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Efficacy of pressure parameters obtained during contrast medium-induced submaximal hyperemia in the functional assessment of intermediate coronary stenosis

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ABSTRACT

Background: Despite evidence demonstrating the superiority of percutaneous coronary intervention guided by fractional flow reserve (FFR), FFR evaluation has not been widely adopted. We sought to determine the diagnostic performance of baseline conditions and contrast medium-induced pressure indices in predicting FFR. We hypothesized that the contrast medium-induced end-diastolic pressure parameter would offer superior diagnostic agreement with FFR, compared to other indices.

Methods & results: Ninety-one intermediate stenoses in 75 patients were studied prospectively. The baseline distal coronary pressure to aortic pressure ratio (Pd/Pa) and end-diastolic instantaneous Pd/Pa 60 ms before the electrocardiographic R-wave (ED-Pd/Pa) were measured; then, after intracoronary injection of 6 mL contrast medium at 3 mL/s, Pd/Pa (C-Pd/Pa) and end-diastolic Pd/Pa (C-ED-Pd/Pa) were obtained. Subsequently, conventional FFR was measured as a reference standard. Of the 91 lesions, 11 (12.1%) were excluded because of suboptimal data acquisition, leaving 80 for final analysis. C-ED-Pd/Pa values (median 0.80 [interquartile range 0.70–0.88]) were significantly lower than conventional FFR (0.83 [0.75–0.89], $P < 0.01$), whereas Pd/Pa (0.93 [0.90–0.96], $P < 0.01$), ED-Pd/Pa (0.91 [0.87–0.93], $P < 0.01$), and C-Pd/Pa (0.85 [0.79–0.90], $P < 0.05$) were significantly higher. Correlation coefficients (R) with conventional FFR were 0.74 (standard error of the estimate [SEE] 0.067, $P < 0.0001$), 0.78 (SEE 0.062, $P < 0.0001$), 0.85 (SEE 0.052, $P < 0.0001$), and 0.93 (SEE 0.037, $P < 0.0001$) for Pd/Pa, ED-Pd/Pa, C-Pd/Pa, and C-ED-Pd/Pa, respectively. Diagnostic accuracy was 81.2%, 83.8%, 87.5% and 93.8% for Pd/Pa, ED-Pd/Pa, C-Pd/Pa, and C-ED-Pd/Pa, respectively.

Conclusions: Among baseline indices and contrast-induced pressure parameters, C-ED-Pd/Pa is a novel, feasible, and high-performance measure for the physiological assessment of intermediate coronary stenosis.

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1. Introduction

Fractional flow reserve (FFR) is an important physiological measure that is accepted and used as the reference standard for assessing the functional significance of epicardial coronary artery stenosis—particularly in intermediate stenosis, where angiography has limited efficacy in identifying the lesions responsible for inducing myocardial ischemia. Despite evidence demonstrating the superiority 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. Recently, with the accumulation of evidence supporting the use of FFR in clinical decision making regarding revascularization, there has been growing interest in simplifying the assessment of physiological lesions. The indices evaluated include the resting baseline distal coronary pressure to proximal aortic pressure ratio (Pd/Pa) and the instantaneous wave-free ratio (iFR) [6,7]. These indices have been investigated extensively [7–10] and 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 [11]. Because these results were not sufficient to justify replacing FFR with these baseline indices, the authors simulated a hybrid approach that restricted the use of FFR to a certain range of thresholds.

A recent study that compared contrast medium-induced Pd/Pa with baseline Pd/Pa found that it showed a better correlation with conventional FFR [12]. Since this technique for evaluating the functional significance of coronary lesions is readily available in the catheterization

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laboratory, further testing of its appropriateness is warranted. More recently, in an 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 [13]. Given the reported results of the 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 performance for functional lesion discrimination compared with baseline Pd/Pa, baseline end-diastolic Pd/Pa, and contrast medium-induced Pd/Pa. The purpose of this study was to evaluate the diagnostic performance of baseline Pd/Pa, baseline end-diastolic Pd/Pa, contrast medium-induced Pd/Pa, and contrast medium-induced end-diastolic Pd/Pa, compared to conventional FFR, as a standard of reference.

2. Methods

2.1. Study population

From September 2014 to Jan 2015, 75 consecutive patients with 91 intermediate lesions 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 with 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

Each patient underwent standard selective coronary and left ventricular (LV) angiography for the assessment of coronary anatomy and LV volume and contractility, after catheterization via the radial artery using a 6-F system. All patients received a bolus of heparin (5000 IU) before the procedure. An intracoronary bolus of nitroglycerin (0.2 mg) was administered at the start of the procedure. Coronary angiograms were quantitatively analyzed with a CMS-MEDIS system (Medis Medical Imaging Systems, Leiden, The Netherlands). The 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 calibration, the PressureWire™ was advanced to the tip of the guiding catheter, so that the sensor pressures by PressureWire™ and by guiding catheter were equalized, and then positioned 8–10 cm distal to the ostium of the studied artery and distally to the target coronary stenosis. The distance of the pressure–temperature sensor-tipped guidewire from the guide catheter tip is a potential source of error for analyzing coronary pressure; therefore, care was taken to maintain the sensor position across all measurements.

2.3. Pressure parameter measurement protocol

At the start of the pressure study, 0.2 mg of intracoronary nitroglycerin was administered. The study consisted of three sequential measurements, separated by at least 3 min, until the hemodynamic status returned to the baseline values.

