

Usefulness of a Pressure Wire for the Diagnosis of Vasospastic Angina during a Spasm Provocation Test

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Abstract

Objectives: We performed spasm provocation tests (SPTs) using a pressure wire and compared the results with those from patients who underwent the same test without a pressure wire.

Background: The SPT is an important examination used to diagnose vasospastic angina; however, it is sometimes accompanied by severe complications.

Methods: We enrolled 190 patients who underwent an SPT: a pressure wire was used in 103 (Group I) and no wire was used in 87 (Group II). We attempted to place the pressure wire in the distal portions of the right coronary artery and left anterior descending coronary artery. The pressure ratio of the distal lesion to the proximal lesion (Pd/Pa index) was monitored continuously during the test. Vasospastic angina was defined as an angiographic vasoconstriction of the coronary artery accompanied by ischemic chest symptoms and/or electrocardiographic changes. The fluoroscopic time, total dose of contrast medium, and frequency of severe complications were investigated in both groups.

Results: The fluoroscopic time was longer in Group I than in Group II (13.0 ± 5.2 min vs. 11.5 ± 5.0 min, $p = 0.0329$). However, the volume of contrast medium used was lower in Group I (127 ± 30 and 138 ± 24 mL, $p = 0.0058$), as was the frequency of severe complications (2% vs. 8%, $p = 0.0484$). The minimal Pd/Pa index during an SPT was 0.74 ± 0.15 in the 119 vessels with spasms and 0.91 ± 0.07 in the 76 vessels without spasms. The Pd/Pa cut-off value for detecting a coronary spasm was 0.84, with a sensitivity of 79% and a specificity of 85%.

Conclusion: The use of a pressure wire during an SPT may help establish a firm diagnosis of vasospastic angina.

Keywords: Vasospastic angina; Coronary spasm; Acetylcholine; Spasm provocation test; Pressure wire; Intracoronary pressure

List of Abbreviations: ACh: Acetylcholine; CAG: Coronary Angiography; ECG: Electrocardiogram; LAD: Left Anterior Descending Coronary Artery; LCA: Left Coronary Artery; LVEF: Left Ventricular Ejection Fraction; NTG: Nitroglycerin; Pd/Pa index, Pressure Ratio of the Distal Lesion to the Proximal Lesion; RCA: Right Coronary Artery; ROC: Receiver Operating Characteristics; SPT: Spasm Provocation Test; VSA: Vasospastic Angina

Introduction

Vasospastic angina (VSA) is characterized by transient narrowing of epicardial coronary arteries and cause myocardial ischemia [1,2]. In these cases, a coronary spasm may not only cause angina at rest but also acute myocardial infarction or sudden ischemic cardiac arrest [1,2]. Therefore, diagnosing VSA is clinically important.

Although the diagnosis of VSA is usually made by the presence of characteristic chest pains and transient ST-segment changes on electrocardiography (ECG), many patients cannot be diagnosed by ECG changes alone and usually require a spasm provocation test (SPT) [3-5]. Despite being clinically important, this examination can be accompanied by severe complications such as shock, ventricular fibrillation, ventricular tachycardia, and bradyarrhythmia [6-9]. A positive SPT is judged by angiographic confirmation of coronary artery spasm combined with ischemic symptoms and ECG changes [3]. Nevertheless, we sometimes experience cases in which the diagnosis of VSA is difficult because coronary spasms occur without symptoms or ECG changes, because changes are only moderate on angiography, or because symptoms are atypical. Thus, there is a need for an alternative clinical measure of coronary spasm in some patients.

In cases of moderate organic coronary stenosis, intracoronary pressure assessment with a pressure wire has been widely used in clinical settings, and has not been associated with severe complications [10,11]. Therefore, we assessed the usefulness, safety, and procedure-related parameters associated with using a pressure wire during an SPT and compared the results with those for standard SPT performed without a pressure wire.

Methods

Study population

In this observations study, we enrolled 190 patients who underwent coronary angiography (CAG) with an SPT from 2012 to 2015 for the evaluation of chest symptoms that were felt mostly at rest. We excluded patients with moderate chronic kidney disease and worse (estimated glomerular filtration ratio <45 mL/min/1.73 m²) and significant coronary stenosis ($>75\%$) from the study. The protocol was approved by the Ethics Committee of our institution, and written informed consent was obtained from all patients.

