Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Impact of additional intracoronary nicorandil administration during fractional flow reserve measurement with intravenous adenosine 5′-triphosphate infusion

Hironori Takami (MD), Shinjo Sonoda (MD, PhD, FJCC)*, Yoshitaka Muraoka (MD, PhD), Yoshinori Sanuki (MD), Kuninobu Kashiyama (MD, PhD), Shota Fukuda (MD, PhD), Yasushi Oginosawa (MD, PhD), Yuki Tsuda (MD, PhD), Masaru Araki (MD, PhD), Yutaka Otsuji (MD, PhD, FJCC)

Second Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan

ARTICLE INFO

Article history:
Received 31 December 2015
Received in revised form 22 January 2016
Accepted 28 January 2016
Available online xxx

Keywords:
Fractional flow reserve
Adenosine 5′-triphosphate
Nicorandil
Cyclic change
Caffeine

ABSTRACT

Background: Fractional flow reserve (FFR) is a useful index for determining the functional severity of epicardial coronary artery stenosis as an invasive physiological method. Although intravenous adenosine 5′-triphosphate (ATP) is generally used as a hyperemic agent for FFR measurement in Japan, there are some concerns about the variability of FFR measurement (short half-life, effect of caffeine, cyclic change). It is difficult to confirm sufficient maximum hyperemia after ATP infusion. Recent studies reported that nicorandil (NIC) could be an alternative to ATP as a hyperemic agent.

Methods: Patients who underwent FFR assessments of angiographically intermediate lesions were included. All patients were asked to refrain from caffeine-containing products more than 12 hours before FFR measurements. All patients first received intravenous (IV) ATP infusion (180 μg/kg/min) for 3 min to measure FFR (ATP-FFR). After additional intracoronary (IC) NIC administration (2 mg/30 s) during ATP infusion, FFR was measured again (NIC-FFR). To check cyclic change in FFR, we measured minimum and maximum FFR values during both ATP and NIC hyperemic phase.

Results: In this study, 94 patients with 94 lesions were enrolled. Mean FFR value was 0.81 ± 0.10 in ATP-FFR infusion and 0.80 ± 0.09 in NIC-FFR, respectively. ATP-FFR and NIC-FFR had a strong correlation on the whole ($r = 0.92, p < 0.001$). In 18 patients (19%), FFR values were significantly lower in NIC-FFR than in ATP-FFR. In one-third of those patients (6%), it was possible to change therapeutic strategy from deferral range (>0.80) to interventional range (≦0.80) after NIC-FFR measurements. Cyclic change in FFR was smaller in NIC-FFR than in ATP-FFR (0.03 ± 0.02 vs. 0.06 ± 0.05, $p < 0.0001$).

Conclusion: Additional IC NIC might be useful to confirm sufficient maximum hyperemia after IV ATP infusion in daily clinical practice. Furthermore, IC NIC could reduce cyclic change in FFR; thus, physicians might find it easier to determine FFR value during the procedure.

Introduction

Fractional flow reserve (FFR) is a useful index for determining the functional severity of epicardial coronary artery stenosis as an invasive physiological method [1]. FFR-guided revascularization strategy has been reported to be better than angiography-guided strategy in the management of coronary artery disease. In the FAME study, FFR-guided percutaneous coronary intervention (PCI) only if FFR was ≦0.80 decreased myocardial ischemia and improved patient outcomes [2–6]. The DEFER study demonstrated that deferred PCI strategy was safe if FFR was ≧0.75 [7]. Recent reports suggested that incidence of target vessel failure after deferral of PCI was significantly higher in patients with FFR 0.75–0.80 than in patients with FFR >0.80 [8,9]. In this situation, we sometimes experienced cases with discrepancy between angiographic findings, FFR assessments, and coronary plaque characteristics [10,11]. Thus, we hope to confirm the achievement of sufficient maximum hyperemia during FFR measurements.

* Corresponding author at: Second Department of Internal Medicine, University of Occupational and Environmental Health, 1-1, Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan. Tel.: +81 93 691 7436; fax: +81 93 691 6913.
E-mail address: s-sonoda@med.uoeh-u.ac.jp (S. Sonoda).

http://dx.doi.org/10.1016/j.jjcc.2016.01.018
0914-5087/

FFR is defined as the ratio of hyperemic flow in the presence of coronary artery disease to normal maximum flow, and it can be obtained by the ratio of the hyperemic distal coronary artery pressure (Pd) to the aortic pressure (Pa) [12]. The measurement of Pd is determined by both epicardial stenosis and microvascular resistance, and maximum hyperemia is a key prerequisite for the accurate measurement of FFR.

Continuous intravenous (IV) infusion of adenosine or adenosine 5′-triphosphate (ATP) via central vein is a gold standard for the induction of hyperemia for invasive physiological assessment. Although adenosine or ATP is generally used as a hyperemic agent for FFR measurement, there are some concerns about the variability of FFR measurements [13–15].

