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REVIEW

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Noninvasive Assessment of Coronary Artery Disease: Fractional Flow Reserved Derived from Coronary Computed Tomography Angiography (FFRCT)

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ABSTRACT

Invasive coronary angiography (ICA) completed by fractional flow reserve (FFR) assessment represents the main procedure that is performed in the decision process for coronary revascularization. Coronary Computed Tomography Angiography (CCTA) is an effective method used in the noninvasive anatomic assessment of coronary artery disease (CAD). However, CCTA tends to overestimate and does not offer hemodynamic data about the coronary lesions. Recent progresses made in the research involving computational fluid dynamics and image modeling permit the evaluation of FFRCT noninvasively, using data obtained in a standard CCTA. Studies have shown an improved precision and discrimination of FFRCT compared to CCTA for the diagnosis of significant coronary artery stenosis. In this review, we aimed to summarize the role of CCTA in CAD evaluation, the impact of FFRCT, the scientific basis of this novel method and its potential clinical applications.

Keywords: FFRCT, computational fluid dynamics, coronary artery disease

BACKGROUND

Cardiovascular disease (CVD) remains the leading cause of death in Europe and around the world. In particular, coronary heart disease (CAD) has the highest incidence among all cardiovascular diseases, representing 46.2%.[1] CAD develops silently over the years, with a long asymptomatic phase before clinical presentation, which has a wide spectrum, ranging from stabile angina to sudden cardiac death. The underlying condition of CAD is represented by coronary stenosis due to vascular atherosclerosis.

CAD investigation and treatment remain points of interest due to the high morbidity and mortality associated. Evaluation of coronary stenosis in order to identify patients, which will develop major cardiovascular events represents a challenging topic in cardiovascular and imaging research, essential in the prevention of CAD. Early recognition of clinically significant coronary stenosis is of great importance in patient work-up.

Invasive coronary angiography (ICA) is the main investigation method in the diagnosis of patients with suspected or known coronary stenosis, having the advantage of guiding interventional revascularization in the same intervention.[2,3] In order to characterize lesions according to their hemodynamic effects, ICA can be aided by functional flow reserve (FFR).

Computed Tomography Angiography (CTA) development offered the possibility of noninvasive evaluation of coronary arteries, and has emerged, nowadays, as an effective method in CAD and cardiovascular risk assessment.[4] CCTA offers data about coronary anatomy and is useful in plaque characterization. However, it does not offer information about the hemodynamic impact of stenotic lesions.

Developments in computational fluid dynamics and image-based simulations have lead to the possibility of obtaining data about the hemodynamic impact of coronary stenosis, by determining FFR noninvasively based on a CCTA examination.[2]

In this review, we aimed to summarize the contribution of CCTA in coronary plaque characterization, the impact of FFRCT in cardiovascular patients evaluation, the scientific basis of this noninvasive method, the benefits in therapeutic decisions of this new technique, and its potential clinical applications.

INVASIVE EVALUATION OF CAD

ICA is considered the standard evaluation used in CAD diagnosis. By visual estimation, it appreciates coronary stenosis according to luminal diameter narrowing. Using X-rays and a radiopaque contrast medium, ICA offers information about occlusion percentage, and provides a road map for therapeutic strategies. However, it is known to have limited value in offering functional information about coronary stenotic lesions.[5]

Besides detecting coronary stenosis, identifying the hemodynamic impact was established as the most important factor in patient outcome.[6] Even if the association between coronary stenosis and coronary flow was demonstrated and was considered more predictable for lumen diameter narrowing over 70%, the degree of coronary stenosis that causes significant reduction in the flow and subsequent ischemia is variable, especially in moderate severity lesions (30–70%).[7–9] Recent studies revealed an unreliable relationship between stenosis severity and ischemia.[5]

Revascularization decision requires objective evidence of ischemia.[5] Percutaneous coronary revascularization is indicated for hemodynamically significant stenotic lesions that produce ischemia, while in hemodynamically nonsignificant lesions, medical therapy is preferred.[10] Therefore, assessing the functional implication of stenotic lesions is the key for therapeutic decision and can be assessed by determination of FFR during ICA.