From 2012 to mid-2013, we performed SPTs without a pressure wire, and from mid-2013 to 2015 we performed SPTs with a pressure wire. However, we sometimes performed SPT without a pressure wire in the latter period because of wire-related problems or time restrictions. For analysis, the patients were divided into 2 groups according to the use of a pressure wire: Group I included 103 patients who underwent SPTs with a pressure wire and Group II included 87 patients who underwent SPTs without a pressure wire.

Coronary angiography and SPT

All antianginal agents were discontinued at least 48 h before catheterization, except for sublingual nitroglycerin (NTG), which was only withheld from 1 h before catheterization. We performed SPTs after standard diagnostic CAG using the percutaneous brachial approach. A 5-French gage (Fr) transient pacing catheter (Bipolar Balloon Catheter, Bebrawn, Melsungen, Germany) was inserted into the right ventricle via the internal jugular vein or medial cubital vein and set at 50 beats/min. Arterial pressure, heart rate, and electrocardiography (ECG) readings were monitored continuously and recorded using a multichannel recorder (Polygraph 1600; Nihon Electric Corporation, Tokyo, Japan).

After initial CAG, 30 and 50 μ g doses of acetylcholine (ACh) were infused into the right coronary artery (RCA) for 20s, with 3 min intervals between consecutive doses. If coronary spasms were expected to occur easily, we used 10 μ g of ACh for the first dose; this requirement was determined according to the patients' symptoms, including the frequency of chest symptoms and the presence of associated symptoms (e.g., syncope or "cold sweating"). If coronary spasms were not induced by 50 μ g of ACh, a maximum dose of 80 μ g was infused into the RCA. CAG was performed immediately after coronary spasms were induced or the maximum ACh infusion finished.

When coronary spasms were provoked but relieved spontaneously, we moved to SPT of the left coronary artery (LCA) without injecting NTG into the RCA. In such cases, after completing SPT of the LCA, we repeated coronary angiograms following an NTG injection into the RCA. When coronary spasms were prolonged or severe enough to cause unstable hemodynamics, 200 μ g of NTG was administered by intracoronary injection to relieve the coronary spasms. Once the coronary spasms were relieved, final coronary angiograms of the RCA were performed. After intracoronary NTG injection into the RCA, we performed further SPT for the LCA. This was because we have experienced many patients with a positive spasm provocation for the LCA despite receiving intracoronary NTG injections in the RCA. If there was a small RCA on angiograms or if the catheter was not engaged into the ostium of the RCA, we omitted SPT of the RCA.

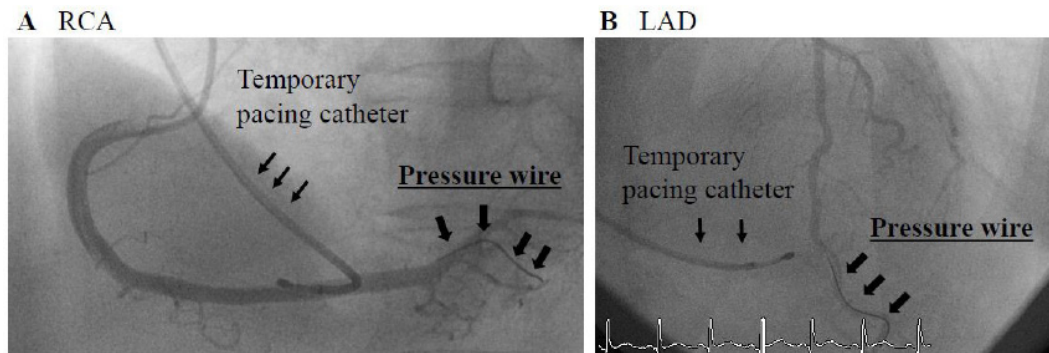
After the spasm provocation for the RCA, we infused 50 and 100 μ g doses of ACh into the LCA for 20 s, with 3 min intervals between doses. If coronary spasms were expected to occur easily, we used 20 μ g of ACh for the first dose in the LCA. If coronary spasms were not induced by 100 μ g of ACh, a maximum of 200 μ g was infused into the LCA, with or without 20, 40, or 60 μ g of ergometrine maleate. CAG was performed immediately after coronary spasms were induced or the maximum ACh infusion finished.

