Introduction

In 1986, intracoronary acetylcholine (ACh) testing was first reported\(^1\). Since then, intracoronary ACh test has become popular as a spasm provocation test as well as ergonovine (ER) test in the world\(^2\)\(^-\)\(^6\). Intracoronary injection of ACh has a short half life of this agent and so intracoronary ACh testing considered to be a relatively safe method. However, we experienced some complications such as ventricular fibrillation or tachycardia necessary for electric cardioversion, severe hypotension or left main trunk equivalent spasm during the ACh tests. Furthermore, we also experienced transient paroxysmal atrial fibrillation (PAF) in a sixth of patients who underwent ACh testing based on the Japanese Circulation Society guidelines\(^7\)\(^-\)\(^8\). ACh-inducible PAF is one of a mechanism of a vagally-mediated PAF\(^7\). There are no reports concerning the reproducibility of ACh-inducible PAF in the same patients. In this article, we retrospectively investigated the reproducibility of ACh-inducible PAF in the same patients.

Methods

Study patients

From January 1991 to February 2019, we performed total 1,864 ACh spasm provocation tests. During these periods, we tried to perform the selective spasm provocation tests to examine the incidence of provoked spasm in patients who had undergone coronary angiography whenever possible. Among 1,864 patients with ACh testing, we enrolled 70 patients who had at least two times of ACh testing, while the remaining 55% of patients revealed the discordance of ACh-inducible PAF. The remaining 11 patients had discordance between the first and the second ACh tests. There were no clinical and angiographical differences except organic stenosis between the first and second ACh testing. All 70 patients had neither past PAF nor future PAF. The rate of coincidence was 84%, while discordance was 16%. ACh-inducible PAF was reproduced in 45% of patients who had two times of ACh testing, while the remaining 55% of patients revealed the discordance of ACh-inducible PAF. Conclusions: Less than half patients disclosed the reproducibility of ACh-inducible PAF.

KEY WORDS: acetylcholine, acetylcholine-induced paroxysmal atrial fibrillation, paroxysmal atrial fibrillation, vagal stimulation
main narrowing (>50%), triple-vessel disease, two-vessel disease with total occlusion, heart failure (New York Heart Association functional class III or IV), renal failure (creatinine > 2.0 mg/dl), if spontaneous spasm was observed or if isosorbide dinitrate was initially used to relieve spasm in the coronary artery tested.

The definition of PAF

We defined positive PAF as at least 30 seconds’ duration of PAF, and also defined spontaneous relief of ACh-induced PAF as < 15 minutes’ duration. When ACh-induced PAF continues for > 15 minutes, 50 mg of disopyramide or cibenzoline 70 mg solved in warmed 0.9% saline solution was administered intravenously for 5 minutes.

The definition of positive spasm and spasm configuration

Generally, we defined positive spasm as ≥ 90% transient stenosis and usual chest symptom or ischemic ECG changes. The degree of ST-segment depression was measured 80 msec after the J point. We considered a result to be positive when at least 1 of the following ischemic ECG changes was demonstrated during and/or after the ACh test: (1) ST-segment elevation of ≥ 0.1 mV in at least 2 contiguous leads; (2) ST-segment depression of 0.1 mV in at least 2 contiguous leads. We also considered negative U wave as positive ischemic ECG change. Focal spasm was defined as a discrete transient vessel narrowing ≥ 90% localized in a major coronary artery, whereas diffuse spasm was diagnosed when transient vessel narrowing ≥ 90%, compared with baseline coronary angiography, was observed in ≥ 2 adjacent coronary segments of epicardial coronary arteries.

Spasm provocation test

All drugs except for nitroglycerine were discontinued for ≥ 24 hours before the study, and nitroglycerine was also discontinued > 4 hours before the study. Cardiac catheterization was performed from 9:00 am to 4:00 pm in the fasting state. After control coronary arteriograms of the left coronary artery (LCA) in the right anterior oblique with caudal projection and of the right coronary artery (RCA) in the left anterior oblique with cranial projection were obtained by injection of 8-10 ml of contrast medium, a temporary pacemaker was inserted into the right ventricle of each ACh testing patient and the pacing rate was set at 40-45 beats/min.

