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Diffuse coronary artery disease among other atherosclerotic plaque characteristics by coronary computed tomography angiography for predicting coronary vessel-specific ischemia by fractional flow reserve

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ABSTRACT

Background and aims: Coronary computed tomography angiography (CCTA) permits effective identification of diffuse CAD and atherosclerotic plaque characteristics (APCs). We sought to examine the usefulness of diffuse CAD beyond luminal narrowing and APCs by CCTA to detect vessel-specific ischemia.
Methods: 407 vessels (n = 252 patients) from the DeFACTO diagnostic accuracy study were retrospectively analyzed for percent plaque diffuseness (PD). Percent plaque diffuseness (PD) was obtained on per-vessel level by summation of all contiguous lesion lengths and divided by total vessel length, and was logarithmically transformed (log percent PD). Additional CCTA measures of stenosis severity including minimal lumen diameter (MLD), and APCs, such as positive remodeling (PR) and low attenuation plaque (LAP), were also included. Vessel-specific ischemia was defined as fractional flow reserve (FFR) ≤0.80. Multivariable regression, discrimination by area under the receiver operating characteristic curve (AUC), and category-free net reclassification improvement (cNRI) were assessed.
Results: Backward stepwise logistic regression revealed that for every unit increase in log percent PD, there was a 58% (95% CI: 1.01−2.48, $p = 0.048$) rise in the odds of having an abnormal FFR, independent of stenosis severity and APCs. The AUC indicated no further improvement in discriminatory ability after adding log percent PD to the final parsimonious model of MLD, PR, and LAP (AUC difference: 0.003, 95% CI: −0.003−0.010, $p = 0.33$). Conversely, adding log percent PD to the base model of MLD, PR, and LAP improved cNRI by 0.21 (95% CI: 0.01−0.41, $p < 0.001$).
Conclusions: Accounting for diffuse CAD may help improve the accuracy of CCTA for detecting vessel-specific ischemia.

1. Introduction

Coronary artery disease (CAD) affects more than 16 million adults in the United States, and is the most prominent cause of death among men and women [1]. The gold standard for evaluating the hemodynamic significance of coronary stenoses is invasively determined fractional flow reserve (FFR). However, abnormal FFR values in the absence of focal epicardial disease are not uncommon, and have been observed in 18% of coronary arteries [2]. Notably, diffuse CAD, which is underestimated by luminal evaluation with invasive coronary angiography (ICA), increases risk of mortality [3,4].

Further enhancements in cardiac imaging modalities have led to the emergence of coronary computed tomography angiography (CCTA), a relatively novel and promising imaging technique for detection and assessment of coronary luminal narrowing and high-risk atherosclerotic plaque characteristics (APCs) that include positive remodeling (PR), low attenuation plaque (LAP), and spotty calcification (SC) [5]. In contrast to invasive angiography, CCTA goes

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beyond coronary "luminology" by directly visualizing coronary plaques located at the vessel wall. In spite of this, however, the impact of CCTA-evaluated plaque diffuseness (PD) beyond conventionally available CCTA measures of CAD severity and APCs has not been determined to date. Using data from a prospective international multicenter study, we therefore set out to examine the usefulness of percent PD above and beyond luminal narrowing and other measures of atherosclerotic plaque by CCTA for detection of vessel-specific ischemia.

2. Patients and methods

2.1. Study population

The DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) Study is a prospective, multicenter, cross-sectional diagnostic accuracy study performed at 17 centers in 5 countries including Canada, Belgium, Latvia, South Korea, and United States. The rationale and design of the DeFACTO study has been previously described [6]. Enrolled patients included adults with suspected CAD who underwent both clinically indicated non-emergent CCTA and ICA. Patients were not deemed eligible for study inclusion if they had a prior history of coronary artery bypass graft (CABG) surgery, percutaneous coronary intervention (PCI) with suspected in-stent restenosis based upon CCTA findings, and suspicion of/or recent acute coronary syndrome (ACS). Further details regarding exclusion criteria have been described elsewhere [6]. Hence, the current analyses included 407 vessels derived from 252 consecutive stable patients, wherein percent PD was retrospectively measured. The institutional review boards at all participating centers approved the study protocol, and further details of the trial are registered at http://www.clinicaltrials.gov (Registration #: NCT01233518).

