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Complications of Pharmacological Spasm Provocation Tests

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Abstract

Background: We investigated the complications of spasm provocation tests, including acetylcholine (ACh) tests, ergonovine (ER) tests and adding ACh after ER tests, retrospectively.

Methods: We performed 1546 ACh tests and 1114 ER tests during 23 years, including 240 adding ACh after ER tests. ACh (RCA: 20/50/(80) g, LCA: 20/50/100/(200) g) was injected incrementally over 20 seconds, whereas ER (RCA: 40 g, LCA: 64 g) was administered over 2-4 minutes. In addition, we administered adding intracoronary injection of ACh (RCA: 50/80 g, LCA: 100/200 g) after ER tests. Serious major complications were defined as ventricular fibrillation, sustained ventricular tachycardia, shock, severe hypotension (< 60 mmHg), cardiac arrest and cardiac tamponade.

Results: Serious major and major complications were higher in ACh tests than ER tests (1.8% vs. 0.4%, p<0.01), whereas serious major complications were not different between ACh and ER tests (0.9% vs. 0.4%, ns). No serious major or major complications were observed in adding ACh after ER tests. Paroxysmal atrial fibrillation was not different between ACh tests and adding ACh after ER tests (16.7% vs. 12.5%, ns). Necessity of nitrates to relive provoked spasms prior to carrying other site tests were significantly higher in ER tests (6.8%) than ACh tests (2.0%) and adding ACh after ER test (2.5%). No death or irreversible complications were recognized in all three spasm provocation tests.

Conclusions: Serious major complications were not different between the two agents, whereas serious major and major complications were significantly higher in ACh tests than ER tests. Although pharmacological spasm provocation tests including adding ACh after ER tests were reliable and relatively safer methods, we should perform these tests positively in the cardiac catheterization laboratory.

Keywords: Complications; Spasm provocation test; Acetylcholine; Ergonovine

Introduction

As pharmacological spasm provocation tests, acetylcholine (ACh) [1-3] and ergonovine (ER) [4,5] are employed in the cardiac catheterization laboratory. However, we often encounter the major and minor complications during performing these procedures. As a diagnostic tool, we should perform spasm provocation tests more safely without major complications. Multiple and proximal spasm documented by the pharmacological agents may occur a hemodynamic instability, such as shock and hypotension. Moreover, irreversible arrhythmia may be recognized. Selective spasm provocation tests such as intracoronary injection of ACh and ER is safer than the intravenous injection of ER. The effect time of ACh is very short and we may have the spontaneous remission of the provoked spasm. Therefore, we can perform a selective right and left coronary artery testing separately. We already reported the major complications during ACh spasm provocation tests in 2000 [6]. Serious major complications were not different from the reports with an intravenous injection of ER. Recently, we employed the sequential spasm provocation tests to document coronary spasm in the clinic [7]. As sequential spasm provocation tests, we first perform intracoronary injection of ACh, second intracoronary administration of ER, and finally adding intracoronary injection of ACh just after ER test if we did not obtain the provoked spasm. However, the majority of cardiologists employed a single spasm provocation test for example ACh alone or ER only in each institution. Thus, they did not experience the difference of coronary artery response and complications between the two pharmacologic agents. We have been routinely used the ACh and/or ER spasm provocation tests to diagnose the presence of coronary artery spasm in the cardiac catheterization laboratory during a quarter century. In the Japanese Circulation Society guidelines, complications during invasive spasm provocation tests were not mentioned [8].

In this article, we investigated the complications of these three spasm provocation tests; first, ACh test, second, ER test and finally adding ACh after ER test retrospectively.

Methods

Study patients

We performed ACh spasm provocation tests in 1546 patients and ER spasm provocation tests in 1114 patients during 23 years from January 1991 and December 2013. We also performed both ACh and ER tests in 461 patients and adding ACh after ER tests in 240 patients in the above patients. Therefore, we carried ACh tests alone in 1085 patients and ER tests alone in 653 patients. During this period, we performed total 7302 coronary angiography procedures including 1872 percutaneous coronary intervention procedures and 5430 diagnostic/follow up cardiac catheterizations as shown in (Figure 1).

