

CT Determination of Fractional Flow Reserve in Coronary Lesions

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ABSTRACT

Invasively determined fractional flow reserve (FFR) represents the gold-standard method for the functional evaluation of coronary lesions. Coronary computed tomography angiography (CCTA) provides characterization of the coronary anatomy, with important morphological information on the atherosclerotic plaques, but does not offer a hemodynamic evaluation of coronary artery lesions. CT evaluation of FFR (FFRCT) is a new noninvasive diagnostic method, which provides anatomical and functional assessment of the whole coronary tree, based on computational techniques, with no more radiation or hyperemic agent administration compared with routine CCTA. Recent studies demonstrated the safety and accuracy of FFRCT and its therapeutic use and cost benefits in real-world clinical use.

Keywords: FFRCT, cardiac computed tomography angiography, coronary angiography, hemodynamics, revascularization, PCI

INTRODUCTION

Numerous diagnostic modalities are available for analyzing the anatomical severity of a coronary stenosis. Coronary computed tomography angiography (CCTA) and invasive coronary angiography (ICA), combined with modern imaging tools including optical coherence tomography (OCT) and intravascular ultrasound (IVUS), are useful methods for identifying anatomically significant lesions, but none of these methods offer information about their hemodynamic consequence.¹

In current clinical practice, fractional flow reserve (FFR) — the maximum blood flow through a stenosed coronary artery, determined invasively as the ratio between distal coronary artery and intra-aortic pressure during maximum hyperemia — is used for the functional estimation of intermediate coronary artery stenoses. An FFR index of <0.8 is considered functionally significant.² The European guidelines for myocardial revascularization indicate FFR as a class Ia recommendation for identifying functional coronary lesions in stable patients

without evidence of ischemia and a class IIa recommendation for the decision-making process of either opting for revascularization or pharmacological treatment.³

USEFULNESS OF FFR IN CLINICAL PRACTICE

Several trials have proved the clinical utility of FFR in guiding the treatment decision. Pijls *et al.* presented the results of the DEFER trial (Deferral of PTCA versus performance of PTCA), which enrolled 325 subjects with single-vessel coronary artery stenosis. FFR was performed for all lesions. If the FFR ratio was >0.75 , the patient was randomized to the Defer group ($n = 91$), with deferral from PTCA, or to the Perform group ($n = 90$), where PTCA was performed immediately. If the FFR was <0.75 , the patient was included in the Reference group ($n = 144$), where PTCA was performed as planned. Clinical follow-up was obtained at 5-years, and no differences were recorded between the Defer and Perform groups regarding the event-free survival rates (80% vs. 73%; $p = 0.52$), but these were higher in the reference group (63%; $p = 0.03$). The rates of cardiac mortality and myocardial infarction did not differ between the two groups (Defer – 3.3% vs. Perform – 7.9%; $p = 0.21$), but were meaningfully inferior in the Reference group (15.7%; $p = 0.003$ vs. the Defer and Perform groups).⁴ This study concluded that deferral from PCI in patients with FFR >0.75 is safe, with good long-term clinical outcomes, and that FFR can recognize patients who will benefit from PTCA. Another benchmark FFR study was performed by Pijls *et al.* in the FAME trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation), which investigated the clinical outcome of FFR-guided PTCA versus the standard, angiography-guided PTCA in patients with multi-vessel coronary atherosclerosis. During the 2-year follow-up, the percentage of deaths and myocardial infarctions (MI) were inferior in the FFR-guided PTCA with drug-eluting stents group (12.9% vs. 8.4%; $p = 0.02$).⁵ The 5-year follow-up proved that FFR-guided PCI is safer.⁶ Further inquiry was performed in the FAME 2 trial, which included 1,220 patients scheduled for DES-PCI and compared the long-term clinical outcome of FFR-guided PCI versus optimal pharmacological therapy in patients with stable coronary artery disease (CAD). Patients with at least 1 functional lesion (FFR ≤ 0.8) were randomized to PCI with optimal drug therapy or pharmacological treatment alone ($n = 888$). Patients with FFR >0.8 were included in the registry group and received optimal medical treatment alone ($n = 332$). At 2-year follow-up, there was no substantial difference between the two randomized groups regarding the

mortality and MI rates, but there was a substantial difference in the rate of emergency revascularization (4.0% vs. 16.3%; $p < 0.001$).^{7,8}

Multiple clinical trials have proven that the routine use of FFR (as gold-standard for the evaluation of hemodynamic significance of a coronary lesion) in guiding and optimizing PCI has improved the clinical outcome of patients and is currently one of the most solid recommendations in current guidelines for a revascularization.⁹

THE NEED FOR NONINVASIVE FFR DETERMINATION

With the evolution of noninvasive imaging techniques in the last decade, CCTA became an important and reliable diagnostic tool for identifying low- and intermediate-risk CAD patients.¹⁰ Current ESC guidelines give CCTA a Class IIa recommendation with C level of evidence in patients with intermediate risk for CAD as a substitute for stress imaging techniques, given its high specificity and sensitivity.^{11–13} CCTA also demonstrated its reliability in the long-standing follow-up period of these individuals, as its high negative predictive value (NPV) can rule out long-term adverse events.^{14,15}

Although CCTA can provide accurate 3D anatomic evaluation of the coronary arteries, determining the extent of luminal stenosis with plaque morphology characterization, numerous studies comparing CCTA- and ICA- assessed stenoses with invasive FFR determination demonstrated that the severity of coronary lesions does not always reflect the hemodynamic significance of a plaque.^{16–19} Meijboom *et al.* evaluated 89 lesions which caused $\geq 50\%$ luminal stenosis assessed by CCTA and concluded that only 49% of these lesions were functionally significant, with a measured FFR <0.75 .²⁰

Having these aforementioned tools, the development of a noninvasive technique that is able to offer both anatomical and functional evaluation of coronary lesions was imperative.

