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CT morphological index provides incremental value to machine learning based CT-FFR for predicting hemodynamically significant coronary stenosis

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ABSTRACT

Aims: To study the diagnostic performance of the ratio of Duke jeopardy score (DJS) to the minimal lumen diameter (MLD) at coronary computed tomographic angiography (CCTA) and machine learning based CT-FFR for differentiating functionally significant from insignificant lesions, with reference to fractional flow reserve (FFR).
Methods and results: Patients who underwent both coronary CTA and FFR measurement at invasive coronary angiography (ICA) within 2 weeks were retrospectively included in our study. CT-FFR, DJS/MLD_{CT} ratio, along with other parameters, including minimal luminal area (MLA), MLD, lesion length (LL), diameter stenosis, area stenosis, plaque burden, and remodeling index of lesions, were recorded. Lesions with FFR ≤0.8 were considered to be functionally significant. One hundred and twenty-nine patients with 166 lesions were ultimately included for analysis. The LL, diameter stenosis, area stenosis, plaque burden, DJS and DJS/MLD_{CT} ratio were all significantly longer or larger in the group of FFR ≤ 0.8 ($p < 0.001$ for all), while smaller MLA, MLD and CT-FFR value were also noted ($p < 0.001$ for all). CT-FFR and DJS/MLD_{CT} ratio showed the largest AUC among all single parameters (AUC = 0.85 and AUC = 0.83, respectively; $p < 0.001$ for both) for diagnosing functionally significant stenosis. Combining CT-FFR and DJS/MLD_{CT} ratio provided incremental value for discrimination between flow-limiting and non-flow-limiting coronary lesions and yielded the best diagnostic performance (accuracy of 83.7%).
Conclusions: The combination of ML-based CT-FFR and DJS/MLD_{CT} allows accurate non-invasive discrimination between flow-limiting and non-flow-limiting coronary lesions.

1. Introduction

Coronary computed tomography angiography (CCTA) has been well established as a reliable non-invasive modality for the detection of obstructive coronary artery disease (CAD) [1–3]. However, it still has limitations in the diagnosis of functionally significant coronary stenosis, which can be accurately assessed by fractional flow reserve (FFR) and is more important for clinical decision-making, in particular with regard to revascularization [4,5].

CT-FFR was introduced as an advanced technique for non-invasive evaluation of hemodynamic status of coronary stenosis. It applies computational fluid dynamics to CCTA, which enabling calculation of FFR value from standard CCTA scan without the need of additional medication, image acquisition or radiation exposures [6–8]. In contrast to its advantages, this sophisticated method requires large computation power and is not routinely available to most institutes. Recently, a machine learning (ML) based CT-FFR approach has been reported to have high predictive power and diagnostic accuracy in detecting positive myocardial ischemia at very short calculation time [9]. In addition to the above methods, other relatively simple morphological index based on Duke jeopardy score has also been revealed to be the potentially useful parameter for predicting hemodynamic status of coronary stenosis [10]. Although CT-based morphological index is easy-to-calculate, however, the incremental value of this method to CT-FFR has not been explored yet. Therefore, we aimed to investigate the diagnostic performance of ML-based CT-FFR combined with CT-based morphological indices for predicting hemodynamically significant coronary stenosis with reference to invasive FFR.

2. Methods and materials

2.1. Patient population

Institutional review board approval was obtained for this retrospective study, and the informed consent was waived. From January 2011 to April 2017, we retrospectively

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included patients with clinically suspected coronary artery disease (CAD) who underwent both CCTA and FFR measurement at ICA. Inclusion criterion was the interval between CCTA examination and FFR measurement within 2 weeks.

Exclusion criteria were: I) patients who had a history of bypass surgery or target vessel revascularization; II) patients who had previous history of myocardial infarction within 3 months; III) patients in whom the CCTA examination was uninterpretable due to poor image quality; IV) target lesion was diffusely calcified (defined as calcium involvement ≧50% of any vessel cross-section within lesion), because such lesions cannot be accurately evaluated neither by CCTA quantification nor by CT-FFR; and V) patients in whom the interval between CCTA and FFR measurement was longer than 2 weeks (Online supplement Fig. E1).