Provocation of coronary artery spasm was performed with an intracoronary injection of ACh, as previously reported. ACh chloride was injected in incremental doses of 20, 50 and 80 µg into the RCA and of 20, 50, 100 and 200 µg into the LCA over 20 seconds with at least a 3-minute interval between each injection. Coronary arteriography was performed when ST-segment changes and/or, chest pain occurred or 1–2 minutes after the completion of each injection. When an induced coronary spasm did not resolve spontaneously within 3 minutes after the comple-

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Table 1  All patient clinical characteristics

|                      | All patients | Both negative PAF | Both positive PAF | Concordance | Discordance |
|----------------------|--------------|------------------|------------------|-------------|------------|
| Number               | 70           | 50               | 9                | 59          | 11         |
| Sex (female)         | 10 (14)      | 6 (12)           | 1 (11)           | 7 (12)      | 3 (27)     |
| Age, y, mean ± SD    | 64 ± 11      | 64 ± 11          | 60 ± 13          | 64 ± 11     | 64 ± 9     |
| Organic stenosis     | 38 (54)      | 28 (56)          | 7 (78)           | 35 (59)     | 3 (27)     |
| Follow-up duration (month) | 54 ± 34    | 52 ± 31          | 44 ± 37          | 51 ± 32     | 71 ± 43    |
| Angina pectoris       | 48 (69)      | 38 (76)          | 5 (56)           | 43 (73)     | 5 (45)     |
| Myocardial infarction | 9 (13)       | 5 (10)           | 3 (33)           | 8 (14)      | 1 (9)      |
| Post percutaneous coronary intervention | 13 (19) | 7 (14)          | 1 (11)           | 8 (14)      | 5 (45)*    |
| LVEF by UCG (%) mean ± SD | 65 ± 9       | 66 ± 9           | 63 ± 10          | 65 ± 9      | 62 ± 11    |

Coronary risk factors

- Hypertension
- Dyslipidemia
- Diabetes mellitus
- History of smoking

Medications before ACh testing

- Calcium channel blocker
- Dihydropyridine
- Benzodiazepine
- Both calcium channel blocker
- Nitrates or nicorandil
- Beta blocker
- ACEI or ARB
- Statin
- Antiplatelet

ACh: acetylcholine, LVEF: left ventricular ejection fraction, UCG: ultrasound cardiography, ARB: angiotensin receptor blocker, ACEI: angiotensin converting enzyme inhibitor, PAF: paroxysmal atrial fibrillation, *: p<0.05 vs. concordance

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perform ACh testing in the hypoplastic RCA posterior descending artery and posterolateral artery. We did not before reaching the crux of the heart and prior to splitting off the RCA when the RCA supplies only to the right ventricle and ends the ethical committee at our institution.

The study protocol complied with the Declaration of Helsinki. Written informed consent was obtained from all patients before performing the pharmacological spasm provocation tests and the protocol of this study was in agreement with the guidelines of the ethical committee at our institution.

### Table 2 Clinical and angiographical findings in patients with both PAF positive

| No | Age | Sex | Diagnosis | First ACh test | Second ACh test |
|----|-----|-----|-----------|----------------|----------------|
| 1  | 56  | M   | Rest AP   | RCA (50)       | RCA (50)       |
|    |     |     |           | 1(d)           | 8 (t)          |
| 2  | 47  | M   | Effort AP | RCA (20/50)    | RCA (20/50/80) |
|    |     |     |           | 2(d) No spasm  | 3 (t) No spasm |
| 3  | 62  | F   | MI        | RCA (80)       | RCA (50)       |
|    |     |     |           | No spasm 8(d)  | 7 (t) No spasm |
| 4  | 64  | M   | MI        | RCA (20/50/80) | RCA (20/50/80) |
|    |     |     |           | 1(d) Disopyramide 50 mg | 3(t) Natural |
| 5  | 60  | M   | Rest AP   | RCA (25/50)    | RCA (50)       |
|    |     |     |           | No spasm 7(d)  | No spasm       |
| 6  | 39  | M   | MI        | RCA (50)       | RCA (50)       |
|    |     |     |           | No spasm 7(t)  | 4(d) Natural   |
| 7  | 72  | M   | Effort AP | RCA (25/50)    | RCA (75)       |
|    |     |     |           | 4(d) Natural   | 4(d) Cibenzoline 70 mg |
| 8  | 63  | M   | Post P    | RCA (50/80)    | RCA (50)       |
|    |     |     |           | No spasm 8(d)  | No spasm       |
| 9  | 85  | M   | Post P    | RCA (25/50/75) | RCA (80)       |
|    |     |     |           | No spasm Cibenzoline 70 mg | No spasm |

