International Journal of Cardiology 208 (2016) 128–136

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Efficacy of pressure parameters obtained during contrast medium-induced submaximal hyperemia in the functional assessment of intermediate coronary stenosis in comparison with instantaneous wave-free ratio

Yoshihisa Kanaji [a], Tadashi Murai [a], Tetsumin Lee [a], Junji Matsuda [a], Eisuke Usui [a], Makoto Araki [a], Takayuki Niida [a], Sadamitsu Ichijyo [a], Rikuta Hamaya [a], Taishi Yonetsu [b], Shigeki Kimura [c], Tsunekazu Kakuta [a,*]

[a] Department of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Tsuchiura, Japan
[b] Department of Cardiology, Kameda Medical Center, Chiba, Japan
[c] Cardiovascular Center, Yokosuka Kyosai Hospital, Yokosuka, Kanagawa, Japan

ARTICLE INFO

Article history:
Received 29 July 2015
Received in revised form 20 January 2016
Accepted 22 January 2016
Available online 25 January 2016

Keywords:
Fractional flow reserve
Atherosclerosis
Ischemia
Angioplasty
Revascularization

ABSTRACT

Background: Despite evidence demonstrating the benefits of percutaneous coronary intervention guided by fractional flow reserve (FFR), FFR evaluation has not been widely adopted. We sought to compare the diagnostic performances of instantaneous wave-free ratio (iFR) to a novel contrast medium-induced index in FFR prediction, hypothesizing that the latter parameter would offer superior diagnostic agreement with FFR.

Methods & results: We studied 132 intermediate stenoses in 97 patients prospectively. iFR was measured first, followed by intracoronary injection of 6 mL contrast medium at 3 mL/s to obtain end-diastolic instantaneous distal coronary pressure/aortic pressure ratio (Pd/Pa) 60 ms before the electrocardiographic R-wave (C-ED-Pd/Pa). Subsequently, conventional hyperemic FFR was measured as a reference standard. Of the 132 lesions, 120 were available for final analysis. The FFR values of 95/120 lesions (79.2%) were between 0.60 and 0.90. C-ED-Pd/Pa values (median 0.79 [interquartile range 0.69–0.87]) were significantly lower than FFR values (0.81 [0.75–0.88], $P < 0.01$), whereas iFR values (0.91 [0.86–0.94], $P < 0.01$) were significantly higher. Correlation coefficients with FFR were 0.78 (standard error of the estimate [SEE] 0.067, $P < 0.0001$) and 0.93 (SEE 0.052, $P < 0.0001$) for iFR and C-ED-Pd/Pa, respectively ($P < 0.001$). The areas under the receiver operating characteristic curves were 0.88 and 0.96 for iFR and C-ED-Pd/Pa, respectively ($P < 0.01$). Diagnostic accuracy was 85.0% and 92.5% for iFR and C-ED-Pd/Pa, respectively ($P = 0.06$).

Conclusions: C-ED-Pd/Pa is a novel, practical, and accurate measure for the physiological assessment of intermediate coronary stenosis compared to iFR.

1. Introduction

Fractional flow reserve (FFR) is an important physiological measure that is used as the reference standard for assessing the functional significance of epicardial coronary artery stenosis. It is particularly useful in intermediate stenosis, where angiography is of limited efficacy in identifying lesions that cause myocardial ischemia. Despite evidence demonstrating the efficacy of FFR-guided percutaneous coronary intervention (PCI) [1–5], it has not been widely adopted, partly because of the expense and potential side effects associated with vasodilator administration, as well as the time and procedural techniques required for FFR determination. With accumulating evidence supporting the use of FFR for guiding revascularization, there has been growing interest in simplifying the assessment of physiological lesion severity. Resting baseline distal coronary pressure to proximal aortic pressure ratio (Pd/Pa) and the instantaneous wave-free ratio (iFR) [6,7] are indices that have been investigated extensively [7–10,11]. A recent independent core laboratory analysis reported that, in comparison with the use of an FFR cut-off of 0.80, iFR and Pd/Pa showed an overall diagnostic accuracy of 80.4% and 81.5%, respectively, with no significant difference between the two measures [12]. Because the results did not justify replacing FFR with these baseline indices, the investigators attempted a hybrid approach that restricted the use of FFR to a certain range of thresholds. Escand et al. reported the results of a prospective, observational, non-randomized double blind global multi-center registry study with an adaptive design (ADVISE II) [11]. In ADVISE II, the diagnostic performance of iFR was analyzed both as a dichotomous index and as part of a hybrid iFR/FFR strategy. iFR showed a diagnostic accuracy of 82.5% in the ADVISE II cohort;

