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Diagnostic accuracy of CCTA-derived versus angiography-derived quantitative flow ratio (CAREER) study: a prospective study protocol

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ABSTRACT

Introduction Coronary CT angiography (CCTA)-derived quantitative flow ratio (CT-QFR) is a novel non-invasive technology to assess the physiological significance of coronary stenoses, which enables fast and on-site computation of fractional flow reserve (FFR) from CCTA images. The objective of this investigator-initiated, prospective, single-centre clinical trial is to evaluate the diagnostic performance of CT-QFR with respect to angiography-derived QFR, using FFR as the reference standard.

Methods and analysis A total of 216 patients who have at least one lesion with a diameter stenosis of 30%–90% in an artery with ≥2.0 mm reference diameter will be enrolled in the study. FFR will be measured during invasive coronary angiography. CT-QFR and QFR will be assessed in two independent core laboratories in a blinded fashion. The primary endpoint is the diagnostic accuracy of CT-QFR in identifying haemodynamically significant coronary stenosis with FFR as the reference standard. The major secondary endpoint is the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions.

Ethics and dissemination The study was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University (2020K192). Outcomes will be disseminated through publications in peer-reviewed journals and presentations at scientific conferences.

Trial registration number NCT04665817.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The diagnostic accuracy of coronary CT angiography (CCTA)-derived versus angiography-derived quantitative flow ratio (QFR) (CAREER) study is a prospective and observational study initiated by investigator.
⇒ This is a non-inferiority study comparing CCTA-derived QFR (CT-QFR) to QFR.
⇒ CT-QFR and QFR will be computed in a blinded fashion and compared with fractional flow reserve.
⇒ Differences in cultural, economic and social factors that affect patients' willingness to participate in the study will limit the inclusivity of the population.
⇒ Due to the tight schedule and insufficient funding, a multicentre study cannot be conducted at this time.

INTRODUCTION

Coronary CT angiography (CCTA) is a non-invasive test that enables visualisation of coronary anatomy and the characteristics of arterial plaques with high sensitivity and negative predictive value.[1] However, conventional CCTA does not allow for physiological assessment of coronary stenosis.[2] Fractional flow reserve (FFR) is the current gold standard for evaluating the physiological significance of coronary stenosis in the catheterisation laboratory.[3] An FFR-guided revascularisation strategy was validated with improved clinical outcomes and cost-effectiveness compared with a traditional invasive coronary angiography-guided strategy.[4–7] The use of FFR is supported by both European guidelines (Class I, Level of Evidence: A) and American guidelines (Class IIa, Level of Evidence: A) in assessing coronary stenosis and guiding revascularisation.[8] However, the adoption of FFR was limited due to prolonged procedural time, increased cost, patient discomfort and operator's confidence in visual assessment from coronary angiograms.

Several computational FFR methods were developed to overcome the above limitations. Quantitative flow ratio (QFR), a new method for fast computation of FFR based on invasive coronary angiography (ICA) and empirical fluid dynamic equations was recently developed.[9] The overall diagnostic concordance between QFR and FFR was reported as 87% in a recent meta-analysis of prospective clinical studies.[10]

More recently, CCTA-derived QFR, namely CT-QFR, has been developed as a method for fast computation of FFR from CCTA images based on a previously validated QFR algorithm. A recent retrospective and

observational study demonstrated a good diagnostic concordance of 87%.[11] In addition, its analysis time has been reduced to less than 5 min per patient on an off-the-shelf workstation. The diagnostic accuracy of this CT-QFR software version for on-site evaluation of coronary stenosis severity remains unknown. Furthermore, the differences in the diagnostic performance of QFR when applied to non-invasive CCTA images and ICA have not been studied. We are therefore planning to prospectively validate the diagnostic performance of on-site CT-QFR analysis compared with QFR, using FFR as the reference standard.

METHODS AND ANALYSIS

Study design

This study is an investigator-initiated, prospective, single-centre clinical trial to validate the diagnostic performance of on-site CT-QFR using FFR as the reference standard. The study is conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University. Before the study starts, a written informed consent form will be obtained from patients willing to participate in the study and approved by the institutional review board/independent ethics committee of Huadong Hospital Affiliated to Fudan University (2020K192). The protocol of the trial has been registered at http://clinicaltrials.gov.

