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Advanced computed tomographic anatomical and morphometric plaque analysis for prediction of fractional flow reserve in intermediate coronary lesions

Maksymilian P. Opolski[a,*], Cezary Kepka[b], Stephan Achenbach[c], Jerzy Pregowski[a], Mariusz Kruk[b], Adam D. Staruch[d], Jacek Kadziela[a], Witold Ruzyllo[b], Adam Witkowski[a]

[a] Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw, Poland
[b] Department of Coronary and Structural Heart Diseases, Institute of Cardiology, Warsaw, Poland
[c] Department of Internal Medicine 2 (Cardiology), University of Erlangen, Erlangen, Germany
[d] Medical University of Warsaw, Warsaw, Poland

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ABSTRACT

Objective: To determine the application of advanced coronary computed tomography angiography (CCTA) plaque analysis for predicting invasive fractional flow reserve (FFR) in intermediate coronary lesions.
Methods: Sixty-one patients with 71 single intermediate coronary lesions (≥50–80% stenosis) on CCTA prospectively underwent coronary angiography and FFR. Advanced anatomical and morphometric plaque analysis was performed based on CCTA data set to determine optimal criteria for significant flow impairment. A significant stenosis was defined as FFR ≤ 0.80.
Results: FFR averaged 0.85 ± 0.09, and 19 lesions (27%) were functionally significant. FFR correlated with minimum lumen area (MLA) ($r = 0.456$, $p < 0.001$), minimum lumen diameter (MLD) ($r = 0.326$, $p = 0.006$), reference lumen diameter (RLD) ($r = 0.245$, $p = 0.039$), plaque burden ($r = -0.313$, $p = 0.008$), lumen area stenosis ($r = -0.305$, $p = 0.01$), lesion length ($r = -0.692$, $p < 0.001$), and plaque volume ($r = -0.668$, $p < 0.001$). There was no relationship between FFR and CCTA morphometric plaque parameters. By multivariate analysis the independent predictors of FFR were lesion length (beta = −0.581, $p < 0.001$), MLA (beta = 0.360, $p = 0.041$), and RLD (beta = −0.255, $p = 0.036$). The optimal cutoffs for lesion length, MLA, MLD, RLD, and lumen area stenosis were >18.5 mm, ≤3.0 mm^2, ≤2.1 mm, ≤3.2 mm, and >69%, respectively (max. sensitivity: 100% for MLA, max. specificity: 79% for lumen area stenosis).
Conclusions: CCTA predictors for FFR support the mathematical relationship between stenosis pressure drop and coronary flow. CCTA could prove to be a useful rule-out test for significant hemodynamic effects of intermediate coronary stenoses.

1. Introduction

Fractional flow reserve (FFR) is an established method for invasive evaluation of the functional significance of coronary stenosis allowing for improved clinical decision-making as compared to two-dimensional invasive coronary angiography (ICA) [1]. However, FFR measurement involves endovascular instrumentation, adds expense to the diagnostic procedure and is not performed routinely in many centers.

Whereas coronary computed tomography angiography (CCTA) has emerged as a widespread noninvasive test to rule out or identify significant luminal coronary obstruction [2], it still has an unfavorable diagnostic performance for identification of lesion-specific ischemia in comparison to functional tests [3,4]. Until now, there is very limited data on the potential use of advanced plaque quantification to depict the functional significance of intermediate coronary stenoses as assessed by prospective CCTA inclusion criteria.

The aims of our study were, therefore, to (1) investigate the relationship between CCTA-derived anatomical and morphometric plaque characteristics and FFR, and to (2) assess whether CCTA measurements can predict the functional significance of intermediate coronary lesions.

* Corresponding author at: Department of Interventional Cardiology and Angiology, Institute of Cardiology, Alpejska 42, 04-628 Warsaw, Poland.
Tel.: +48 501 444 303; fax: +48 22 343 4506.
E-mail addresses: opolski.mp@gmail.com (M.P. Opolski), c.kepka@ikard.pl (C. Kepka), stephan.achenbach@uk-erlangen.de (S. Achenbach), jerzypregowski74@gmail.com (J. Pregowski), mariuszkruk2000@yahoo.com (M. Kruk), adstarman@gmail.com (A.D. Staruch), j.kadziela@ikard.pl (J. Kadziela), w.ruzyllo@ikard.pl (W. Ruzyllo), witkowski@hbz.pl (A. Witkowski).

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2. Materials and methods

2.1. Study design and population

Between January 2010 and October 2012, 61 stable patients with 71 single coronary artery lesions of intermediate severity (≥50–80% stenosis) in major coronary arteries as judged by visual assessment in CCTA were prospectively included in the study and scheduled for ICA with FFR in the Institute of Cardiology in Warsaw. CCTA was performed within 4 weeks preceding the ICA. Exclusion criteria were multiple stenoses within a target vessel, target vessel of <2 mm diameter, severe calcification (defined as an arc of ≥180° in >1 cross-sectional image and/or calcium content ≥70% of total plaque volume in CCTA) precluding reliable plaque evaluation [5,6], left main coronary disease (defined as ≥50% luminal narrowing by visual assessment on CCTA), prior percutaneous coronary intervention at the target vessel, prior *Q*-wave myocardial infarction in the coronary territory, previous coronary bypass grafting, hemodynamic instability, and renal insufficiency. The study was approved by local ethics committee and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