* Corresponding author at: Department of Cardiology, Tsuchiura Kyodo General Hospital, 11-7, Manabeshin-machi, Tsuchiura, Ibaraki 300-0053, Japan.
E-mail address: kaz@joy.email.ne.jp (T. Kakuta).

http://dx.doi.org/10.1016/j.ijcard.2016.01.205
0167-5273/

the hybrid iFR/FFR approach correctly classified 94.2% of coronary stenoses without the need for adenosine administration in 65.1% of patients (69.1% of stenosis).

A recent study comparing contrast medium-induced Pd/Pa with baseline Pd/Pa found that this value showed a better correlation with conventional FFR [13]. Since this technique is readily available in catheterization laboratories and does not require hyperemic induction by drugs, further evaluation of its potential is warranted. In a recent animal study, Chalyan et al. reported that instantaneous hyperemic end-diastolic Pd/Pa measured 60 ms before the R-wave had a better correlation with FFR obtained directly by an ultrasound flow-probe than did conventional FFR [14]. Given the reported efficacy of contrast medium-induced Pd/Pa and the diagnostic value of hyperemic end-diastolic Pd/Pa, we hypothesized that instantaneous end-diastolic Pd/Pa, obtained at submaximal hyperemia caused by intracoronary contrast medium injection, could offer superior functional lesion discrimination compared to resting iFR. In this study, we compared the diagnostic performance of iFR to that of contrast medium-induced end-diastolic Pd/Pa, using conventional FFR as a standard of reference.

2. Methods

2.1. Study population

Between September 2014 and January 2015, 97 consecutive patients with 132 intermediate lesions who were undergoing diagnostic cardiac catheterization for suspected coronary artery disease were enrolled prospectively. All patients had lesions in at least one epicardial proximal coronary artery that were angiographically intermediate (defined as a diameter stenosis of 30% to 80% by visual estimation). The exclusion criteria were a history of coronary artery bypass surgery, extremely tortuous coronary arteries, severely calcified arteries, acute coronary syndrome, a history of myocardial infarction, occluded coronary arteries, left main disease, coronary ostial stenosis, congestive heart failure, significant arrhythmia, renal insufficiency (creatinine > 1.5 mg/dL), or an absolute contraindication to adenosine. Cardiovascular medications were not withheld before the study. The study was approved by the local ethics committee and conformed to the Declaration of Helsinki on human research. Informed consent was obtained from all participants after a complete explanation of the protocol and potential risks.

2.2. Cardiac catheterization and hemodynamic measurements

Upon catheterization via the radial artery using a 6-F system, each patient underwent standard selective coronary and left ventricular angiography for the assessment of coronary anatomy and ventricular volume and contractility. All patients received a heparin bolus (5000 IU) before the procedure and an intracoronary bolus of nitroglycerin (0.2 mg) at its start. Coronary angiograms were quantitatively analyzed with a CMS-MEDIS system (Medis Medical Imaging Systems, Leiden, The Netherlands). Lesion length, minimum lumen diameter, reference lumen diameter, and percent diameter stenosis were measured at the target lesion.

Physiological measurements of coronary stenoses were performed using a RadiAnalyzer Xpress instrument with a Certus coronary pressure wire (St. Jude Medical, Uppsala, Sweden). A coronary 0.014-in. PressureWire Certus™ (St. Jude Medical, MN) was used to measure the distal coronary pressure. After the pressure wire was zeroed and equalized to aortic pressure, the PressureWire™ was advanced to the tip of the guiding catheter to equalize the sensor pressures of the PressureWire™ and the guiding catheter. The PressureWire™ was then positioned 8–10 cm distal to the ostium of the intended artery and distally to the target coronary stenosis. Care was taken to maintain the same sensor position across all measurements to avoid variability.