Study objectives

The primary endpoint of the study is the patient-level diagnostic accuracy of on-site CT-QFR in identifying physiologically significant coronary artery stenosis, using FFR as the reference standard. The major secondary endpoint is the non-inferiority of CT-QFR compared with QFR in the vessels without extensively calcified lesions defined by the combination of a cross-sectional calcium arc >90° and a thickness >1.5 mm. Other secondary objectives of the study will include the following: (1) Other common measures of diagnostic performance of CT-QFR, including sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at the patient level compared with FFR as the reference standard. (2) Correlation between CT-QFR and FFR. (3) The comparison of the discrimination ability between CT-QFR, CCTA-derived per cent diameter stenosis (CTA-DS%) and quantitative coronary angiographic (QCA)-derived DS% for identifying physiologically significant stenosis with FFR as the reference standard.

Patient population

Patients with stable or unstable angina pectoris or non-acute phase of myocardial infarction who are undergoing CCTA examination and scheduled for coronary angiography within 30 days will be screened. We require the interval between ICA and CCTA to be less than 30 days which was in line with previous studies on CCTA-based FFR[12 13] to avoid a mismatch between CCTA images and invasive coronary angiography images due to the progression of the patient's coronary artery stenosis. Inclusion criteria are: (1) at least one lesion with DS% between 30% and 90% in a coronary artery with a ≥2.0 mm reference vessel diameter by visual estimation; (2) invasive coronary angiography performed less than 30 days after CCTA; (3) age over 35 years but less than or equal to 85 years. Exclusion criteria are: (1) prior percutaneous coronary intervention or coronary artery bypass graft of the interrogated lesion; (2) myocardial bridge involved in the interrogated vessel; (3) presence of collateral flow; (4) severe heart failure (New York Heart Association (NYHA) ≥III); (5) known severe renal failure (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2); (6) contraindicated to use contrast agents, beta-blockers, nitrates or adenosine drugs; (7) recent prior myocardial infarction within 1 month of CCTA; (8) low image quality CCTA or coronary angiography to be assessed such as motion artefacts, poor filling of contrast agent and so on; (9) any factors that affect the image quality of CCTA and coronary angiography, such as frequent premature contractions, atrial fibrillation and so on. Patients with comorbidities such as diabetes mellitus, hypertension or other chronic diseases, in particular, will not be excluded in this study because the coronary haemodynamics and image quality of CCTA and ICA will not be significantly influenced by these comorbidities.

Statistical hypotheses and sample size calculation

The primary endpoint is the diagnostic accuracy of CT-QFR ≤0.8 to identify haemodynamically significant coronary stenosis with FFR ≤0.8 as the reference standard. The trial is powered for testing the significance of the primary endpoint. The primary null and alternative hypotheses to be tested are H0, diagnostic accuracy of CT-QFR ≤0.72, and H1, diagnostic accuracy of CT-QFR >0.72. Estimates for the sample size calculation are based on the results from the retrospective study of CT-QFR,[11] where an accuracy of 87% at the patient level was found. In this prospective study, the accuracy is conservatively estimated as 82% for the consecutively enrolled patient population, and with a target value set as 72%, which is chosen to be higher than the one in the DeFACTO study.[14] The sample size is analysed for paired proportions using the following formula:

$$N = \frac{\left[Z_{1-\alpha/2}\sqrt{P_0(1-P_0)} + Z_{1-\beta}\sqrt{P_T(1-P_T)}\right]^2}{(P_T - P_0)^2}$$

With power=0.90, two-tailed alpha=0.05, a total of 188 patients with paired CT-QFR and FFR are required to reject the null hypothesis for diagnostic accuracy. To account for incomplete CT-QFR/CT-DS%/FFR/QFR/QCA data of 15% at most, a total of 216 patients needs to be enrolled.

