Coronary Computed Tomographic Angiography-Derived Fractional Flow Reserve for Therapeutic Decision Making

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This study investigated the performance of coronary computed tomography angiography (cCTA) with cCTA-derived fractional flow reserve (CT-FFR) compared with invasive coronary angiography (ICA) with fractional flow reserve (FFR) for therapeutic decision making in patients with suspected coronary artery disease (CAD). Seventy-four patients (62 ± 11 years, 62% men) with at least 1 coronary stenosis of ≥50% on clinically indicated dual-source cCTA, who had subsequently undergone ICA with FFR measurement, were retrospectively evaluated. CT-FFR values were computed using an on-site machine-learning algorithm to assess the functional significance of CAD. The therapeutic strategy (optimal medical therapy alone vs revascularization) and the appropriate revascularization procedure (percutaneous coronary intervention vs coronary artery bypass grafting) were selected using cCTA-CT-FFR. Thirty-six patients (49%) had a functionally significant CAD based on ICA-FFR. cCTA-CT-FFR correctly identified a functionally significant CAD and the need of revascularization in 35 of 36 patients (97%). When revascularization was deemed indicated, the same revascularization procedure (32 percutaneous coronary interventions and 3 coronary artery bypass grafting) was chosen in 35 of 35 patients (100%). Overall, identical management strategies were selected in 73 of the 74 patients (99%). cCTA-CT-FFR shows excellent performance to identify patients with and without the need for revascularization and to select the appropriate revascularization strategy. cCTA-CT-FFR as a noninvasive "one-stop shop" has the potential to change diagnostic workflows and to directly inform therapeutic decision making in patients with suspected CAD. **(Am J Cardiol 2017;120:2121–2127)**

Coronary computed tomography angiography (cCTA) is a robust method to safely rule out obstructive coronary stenosis in the workup of patients suspected of having coronary artery disease (CAD).[1,2] However, a purely anatomic evaluation has been shown to be a poor predictor in identifying the functional significance of a coronary lesion.[3] This has driven an interest in the addition of add-on approaches based on computed tomography (CT), which may yield a more comprehensive noninvasive imaging test for CAD. The recently introduced cCTA-derived fractional flow reserve (CT-FFR) has been validated in previous multicenter trials as a reliable method for the noninvasive detection of functionally significant stenosis in comparison with invasive fractional flow reserve (FFR).[4–6] We sought to investigate the performance of cCTA combined with machine–learning-based CT-FFR for therapeutic decision making in patients suspected of CAD, compared with invasive coronary angiography (ICA) with invasive FFR.

Methods

The present study was approved by the local Institutional Review Board with a waiver of informed consent and was conducted in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A retrospective analysis was performed on a patient cohort with suspected CAD who had undergone dual-source cCTA as part of their diagnostic workup followed by ICA with invasive FFR within 3 months for the assessment of CAD from November 2009 to December 2014. Indications for cCTA were

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abnormal exercise testing (n = 14), abnormal nuclear stress testing (n = 23), or chest pain (n = 37). The decision to perform ICA was based on clinical parameters, cCTA data, as well as other noninvasive functional test results, in accordance with clinical guidelines.[7] All CT-FFR values were computed as a procedure of this retrospective investigation and were not available to the patient's cardiologist at the time of treatment. All patients in the present study had at least 1 coronary stenosis of ≥50% on cCTA. Patients who previously underwent percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or cCTA datasets with nondiagnostic image quality were excluded from this analysis. Furthermore, patients with renal insufficiency (glomerular filtration rate <30 ml/min/1.73 m^2) or an allergy to iodine contrast media were excluded. Covariates, including cardiac risk factors and patient baseline characteristics, were obtained from medical records. Imaging was performed using a first- or a second-generation dual-source CT system (SOMATOM Definition or SOMATOM Definition Flash; Siemens Healthineers, Forchheim, Germany). All patients initially underwent a non–contrast-enhanced calcium scoring study. For the subsequent contrast-enhanced cCTA, scan parameters were a retrospectively electrocardiography-gated protocol for the first-generation dual-source CT scanner and a prospectively electrocardiography-triggered sequential scan protocol with a padding window for the second-generation dual-source CT scanner; a tube voltage of 100 to 120 kV, a tube current of 320 to 412 mA, a temporal resolution of 83 or 75 ms, and a $2 \times 32 \times 0.6$ mm or $2 \times 64 \times 0.6$ mm collimation with a z-flying focal spot. Fifty to eighty milliliters of iopromide (Ultravist 370 mgI/ml; Bayer, Wayne, New Jersey) was injected at 4 to 6 ml/s followed by a 30 ml saline bolus chaser at the same flow rate to provide contrast enhancement. The attending physician of the day individually determined the use of β blockers and nitroglycerin. A total of 47 patients (64%) were administered nitroglycerin and 24 patients (32%) were administered β blockers. Weighted filtered back-projection image reconstruction was performed in the cardiac phase with the least motion: a section thickness of 0.75 mm, a reconstruction increment of 0.5 mm, and a smooth convolution kernel (B26f). The mean dose-length product was 474 ± 52.8 mGy·cm. The effective radiation dose was estimated by multiplying the dose-length product with a standard conversion factor of 0.014 mSv/mGy·cm,[8] resulting in a mean effective radiation dose equivalent of 6.5 ± 0.7 mSv.