After intracoronary injections of 200 μ g NTG, we performed the final CAG for the LCA. The 80 μ g dose in the RCA and the 200 μ g dose in the LCA were defined as "higher" ACh doses.

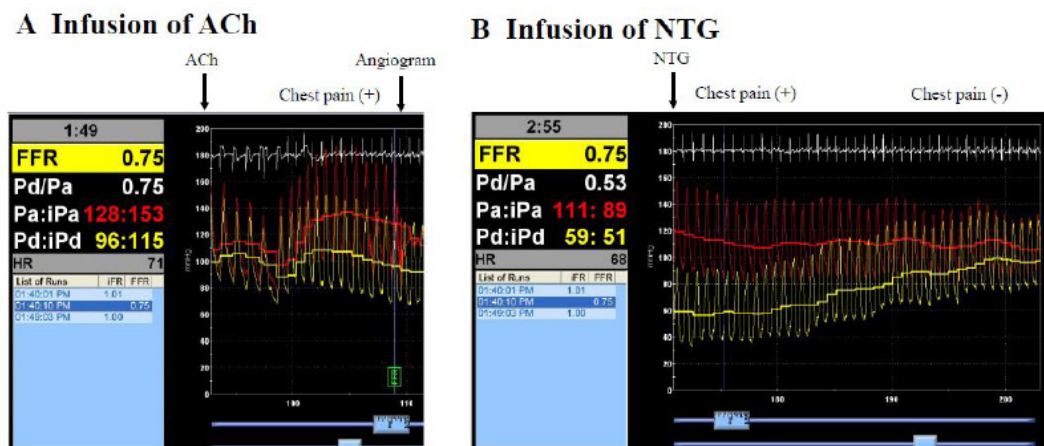
Each coronary angiogram was performed using an autoinjector (ZoneMaster, Sheen Man, Osaka) to inject 5 mL contrast medium at 2.5 mL/s. If a moderate atherosclerotic lesion was recognized on angiograms, we measured the fractional flow reserve (FFR) by intravenous infusion of adenosine triphosphate to assess the organic stenosis functionality. If unstable hemodynamics occurred (systolic blood pressure <90 mmHg) and/or ST-segment elevations continued on ECG during an SPT, we added another intracoronary injection of NTG and maximized the speed of intravenous volume injection. If unstable hemodynamics and ST-segment elevations continued despite these countermeasures, we infused small doses (2–10 μ g) of intracoronary or intravenous adrenaline [9].

SPT with a pressure wire

In Group I, a 0.014-inch pressure wire (PrimeWire Prestige Plus Guide Wire or Verrata Pressure Guide Wire; Volcano Therapeutics Inc., Rancho Cordova, CA, United States) was advanced through a 5-Fr catheter into the distal segments of the RCA and the left anterior descending coronary artery (LAD). Before this, we performed pressure calibration between the tips of the catheters and the pressure wire at the ostium of the coronary arteries (Figure 1). The ratios of distal intracoronary pressure, derived from the pressure wire, to the aortic pressure, derived from the catheter tips (Pd/Pa index), were monitored continuously. The minimal Pd/Pa index in response to each ACh dose was recorded, and when the Pd/Pa index reduced during the coronary spasm [12], the values from just before the angiograms were adopted (Figure 2).