The major secondary endpoint is to validate the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions. Analysed by the

enrolment of 216 patients, about 158 patients will be calculated according to the proportion, 26.9%, of extensively calcified lesions from the retrospective study.[11] It will be tested for the capability of achieving the major secondary endpoint. The accuracy of 89.5% for CT-QFR in non-severe calcified lesions[11] and the accuracy of 92.7% for QFR[15] are used to calculate the sample size. We set the non-inferiority threshold as 15%. It will be analysed by the following formula:

$$N_T = \frac{(Z_{1-\alpha/2}+Z_{1-\beta})^2\left[P_C(1-P_C)+P_T(1-P_T)\right]}{(D-\Delta)^2}$$

With power=0.90, two-tailed alpha=0.05, a total of 122 patients are required to validate the non-inferiority. To account for incomplete CT-QFR/CTA-DS%/FFR/QFR/QCA data of 15% at most, 141 patients need to be enrolled. Therefore, 158 patients without extensively calcified lesions meet the sample size of the major secondary endpoint. Thus, the sample size is set as 216 patients to satisfy the requirements for validating both primary and major secondary endpoints.

CCTA and CTA-DS% Analysis

CCTA will be performed on a dual-source CT system (SOMATOM Drive; Siemens Healthineers, Erlangen, Germany) or a 256 detector row scanners CT system (Revolution CT; GE Healthcare) with prospective or retrospective electrocardiographic gating in accordance with Society of Cardiovascular CT guidelines.[16] Image interpretation of CCTA will be conducted in a blinded fashion by an experienced investigator. Images with coronary artery stenosis detected visually will be further analysed (CtaPlus; V.1.0, Pulse Medical Imaging Technology, Shanghai, China). Coronary stenosis will be quantified by using the following parameters: (i) the minimal lumen area (MLA) and the minimal lumen diameter (MLD) and (ii) the DS% and the percentage area stenosis (AS%).

CT-QFR computation

CT-QFR computation will be performed by experienced analysts using a recently developed software package (CtaPlus, V.1.0; Pulse Medical Imaging Technology, Shanghai, China), blinded to both QFR and FFR data. Detailed methodologies for CT-QFR computation have been published previously.[11] A recent upgrade in the CT-QFR algorithm integrated deep learning technique into the coronary segmentation method to improve the computation efficiency. Manual corrections are allowed if the automated delineation lumen contour is suboptimal, particularly at the segment with calcified plaques. All coronary artery segments with reference lumen diameter ≥1.5 mm are analysed. Subsequently, all the delineated coronary branches are automatically merged for the reconstruction of the entire coronary tree, based on which the healthy reference lumen is also reconstructed. Finally, the CT-QFR value at each position of the coronary tree is computed using the previously validated QFR algorithm.[9 17]

Coronary angiography

Coronary angiography will be performed by using a 5-F or 6-F catheter with a transfemoral or transradial approach. All patients will receive an intravenous injection of heparin 100 IU/kg before angiography. Contrast media (Omnipaque 350 injection, GE Healthcare, Shanghai, China) will be injected manually with a forceful and stable injection. Coronary angiograms will be obtained from standard series of six to eight projections for the left coronary artery and two or three projections for the right coronary artery by using a monoplane or biplane radiographic system (AXIOM Artis FC and Artis zee Biplane MN, Siemens) at 15 frames/s. All images will be digitally stored for analysis.

FFR measurement

Intracoronary pressure will be measured by using a RadiAnalyzer Xpress instrument and Certus pressure wire (St. Jude Medical, Plymouth, Minnesota, USA). The pressure guidewire will be introduced into the coronary artery and positioned distal to the coronary stenosis. The position of the sensor of the pressure guidewire will be recorded on cine fluorography. Hyperaemia will be induced by ATP infusion (160 µg/kg/min) through an antecubital vein over a minimum of 2 min. During steady-state hyperaemia, mean proximal aortic pressure and mean intracoronary pressure distal to the target stenosis will be measured. Subsequently, the pressure guidewire will be slowly pulled back from the most distal to the proximal part of the artery by manual procedure during steady-state maximal hyperaemia. If the pressures are not equalised at the end of the pullback (ie, the pressure drift |Pa-Pd|>3 mm Hg), the whole FFR measurements should be repeated from the beginning.