ACAT: acetylcholine, AP: angina pectoris, MI: myocardial infarction, Post P: post percutaneous coronary intervention, RCA: right coronary artery, LCA: left coronary artery, (d): diffuse spasm, (f): focal spasm, (t): total spasm, PAF: paroxysmal atrial fibrillation, bold number: PAF induced dose of ACh

### Statistical analysis

Data analysis was carried out with SPSS (version 22.0, IBM Japan, Ltd., Tokyo, Japan). All data were presented as the mean±1 SD. Clinical characteristics among three groups and angiographical findings and medications between the first and second tests were analyzed by the Fisher’s exact test with correction or the Mann-Whitney test. P < 0.05 was considered significant.

### Results

During the follow-up periods (64±11 months), we found no previous PAF and no future PAF in all 70 patients. According to the response of ACh testing, we classified 70 patients into the three groups: 50 patients with both sinus rhythm, 9 patients with both positive PAF, and 11 patients with either of one PAF positive. We could not perform ACh tests in 5 RCAs (hypoplastic RCA: 2 vessels, obstructive stenosis > 90%: 2 vessels, after the administration of nitroglycerine into the LCA: 1 vessel) and one LCA (after the administration of nitroglycerine into the RCA) of the first ACh testing, whereas we also could not perform these tests in 2 RCAs (hypoplastic RCA) and one LCA (after the administration of nitroglycerine into the RCA) of the second ACh tests. We could perform both times and both coronary ACh testing in 63 patients (90%) of the study subjects.

### Concordance of PAF or sinus rhythm

As shown in Table 1, 59 patients had the same response be-
between the two ACh testing. There was no clinical difference between both sinus rhythm and both positive PAF. Table 2 showed the clinical and angiographical findings in patients with both occurrence of PAF. PAF was observed in all 9 patients in the first RCA ACh testing, whereas, PAF was observed in all 9 RCA ACh testing and two LCA ACh tests in the second ACh test. Positive spasm in 59 patients with concordance groups was observed in 49 patients (83%) in the first ACh testing, while positive spasm in the second ACh test was recognized in 41 patients (69%). In 9 patients with both PAF, positive spasm of first ACh testing was observed in 8 patients (89%), whereas positive spasm in the second ACh test was found in 4 patients (44%).

Comparisons of concordance and discordance PAF

Discordance occurrence of PAF between the two ACh tests was found in 11 patients, as shown in Table 3. In the first ACh testing, 7 patients had PAF including 4 RCA ACh tests, 2 LCA ACh tests and one both ACh test, while 4 patients had PAF including 3 RCA ACh tests and one LCA ACh test in the second ACh testing. Positive spasm was found in 7 patients (64%) in the first ACh testing, whereas positive spasm in the second ACh test was revealed in 6 patients (55%). However, there were no clinical differences between the concordance group and discordance group as shown in Table 1.

Comparisons between first and second ACh testing

As shown in Table 4, the frequency of organic stenosis in second ACh testing was significantly lower than that in first ACh tests. However, there was no differences concerning the provoked spasm and medications between the two ACh testing.

Complications of ACh testing

Left amin trunk equivalent spasm was observed in just one patient. However, no irreversible complications were observed in this study.

Discussion

In this article, we found no correlation of reproducibility of PAF between first ACh testing and second ACh tests. Discordance of ACh-inducible PAF was observed in 14% of patients who had two times ACh tests apart from more than one month. Furthermore, during the follow-up periods (64±11 months), we found no previous PAF and no future PAF in these 70 patients.