The pressure wire is inserted into the distal portion of the right coronary artery (RCA, A) and distal portion of the left anterior descending coronary artery (LAD, B). The thick arrows indicate the tip of the pressure wire and the thin arrows indicate a temporary pacing catheter. Abbreviations: LAD: left anterior descending coronary artery; RCA: right coronary artery
Figure 1: Positions of a pressure wire during spasm provocation testing



During the SPTs, the Pd/Pa index decreased gradually during a coronary spasm (A). After an intracoronary injection of NTG, the Pd/Pa index returned to the baseline value. Abbreviations: ACh: acetylcholine; NTG: nitroglycerin; Pd/Pa index, pressure ratio of the distal lesion to the proximal lesion; SPT: spasm provocation test
Figure 2: A representative case

Quantitative CAG

The method for measuring coronary artery diameter has been described previously [13,14]. We selected spastic and atherosclerotic segments for quantitative analysis. In all cases, the luminal diameters were then measured by a single investigator who was blinded to the clinical data, using an end-diastolic frame in a computer-assisted coronary angiographic analysis system (CAAS II/QUANTCOR; Siemens, Berlin, Germany). Measurements were performed 3 times and the average value was used for analysis. Changes in coronary artery diameter in response to ACh and NTG infusions were expressed as percentage changes from baseline angiographic measurements. The intra- and inter-observer validity of this method are reported to be excellent [15]. Lesions with >20% stenosis were defined as atherosclerotic. Angiographic spastic segments were classified by the severity of vasoconstriction as ≥90%, subtotal occlusion, and total occlusion.

Definitions of VSA and related parameters

VSA was defined as a ≥90% narrowing of the epicardial coronary arteries on angiography during SPT, the presence of characteristic chest pain, and/or the presence of ST-segment deviation on ECG [3]. Focal spasm was defined as discrete transient vessel narrowing of ≥90% localized to major or branch coronary arteries. Diffuse spasm was defined as 90% transient, severe, diffuse vasoconstriction observed in more than 2 adjacent coronary segments of the epicardial coronary arteries and branches [16]. If focal

spasm occurred in one vessel and a diffuse spasm occurred in another vessel, only focal spasm was assessed for that patient. The presence of multi-vessel spasms was defined as coronary spasms that occurred in more than 2 major coronary branches. We did not assess for the presence of multi-vessel spasms when an SPT was not performed for the RCA because of a small RCA, because we could not engage the catheter into the coronary ostium, or because intracoronary NTG was infused to relieve spasm and the subsequent SPT was negative.

Angiogram-related parameters and SPT-related complications

The angiogram-related parameters measured in each patient were the total dose of a contrast medium (mL) and the total fluoroscopic time (min). The frequency of FFR measurements was also checked. The frequencies of the following SPT-related complications were measured: paroxysmal atrial fibrillation, prolonged coronary spasm, and prolonged hemodynamic instability, especially requiring the use of adrenaline.

Assessment of biochemical markers and coronary risk factors

Fasting blood samples were obtained on the day of CAG. Patients were questioned about their smoking status and classified as a current smoker, past smoker (who had stopped smoking for at least 1 month), or nonsmoker. Family history of coronary artery disease was recorded. Blood pressure was measured and hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, and/or treatment with antihypertensive drugs. Blood chemistry parameters, including total cholesterol, triglycerides, high-density lipoprotein cholesterol, fasting blood sugar, insulin, hemoglobin A1C, and creatinine levels were measured. Low-density lipoprotein cholesterol levels were calculated using the Friedewald equation [17]. Hyperlipidemia was defined as a low-density lipoprotein cholesterol level ≥ 120 mg/dL and/or treatment with antihyperlipidemic medication. Diabetes mellitus was defined as a fasting blood sugar level ≥ 126 mg/dL, a hemoglobin A1C $\geq 6.5\%$, and/or treatment with antidiabetic medication. Finally, the left ventricular ejection fraction (LVEF) was checked.

Statistical analysis

All data are expressed as mean \pm SD. Baseline characteristics of the 2 groups were compared by Student's unpaired *t*-test or χ^2 analysis, as appropriate. The Pd/Pa cut-off value for the presence of a coronary spasm was measured by receiver operating characteristics (ROC) analysis. Logistic regression analysis was used to clarify the factors associated with a positive SPT. A *P*-value < 0.05 was considered statistically significant.