2.3. Pressure parameter measurement protocol

At the start of the pressure study, 0.2 mg of intracoronary nitroglycerin was re-administered. The study consisted of three sequential measurements, separated by at least 3 min, until the hemodynamic status returned to baseline values. Data acquisition included electrocardiographic recording for the iFR calculation algorithm.

1. Baseline pressure recording for iFR determination: baseline pressures were recorded for at least 30 s to calculate iFR.
2. Contrast medium-induced pressure indices: a single contrast medium injection of 6 mL (Iomeron 400; Eizai, Japan; used routinely as a nonionic low-osmolar contrast medium for cardiac catheterization) at a flow rate of 3 mL/s was performed using a power injector system (ACIST CVi®system; ACIST Medical Systems, Inc., US). Afterwards, a saline flush was performed to avoid pressure damping of the guiding catheter due to contrast medium viscosity. C-ED-Pd/Pa, defined as the instantaneous end-diastolic Pd/Pa obtained 60 ms before the R-wave on the electrocardiogram (ECG), was calculated as the mean value of 3 measurements, including the lowest C-ED-Pd/Pa value and 2 adjacent cardiac cycles after contrast medium injection.
3. Conventional FFR measurement: steady-state maximal hyperemia was induced by intravenous infusion of adenosine at a rate of 140 μg/kg for a minimum of 2 min via a central vein. FFR was defined as the lowest stable value of the Pd/Pa ratio during maximal hyperemia. After FFR measurement, a pullback maneuver of the pressure wire transducer into the guiding catheter to detect pressure sensor drift was mandatory.

Representative pressure waveform tracings of C-ED-Pd/Pa are shown in Fig. 1. Multiple measurements under contrast medium injection, and measurements of contrast medium-induced and conventional adenosine-induced hyperemic states in inverted order, were tested in a separate set of 20 patients. Contrast medium-induced indices showed good reproducibility ($r = 0.98$, $P < 0.001$; intraclass correlation coefficient: 0.97). Consistent with a previous study by Leone et al., [13] there was no significant effect of contrast medium on FFR measurements.

All pressure and ECG tracings of the console, as well as the multichannel ECG recorder included in the catheterization laboratory's monitoring system (RMC-4000 Cardio Master with EP amplifier system JB400G; Nihon Koden, Tokyo, Japan), were submitted to the independent in-hospital core cardiac physiology and morphological analysis laboratory. By automatic identification of the cardiac cycle after phase adjustment of Pa and Pd, the diastolic window for pressure measurement was calculated beginning at 25% into diastole and ending 5 ms before the end of diastole (Fig. 2). iFR was obtained as a Pd/Pa ratio during this pre-specified time window within mid to late diastole under a non-hyperemic resting state (the wave-free period), when microvascular resistance is stable and minimized [7,15]. Waveform tracings with phase adjustments meeting the following exclusion criteria were not analyzed: loss of pressure signal at any point during measurement (other than contrast medium and saline flush injection); ECG signal loss; significant arrhythmia (including atrial fibrillation that might preclude appropriate waveform analysis); bradycardia with a heart rate < 50 beats/min or tachycardia at >120 beats/min (suggestive of catheter-damped Pa recording); inappropriate Pd waveform quality; or sensor drift (defined as a pressure difference >3 mm Hg between Pd and Pa after pullback of the pressure wire transducer into the guiding catheter). For all analyses, a minimum of 5 stable and assessable waveforms without significant artifacts were required. All analyses were performed semi-automatically. The C-ED-Pd/Pa value was calculated 60 ms before the R-wave on the ECG, and the location of the measurement time point was determined semi-automatically from the R-wave trigger of the synchronized ECG signal. For iFR, the end-diastolic point was confirmed and adjusted manually. Independent in-hospital analyses were performed in a blinded fashion. FFR data were compared with the original