1. Baseline pressure recording: Pd/Pa was defined as the ratio of mean distal coronary pressure to mean aortic pressure. End-diastolic Pd/Pa (ED-Pd/Pa) was defined as the instantaneous end-diastolic Pd/Pa obtained 60 ms before the R-wave on the electrocardiogram (ECG). ED-Pd/Pa was calculated as the mean value from 3 stable measurements.
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 our institution) at a flow rate of 3 mL/s was performed using a power injector system (ACIST CVi®system; ACIST Medical Systems, Inc., US). After contrast injection, a saline flush was immediately performed to avoid pressure damping of the guiding catheter due to contrast medium viscosity. C-Pd/Pa was defined as the mean ratio calculated from 3 Pd/Pa measurements, including the minimal Pd/Pa value and 2 adjacent cardiac cycle Pd/Pa values. C-ED-Pd/Pa was defined as the instantaneous end-diastolic Pd/Pa obtained 60 ms before the R-wave on ECG. C-ED-Pd/Pa was also calculated as the mean value from 3 measurements, including the lowest C-ED-Pd/Pa value and 2 adjacent cardiac cycles.
3. Conventional FFR measurement: steady-state maximal hyperemia was induced by intravenous infusion of adenosine 50-triphosphate (ATP; 160 μg/kg/min) via a central vein. FFR was defined as the lowest stable value of the Pd/Pa ratio during maximal hyperemia.

Representative pressure waveform tracings of C-Pd/Pa and C-ED-Pd/Pa are shown in Fig. 1. Multiple measurements under contrast medium injection and measurements of contrast medium-induced and conventional ATP-induced hyperemic states in inverted order were tested in a different set of 20 patients. Contrast medium-induced indices showed good reproducibility ($r = 0.98$, $P < 0.001$, intraclass correlation coefficient: 0.97) and no significant effect of contrast medium on FFR measurements, in line with the results shown in a study by Leone et al. [12].

All pressure and ECG tracings of the console and 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 in-hospital core cardiac physiology and morphological analysis laboratory, which is operated independently by expert medical engineers and cardiologists. Waveform tracings with phase adjustments meeting the following exclusion criteria were excluded from the analysis: loss of pressure signal at any point during the measurement phase, apart from contrast medium and saline flush injection; 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 mean pressure difference ≥3 mmHg between Pd and Pa after pullback of the pressure wire transducer into the guiding catheter. For all analyses of indices, a minimum 5 waveforms of stable and assessable recording without significant artifacts on the tracing were required. All analyses were performed in a fully automated manner, except for ED-Pd/Pa and C-ED-Pd/Pa, where the 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 automatic R-wave trigger of the synchronized ECG signal. Independent in-hospital analyses were performed in a blinded fashion. These data were compared with the original readout in the catheterization laboratory, and consensus reading was performed by two expert physicians if there were discordant values.

2.4. Statistical analysis

SPSS version 22.0 (SPSS Inc, Chicago, IL, USA) was used for baseline descriptive analyses. The normality of the data was verified using the Kolmogorov–Smirnov test. Categorical data were expressed as absolute frequencies and percentages and were compared using the χ^2 or Fisher's exact test, as appropriate. Continuous variables were expressed as mean ± standard deviation for normally distributed variables and as median with interquartile range (IQR) for non-normally distributed variables. Comparisons between multiple groups were performed by Friedman test followed by post hoc tests for pairwise comparison of variables according to Conover correction. Linear regression analysis was performed to examine the relationship between Pd/Pa and FFR, ED-Pd/Pa and FFR, C-Pd/Pa and FFR, and C-ED-Pd/Pd and FFR, respectively. The correlation coefficient (R) and standard error of estimate (SEE) were determined. Agreement between the studied indices was evaluated by Bland–Altman plots with 95% limits of agreement. The receiver operating characteristic (ROC) curve analyses were conducted for conventional FFR cut-off of 0.80. The area under the ROC curve was also calculated for each index. Comparison of ROC curves to test the statistical significance of the difference between the areas under ROC curves were made by the method of DeLong et al. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of each index relative to FFR cut-off of 0.80 were determined. Optimal cut-off values of Pd/Pa, ED-Pd/Pa, C-Pd/Pa, and C-ED-Pd/Pa relative to FFR of 0.80 were also calculated to maximize the sum of sensitivity and specificity, equivalent to maximization of Youden's statistics J. Thresholds to achieve the diagnostic accuracy >95% were determined, and the proportions of lesions beyond these cut-off values were calculated. A value of $P < 0.05$ was considered significant.

3. Results

Of a total of 91 lesions in the 75 patients initially evaluated, 11 met at least one of the predefined exclusion criteria, leaving 80 lesions in 65 patients for final analysis. The most common reasons for exclusion were insufficient waveform quality and sensor drift, predefined as above. Intracoronary injection of contrast medium for C-Pd/Pa and C-ED-Pd/Pa assessment was feasible and was performed without symptoms in all patients. In contrast, ATP infusion for conventional FFR induced a chest burn sensation, chest pain, or dyspnea in 15 patients (23.1%) and transient atrioventricular block in 4 patients (6.2%), while in 2 patients (3.1%) FFR assessment could not be completed.

The patients' characteristics are summarized in Table 1. Quantitative coronary angiography yielded a diameter reduction of 48.9 ± 15.6% for all lesions. Values of Pd/Pa, ED-Pd/Pa, C-Pd/Pa, C-ED-Pd/Pa, and FFR are shown in Fig. 2. The median (IQR) values for Pd/Pa, ED-Pd/Pa, C-Pd/Pa, C-ED-Pd/Pa, and FFR were 0.93 (0.90–0.96), 0.91 (0.87–0.93), 0.85

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