Intracoronary (IC) nicorandil (NIC) bolus administration has been demonstrated as a novel hyperemic agent for invasive physiological evaluation in coronary artery disease [16,17]. Although a strong linear correlation was observed between FFR with ATP and NIC, some cases indicated relatively large FFR discrepancy between ATP and NIC [18].

Based on these findings, we evaluated FFR changes with additional IC NIC administration during IV ATP infusion in Japanese patients with intermediate coronary artery stenosis.

Methods

Study population

Patients with angiographically intermediate lesions (visual estimation: 40–70%) in major epicardial coronary arteries were prospectively and consecutively enrolled. Patients who underwent PCI and/or coronary artery bypass graft (CABG) for target vessel within one year, and device implantation [pacemaker (PM), implantable cardioverter-defibrillator (ICD), and cardiac resynchronization therapy-defibrillator] were excluded. Patients with valvular disease, non-ischemic cardiomyopathy, congestive heart failure, and contraindications to ATP and NIC were also excluded. Furthermore, patients with bronchial asthma were excluded from this study along with patients experiencing induced or worsened bronchial asthma. All patients provided informed consent.

Study protocol (FFR measurement)

Coronary angiography was performed using 4–7 French guide catheters without side holes by a radial or femoral approach. Pressure measurements were performed using a 0.014-inch pressure guide wire (PressureWire Verrata, Volcano, San Diego, CA, USA, or PressureWire Aeris, St. Jude Medical, St. Paul, MN, USA). Pd and Pa were recorded from baseline to hyperemia with ATP and then to hyperemia with ATP and NIC. Maximal hyperemia was presumed to have occurred when the maximal drop in distal pressure was identified.

All patients were asked to refrain from caffeine-containing products more than 12 h before FFR measurements. All patients first received IV ATP infusion (180 μg/kg/min) continuously via left or right cubital vein (20G needle) for 3 min to measure FFR (ATP-FFR). After additional IC NIC bolus administration (2 mg/30 s) during IV ATP infusion, FFR was measured again (NIC-FFR).

We assessed changes in FFR values and hemodynamics during FFR measurement. Then, we measured not only adequate FFR values but also cyclic changes in FFR values.

A 12-lead electrocardiogram was performed at baseline, during IV infusion of ATP and additional IC bolus of NIC. We also assessed baseline echocardiographic findings.

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. Cases with discrepancy in FFR between ATP and NIC were defined by more than 2 standard deviations (SD) according to Bland–Altman plot analysis in previous studies.

These data were statistically analyzed by JAMP 11.0 (SAS Institute Japan Ltd., Tokyo, Japan). A value of $p < 0.05$ was considered statistically significant.

Results

Between March 2013 and July 2015, 111 patients were prospectively enrolled from our institution. Although some patients had more than two moderate stenotic coronary vessels, we included only main target vessels. A total of 17 patients were excluded from this study: target vessel revascularization within 1 year ($N = 2$), valvular disease ($N = 5$), 2 non-ischemic cardiomyopathy (hypertrophic obstructive cardiomyopathy: $N = 1$, hypertensive heart disease: $N = 1$), 5 device implantation (4 PM, and 1 ICD), and congestive heart failure ($N = 3$). Finally, 94 patients with 94 lesions consisting of 66 left anterior descending artery, 14 left circumflex artery, and 14 right coronary artery were included. Clinical characteristics of study subjects are summarized in Table 1.

Hemodynamic changes during induction of maximal hyperemia

In this study, IV ATP infusion (180 μg/kg/min for 3 min) produced significant decreases in systolic (15%), diastolic (12%), and mean blood pressure (12%), but a significant increase in heart rate (4%) compared to baseline. Moreover, additional IC NIC administration produced a further drop in blood pressure (systolic: 3%, diastolic: 5%, mean: 4%) compared to post IV ATP infusion (Table 2). There were no arrhythmic changes such as transient

Table 1
Baseline clinical characteristics ($N = 94$).

Characteristics	*n* (%)
Age (yrs)	70 ± 9
Male	71 (76)
BMI (kg/m^2)	24 ± 4
Hypertension	75 (80)
Dyslipidemia	78 (83)
Diabetes	50 (53)
Smoker	59 (63)
Symptom	
Silent ischemia	52 (55)
Angina	42 (45)
Target vessel	
LAD	66 (70)
LCX	14 (15)
RCA	14 (15)
eGFR	57 ± 26
Hemodialysis	11 (11)
LVEF (%)	56 ± 15
LVMI (g/m^2)	104 ± 34
E/e′	15 ± 5
E/A	0.87 ± 0.35
DcT (ms)	228 ± 66

BMI, body mass index; LAD, left anterior ascending artery; LCX, left circumflex artery; RCA, right coronary artery; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; DcT, deceleration time.
Values are mean ± SD or *n* (%).

Please cite this article in press as: Takami H, et al. Impact of additional intracoronary nicorandil administration during fractional flow reserve measurement with intravenous adenosine 5′-triphosphate infusion. J Cardiol (2016), http://dx.doi.org/10.1016/j.jjcc.2016.01.018