QCA analysis and QFR computation

QCA analysis and QFR computation will be performed in a blinded fashion by using the recently developed QFR analysis system (AngioPlus Core; Pulse Medical Imaging Technology, Shanghai, China). The computational methods were previously described.[9 15] Same as CT-DS% analysis, QCA analysis includes the following parameters: (i) MLA and MLD, and (ii) DS% and AS%. It will be analysed by well-trained technicians who have successfully completed QFR training. Before QFR analysis, the technicians will be informed about the location where the operators measured FFR so that QFR could be measured at the same vessel site. The QFR measure will be performed on the system placed in the control room. The investigators will be blinded to the FFR results.

Study flowchart

A study flowchart is shown in figure 1.

Statistical analysis

Continuous variables are presented as mean±SD, and categorical variables will be presented as counts and percentages. Sensitivity and specificity to predict functionally significant stenosis (FFR ≤0.80). The performance

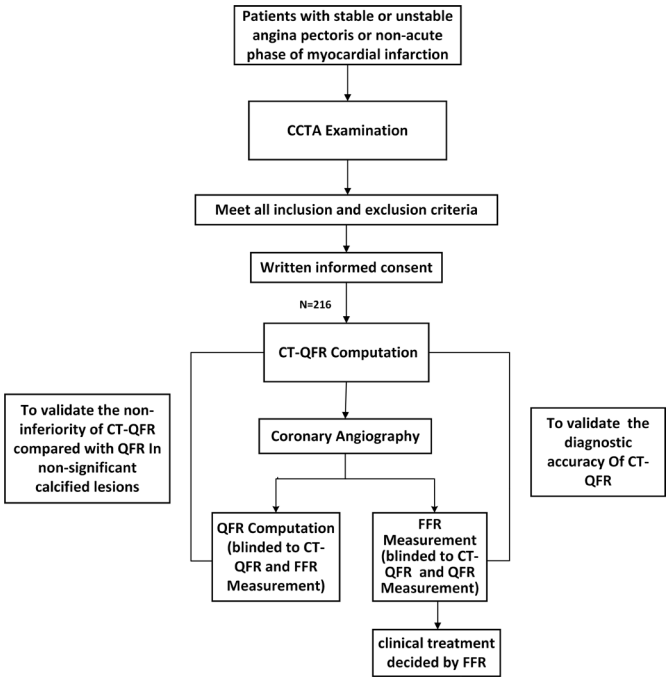

Figure 1 Study flowchart. CCTA, coronary CT angiography; CT-QFR, CCTA-derived QFR; FFR, fractional flow reserve; QFR, quantitative flow ratio.

of QFR ≤0.80 and CT-QFR ≤0.80 for predicting FFR ≤0.80 will be assessed by using sensitivity, specificity, PPV, NPV, positive likelihood ratio, negative likelihood ratio and diagnostic accuracy, together with their 95% CIs. Pearson correlation or Spearman's correlation will be used to quantify the correlations between QFR, CT-QFR and FFR. Agreements between QFR, CT-QFR and FFR will be assessed by the Bland-Altman plot. The Bland-Altman plot depicts the differences of each pair of measurements versus their mean values with reference lines for the mean difference of all paired measurements. The limits of the agreement will be defined as mean±1.96 SD of absolute difference. The receiver operating characteristic (ROC) curve analysis will be performed to assess the area under the curve of CT-QFR, QFR, CT-derived %DS and QCA-derived %DS for predicting FFR ≤0.80. The ROC curves will be compared by using the DeLong method. A two-sided p value<0.05 will be considered to indicate statistical significance.

Current status

The study has been approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University. Five analysts have successfully completed the International Course on Coronary Image Analysis and Computational Physiology which covers FFR, QFR and CT-QFR. All of them have passed the final examinations (with the diagnostic accuracy higher than 85% and the SD of mean difference less than 0.05 between image-based FFR and invasive FFR) and obtained qualification certificates for relevant analysis. Recruitment is ongoing at Huadong Hospital Affiliated to Fudan University, Shanghai, China. At the time of submission of this manuscript, 35 participants have been recruited for the study.

DISCUSSION

The CAREER study will for the first time prospectively evaluate the diagnostic accuracy of on-site CT-QFR analysis in identifying patients with physiologically significant coronary stenosis. In addition, the diagnostic performance of CCTA-based versus angiography-based QFR in vessels without significantly calcified lesions will be compared. The study findings will provide pivotal data to support the clinical applications of CT-QFR in the management of patients with coronary artery disease (CAD).

