Usefulness and Safety of Intracoronary Administration of Nicorandil for Evaluating Fractional Flow Reserve in Japanese Patients

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ABSTRACT

Background: Fractional flow reserve (FFR) is useful for determining the functional significance of epicardial coronary stenosis and may facilitate clinical decision making in patients with an equivocal coronary stenosis for coronary revascularization. Therefore, determining an efficient and safe method to achieve hyperemia is important for evaluating FFR. We investigated the usefulness and safety of intracoronary bolus administration of nicorandil compared with intravenous administration of adenosine triphosphate (ATP) for evaluating FFR in Japanese patients with suspected angina pectoris.

Methods: First, we evaluated the most appropriate hyperemic dose of nicorandil in the first 11 consecutive patients out of 101 Japanese patients. Next, we compared the FFR induced by ATP and by 2 mg of nicorandil in 130 vessels of the 101 patients.

Results: FFR was measured according to nicorandil dose in 14 vessels among 11 of the 101 patients; 92.9% of the patients achieved hyperemia with 2 mg of nicorandil. The FFR values obtained with ATP were significantly correlated with those obtained with 2 mg of nicorandil (regression coefficient = 0.974, $R^2 = 0.933$, $P < 0.001$). There were no hypotension cases needing a vasopressor after ATP or nicorandil administration, and there was 1 case of transient second-degree atrioventricular block after ATP administration. The time taken to achieve hyperemia after nicorandil administration (18.9 ± 9.6 seconds) was significantly shorter than that after ATP administration (197.9 ± 23.8 seconds) ($P < 0.001$).

Conclusions: Intracoronary nicorandil administration is more useful than and as safe as intravenous administration of ATP for evaluating FFR in Japanese patients.

Introduction

Patients with cardiac abnormalities on single photon-emission computed tomography (SPECT) have an intermediate-to-high risk for future cardiac events, depending on the degree of the abnormality.¹ Compared with medical therapy, SPECT-based revascularization had a greater survival benefit in patients with moderate-to-large amounts of inducible ischemia.^{2,3} SPECT has limited ability to accurately locate ischemia-producing lesions in patients with multivessel coronary artery diseases.⁴

The physiologic effects of the majority of coronary obstructions cannot be determined accurately using conventional angiographic approaches.⁵ Neither visual assessment of an angiogram by experienced interventional cardiologists nor quantitative coronary angiography (QCA) can accurately predict the significance of a moderate narrowing.⁶

Fractional flow reserve (FFR) is a useful index for determining the functional severity of stenosis and the need for coronary revascularization.⁷ A cutoff value of 0.75 FFR has been recommended to distinguish patients with positive SPECT imaging from those with negative SPECT imaging after myocardial infarction.^{8,9} FFR-guided percutaneous coronary intervention (PCI) with a cutoff value of 0.80 was reported to decrease the need for urgent revascularization in patients with suspected angina pectoris¹⁰ and reduces the rate of death, nonfatal myocardial infarction, and repeat revascularization.^{11,12} Although a standard method to achieve maximal hyperemia is infusion of adenosine through a central vein,^{10,11,13} continuous intravenous infusion of adenosine via the forearm vein is reported to be a convenient and effective way to induce steady-state hyperemia in the same way as through a central vein.¹⁴ However, it takes a long time to achieve hyperemia using both methods; consequently, it also takes a longer time to complete the examination by cardiac catheterization. Adenosine titer is about 1.1 times compared to adenosine triphosphate (ATP) via the forearm vein.¹⁵ In Japan, ATP is used to evaluate FFR because it is less expensive compared to adenosine.

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Additional Supporting Information may be found in the online version of this article.