Results

Patient characteristics, angiogram-related parameters, and complications

There were 103 patients in Group I and 87 patients in Group II (Table 1), with no difference in characteristics between the 2 groups. However, there were some differences in the angiographic findings and complications (Table 2).

| | Group I | Group II | p-value |
|---------------------------|----------------|----------------|---------|
| Number | 103 | 87 | |
| Age (yrs.) | 67 \pm 11 | 68 \pm 11 | 0.4273 |
| Male / Female | 52/51 | 47/40 | 0.6267 |
| Body mass index | 24.2 \pm 4.6 | 24.7 \pm 4.3 | 0.5173 |
| Coronary risk factors (%) | | | |
| Smoking (%) | 20 (19) | 17 (20) | 0.983 |
| Current / Past | 20 / 25 | 17 / 25 | 0.6561 |
| Hypertension (%) | 74 (72) | 62 (72) | 0.9296 |
| Lipid disorder (%) | 65 (63) | 48 (55) | 0.2627 |
| Diabetes mellitus (%) | 22 (21) | 19 (22) | 0.903 |
| Family history of CAD (%) | 25 (24) | 16 (18) | 0.3262 |
| Taking statins (%) | 37 (36) | 31 (36) | 0.9668 |
| LVEF on UCG (%) | 67 \pm 9 | 66 \pm 10 | 0.4877 |

Data were expressed as the mean \pm standard deviation or n (%)

*Significant at $p < 0.05$

List of abbreviations: CAD, coronary artery disease; LVEF left ventricular ejection fraction; UCG, echocardiography

Table 1: Patient's characteristics

| | Group I | Group II | p-value |
|---|------------|------------|-----------|
| Provocations | | | |
| 1) Use of higher doses of ACh (%) | 15 (15) | 3 (3) | 0.0091* |
| 2) Use of additional EM (%) | 7 (7) | 5 (6) | 0.7671 |
| 1) + 2) | 21 (20) | 8 (9) | 0.0326* |
| Positive SPT (%) | 78 (76) | 51 (59) | 0.0119* |
| Diffuse / focal | 57/21 | 41/10 | 0.3417 |
| Multivessel spasm (%) | 47/67 (70) | 27/41 (66) | 0.6469 |
| Atherosclerotic lesions (%) | 63 (61) | 52 (60) | 0.8449 |
| Frequency of measuring FFR (%) | 36 (35) | 9 (10) | < 0.0001* |
| Total fluoroscopic time (min) | 13.0±5.2 | 11.5±5.0 | 0.0329* |
| Total volume of contrast medium (ml) | 127±30 | 138±24 | 0.0058* |
| Complications (%) | 14 (14) | 11 (13) | 0.8472 |
| 1) Ventricular fibrillation (%) | 0 (0) | 1 (1) | 0.2753 |
| 2) Hemodynamics instability requiring adren | 2 (2) | 6 (7) | 0.0902 |
| 1) + 2) | 2 (2) | 7 (8) | 0.0484* |
| 3) Hemodynamics instability (%) | 3 (3) | 1 (1) | 0.399 |
| 4) Paroxysmal atrial fibrillation | 10 (10) | 4 (5) | 0.1791 |

Data were expressed as n (%) or the mean ± standard deviation

*Significant at $p < 0.05$

List of abbreviations: ACh, acetylcholine; EM, ergometrine maleate; SPT, spasm provocation test; FFR, fractional flow reserve

Table 2: Angiographic-related parameters and complications

Regarding provocative drug use, higher ACh doses were used significantly more in Group I ($p = 0.0091$). The frequency of positive SPTs was significantly higher in Group I (76% vs. 59%, $p = 0.0119$). Although the frequency of atherosclerotic lesions was also similar, the FFR was measured more frequently in Group I ($p < 0.0001$), which led to a longer total fluoroscopic time in Group I ($p = 0.00329$). Among the patients in whom FFR was not measured, the total fluoroscopic time also tended to be longer in Group I ($n = 67$, 12.7 ± 4.4 min) compared with Group II ($n = 78$, 11.3 ± 5.1 min) ($p = 0.0935$). By contrast, the volume of contrast medium was smaller in Group I ($p = 0.0058$).