In this study, we defined serious major complications as ventricular

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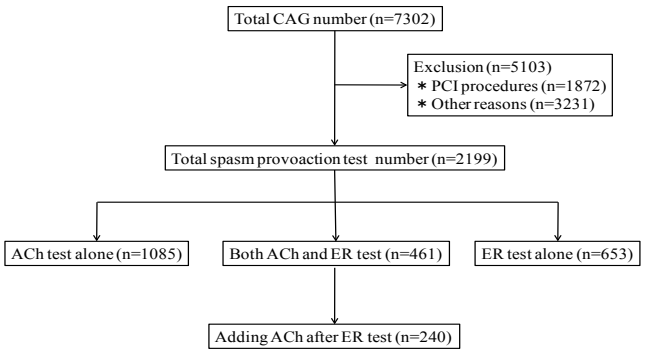

(CAG: coronary arteriography, PCI: percutaneous coronary intervention, ACh: acetylcholine, ER: ergonovine)

Figure 1: Flow chart of the pharmacological spasm provocation tests.

fibrillation (VF), sustained ventricular tachycardia (VT), shock, severe hypotension (< 60 mmHg), cardiac arrest and cardiac tamponade. We also defined a major complication as non-sustained VT and a minor complication as paroxysmal atrial fibrillation.

Indication and exclusion criteria for pharmacological spasm provocation tests

We tried to perform the selective spasm provocation tests to examine the incidence of provoked spasm in patients who had undergone coronary angiography as much as possible over 23 years in the same manner. The provocation test was not performed, if patients had left main narrowing (>50%), triple-vessel disease, two-vessel disease with total occlusion, heart failure (New York Heart Association class III or IV), renal failure (creatinine >2.0 mg/dl), if spontaneous spasm was found, or if nitrate was initially used to relieve spasms in the coronary artery tested. We also did not perform spasm provocation tests if the patients will undergo multiple coronary angioplasties or bypass surgery. We firstly selected ACh tests in patients who were strongly suspected of having the coronary artery spasms as much as possible. If we did not obtain the provoked spasms, we employed the ER tests as a second test. Lastly, we performed the adding ACh after ER tests if we did not obtain the provoked spasm by the ACh or ER tests in patients who were suspected of coronary artery spasms.

Spasm provocation tests

Coronary arteriography was obtained by injection of 8-10 ml of contrast medium with the Sones technique from 10:00 to 16:00 without medication for at least 24 hours. A bipolar electrode catheter was inserted into the right ventricular apex through the femoral vein or antecubital vein and was connected to a temporary pacemaker set at the rate of 45 beats/minutes. Provocation of coronary artery spasm was performed with an intracoronary injection of ACh and ER, as previously reported [9-14]. ACh chloride (Neucholin-A, 30 mg/2 mL; Zeria Seiyaku, Tokyo, Japan) was injected in incremental doses of 20, 50 and 80 g into the right coronary artery and of 20, 50 and 100 (200) g into the left coronary artery over 20 second with at least a 3 minutes interval between each injection. Each injection was approximately 10 ml solved 0.9% warm saline. Coronary arteriography was performed when either ST-segment changes or chest pain (or both) occurred, or after one minute following the completion of each injection. Intracoronary injection of ACh into the responsible vessel was not performed if coronary artery spasm occurred spontaneously during coronary angiography. ER (Ergometrine injection F, 0.2 mg/mL; Fuji Seiyaku, Tokyo, Japan) in 0.9% warm saline solution was injected in 10 g/min for 4 minutes for a maximal dose of 40 g into the right coronary artery and 16 g/min over 4 minutes for a total dose of 64 g into the left coronary artery, with at least a 5-minute interval between each injection. If systolic blood pressure was >190 mmHg prior to performing ER tests, we did not perform ER tests in these patients. Coronary arteriography was performed when ST-segment changes, chest pain (or both), occurred, or following 2 minutes after the completion of each injection. In addition, we performed the adding intracoronary injection of ACh after ER tests if not provoked spasm by either ACh or ER test. The dose of adding ACh was 50/80 g into the RCA and 100/200 g into the LCA over 20 second with at least a 3-minute interval between each injection. Adding ACh injection was approximately 10 ml solved 0.9% warm saline. When a coronary spasm was induced and did not resolve spontaneously within 3 minutes after the completion of ACh/ER and adding intracoronary injection of ACh after ER tests, or when hemodynamic instability due to coronary spasms occurred, 2.5 to 5.0 mg of nitrate was injected into the responsible vessel. During the study, arterial blood pressure and a standard 12 lead electrocardiogram were continuously monitored on an oscilloscope using a Nihon-Kohden polygraph. A standard 12 lead electrocardiogram was recorded every 30 second. In this study, we performed frequent test shots at about 30 second intervals with a contrast medium during these three testing, whenever possible. We tried to perform coronary angiography before coronary spasm with complete obstruction was induced by pharmacologic agents.