THE CONCEPT OF FFRCT

Fractional flow reserve derived from CCTA (FFRCT) is calculated using the same images as for the reconstruction of coronary arteries, without additional radiation exposure, acquisition protocol modifications or administration of hyperemic agents, using computational flow dynamics and can be determined in any point of the coronary artery system.²¹

Currently two methods are available for determining FFRCT. The first one is based on an off-site supercomputer

system analysis developed by HeartFlow Inc. (Redwood City, California, USA), which provides 3D modeling anatomical and functional evaluation of the whole coronary tree in approximately 1 or 2 days. The second one is an on-site workstation by Siemens (Forchheim, Germany), which provides 1D anatomical and functional analysis.²²

The calculation for FFRCT requires: (A) a patient-specific anatomic model of the coronary artery system, obtained and processed (with segmentation algorithms, luminal boundary extraction of the main and side branches, identifying and analyzing coronary plaques in every artery, followed by generation of a geometric modeling mesh fitted to the segmented data) from the recorded CCTA images;^{23,24} (B) a physiological model of the coronary blood flow, which requires the CCTA determination of the myocardial wall volume, the coronary resistance of each vessel (which is inversely proportional to the dimension of the artery), the pressure in the aorta (approximated from the average brachial artery pressure), and simulation of a maximum hyperemic state, when the resting microcirculation resistance is reduced; (C) a numerical equation to analyze the laws that govern fluid dynamics. These computations can be done by modeling fluid dynamics using the Navier-Stokes equations.²⁴

Good-quality CCTA images are essential for FFRCT determination, as all computations are based on the acquired images. Appropriate patient selection and preparation is necessary for reduction of technical errors and artifacts. Even with recent advanced techniques, 10–13% of patients included in large studies were excluded due to poor image quality.²²

ACCURACY OF FFRCT

Several multi-center studies were conducted in the past years for assessing the diagnostic precision of FFRCT compared to the standard, invasively measured FFR.^{25–27}

A meta-analysis on three prospective multi-center FFRCT trials (NXT – Analysis of Coronary Blood Flow Using CT Angiography: Next Steps; DISCOVER-FLOW – Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive Fractional Flow Reserve, and DeFACTO – Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography) was recently published by Li *et al.*, analyzing the diagnostic accurateness of FFRCT compared to invasively determined FFR (gold standard) and CCTA. The meta-analysis concluded that FFRCT demonstrated a high diagnostic capacity in determining coronary ischemia, with improved accuracy and specificity compared to CCTA. FFRCT may also reduce

the false-positive results for patients with functionally non-significant lesions.²⁸

The most recent and also largest NXT study, which included 254 patients revealed a significantly higher diagnostic accuracy for FFRCT compared to CCTA alone, with a higher specificity (79% vs. 34%, $p < 0.001$) and similar sensitivity (86% vs. 94%, $p = \text{NS}$). The link between FFRCT and FFR was also more significant than in previous studies.²⁷

Severe calcifications can alter the acquisition of CCTA images, with lower specificity and sensitivity causing a reduction in its diagnostic accuracy. In patients with an Agatston score of >400–600, the specificity of CCTA can drop down to 35–48%.^{29,30} In a substudy of the NXT trial for patients with Agatston scores of over 400, no significant drop in accuracy, sensitivity and specificity was recorded in the FFRCT group compared to the CCTA group (75%, 88% and 69% vs. 44%, 94% and 23%, respectively).²⁷ This benefit was maintained at higher Agatston scores in favor of FFRCT compared to CCTA alone.³¹

In a study that analyzed 44 patients with pre- and post-virtual PCI FFR values using computational fluid dynamics, Kim *et al.* detected a 96% sensitivity with a 100% specificity of CT-derived FFR. Thus, FFRCT may be useful for identifying patients who may benefit from revascularization and for prediction and optimization of PCI outcomes.^{32–34}

CLINICAL BENEFITS OF FFRCT

In the recent PLATFORM trial (Prospective Longitudinal Trial of FFRCT: Outcome and Resource Impacts), which enrolled 584 patients with stable CAD, Hlatky *et al.* assessed the outcomes and resource use of FFRCT compared to other invasive and noninvasive techniques for a 90-day follow-up period. Seventy-three percent of patients that had been referred directly for ICA, had no significant coronary lesions (>50% stenosis), compared to only 12% in the FFRCT group. FFRCT results changed the therapeutic approach in 61% of cases, with cancelling of invasive diagnostic procedures, but the rate of revascularization by PCI or coronary artery bypass grafting was not significantly different between the two study lots (31.6% in the ICA group vs. 28.5% in the FFRCT group). No MACE were registered in subjects in whom ICA was different based on the FFRCT results.^{35,36}

A substudy of the PLATFORM trial assessed the costs and quality of life for patients undergoing FFRCT compared to other invasive and noninvasive techniques for a 90-day follow-up period. FFRCT was associated with bet-

ter improvement in quality of life compared to other non-invasive techniques. FFRCT costs and resource use were 20% lower compared to ICA during the follow-up period.³⁷

CONCLUSIONS

Among the current noninvasive diagnostic techniques, FFRCT represents the only reliable method for anatomical and functional assessment of CAD patients. There are no current guideline recommendations on the use of FFRCT, but current studies have demonstrated the safety and usefulness of this new technique. FFRCT can reduce the number and cost of unnecessary invasive diagnostic procedures and can provide useful information on the decision for revascularization and optimization of treatment. Further studies are required for the elaboration of guideline recommendations.

CONFLICT OF INTEREST

Nothing to declare.

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