Regarding SPT-related complications, the frequency of hemodynamic instability requiring adrenaline tended to be lower in Group I ($p = 0.0902$). In addition, the frequency of severe complications, including ventricular fibrillation and hemodynamic instability requiring adrenaline, were lower in Group I ($p = 0.0484$).

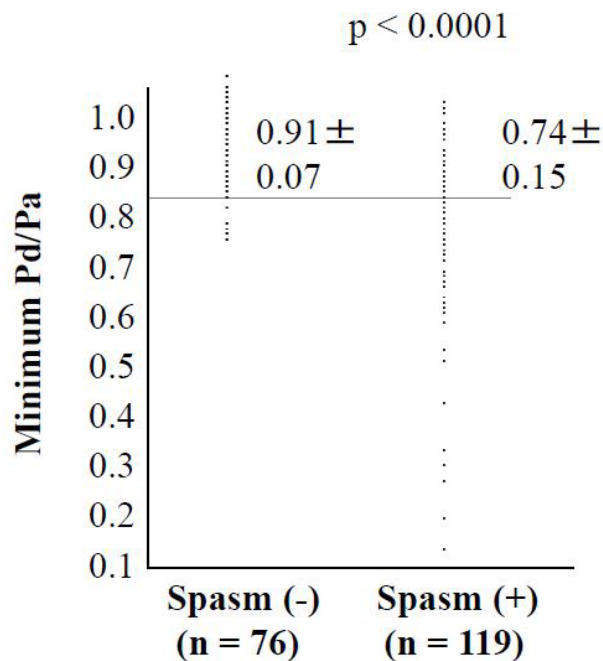
SPT using a pressure wire

Insertion of the pressure wire itself did not cause vascular trauma or wire-induced coronary spasm. SPT was only attempted in 96 RCA vessels because RCAs were small in 5 patients and we could not engage the catheter in the RCA ostium in 2 patients. The pressure wires were successfully inserted into the distal RCAs in 94 of these 96 vessels (98%). SPT was attempted in 103 LCA vessels and was successfully inserted into the distal LAD in 101 (98%). Pd/Pa index monitoring was done for 101 LAD vessels because the pressure wire could not be placed within the LAD in 2 patients.

Of the 195 vessels in which a pressure wire could be inserted distally, the SPT was positive in 119 (61%) and negative in 76 (39%). Of the positive cases, 54 were in RCA vessels (57%) and 65 were in LAD vessels (64%). Coronary spasm was induced at low ACh doses in 43 vessels (36%), at high ACh doses in 72 vessels (61%), and at higher ACh doses (or with additional ergometrine maleate) in 4 vessels (3%). Angiographic narrowing of spastic segments was $\geq 90\%$ in 88 lesions (74%), subtotal occlusion in 23 lesions (19%), and total occlusion in 8 segments (7%).

Intracoronary pressure cut-off value for the detection of a coronary spasm

The minimum Pd/Pa indexes during SPT were 0.74 ± 0.15 in the 119 spastic vessels and 0.91 ± 0.07 in the 76 non-spastic vessels (Figure 3, $p < 0.0001$). The ROC analysis showed that the optimal cut-off value for the presence of a coronary spasm was 0.84, and that this had a sensitivity and specificity of 78% and 84%, respectively (area under the ROC curve, 0.878). The Pd/Pa index was 0.77 ± 0.12 in spastic vessels with $\geq 90\%$ narrowing, 0.70 ± 0.15 in the spastic vessels with subtotal occlusion, and 0.54 ± 0.25 in the spastic vessels with total occlusion ($p < 0.0001$). More RCA vessels ($n = 18$) than LAD vessels ($n = 8$) had a Pd/Pa index > 0.84 , whereas all non-spastic vessels with a Pd/Pa index < 0.84 were recognized in LAD vessels ($n = 11$).



The minimum Pd/Pa during an SPT was 0.74 ± 0.15 in the spastic vessels ($n = 119$) and 0.91 ± 0.07 in the non-spastic vessels ($n = 76$) ($p < 0.0001$). Based on the ROC analysis, the cut-off value for the presence of a coronary spasm was 0.84, with a sensitivity of 0.78 and a specificity of 0.84. Abbreviations: Pd/Pa index, pressure ratio of the distal lesion to the proximal lesion; ROC: receiver operating characteristics; SPT: spasm provocation test

Figure 3: Minimal Pd/Pa index during the SPT in spastic and non-spastic vessels

Discussion

We showed that using a pressure wire during SPT was associated with reductions in the total dose of contrast medium and the frequency of severe complications. Furthermore, we showed that the pressure wire during SPT provided additional information that could be useful when diagnosing VSA.