Positive coronary artery spasm was defined as transient luminal narrowing >99% and usual chest pain or ischemic ECG findings. Focal spasm was defined as a discrete transient vessel narrowing of >99% localized in the major coronary artery. Diffuse spasm was diagnosed when a transient vessel narrowing was >99% compared to the baseline coronary angiography observed from the proximal to the distal segment in the three major coronary arteries. The procedure was explained in detail to each patient, informed consent was obtained and the protocol of this study was in agreement with the guidelines of the ethical committee at each our institution.

Angiographic analysis

The coronary arteriograms were analyzed separately by two independent observers. The percent luminal diameter narrowing of coronary arteries was measured by an automatic edge-contour detection computer analysis system. The size of the coronary catheter was used to calibrate the image in millimeters, and the measurement was performed in the same coronary angiography projection at each stage. Coronary artery spasm was assessed >99% luminal narrowing. Patients with catheter-induced spasms were excluded from this study. Significant organic stenosis was defined as >75 percent luminal narrowing according to the American Heart Association (AHA) classification [15]. Coronary arteries were measured after intracoronary administration of nitrate (ISDN) (5.0mg) to evaluate coronary atherosclerosis.

Statistical analysis

All values were expressed as mean ± SD. The chi square test was used for differences in the prevalence of complications. A value of $P<0.05$ was considered statistically significant.

Results

Serious major complications

Serious major complications were not different between ACh tests

and ER tests (0.9% vs. 0.4%, ns), as shown in (Table 1). In ER tests, VF occurred in two patients who recovered with thump version and cardiac massage, and another two patients presented cardiac arrest, which lead to cessation of ER tests. Meanwhile, in ACh tests, there were 14 serious major complications including four VF, one sustained VT, six shocks, two severe hypotensions and one cardiac tamponade. However, we experienced no serious major complications in the adding ACh after ER tests.

Major complications

As shown in Table 1, major complications in ACh tests were significantly higher than those in ER tests (1.8% vs. 0.4%, p<0.01). VT and VF were recognized in 24 patients in ACh tests, while VF was only two patients by ER testing. Moreover there was no VT/VF when performed adding ACh after ER tests. Non-sustained VT was 19 and sustained VT was one in ACh testing. Shock due to like left main trunk spasm was observed in six patients and severe hypotension was found in nine patients with ACh testing. Two patients with ER testing presented cardiac arrest, and improved after cardiac massage and cessation of administering ER. We experienced one patient with cardiac tamponade after ACh tests. In patients with adding ACh after ER tests, there were no major complications, such as VF, shock, hypotension, cardiac arrest or cardiac tamponade.

Minor and other complications

Paroxysmal atrial fibrillation was often observed in ACh testing and adding ACh after ER tests, but there was no difference between the two tests. Meanwhile, no paroxysmal atrial fibrillation was recognized after ER tests. Provoked positive spasm was recognized in 40.3% (104/258) patients with ACh-induced paroxysmal atrial fibrillation, whereas the frequency of provoked spasm was 55.6% (685/1233) in patients with sinus rhythm following ACh tests. Reciprocal ST-elevation was frequently observed in ACh tests compared with that in ER tests (1.2% vs. 0.3%, p<0.05).