cCTA datasets were transferred to a postprocessing workstation (syngo.via VB10, Siemens, Forchheim, Germany) for further analysis. Transverse sections and automatically generated curved multiplanar reformations were assessed. Two observers independently evaluated all datasets for the presence of CAD and stenosis severity using the Coronary Artery Disease Reporting and Data System (CAD-RADS) classification: 1, none (0%) or minimal (1% to 24%); 2, mild (25% to 49% stenosis); 3, moderate (50% to 69% stenosis); 4, severe (70% to 99% stenosis); and 5, total occlusion (100%). Nondiagnostic studies (CAD-RADS N classification) were excluded from further analysis.[9] Obstructive CAD was defined as ≥50% luminal narrowing (CAD-RADS classification ≥3). All discordant cases were resolved by a consensus reading. Functional stenosis severity assessment was performed in all lesions with ≥50% luminal narrowing on cCTA (CAD-RADS classification ≥3). For the CT-FFR analysis, an artificial intelligence research prototype (Siemens cFFR, version 2.1, Siemens; not currently commercially available) was used as previously described.[10,11] The software resides on-site on a regular workstation and allows for the physician-driven creation of a patient-specific anatomic model of the coronary tree using a semiautomatic approach. CT-FFR values were computed using a recently introduced machine-learning algorithm.[12] This approach is based on a deep learning framework to determine the functional severity of the lesion. The deep learning algorithm employs a multilayer neural network architecture that was trained offline to learn the complex relation between the anatomy of the coronary tree and its corresponding hemodynamics. Model training utilized a large database of synthetically generated coronary anatomies and their corresponding hemodynamic conditions from a computational fluid dynamics simulation. Based on the geometric features of the patient's coronary anatomy on cCTA, such as the vessel radius, the degree of tapering, and the branch length, the algorithm uses the learned relation to calculate the machine–learning-based CT-FFR values. This relation is based on input data, for example, the anatomy of a vascular tree. The quantity of interest (e.g., FFR) is represented by a model built from a database of samples with known characteristics and outcome derived from the computational fluid dynamic approach. For any point available within the coronary tree, CT-FFR was generated by computing the ratio of the average local pressure over a cardiac cycle to the average aortic pressure, resulting in a color-coded 3-dimensional mesh allowing for the determination of the CT-FFR value at arbitrary locations. Functionally significant CAD was defined as a CT-FFR of ≤0.80.[10] Both observers independently decided whether functionally significant stenosis was present for each coronary lesion based on cCTA-CT-FFR (≥50% stenosis on cCTA + CT-FFR ≤0.80). Furthermore, the observers determined whether optimal medical treatment or revascularization was indicated for each patient and, in cases of revascularization, the appropriate revascularization procedure (PCI or CABG) according to societal guidelines.[13] Briefly, patients with a functionally significant 1- or 2-vessel disease without ostial left anterior descending coronary artery involvement were considered for PCI. Patients with an isolated left main disease or left main disease and additional stenosis elsewhere and patients with 3-vessel disease were considered for CABG. A consensus was reached between reviewers in all discordant cases.

ICA was performed by an experienced interventional cardiologist according to societal guidelines.[14] The presence of at least 50% diameter stenosis was evaluated in at least 2 views of each major epicardial vessel in the same projections using the 16-segment American Heart Association coronary model used for the cCTA analysis.[15] Invasive FFR measurement was performed at the discretion of the treating physician to evaluate the functional relevance of CAD seen at angiography (≥50% stenosis). FFR measurement was performed using the QUANTIEN platform (St. Jude Medical, St. Paul, Minnesota), whereas a pressure wire (Aeris, St. Jude Medical) was used to obtain baseline pressure proximal and distal to the particular lesion. Hyperemia was induced by the continuous application of intravenous adenosine (140 μg/kg/min) and distal pressure measurement was reassessed. An FFR value