An SPT is an important clinical diagnostic tool for VSA, and remains so despite reports of severe complications [3,6-9]. These complications may be caused by prolonged hemodynamic instability, severe and prolonged myocardial ischemia, or NTG overdose. Accompanied chest symptoms and ST-segment changes during an SPT are generally reliable indices of myocardial ischemia, but are not always accompanied by a positive SPT. Therefore, to improve the safety and convenience of SPT, indices other than chest symptoms and ECG changes need to be developed to facilitate the prompt detection of myocardial ischemia and recovery.

The usefulness of pressure wires has been established for the functional assessment of organic coronary stenosis, and they are used without severe complications in many clinical settings [10,11]. Consistent with this, pressure wire use did not cause any complications, including coronary spasm, in this study. Naturally, a pressure wire should be inserted into the coronary artery more carefully and slowly during an SPT to avoid guidewire-induced coronary spasm. In this study, using a pressure wire was associated with reductions in both the total contrast medium dose and the frequency of severe complications.

When using a pressure wire during an SPT, it is important to monitor the Pd/Pa index continuously. If chest symptoms, ECG changes, and a reduced Pd/Pa index were absent, we moved to the next provocation with an increased ACh dose, without performing further angiograms. If the Pd/Pa index decreased gradually during the SPT, the occurrence of coronary spasm was anticipated. Furthermore, if a coronary spasm occurred with the reduction in the Pd/Pa index, an intracoronary infusion of NTG was given to relieve the spasm and promptly elevate the Pd/Pa index to the baseline level. If the Pd/Pa index increased after an NTG injection, we waited without an additional angiogram or NTG injection. An SPT using a pressure wire can, therefore, promptly detect myocardial ischemia and its recovery. Indeed, given the process of myocardial ischemia, a change in the Pd/Pa index may be the earliest marker of myocardial ischemia, preceding even ECG changes. This, in turn, may have contributed to the reductions seen in the total contrast medium dose and the frequency of severe complications.

In the present study, the frequency of SPT positivity was higher in Group I. A positive SPT was defined as the presence of angiographic vasospasm accompanied by ischemic findings [3], and was not judged based on the Pd/Pa index. The insertion of a pressure wire may allow the catheter to engage into the ostium of the coronary artery, especially in the RCA, thereby increasing the ACh dose delivered into that artery. But, this may not be the main cause for the higher frequency of positive SPTs. In our study, the period of pressure wire use (Group I) followed the period without pressure wire use (Group II). Although the patient characteristics were not different between the groups, in the latter period we may have judged patients with a lower likelihood of VSA as inappropriate for SPT and patients with a higher likelihood of VSA as suitable for SPT.

Recently, the usefulness of higher ACh doses in SPTs has been reported [5,18,19]. Since these reports, SPTs using higher ACh doses have been done more frequently, even at our institution. It may be that the higher ACh doses contributed to the differences in the frequency of positive SPT results. Despite adopting higher ACh doses in Group I, reductions in the total contrast medium dose and the frequency of severe complications may be important advantages of SPT with a pressure wire. In addition, the total fluoroscopic time was longer in Group I because of both the time needed to insert the pressure wire and the higher frequency of FFR measurement.

The ROC analysis showed that the Pd/Pa cut-off value for detecting the occurrence of a coronary spasm during an SPT was 0.84, which is similar to the FFR of 0.80 reported for detecting myocardial ischemia [11]. This may therefore be an acceptable value. However, the Pd/Pa index should be interpreted carefully because the RCA vessel had a higher index (>0.84) more frequently than the LAD (RCA: 18, LAD: 8), and because coronary spasm occurred at the distal segments of all RCA vessels. Thus, SPT using a pressure wire may be weak in the spasm, which occurred at the distal RCA. When the pressure wire was inserted into one branch of the RCA, but coronary spasm occurred at another branch, the Pd/Pa index was not reduced. In addition, 11 non-spastic vessels with a lower Pd/Pa index were all in the LAD. In general, the baseline Pd/Pa index in the LAD vessel was lower than that in the RCA because of its anatomical position. Thus, the Pd/Pa index in the LAD may be reduced by ACh infusions in the absence of significant coronary spasms.