Procedures for complications

As shown in (Table 2) direct current was necessary to recover sinus rhythm in five patients with ACh tests and two patients with ER tests, while we performed cardiac massage in eight patients with ACh tests and one patient with ER tests. Thump version recovered five ventricular tachycardias in ACh testing and one ventricular fibrillation in ER tests. Surgical drainage for cardiac tamponade was necessary in one patient with ACh tests in order to maintain blood pressure. Cessations of tests were necessary in one ACh test due to the stimulation of the temporary pace maker induced ventricular fibrillation and two patients with ER tests due to cardiac arrest. Intra-arterial administration of norepinephrine and nitrate gradually relieved coronary spasm and the hypotension and shock improved in four patients with ACh tests. Administration of anti-arrhythmic agents for recovering sustained ventricular tachycardia to sinus rhythm was carried in one patient with ACh test but failed to recover sinus rhythm. The incidence of Injection of anti-arrhythmic agents for recovering paroxysmal atrial fibrillation to sinus rhythm was not different between ACh tests and adding ACh after ER tests (5.3% vs. 3.3%, ns). Necessity of nitrates prior to another vessel to relieve provoked coronary spasm was significantly higher in ER tests than that in ACh tests and adding ACh after ER tests (6.8% vs. 2.0%/2.5%, p<0.001/p<0.05).

Discussion

In this article, we reported the serious major, major, minor and other complications during pharmacologic spasm provocation tests, including ACh, ER and adding ACh after ER tests. Serious major complications were not different between the two agents, whereas serious major and major complications during ACh testing were significantly higher than those of ER tests. Most powerful spasm provocation test of adding ACh just after ER test had no major complications in this series when we performed these tests in patients with negative ACh and/or ER tests. In the cardiac catheterization laboratory, we could perform the three sequential spasm provocation tests without death or irreversible complications. In addition, we may also pay attention to the pseudo-negative of the pharmacological spasm provocation tests, although we take great care of the pseudo-positive after the pharmacological tests in the clinic. This sequential spasm provocation tests may fill a limitation of the standard spasm provocation tests without irreversible major complications.

	ACh (n=1546)	ER (n=1114)	Adding ACh after ER test (n=240)
Serious major complications	14 (0.9%)	4 (0.4%)	0
VF	4	2	0
Sustained VT	1	0	0
Shock (like left main trunk spasm)	6	0	0
Hypotension (severe <60 mmHg)	2	0	0
Cardiac arrest	0	2	0
Cardiac tamponade	1	0	0
Major complications	28 (1.8%)**	4 (0.4%)	0
VF	4 [2]	2	0
VT	20 [4]	0	0
Shock (like left main trunk spasm)	6	0	0
Hypotension (severe < 60 mmHg)	9 (6)	0	0
Cardiac arrest	0	2	0
Cardiac tamponade	1	0	0
Minor complications			
Paroxysmal atrial fibrillation	258 (16.7%)	0	30 (12.5%)
Other complications			
Reciprocal ST elevation	19 (1.2%)*	3 (0.3%)	0

(ACh: acetylcholine, ER: ergonovine, VF: ventricular fibrillation, VT: ventricular tachycardia, susVT: sustained VT, [ ]: include hypotension, ( ): include shock, *p<0.05, **p<0.01, vs. ER)

Table 1: Serious major, major and minor complications among three spasm provocation tests.

	ACh (n=1546)	ER (n=1114)	adding ACh after ER test (n=240)
Procedures			
Direct current	5 (0.32%)	2 (0.18%)	0
Cardiac massage	8 (0.52%)	1 (0.09%)	0
Thump version	5 (0.32%)	1 (0.09%)	0
Surgical drainage	1 (0.06%)	0	0
Cessation of tests	1 (0.06%)	2 (0.18%)	0
Administration			
Noradrenaline (intra aorta)	4 (0.26%)	0	0
Anti arrhythmic agents (VT/VF)	1 (0.06%)	0	0
Anti arrhythmic agents (Paf)	82 (5.3%)	0	8 (3.3%)
Nitrate (intra coronary) before another vessel	31 (2.0%)**	76 (6.8%)	6 (2.5%)*

(ACh: acetylcholine, ER: ergonovine, VT: ventricular tachycardia, VF: ventricular fibrillation, Paf: paroxysmal atrial fibrillation,
*p<0.05, **p<0.01 vs. ER)

Table 2: Procedures and administrations for major and minor complications.