The previously presented FFR computation method derived from CT (FFR_{CT}), a non-invasive technology, is a computational fluid dynamic modelling technique that enables the calculation of FFR from a coronary computed tomographic angiographic data set.[18] The diagnostic performance of FFR_{CT} has been validated in several multicentre prospective clinical trials.[12 19 20] The application of FFR_{CT} can reduce unnecessary invasive coronary angiography.[21 22] However, it heavily relies on the quality of the underlying computational models and sophisticated boundary conditions and required a few hours for computation.[20] Moreover, severely calcified lesions might affect the calculation results of FFR_{CT}.[23]

Recently, a novel technique for the rapid computation of FFR from radiographic coronary angiography, named QFR, was accomplished by estimating the pressure drop due to coronary stenosis according to coronary lumen morphology and virtual hyperaemic flow derived from contrast frame count without the use of pressure wire and drug-induced hyperaemia.[9] The diagnostic performance of this minimally invasive technique has been validated by several studies.[9 15 24 25] More recently, the novel QFR algorithm has been applied to CCTA-images, and namely CT-QFR, has been derived as a non-invasive technology to assess the physiological significance of coronary stenoses.[10] The patient-specific virtual hyperaemic flow was used to compute the CT-QFR value at every position of the reconstructed coronary tree. A recent retrospective and observational study with 156 vessels from 134 patients demonstrated good correlation (r=0.79; p<0.001) and agreement (0.00±0.06; p=0.823) between CT-QFR and wire-based FFR, with a vessel-level diagnostic concordance of 87%.[11] The average analysis time for CT-QFR was reported as less than 20 min, with the CT-QFR pullback curve computed in less than 20 s.[11]

A recent upgrade in the CT-QFR algorithm integrated deep learning technique into the coronary segmentation method thus improving the accuracy of automatic lumen delineation and reducing the analysis time to less than 5 min per patient on an off-the-shelf workstation. The incorporation of the deep learning techniques in the CT-QFR algorithm had the potential to improve the calculation efficiency significantly. Large-scale studies have shown that the application of CT-FFR can reduce

unnecessary invasive coronary angiography. At the same time, it brings higher health and economic benefits.[21 26] The 1 year follow-up of the ADVANCE study showed that the Major Adverse Cardiovascular Events (MACE) of patients with a CT-FFR value ≤0.8 was significantly higher than that of patients with a CT-FFR value >0.8[27]. Therefore, a kind of strategy pertaining more to a rapid diagnosis, reduced invasive strategy and lower costs is particularly important. This study will prospectively validate the diagnostic efficacy of such a faster computational approach to derive FFR from CCTA with can be onsite for the first time.

Furthermore, severe calcification will affect the diagnosis of lesions on CT images. It was proved that the presence of extensively calcified lesions influenced the diagnostic accuracy and analysis variability.[11] Therefore, we intend to avoid the effects of severe calcification so as to define whether CT-QFR is equivalent to QFR. It's also the first time to compare the diagnostic performance of CCTA-derived QFR with angiography-derived QFR. Therefore, the major secondary endpoint was intended to investigate the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions.

This study will lay the foundation for future studies to look at the potential value of CT-QFR technology in patient management. If the study achieves the expected objectives, outpatients can receive coronary artery functional evaluation while undergoing CCTA examination. It can greatly reduce unnecessary invasive coronary angiography and coronary interventions.

ETHICS AND DISSEMINATION

This research will not increase the risk and economic burden on patients and the patients' rights will be fully protected. The study is conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University (ref. number 2020K192). All patients will provide written informed consent. The results of this study are to be published in respected, peer-reviewed journals and the findings presented at scientific conferences in the field of cardiology.

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Contributors XQ and ST participated in study design, statistical hypotheses and sample size calculation. TW and QG participated in manuscript preparation, sample size calculation and writing the protocol of fractional flow reserve (FFR) measurement. ZL was involved in manuscript preparation, writing the protocol of quantitative flow ratio (QFR) computation and CT-QFR computation. XZ was involved in writing the protocol of FFR measurement. ML, LQ and CL participated in writing the protocol of coronary CT angiography analysis. SG, WH, YC, LZ, XC was involved in writing the protocol of coronary angiography.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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