2.2. CCTA protocol

A 128-slice multidetector CT (Definition AS, Siemens Medical Solutions, Forchheim, Germany) was employed for scanning. β-Blocker (25–75 mg) was administrated orally 1 h prior to the examination in patients with heart rate >65 bpm. Nitroglycerin was given sublingually in all patients. Retrospective ECG-gated CTA was performed in patients with final heart rate ≥70 bpm whereas prospective ECG-triggered sequential acquisition was performed in patients with final heart rate <70 bpm. The details of CCTA acquisition were given in online appendix.

2.3. Reconstruction and CCTA analysis

Data were transferred to an offline workstation (Syngo, Siemens) for further analyses. Axial images, cross-sectional view, curved planar reformation (CPR), multi-planar reformation (MPR), three-dimensional (3D) volume rendering (VR) and 3D maximum intensity projection (MIP) images were available for evaluation.

Parameters were measured as follows. Total lesion length (LL) was measured on CPR images and was defined as the length from the proximal to the distal shoulder of the lesion, where no plaque could be detected. The minimal lumen area (MLA) and the minimal lumen diameter (MLD) were all measured manually with a digital caliper at the narrowest level of the lesion on the cross-sectional images. The proximal and distal vessel diameter/area was measured manually with a digital caliper on cross-sectional images, immediately proximal/distal to the lesion where no plaque could be detected. The reference diameter and reference area were determined as an average of proximal and distal vessel diameter/area. The MLD and proximal/distal vessel diameters were determined as the shortest diameters in eccentric lesions. The diameter stenosis was defined as (reference diameter − MLD) / reference diameter; the area stenosis was defined as (reference area − MLA) / reference area; plaque burden was defined as (vessel cross-sectional area − MLA) / cross-sectional area; the remodeling index was defined as the ratio of vessel cross-sectional area of the lesion to the proximal reference area.

Two cardiovascular radiologists (observer 1, with 8 years of experience in cardiac imaging, and observer 2, with 6 years of experience in cardiac imaging) who were blinded to clinical histories and CT-FFR results independently analyzed the data. The intra-observer and inter-observer variabilities for the two observers were tested and are expressed by using Cohen *k* values and Bland–Altman plots. Any disagreement between the two observers was resolved by consensus. The mean values of various parameters measured by two observers were used for analysis.

2.4. The DJS/MLD_{CT} ratio calculation

The amount of perfused myocardium subtended by the target stenosis was assessed using the Duke jeopardy score [11,12]. The coronary tree was divided into 6 segments: left anterior descending (LAD), the major diagonal branch of LAD, the major septal perforating branch, the left circumflex artery, the major obtuse marginal branch, and posterior descending artery. Two points are assigned to each of these segments (Online supplement Fig. E2). More details of point's assignment and calculation are given in online appendix.

2.5. CT-FFR analysis

As introduced recently, we used a machine-learning based algorithm for FFR simulation (cFFR, version 3.0, Siemens Healthcare, Germany) [9]. It's an alternative to physics-based approach and can be used on-site to calculate CT-FFR value. More details regarding the mechanism of this algorithm can be found in online appendix.

For the on-site processing, after CCTA data were successfully loaded, the centerline and luminal contours for whole coronary tree were automatically generated. They were manually adjusted when needed. Users then manually identified all stenotic lesions to extract their geometrical features required for cFFR algorithm. Finally, those data were input into the pre-learned model and cFFR was computed automatically at all locations in the coronary arterial tree, and the resulting values were visualized by color-coded 3D coronary maps. The lesion specific CT-FFR values were measured within 2 cm distal to the stenosis [13]. The cFFR values of all targeting lesions were calculated independently by two observers and the mean values were used for analysis.

2.6. ICA and FFR measurement

ICA was performed with standard method and at least two views were obtained for each major vessel. All segments were evaluated by two skilled observers (26-years and 20-years experience of coronary intervention), who were blinded to the results of CCTA. The stenotic extent of each lesion was visually assessed and recorded. The indication for FFR measurement was the clinical necessity to assess hemodynamic significance of coronary stenosis in order to optimize treatment strategy (revascularization or medical treatment). FFR was measured by using a 0.014-inch pressure guidewire (St Jude Medical, Minneapolis, Minn.) as previously described [14]. Hyperemia was induced by means of intravenous infusion of 140 μg per kilogram of body weight per minute of adenosine. An FFR value ≤0.8 was considered physiologically significant stenosis.