By definition, FFR is the ratio between the maximum blood flow in a narrowed artery and the maximum blood flow in the same artery in the absence of stenosis. It is measured using a catheter with a pressure sensor that records the gradient across a stenosis, after the induction of maximal hyperemia with vasodilating agents (usually adenosine), the normal value being 1.0, regardless of the patient, the vessel or the blood pressure.[11] FFR values lower than 0.75 are considered to associate ischemia, while values over 0.80 are considered negative for ischemia.[12] Studies have shown that revascularization of positive FFR stenosis significantly decreased ischemia and improves patient outcome, while postponing the stenting of negative FFR stenosis is safe and has an excellent outcome.[13,14] Also, reperfusion therapy for lesions that do not induce ischemia, has no clinical or survival benefits compared to pharmacological treatment only, and it exposes patients to unnecessary procedure risks, highlighting the need of functional evidences prior to revascularization.[15]

As it indicates ischemia determined by a specific lesion, FFR emerged as an independent predictor in patient outcome and is currently considered the gold standard for revascularization decision.[2,4] Interventions guided by invasive FFR had an improved event-free survival and reduced costs, compared with revascularization based only on ICA.[16,17]

However, ICA is an invasive method with limitations, including underestimation of stenosis due to lack of visualization, extended costs for the numerous resources used in FFR measurement, and known risks that include radiation and a small possibility of secondary major complications.[18]

NONINVASIVE CCTA EVALUATION OF CAD

CCTA has emerged as a valuable instrument in the noninvasive evaluation of patients with low and intermediate risk of CAD. Recent technological progression, including mechanical and software advances, improved not only CCTA acquisition parameters, which can be obtained now during a single breath-hold with reduced radiation dose, but also reconstruction image quality.[19]

Lesion complexity (including location, vessel tortuosity and major calcifications) was indicated to influence not only interventional treatment procedure complexity, but also short- and long-term outcomes, and preprocedural CCTA patient evaluation and lesion characterization became an important step in PCI planning.[20,21]

With improved spatial and temporal resolution, CCTA offers three-dimensional images of the coronary arteries and may characterize stenotic lesions. CCTA provides a detailed anatomic evaluation of coronary artery lesions, identifying the extent of the stenosis and its severity. More than 70% luminal narrowing of the coronary arteries is widely accepted as the anatomical threshold for significant CAD.[12] However, studies showed that CCTA severe stenoses are only modestly predictive of ischemia.[4] CCTA is also useful to assess stenotic lesions according to plaque morphology.[22] By measuring tissue densities, CCTA is useful in evaluating the content of coronary lesions, appreciating low-attenuation components and spotty calcifications, identified as indicators of high risk plaque, as well as other characteristics such as positive remodeling and aggregate plaque volume, factors that may relate to lesion-specific ischemia.[23,24]

CCTA is an accurate procedure; a recent meta-analysis which quantified the diagnostic performance of CCTA by using ICA as reference, reported high sensitivity, specificity, positive and negative predictive values of 97%, 90%, 93% and 96% respectively.[25] A limitation of CCTA is overestimation of CAD incidence and degree, due to blooming artifacts from calcium deposits or moving artifacts. This may significantly increase false positive diagnosis rates, and leads to unnecessary ICA and revascularization.[26]

Assessing the hemodynamic significance of coronary stenosis is a critical step in therapeutic decision.[9] Several noninvasive methods including MRI, IVUS and SPECT provide functional information about CAD, but they do not visualize coronary stenosis directly, offering a complex assessment of coronary lesions. In order to have a complete characterization of CAD, hybrid imaging was developed, but it requires two methods: CCTA for the anatomic evaluation and stress tests for physiologic information.

Obtaining functional information and an anatomic characterization of coronary lesions using a single noninvasive method is one of the most challenging topics in recent cardiovascular imaging research.