2.2. Image acquisition and analysis for ICA

ICA with intended FFR were performed within 60 days of CCTA. No events occurred between CCTA and the invasive procedures. Selective ICA was performed by standard catheterization in accordance with the American College of Cardiology guidelines for coronary angiography [7]. FFR was performed at the time of ICA (PressureWire Certus, St. Jude Medical Systems, St. Paul, Minnesota; ComboWire, Volcano Corp, San Diego, California) in vessels deemed clinically indicated for evaluation and demonstrating a stenosis between 30% and 90%. After administration of intracoronary nitroglycerin, a pressure-monitoring guide wire was inserted distal to a stenosis. Hyperemia was induced with intravenous (140 μg/kg/min) administration of adenosine. FFR was calculated by dividing the mean distal coronary pressure by the mean aortic pressure during hyperemia. In accordance with prior studies, a FFR $\leq$0.80 was considered indicative of vessel-specific ischemia [8].

2.3. Image acquisition and analysis for CCTA

CT-based coronary angiography was performed using 64− or higher detector row scanners in accordance with the Society of Cardiovascular Computed Tomography (SCCT) guidelines [9,10]. An intravenous contrast agent (approximately 80–100 ml), followed by saline (50–80 ml), was injected at a flow rate of 5 ml/s. The scan parameters included heart-rate dependent pitch (0.20–0.45), 330 ms gantry rotation time, 100-kVp or 120-kVp tube voltages, and 350-to-800 mA tube current. Radiation dose reduction strategies were employed when feasible. Radiation dose for CCTA was determined using the dose-length product with an organ-specific conversion factor k of 0.014 mSv/mGy/cm [11]. Transaxial images were reconstructed with 0.5- to 0.75-mm slice thickness, 0.3-mm slice increment, 160- to 250-mm field of view, 512 × 512 matrix, and a standard kernel. All CCTAs were interpreted in an intention-to-diagnose approach. CCTA was analyzed using a dedicated 3-dimensional workstation (Ziosoft, Redwood City, California; Advantage AW Workstation, GE Healthcare, Milwaukee, Wisconsin) by independent level III experienced readers in a blinded fashion.

All CCTAs were evaluated by an array of post-processing techniques, as previously described elsewhere [5]. Coronary arteries and branches were categorized into 1 of 3 vascular territories: left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), and right coronary artery (RCA). The left main coronary artery and diagonal branches were considered part of the LAD, while the obtuse marginal branches were assigned to the LCX in our analysis. The posterior descending artery was considered part of either the RCA or LCX system, depending upon the coronary artery dominance. Stenosis severity was graded in accordance with SCCT guidelines, and categorized as 0%, 1%–24%, 25%–49%, 50%–69%, and $\geq$70%.

The individual lesion length in the coronary artery was measured as the length of the significantly narrowed segment from the proximal to the distal end of an individual lesion in the multiplanar reformat images. Total lesion length was obtained by summation of all lesion lengths in the coronary artery (Fig. 1). Percent PD was then calculated by total lesion length divided by the total vessel length. Percent PD was therefore obtained on a per-vessel level regardless of the number of lesions. Hence, a single value of percent PD for individual vessel was utilized in this study and a single FFR measurement was performed by investigators on a per-vessel level in vessels with significant ischemia that were deemed clinically indicated for evaluation. Diameter stenosis (%) and area stenosis (%) were calculated using proximal and distal reference segments, which were selected to be the most adjacent points to the maximal stenosis in which there was minimal or no plaque. Minimal lumen diameter (MLD) and minimal lumen area (MLA) were measured from the long-axis and short-axis views of double-oblique reconstructions at the site of the maximal stenosis, respectively. Longitudinal inner lumen and outer vessel wall contours were detected using an automatic algorithm. However, manual editing was performed for both inner lumen and outer vessel wall delineations, wherever needed. As previously described, non-evaluable CCTAs with poor scan quality were excluded from this study and the scan quality was excellent to good in the majority of patients [6].

Percent aggregate plaque volume (percent APV) was calculated as previously described [12]. Briefly, plaque area was computed as the vessel area minus the lumen area of each cross section. APV was then obtained by summation of all contiguous plaque areas in the coronary artery from the proximal to the distal end of an individual lesion in a vessel. Percent APV was calculated as: APV divided by the sum of vessel volume from the proximal to the distal end of an individual lesion in a vessel.

Qualitative coronary APCs including positive remodeling (PR), low attenuation plaque (LAP), and spotty calcification (SC) were evaluated for coronary vessels directly interrogated by invasive FFR. These coronary APCs are also referred to as high-risk plaque (HRP) characteristics [13,14]. A remodeling index was defined as a maximal lesion vessel diameter divided by proximal reference vessel diameter, with PR defined as a remodeling index >1.10. LAP was defined as any voxel <30 Hounsfield units within a coronary plaque. SC was defined by an intralesion calcific plaque <3 mm in length that comprised <90° of the lesion circumference. Quantitative coronary atherosclerotic plaque analysis was performed using semi-automated plaque analysis software (QAngio CT Research Edition v2.02, Medis Medical Imaging Systems, Leiden, the

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