2.7. Statistical analysis

Statistical analysis was performed by using commercially available statistical software (MedCalc Statistical Software version 15.2.2, MedCalc Software bvba, Ostend, Belgium). Quantitative variables were depicted as means ± standard deviations or median with 25–75% inter-quartile range (IQR), as appropriate. Normally distributed variables were compared with the independent samples *t*-test. Non-normally distributed variables were compared with the Mann–Whitney *U* test for two groups. Inter-observer agreements were expressed in Cohen *k* values. Correlation between FFR and CT-FFR was calculated using Pearson correlation coefficient. Bland–Altman analysis was performed to test the difference between CT-FFR and FFR. Variables that were significant at univariate analysis were included for further receiver operating characteristic (ROC) curve analysis. The best cutoff values of various parameters were determined by the Youden index, the maximum sum of sensitivity and specificity at ROC curve analysis. The areas under curves (AUCs) were compared based on the method developed by Hanley and McNeil [15]. To determine the optimal model for predicting hemodynamic significant stenosis, a multivariable logistic regression analysis was conducted with the "forward" approach. The model included variables with $p < 0.05$ in the univariate analysis. AUC was used to assess the model's discrimination ability, and the Hosmer–Lemeshow (H–L) test was used to assess the model's calibration ability. The combined diagnostic performance of CT-FFR and DJS/MLD_{CT} ratio was investigated by binary logistic regression (online appendix). Sensitivity, specificity, positive predict value, negative predict value and accuracy were recorded. A fivefold cross validation was then performed, for which the data set was randomly divided into 5 subgroups (A, B, C, D and E). Four subgroups (e.g., A, B, C and D) were used to develop a regression model and the resulting prediction equation was applied to their corresponding fifth subgroup (E). A 2-tailed $p < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics

A total of 148 patients undergoing both CCTA and FFR measurement at ICA were initially reviewed. Nineteen patients were excluded according to exclusion criteria (Fig. 1). Finally, 129 patients with 166 lesions were included in our study. The mean interval between ICA and CCTA was 6.3 ± 3.1 (range 1 to 14 days). The mean effective dose of coronary CTA was 7.3 ± 1.6 (range, 3.4–11.3) mSv. Detailed demographic data was given in online supplement table E1. The mean processing time for CT-FFR calculation (segmentation of lumen contouring, define vessel centerline/lumen/stenosis and computation) was 10.4 ± 2.6 min.

3.2. Correlation of CCTA-derived morphological parameters and CT-FFR with functionally significant stenosis (FFR ≤ 0.8)

Lesions were divided into two subgroups for further analysis, by using an FFR value of 0.8 as cutoff. The diameter stenosis, area stenosis, plaque burden, total lesion length, ICA-based stenosis, Duke jeopardy score as well as DJS/MLD_{CT} ratio were all significantly longer or larger in the group of hemodynamically significant lesions (FFR ≤ 0.8) than in the group of insignificant lesions (FFR > 0.8) ($p < 0.001$ for all), as shown in Table 1. In addition, smaller MLD, MLA and CT-FFR were associated with functionally significant lesions (1.20 ± 0.31 vs 1.53 ± 0.48; 2.0 ± 0.89 vs 2.65 ± 1.04; 0.73 ± 0.10 vs 0.86 ± 0.08, respectively; $p <$ 0.001 for all) (Fig. 1 and Online supplement Figs. E3–E4). However, vessel remodeling was shown to have similar extent between the two subgroups (1.84 ± 1.1 vs 1.75 ± 0.69, $p = 0.54$).

The inter-observer agreement for DJS/MLD_{CT} ratio and CT-FFR was 0.79 and 0.82, respectively. According to the Pearson correlation analysis, CT-FFR correlated well with FFR value ($r = 0.69$, 95% CI: 0.60 to 0.76, $p < 0.001$) (Online supplement Fig. E5). The Bland–Altman analysis showed good agreement between FFR and CT-FFR with a mean difference of 0.01 (95% CI: 0.18 to −0.15) (Online supplement Fig. E6).