Nicorandil is a vasodilator medication that has the dual properties of a nitrate and an ATP-sensitive K⁺-channel agonist. At low plasma concentration, nicorandil dilates large coronary arteries, and it promotes reduction of coronary vascular resistance at high plasma concentrations, an action associated with increased ATP-sensitive K⁺-channel opening.¹⁶ Nicorandil reduces major coronary events in patients with stable angina.¹⁷ Combined intravenous and intracoronary administration of nicorandil reduces reperfusion injury during PCI.¹⁸ Administration of intracoronary nicorandil reduces the occurrence of no-reflow, slow-reflow, and reperfusion arrhythmia; improves the myocardial perfusion grade (Thrombolysis in Myocardial Infarction flow grade) during PCI; and improves clinical outcomes in patients with acute myocardial infarction.¹⁹

We investigated the usefulness and safety of intracoronary bolus administration of nicorandil compared with intravenous administration of ATP for evaluating FFR in Japanese patients with suspected angina pectoris.

Methods

The study design was approved by the ethical review board of our center.

Study Patients

From April 2012 to August 2013, 101 Japanese patients with suspected angina who visited our hospital were enrolled in our study. We excluded patients with cancer and advanced renal, liver, or other serious disorders.

Coronary Angiography and FFR Measurement

After written informed consent was obtained from all the patients, coronary angiography was performed. Coronary angiograms were recorded after intracoronary administration of 2 to 5 mg of isosorbide dinitrate with a cineangiography system (INFX-800V Toshiba, Tokyo, Japan; AXIOM Artis dBC Siemens, Munich, Germany). Coronary artery disease was defined as >50% stenosis of the coronary artery. If angiography showed moderate coronary stenosis, we estimated FFR using a pressure wire (PrimeWire Prestige PLUS; Volcano Corp., San Diego, CA or PressureWire Aeris G8; St. Jude Medical Japan Co., Ltd., Tokyo, Japan). FFR was calculated as the mean distal coronary pressure (Pd) divided by the mean aortic pressure (Pa) during maximal hyperemia by intravenous or bolus administration of ATP or nicorandil, respectively (see Supporting Figure 1 in the online version of this article). In brief, FFR was measured with a coronary pressure guidewire at maximal hyperemia that was induced by ATP administered at 150 µg/kg/min for at least 3 minutes through a large forearm vein using a rate-controlled infusion pump, until the heart rate began increasing and the Pd/Pa ratio remained steady. FFR was generally calculated by the method based on SPECT,²⁰ using adenosine administered at 140 µg/kg/min, as reported in landmark trials.^{10,11} Because there was neither a further decrease in Pd/Pa ratio nor a further increase in coronary flow velocities at doses over 140 µg/kg/min of adenosine,²¹ and continuous intravenous infusion of adenosine via the forearm vein has been reported as a convenient and effective way to induce

Figure 1. Dose-up study. The dose of nicorandil was elevated in the following sequence: 0 mg, 0.5 mg, 1.0 mg, 2.0 mg, and 4.0 mg. This procedure was performed within a few minutes.

steady-state hyperemia in the same way through the central vein,¹⁴ we used ATP at 150 µg/kg/min via the forearm vein. After the initial Pd/Pa ratio recovered without ATP (half-life of ATP <10 seconds), the Pd/Pa ratio induced by intracoronary bolus administration of nicorandil was measured. At first, we evaluated the most appropriate hyperemic dose of nicorandil in 14 vessels among the first 11 consecutive patients of the 101 total patients (dose-up study, Figure 1). Each Pd/Pa ratio was recorded at 0 mg, 0.5 mg, 1.0 mg (plus 0.5 mg to preinjected 0.5 mg), 2.0 mg (plus 1.0 mg to preinjected 1.0 mg), and 4.0 mg (plus 2.0 mg to preinjected 2.0 mg) of nicorandil. This procedure was performed within a few minutes, because the half-life of nicorandil is 6 minutes. Next, we compared the FFR induced by ATP and by 2 mg of nicorandil in 130 vessels of the 101 Japanese patients.