Safety of three sequential spasm provocation tests

We already reported major complications during spasm provocation tests with an intracoronary injection of ACh in 2000. Serious major complication rate was 0.56% (4/715), which was not different compared with those of intravenous ER testing by Bertrand (0.46%) [16]. However, Harding et al reported that major complication rate was 0.03% (11/3447) including four patients (0.01%) with myocardial infarction and seven patients (0.02%) with ventricular tachycardia or fibrillation by carrying intravenous ER testing in patients without significant coronary artery disease or Prinzmetal's variant angina [17]. Takagi et al. reported the high prevalence of arrhythmic complications during coronary spasm provocation tests in ACh test than that in ER testing (9.3% vs. 3.2%, $p<0.001$) [18], although our small data included in this report. The incidence of VT/VF was significantly higher in ACh tests than in ER testing (4.9% vs. 0.8%, $p<0.001$). However, the frequency of VT/VF in our study was remarkably lower than the report by Takagi et al (ACh: 1.6%, $p<0.001$, ER: 0.2%, ns). Ong et al. also reported the minor complications (1%) without any fatal or serious nonfatal complications in ACh testing without temporary pace maker insertion in consecutive 847 white patients with unobstructed coronary arteries [19,20]. Serious major complication rate of ACh tests was 0.9% and 0.4% in ER tests in this study. We mainly selected ACh tests in patients with suspecting of high disease activity whenever possible. If we did not obtain the provoked spasms, we secondary employed ER tests in approximately 40 % of ER study patients. Therefore, disease activity might be lower in patients with ER than those with ACh tests. In order to perform spasm provocation tests strictly, we firstly employed ACh tests whenever possible and secondary used ER tests, and lastly performed adding ACh after ER tests. Therefore, we could perform adding ACh after ER tests in 240 patients. We experienced no major complications during performing adding ACh after ER tests. We performed this powerful tests in patients with very low disease activity whose spasm were not provoked by maximal ACh and ER doses. Disease activity was very low in patients who had undergone adding ACh after ER tests. We believe that sequential spasm provocation tests, first ACh tests, second ER tests and last adding ACh after ER tests are clinical useful and reliable method.

Clinical implications

Spasm provocation tests should be performed without complications. However, we always encounter major and minor complications when carrying these tests in the cardiac catheterization laboratory in the real world. Therefore, prior to performing the spasm provocation tests, we should have detailed preparations for strategies to deal with major and minor complications. If major and minor complications occurred, we should cope with these situations without loss time. Frequent test shots are useful to obtain severe spasms quickly. During spasm provocation tests, over infusion is useful to avoid hypotension due to volume loss. Incremental dose-up should be employed to decrease the risk of severe complications and you should administer less than 20 g of ACh if a case with suspecting of high disease activity. If shock or left main trunk like spasm is observed, we should administer small amount of noradrenaline into the ascending aorta or responsible vessel to keep the hemodynamics. It is useful to administer cibenzoline or disopyramide when ACh induced paroxysmal atrial fibrillation occurred [21]. It is very important to make an effort to lessen complications when performing spasm provocation tests [22].

Study limitations

Our study has several limitations. The first limitation is the retrospective study. We did not perform ACh and ER spasm provocation tests randomly in consecutive patients who had diagnostic catheterization. We performed pharmacological spasm provocation tests in only 40.5% (2199/5430) patients with diagnostic and follow up angiography. The second limitation is small sample size. During 23 years, we performed 1546 ACh and 1114 ER spasm provocation tests and adding ACh after ER spasm provocation tests were performed in only 240 same patients. The third limitation is the dose of ACh and ER used in this study. If higher doses were administered, the incidence of complications may have been higher. Further studies are needed to perform spasm provocation tests safely in the future.

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