Although the presence of silent VSA is not described in relevant guidance, we found that some vessels judged as non-spastic based on the absence of ischemic symptoms and ECG changes actually showed angiographic evidence of vasoconstriction. These findings suggest the possibility of silent VSA. However, we did not check the lactate concentration in the coronary sinus during SPT [3,20]. If a relationship between the Pd/Pa index and myocardial lactate concentration can be clarified, it may be possible to confirm the presence of silent VSA in the future.

An SPT using a pressure wire undoubtedly has higher costs and requires a longer fluoroscopic time than the usual procedure. In addition, the pressure wire cannot detect coronary spasm in coronary branches in which the wire is not inserted, such as the distal branches of the RCA or the left circumflex coronary artery. However, the procedure can promptly detect coronary spasm and its recovery, and may be associated with fewer severe complications. Given the costs, though, it may be best to reserve the procedure for use in the following situations: 1) when hemodynamic instability may be precipitated by coronary spasm, such as when patients have hypertrophic cardiomyopathy or left ventricular dysfunction; 2) when patients have chronic kidney disease; and 3) when cardiologists seek to clarify the disease status through a second SPT [21-24]. In addition to showing that the Pd/Pa index can be measured using ACh as a provocation drug, we have data showing a comparable response to ergometrine maleate (not shown). The Pd/Pa index could, therefore, be relevant when used with different provocation drugs.

Limitations

There were several limitations to the present study. First, this study was observational and not randomized, and the SPT was not performed at the same time in the 2 groups. SPT using a pressure wire was associated with higher ACh doses at that time, and it is possible that this combination caused the better SPT results in the second period. However, other clinical factors, such as patient characteristics and the SPT protocol (excluding the differences in pressure wire use and the higher ACh doses), were similar between the periods, increasing the likelihood our comparison is meaningful.

Second, our SPT deviated in terms of the testing order (i.e., RCA first, LCA second) and the ACh doses (30 and 50 μg for the RCA and 50 and 100 μg for the LCA). At the 30 μg dose in the RCA and the 50 μg in the LCA, we skipped the angiograms if patients had no chest symptoms or ST-segments changes on ECG. This method has been used at our institution for some time, and was familiar to the cardiac catheterization staff. The maximum ACh doses in our method were no different to those used in standard methods, so the Pd/Pa index may not be different during coronary spasm when comparing the methods. However, the different method of SPT may cause differences in the frequency of multi-vessel spasm, total fluoroscopic time, and total contrast medium dose.

There are other important limitations. For example, FFR was measured more often in patients who underwent SPT with a pressure wire. However, we conclude that this resulted from using a pressure wire, with the frequency of atherosclerotic lesions being comparable between the groups. Another limitation is that we did not investigate the association between values obtained from pressure wires and the lactate concentration in the coronary sinus, which is a reliable marker of myocardial ischemia. We also showed that the Pd/Pa index decreased promptly during a coronary spasm and that the minimal Pd/Pa index could not be easily determined in some patients. Indeed, the Pd/Pa index instantly decreased to 0.2-0.3 in some patients, and had we waited longer, the minimal Pd/Pa index could have been even lower. The Pd/Pa index was measured just before the angiograms to obtain the minimal value. Finally, we adopted the 5-Fr coronary catheters in this study, and it is possible that using the recommended 6-Fr catheters may produce slightly different Pd/Pa results.

Conclusion

We conclude that using a pressure wire during an SPT may reduce the total dose of contrast medium and the frequency of severe complications by improving the detection of myocardial ischemia and its recovery. This procedure can also provide valuable data for use when diagnosing VSA, making it a useful adjunct to SPT in specific cases.

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