Statistical Analysis

Data are expressed as mean ± standard deviation for continuous variables and as numbers (%) for categorical variables. Continuous variables were compared using the 2-tailed Student *t* test. Correlation of continuous variables was assessed using simple linear regression analysis. These data were statistically analyzed by SPSS II for Windows (SPSS Japan Inc., Tokyo, Japan). A value of *P* < 0.05 was considered statistically significant.

Results

Patient and Catheter Characteristics

Patient characteristics are shown in Table 1. Multivessel stenosis was defined angiographically (32.7%) (see Supporting Table 1 in the online version of this article for catheter characteristics). A total of 130 vessels were investigated: 84 left anterior descending arteries (LADs), 27 left circumflex arteries (LCXs), and 19 right coronary arteries (RCAs).

Appropriate Dose of Nicorandil for FFR Measurement

FFR was measured according to nicorandil dose in 14 vessels of the first 11 consecutive patients of the 101 total patients (Figure 2). There was no further decrease in Pd/Pa ratio in nicorandil doses over 2 mg.

Table 1. Patient Characteristics (N = 101)

Age, y	70.3 ± 10.0
Male	72 (71.3)
BMI, kg/m ²	23.5 ± 3.4
Diabetes mellitus	46 (45.5)
Hypertension	77 (76.2)
Dyslipidemia	69 (68.3)
Smoking	26 (25.7)
Old myocardial infarction	15 (14.9)
Multivessel stenosis	33 (32.7)
Antiplatelets	53 (52.5)
Lipid-lowering drugs	49 (48.5)
Statin	48 (47.5)
Antihypertensive drugs	75 (74.3)
Calcium channel blocker	48 (47.5)
Antidiabetic medication	31 (30.7)
Nicorandil	16 (15.8)
Systolic blood pressure, mm Hg	132 ± 17
Diastolic blood pressure, mm Hg	71 ± 13
Total cholesterol, mmol/L	4.61 ± 1.14
LDL-C, mmol/L	2.69 ± 0.91
HDL-C, mmol/L	1.22 ± 0.34
Triglyceride, mmol/L	1.55 ± 0.88
Glycated hemoglobin, proportion of total hemoglobin	0.06 ± 0.01
eGFR, mL/min/1.73 m ²	66.5 ± 16.0

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Data are expressed as n (%) for categorical variables and mean ± standard deviation for continuous variables. BMI was calculated as body weight/body height × body height. Diabetes mellitus was defined as having a glycated hemoglobin level of 6.2% (as defined by the National Glycohemoglobin Standardization Program) or taking antidiabetic medication. Hypertension was defined as >140 mm Hg of systolic blood pressure or/and 90 mm Hg of diastolic blood pressure or taking antihypertensive medication. Dyslipidemia was defined as >3.63 mmol/L (>140 mg/dL) of LDL-C, and/or >1.69 mmol/L (>150 mg/dL) of triglycerides, and/or <1.04 mmol/L (40 mg/dL) of HDL-C, or taking a lipid-lowering drug. A positive smoking status was defined as being a current smoker or having quit smoking since <1 year at the time of evaluation. eGFR was calculated as $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ for men and $\times 0.739$ for women using the estimate equation by the Japanese Society of Nephrology. Serum lipids, glycated hemoglobin, and serum creatinine were measured by standard laboratory methods.

Figure 2. Fractional flow reserve (FFR) values according to nicorandil dose. FFR values were measured according to increasing nicorandil dose in 14 vessels of the first 11 consecutive patients of the 101 total patients. Abbreviations: Pd, distal coronary pressure; Pa, mean aortic pressure.

Correlations Between FFR Values and the Administration of ATP or Nicorandil in Each Vessel

FFR values using nicorandil were strongly related with those using ATP in all vessels (regression coefficient [β] = 0.974, $R^2 = 0.933$, $P < 0.001$) (Figure 3). The accordance between ATP-FFR and nicorandil-FFR was good, with a mean difference of -0.0003 and a standard deviation of 0.032 (Figure 3). This relationship of FFR values obtained with ATP and nicorandil was found in all vessels (LADs, LCXs, and RCAs) (Figure 3).

