also recorded.

2.4. Statistical Analysis

Statistical analysis was performed with SAS statistical software package version 9.4 (SAS Institute, Cary, NC, USA). Continuous variables are expressed as mean ± standard deviation when normally distributed, and as median and interquartile range when non-normally distributed. Categorical data are presented as absolute numbers and percentages. Continuous variables were compared using unpaired Student's t-test or Mann-Whitney U-test, as appropriate. Categorical variables were compared with chi-square test or Fisher's exact test. A value of $p < 0.05$ was considered statistically significant.

3. Results

Clinical characteristics of the study population and ACh provocation test are shown in Table 1. There were no significant differences between the groups of emergency and non-emergency ACh provocation test. Although patients with emergency ACh test developed either MINOCA or unstable angina (Table 1), the characteristics in subjects with MINOCA did not significantly differ compared to those with unstable angina except for a history of AF (25% vs. 7%, p=0.04). Additionally, in the emergency group, 5 out of 28 patients (18%) with MINOCA had ST-segment elevation on arrival. Table 2 shows adverse events in patients with emergency and non-emergency ACh provocation test. The rate of major cardiovascular complications did not significantly differ between the 2 groups. There was 1 case of VF induced by ACh injection into the RCA, which was immediately terminated by electrical cardioversion, and 1 case of acute MI possibly due to prolonged coronary spasm in the distal RCA, in patients with non-emergency ACh test. Cardiogenic shock induced by severe vasospasm occurred in 3 patients. In addition, there were 2 cases of ischemic stroke presented partial visual field impairment and mild dysarthria in patients with non-emergency ACh provocation test. Both cases of stroke were confirmed by magnetic resonance imaging. The incidence of non-sustained VT and paroxysmal AF was also similar between the 2 groups (Table 2).

4. Discussion

The main findings of the present study is that in patients undergoing ACh provocation test during the same angiographic session of emergency CAG, the rate of adverse events was low and comparable to those on non-emergency settings.

4.1. Safety of Emergency Acetylcholine Test

Previous studies have reported low rates of complications with ACh provocation test [12-14]. However, the safety of ACh provocation tests have been established mostly based on those with elective status. Ong et al. showed coronary spasm could be documented by ACh test in nearly half of the patients with suspected ACS and no culprit lesions [15]. ACh provocation test in that study was performed either at primary catheterization or in a second session, and the complications were not reported. Montone et al. recently demonstrate that intracoronary provocative test with ACh or ER was safe and can identify a high-risk subset of patients presenting with MINOCA [5]. In this study, intracoronary ACh test was performed in 43 patients without any complication. Although there were some previous reports which suggested the usefulness of ACh provocation test in ACS patients without culprit lesions [16,17], no studies have directly compared ACh test in the emergency (i.e. ACS) versus non-emergency settings. In the present study, we focused on the safety of intracoronary ACh provocation test during emergency CAG performed within 24 hours after hospital admission due to ACS, compared to those with the elective tests. ACh provocation test is not recommended during emergency CAG performed in patients with ACS in the Japanese Circulation Society guidelines [2]. Similarly, the American Heart Association and American College of Cardiology guidelines also indicated that intracoronary provocative test may be undertaken after a period of stabilization [4]. In addition, although a recent position paper recommends provocative testing for the MINOCA patients, it is also mentioned that the procedure should generally be avoided in the acute phase of MI [18]. However, the present study suggested that ACh

provocation test during the same angiographic session of emergency CAG can be safely performed as on non-emergency CAG.

Interestingly, the incidence of positive ACh provocation test in the emergency group was comparable to those in the non-emergency group, although 35% of patients in the emergency group were under continuation of vasodilators. The findings may allow to avoid the second CAG with provocative test, possibly leading to the reduced medical cost and catheterization complications. Additionally, in patients with MINOCA, AF was more prevalent compared to those with unstable angina who had no culprit lesions (25% vs. 7%). Tachycardia including AF can account for MINOCA [4], thus there is a possibility that some patients with negative emergency ACh test developed MINOCA actually due to AF.

4.2. Study Limitations

There are some limitations in the present study. First, this is the single center retrospective study. Since the adverse events were not frequent, the sample size was relatively small. Second, although the incidence of AF was higher in patients with MINOCA compared to those with unstable angina, the finding is probably due to selection bias. Third, patients with resuscitated cardiac arrest were excluded in the present study. VSA was reported as an important cause of cardiac arrest, with the prevalence ranging from 3% to 11% of patients with out-of-hospital cardiac arrest survivors [19,20].