| No | Age | Sex | Diagnosis | First ACh test | Second ACh test |
|----|-----|-----|-----------|---------------|---------------|
| 1  | 54  | M   | Post P    | RCA (50/80)    | RCA (50/80)    |
|    |     |     |           | RCA (50/100)   | RCA (50/100)   |
| 2  | 71  | M   | R & E AP  | RCA (50)       | RCA (50)       |
|    |     |     |           | LCA (100)      | LCA (100)      |
| 3  | 65  | F   | Post P    | RCA (20/50/80)| RCA (20/50/80)|
|    |     |     |           | LCA(20/50/100)| LCA(20/50/100)|
| 4  | 72  | M   | MI        | RCA (20/50)    | RCA (20/50/100)|
|    |     |     |           | LCA (100)      | LCA (100)      |
| 5  | 69  | F   | Rest AP   | RCA (20/50)    | RCA (80)       |
|    |     |     |           | LCA (20/50/100/200) | LCA (20/100/200) |
| 6  | 73  | M   | Post P    | RCA (50/50)    | RCA (25/50)    |
|    |     |     |           | LCA (25/50/100)| LCA (50/100)   |
| 7  | 45  | M   | Rest AP   | RCA (20/50/100)| RCA (80)       |
|    |     |     |           | LCA (20/50/100)| LCA (20/100/200)|
| 8  | 66  | F   | Post P    | RCA (50/50)    | RCA (50/50)    |
|    |     |     |           | LCA (50/100)   | LCA (50/100)   |
| 9  | 69  | M   | Post P    | RCA (25/50)    | RCA (75)       |
|    |     |     |           | LCA (25/50/100)| LCA (50/100)   |
| 10 | 54  | M   | MI        | RCA (20)       | RCA (20/50)    |
|    |     |     |           | LCA (20/50/100)| LCA (20/50/100)|
| 11 | 65  | M   | R & E AP  | RCA (20/50)    | RCA (50)       |
|    |     |     |           | LCA (50/100)   | LCA (100)      |

ACh: acetylcholine, AP: angina pectoris, MI: myocardial infarction, Post P: post percutaneous coronary intervention, RCA: right coronary artery, LCA: left coronary artery, (d): diffuse spasm, (f): focal spasm, (t): total spasm, PAF: paroxysmal atrial fibrillation, bold number: PAF induced ACh dose, under PAF test
Table 4  Angiographical findings and medications before acetylcholine tests

|                        | First ACh testing | Second ACh testing | p value |
|------------------------|-------------------|--------------------|---------|
| Number                 | 70                | 70                 |         |
| Organic stenosis       | 38 (54)           | 16 (23)            | <0.001  |
| Right coronary artery  | 13 (19)           | 6 (9)              | 0.1387  |
| Left circumflex artery | 19 (27)           | 3 (4)              | <0.001  |
| Left anterior artery   | 48 (69)           | 8 (11)             | <0.001  |
| 1 vessel disease       | 33 (47)           | 15 (21)            | <0.01   |
| 2 vessel disease       | 5 (7)             | 1 (1)              | 0.2106  |
| Provoked positive spasm| 54 (77)           | 46 (66)            | 0.1344  |
| Right coronary artery  | 36 (51)           | 32 (46)            | 0.4987  |
| Left circumflex artery | 17 (24)           | 13 (19)            | 0.4100  |
| Left anterior artery   | 45 (64)           | 37 (53)            | 0.1698  |
| 1 vessel spasm         | 23 (33)           | 19 (27)            | 0.4606  |
| 2 vessel spasm         | 19 (27)           | 19 (27)            | 1.0000  |
| 3 vessel spasm         | 12 (17)           | 8 (11)             | 0.3339  |
| Medications before ACh testing |           |                    |         |
| Calcium channel blocker| 50 (71)           | 57 (81)            | 0.1633  |
| Dihydropyridine r      | 40 (57)           | 43 (61)            | 0.6058  |
| Benzodiazepine         | 22 (31)           | 21 (30)            | 0.8546  |
| Both calcium blocker   | 12 (17)           | 7 (10)             | 0.2172  |
| Nitrate or nicorandil  | 40 (57)           | 44 (63)            | 0.4901  |
| Beta blocker           | 6 (9)             | 3 (4)              | 0.4907  |
| ACEI or ARB            | 10 (14)           | 12 (17)            | 0.6423  |
| Statin                 | 19 (27)           | 20 (29)            | 0.8504  |
| Antiplatelet           | 42 (60)           | 44 (63)            | 0.7284  |

ACh: acetylcholine, ARB: angiotensin receptor blocker, ACEI: angiotensin converting enzyme inhibitor

This may suggest that ACh-inducible PAF is a reaction of individual response to just ACh at that time. The clinical implications of ACh-inducible PAF may have limitations of estimating previous and future occurrence of PAF:

**ACh-inducible PAF in Western and Japanese populations**

In the past report of ours, we had no correlation between the daily PAF and ACh-inducible PAF. Among 717 patients without persistent atrial fibrillation, we experienced transient PAF during ACh testing in 116 patients (16.2%). Daily PAF in patients with ACh-induced PAF was not different from that in those with ACh-induced no PAF (2.6% (3/116) vs. 1.0% (6/601), ns). However, Saito et al. reported that a history of PAF and body mass index were independent predictors for occurrence of PAF during intracoronary ACh provocation test by multivariate logistic regression analysis. PAF during ACh testing was observed in just 8% (31 patients) among 377 patients without persistent atrial fibrillation who underwent intracoronary ACh provocation tests. The occurrence rate of PAF during ACh testing was lower than the data of previous ours. Maximum ACh dose of 80µg into the RCA and 200µg into the LCA of our study might be concerned. They employed maximum ACh dose of 50µg into the RCA and 100µg into the LCA. In contrast, in a Western report, one patient had fast PAF that resolved spontaneously after discontinuing the ACh injection. The observation of short phases of PAF during ACh testing was not uncommon, but was not registered as a complication in their study. Incremental doses of 2, 20, 100, and 200µg of ACh were manually infused over a period of 3 minutes into the LCA without a pacemaker. If no proved spasm in the LCA was revealed, 80µg of ACh was injected into the RCA. However, intracoronary RCA ACh testing was performed in just 34.4% (291/847) of their study. Accurate occurrence of PAF in their study was obscure. In another Caucasian report, PAF is a rare complication with ACh infusion over 1 minute into the LCA (1.1%). While 6.9% of patients developed atrioventricular block and 3.3% developed significant bradycardia, these conditions readily reversed once the administration of ACh was stopped. Western cardiologists administered intracoronary ACh over 1–3 minutes without a pacemaker, whereas we injected intracoronary ACh within 20 seconds under pacemaker. Intracoronary RCA ACh testing without a pacemaker is difficult to perform possibly due to bradycardia and block. According to our previous report, PAF was observed in 109 patients (94%) in the RCA ACh testing, whereas 9 patients (8%) had PAF in the LCA ACh tests. Two patients (2%) had PAF on both coronary arteries. In this study, PAF was recognized in 26 RCAs, while 6 LCAs had PAF. PAF was observed in 3 patients on both coronary arteries (one patient with discordance PAF of first ACh test & two patients with concordance PAF of second ACh tests).
Clinical implications of ACh-inducible PAF

The majority of ACh-inducible PAF was observed in the RCA ACh testing. However, the occurrence of ACh-inducible PAF in Western reports was unclear. Furthermore, we could not find the reproducibility of ACh-inducible PAF in the previous reports. This is the first report regarding the reproducibility of ACh-inducible PAF. In this study, we could perform both times and both coronary ACh testing in 90% of study populations. The administration time of ACh may contribute to the occurrence of PAF and vagally mediated PAF is a mechanism of ACh-inducible PAF. In this study, a previous history of PAF or future PAF in patients with ACh-induced PAF was not found. We suggest that ACh-induced PAF may react the individual response of ACh in the cardiac catheterization laboratory at that time. Mechanism favoring the occurrence of PAF are complex and the occurrence of PAF greatly depends on variation of the autonomic tone, with a primary increase in adrenergic tone followed by an abrupt shift toward vagal predominance. It may be difficult to estimate the occurrence of clinical daily PAF or persistent atrial fibrillation in the future by intracoronary ACh-inducible PAF alone. Further research is necessary to clarify the reproducibility of the occurrence of ACh-inducible PAF in Western and Japanese subjects.

Limitations

Several limitations were recognized in this study. First is a single center, retrospective, small study sample and not prospective study. Second, we could not perform Holter monitoring in all patients during follow-up periods at a constant examination. We may miss a transient silent PAF. Third, follow-up duration was short to verify the correlation between ACh-inducible PAF alone. This is the first report regarding the reproducibility of ACh-inducible PAF in the previous reports. Western reports was unclear. Furthermore, we could not find the reproducibility of ACh-inducible PAF in the previous reports. This is the first report regarding the reproducibility of ACh-inducible PAF. In this study, we could perform both times and both coronary ACh testing in 90% of study populations. The administration time of ACh may contribute to the occurrence of PAF and vagally mediated PAF is a mechanism of ACh-inducible PAF.

Conclusions

There was no correlation regarding the reproducibility between first and second ACh-inducible PAF. This study suggests that it may be difficult to estimate the past and future occurrence of PAF according to the ACh-inducible PAF alone.

Conflicts of interest

The authors declare that they have no conflict of interest.

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