Safety

Additionally, we checked side effects and the time to evaluate FFR values by administering ATP or nicorandil. There were no hypotension cases requiring vasopressor with either ATP or nicorandil administration, and there was 1 transient second-degree atrioventricular block after ATP administration; however, this event was transient and did not require injection of atropine or pacing, and it was not statistically significant. The time taken to achieve hyperemia after ATP administration was significantly longer than that after nicorandil administration (197.9 ± 23.8 seconds vs 18.9 ± 9.6 seconds, respectively; $P < 0.001$) (Table 2).

Discussion

In this study, we compared whether intracoronary bolus administration of nicorandil or intravenous administration of ATP is better for assessing FFR in Japanese patients with suspected angina pectoris.

The COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial substudy suggested that ischemia reduction to >5% should be targeted, as determined using SPECT with or without PCI.³ However, SPECT cannot accurately locate ischemia-producing lesions in patients with multivessel coronary artery diseases.⁴

The physiologic effects of the majority of coronary obstructions cannot be determined accurately by conventional angiographic approaches.⁵ Neither visual assessment of an angiogram by experienced interventional cardiologists nor QCA can accurately predict the significance of

Figure 3. Correlation between adenosine triphosphate (ATP)-fractional flow reserve (FFR) and nicorandil (NIC)-FFR (total vessels, left anterior descending artery [LAD], circumflex artery [CX], and right coronary artery [RCA]). Left panels show correlation, and the right panels show Bland-Altman plot of ATP-FFR and NIC-FFR.

Table 2. Time Taken to Achieve Hyperemia and the Observed Side Effects

	ATP	Nicorandil	P Value
Time to reach hyperemia (second)	197.9 ± 23.8	18.9 ± 9.6	<0.001
Side effect, n (%)			
Hypotension requiring any vasopressor	0	0	—
Second-degree AV block, n (%)	1 (0.8)	0	0.319

Abbreviations: ATP, adenosine triphosphate disodium hydrate; AV, atrioventricular.

moderate narrowing.⁶ There were visual-functional mismatches between angiography and FFR.^{22,23}

FFR has been established as a useful index for determining the functional severity of a stenotic lesion, the need

for coronary revascularization,⁷ and for reducing the event rate.^{10–13,24}

The results of a recent study on the safety and efficacy of intracoronary nicorandil as a hyperemic agent to evaluate FFR were in some ways consistent with our results.²⁵ In addition to this consistency between results, our study revealed more about the hyperemic dose of nicorandil for FFR. Although the time taken for evaluating FFR after ATP administration in our study was longer than that found in that study and other reports,^{21,26} this discrepancy may have been caused by the difference of judgment of lowest FFR and the differences in the administration method/route of ATP. For example, in our study, the femoral vein was not used to administer ATP, and we administered 5 mg/mL of ATP without other fluids, whereas other studies may have included other fluids when administering ATP; thus, the drip speed in these studies may differ.

Our results showed that an intracoronary bolus of 2 mg of nicorandil is sufficient to achieve hyperemia, and that it is better than intravenous administration of ATP because the use of nicorandil reduces the handling time for FFR. Moreover, intracoronary bolus administration of 2 mg of nicorandil was as safe as the intravenous administration of ATP.

Conclusion

Intracoronary administration of nicorandil to evaluate FFR is more useful than and as safe as intravenous administration of ATP.

Limitations

Our study had some limitations. The present study was limited by its single-center study design, not calculating statistical power, and was not a blinded study. There is selection bias regarding selecting vessels with moderate stenosis to evaluate FFR. This dose-up study may have underestimated FFR values because some of the nicorandil administered may have been catabolized during hyperemic dose evaluation.

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