5. Conclusion

ACh provocation test can be safely performed in ACS patients with no obstructive culprit

lesions on emergency CAG, and may be useful to diagnose VSA in those patients.

Acknowledgements

We gratefully thank all of the hospital staff who assisted in data collection.

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Table 1. Patient and ACh Provocation Test Characteristics

Variable	All (n=529)	Emergency (n=84)	Non-Emergency (n=445)	P value
Age (years)	64.1±12.5	64.8±13.4	64.0±12.6	0.30
Male	275 (52%)	43 (51%)	232 (52%)	0.87
Hypertension	329 (62%)	59 (70%)	270 (61%)	0.10
Diabetes mellitus	96 (18%)	16 (19%)	80 (18%)	0.82
Dyslipidemia	349 (66%)	53 (63%)	296 (67%)	0.54
Current smoker	96 (18%)	14 (17%)	82 (18%)	0.70
Prior myocardial infarction	47 (9%)	7 (8%)	40 (9%)	0.85
eGFR (ml/min/1.73 m^2)	76.0±19.5	76.9±22.3	75.9±19.3	0.33
History of AF	41 (8%)	11 (13%)	30 (7%)	0.24
Clinical presentation				
MINOCA	28 (5%)	28 (33%)	-	-
Unstable angina	56 (11%)	56 (67%)	-	-
Rest angina	325 (61%)	-	325 (73%)	-
Effort angina	11 (2%)	-	11 (2%)	-
Rest and effort angina	91 (17%)	-	91 (20%)	-
Other	18 (3%)	-	18 (4%)	-
Medical treatment				
Calcium channel blocker	244 (46%)	23 (27%)	221 (50%)	<0.001
Long-acting nitrate	95 (18%)	10 (11%)	85 (19%)	0.12
Nicorandil	42 (8%)	4 (5%)	38 (9%)	0.38
β blocker	80 (15%)	17 (20%)	63 (14%)	0.15
ACE-I or ARB	178 (34%)	33 (39%)	145 (33%)	0.23
Antiplatelet	165 (31%)	23 (27%)	142 (32%)	0.41
Anticoagulant	31 (6%)	10 (11%)	21 (5%)	0.01
Statin	199 (38%)	27 (32%)	172 (39%)	0.26
Coronary artery with provoked spasm				
Right	155 (29%)	21 (25%)	134 (30%)	0.35

Left anterior descending	249 (47%)	43 (51%)	206 (46%)	0.41
Left circumflex	94 (18%)	18 (21%)	76 (17%)	0.34
Multivessel spasm	150 (28%)	21 (25%)	129 (29%)	0.46
Signs of ischemia				
Electrocardiographic change	204 (39%)	38 (45%)	166 (37%)	0.17
Chest pain	292 (52%)	48 (57%)	244 (55%)	0.70
Positive ACh provocation test	258 (49%)	42 (50%)	216 (49%)	0.81

ACE-I, angiotensin converting enzyme inhibitor; ACh, acetylcholine; AF, atrial fibrillation; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; MINOCA, myocardial infarction with non-obstructive coronary arteries.

Table 2. Adverse Events

Variable	All (n=529)	Emergency (n=84)	Non-Emergency (n=445)	P value
Major adverse events	7 (1.3%)	1 (1.2%)	6 (1.3%)	1.00
Death	0 (0%)	0 (0%)	0 (0%)	-
VF or sustained VT	1 (0.2%)	0 (0%)	1 (0.2%)	1.00
Myocardial infarction	1 (0.2%)	0 (0%)	1 (0.2%)	1.00
Cardiogenic shock	3 (0.6%)	1 (1.2%)	2 (0.4%)	0.41
Cardiac tamponade	0 (0%)	0 (0%)	0 (0%)	-
Stroke	2 (0.4%)	0 (0%)	2 (0.4%)	1.00
Non-major adverse events				
Non-sustained VT	4 (0.8%)	1 (1.2%)	3 (0.7%)	0.50
AF	54 (10.2%)	11 (13.1%)	43 (9.7%)	0.33

AF, atrial fibrillation; VF, ventricular fibrillation; VT, ventricular tachycardia.

International Journal of Cardiology, Vol. 269, 15 October 2018, Pages 27～30
平成 30 年 10 月 15 日　公表済