2.2. CCTA imaging and data analysis

Image acquisition was performed using a dual-source CT scanner (Somatom Definition, Siemens Healthcare, Forchheim, Germany), with a beam collimation of 64 × 0.6 mm, a gantry rotation time of 330 ms, a tube voltage of 100–120 kV, a tube current of 330–438 mAs/rotation, and a pitch of 0.2–0.3. Unless contraindicated, intravenous metoprolol (sequential doses of 2.5 mg) was administered to target a heart rate <65 beats/min, and sublingual nitroglycerin (0.4 mg) was given directly before CT scan. For acquisition of the volume data set, a bolus of 80–120 ml iodinated contrast material (Iomeron 400, Bracco Altana Pharma, Konstanz, Germany) was administered through an antecubital vein at a rate of 6 ml/s. A retrospectively electrocardiogram-gated or prospectively electrocardiogram-triggered acquisition protocol was used depending on patient's heart rate and body mass index at the operator's discretion. Radiation dose reduction strategies were employed if feasible, and the mean effective dose was 12.1 ± 6 mSv. Image data were reconstructed routinely in mid-to-end systole and diastole (35–45% and 65–75% of the *R–R* interval). The slice thickness was 0.6 mm with an increment of 0.4 mm. All CCTA data were acquired in a single high-volume center performing approximately 2500 CCTA examinations per year.

All CT data were analyzed by a highly experienced observer blinded to the results of ICA and FFR using a dedicated software tool, SurePlaque™ (Vitrea, version 6.3, Vital Images Inc., Toshiba Medical Systems, Japan) previously validated against intravascular ultrasound (IVUS) [7]. Automatic vessel tracking was used to locate the vessel centerline based on the opacification of the lumen. The location and extent of the coronary lesion were manually assigned as previously reported, and the minimum lumen diameter (MLD), minimum lumen area (MLA), proximal and distal lesion edge sites, and proximal and distal reference sites were determined according to IVUS consensus recognized as the gold-standard guidance for quantitative plaque assessment [8]. In ostial lesions only one reference site was used. The direct anatomic measurements included vessel and lumen cross-sectional areas, and lumen diameters that were automatically calculated by the software based on lumen and vessel boundaries. In addition, the lesion length and directional lesion tortuosity were measured automatically. The reference lumen diameter (RLD) was computed as an average value of the mean lumen diameters at the proximal and distal reference sites. The derived anatomical and volumetric measurements were calculated for the traced lesion region and were defined as: lumen eccentricity = (maximum lumen diameter–minimum lumen diameter)/maximum lumen diameter, atheroma eccentricity = (maximum plaque thickness–minimum plaque thickness)/maximum plaque thickness, lumen area stenosis (%) = (mean reference lumen area–MLA)/mean reference lumen area, plaque burden (%) = (mean vessel area–mean lumen area)/mean vessel area, plaque volume (mm^3) = sum of all contiguous voxels between the outer vessel contour and the lumen border and remodelling index (%) = vessel area at MLA/mean vessel area at reference segments [8,9]. According to Sun et al., the morphometric plaque analysis was based on preset Hounsfield unit (HU) ranges of the voxels in the traced lesions [7]. Specifically, the lipid, fibrous, and calcified plaque composition were represented by voxels in the ranges between −100 and 29 HU, 30 and 189 HU, and 350 and 1,000 HU, respectively. Voxels in the range between 190 and 349 HU corresponded to lumen density. In all cases manual corrections of lumen and vessel boundaries on transverse images at 0.5 mm intervals were necessary, and the image quality was sufficient for evaluation. The CCTA analysis required approximately 1.5 h/exam. The interobserver variability was assessed by a second experienced reader in 35% of randomly selected lesions.

2.3. Angiographic protocol and data analysis

ICA was performed using standard techniques and projections. FFR was measured with 2 commercially available coronary pressure guidewires (Prime Wire Prestige, Volcano Corporation, San Diego, California, and Pressure Wire 4, Radi Medical Systems, Uppsala, Sweden) chosen at the discretion of the operator. Calculation of FFR was performed as the ratio between mean distal coronary pressure (measured distal to a stenosis with the pressure wire) and mean aortic pressure (measured simultaneously with the guiding catheter) at maximal hyperemia induced by continuous infusion of adenosine administered at 160 μg/kg/min through an antecubital vein. An FFR ≤ 0.80 was considered functionally significant [1,10]. Angiographic analysis was performed offline by a single independent reader blinded to the results of CCTA and FFR using a commercially available software (CASS QCA, Pie Medical Imaging, Maastricht, The Netherlands). Using the computerized edge-detection system, the reference diameters, MLD, and the percentage diameter stenosis were calculated.

2.4. Statistical analysis

Data are presented as mean ± SD for continuous variables and frequency for categorical variables. Comparison of continuous variables was performed by Student's *t* test or Mann-Whitney test as appropriate. Differences in categorical data were analyzed by the Fisher exact test. Agreement between CCTA and FFR was assessed using Pearson's correlation coefficient. To determine the independent predictors of FFR as a continuous and binary variable (FFR ≤ 0.8), multivariable linear and logistic regression models were used, respectively. Receiver operating characteristics analysis was performed to establish the optimal CCTA cut-off values to predict FFR ≤ 0.8. The diagnostic performance of CCTA for the detection of significant stenoses with FFR as the standard of reference was presented as sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy (true positives + true negatives)/(true positives + true negatives + false positives + false negatives), with the corresponding 95% confidence intervals. Intraclass correlation coefficient (a method of agreement for continuous variables) was used to assess interobserver variability in CCTA-derived parameters. Statistical significance was defined as a *p* value of <0.05. Statistical analyses were performed with SPSS 15.0 (SPSS