Recent improvements in computational fluid dynamics applied for the coronary flow, and development of image-based modeling enabled calculation of FFR noninvasively, using data acquired during a standard CCTA, without additional imaging, medication, contrast or radiation.[27]

Scientific Basis for FFRCT

Developers of this new method established that FFRCT computation requires three elements: (1) construction of a 3D anatomical prototype of the coronary arteries; (2) a mathematical model of coronary physiology and (3) a numerical formula to explain the laws of physics involved in fluid dynamics.[27] The first two elements are specific to each patient, while the equations describing blood flow dynamics are universal and can be applied in different patients.

The 3D patient-specific anatomic model is obtained by processing image data acquired during CCTA. Construction involves segmentation algorithms, which extract the luminal boundary of coronary arteries and their branches, followed by the discretization phase, when a geometrical triangular network is fitted to the segmented data.[12] Good quality images are the key element of a valuable FFRCT as all the following computations are based on them.

Computational simulations of flow and pressure in the coronary tree are based on the universal Navier-Stokes equations that rule fluid dynamics. They describe the correlation between conservation of mass and balance of momentum, explaining coronary flow and pressure as a function of three spatial coordinates and time, with blood considered as a Newtonian fluid. Because they are nonlinear partial differential equations, they can only be elucidated under ideal conditions. For a coronary model specific for a patient, a mathematical approximation method must be used for velocity and pressure at a finite number of points. This entails resolving millions of equations and repeating the process thousands of times during one cardiac cycle.[7] To facilitate these calculations, boundary conditions need to be set.

In order to generate a personalized prototype for coronary physiology, the boundary conditions include: cardiac output, aortic pressure and microcirculatory resistance, and they have to be assigned taking into account three underlying principles. Firstly, the total coronary blood stream at rest can be quantified from the myocardial mass determined by CCTA. The second principle states that the microvascular bed at rest is inversely proportional to the coronary artery dimension, thus the vascular caliber adapts to the amount of flow they carry. Thirdly, the microcirculation has a foreseeable vasodilatatory answer to adenosine, which allows the simulation of maximal hyperemia state in the computational model.[28]

Finally, the integration of the dynamic physiological model of coronary flow to patient-specific anatomy allows FFRCT computation as the ratio of coronary pressure to aortic pressure under simulated maximal hyperemic conditions.

Clinical Performance of FFRCT

The diagnostic capacity of FFRCT in patients with assumed CAD has been tested in four multicenter prospective studies: DISCOVER-FLOW — 'Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive Fractional Flow Reserve', DeFACTO — 'Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography', NXT — 'Analysis of coronary Blood Flow Using CT Angiography, Next Steps' and PLATFORM — 'Prospective Longitudinal Trial of FFRCT: Outcome and Resource Impacts'.

The first trial, DISCOVER-FLOW was conducted in 4 centers and it compared the diagnostic performance of FFRCT versus CT in assessing stenosis severity, using invasive FFR as a reference. The study included 103 patients with known or suspected CAD, for which CT, ICA, invasive FFR measurements and computation of FFRCT was performed. The results showed a superior diagnostic performance of FFRCT compared with CCTA alone, with a diagnostic accuracy of 84% for FFRCT compared with 59% for CCTA.[29]

Subsequently, the DeFACTO trial, which included 252 patients with known or suspected CAD, from 17 centers, compared the diagnostic performance of FFRCT in identifying hemodynamically significant coronary stenosis, to the standard FFR, assessed invasively. By individually analyzing each patient, FFRCT was superior to CCTA in identifying ischemic lesions, in terms of sensitivity (90% vs. 84%), specificity (54% vs. 42%), PPV (67% vs. 61%) and NPV (84% vs. 72%). The trial showed an improved accuracy in diagnosis for ischemia-causing stenosis of FFRCT (73%) compared to CCTA alone (64%). Also, FFRCT presented superior ability to discriminate between patients with or without ischemia. A particular aspect was demonstrated in patients with intermediate stenosis, where sensitivity increased more than 2-fold, with no loss of specificity.[30]

The NXT trial is the largest one, incorporating results from two previous studies that used FFRCT computation as the latest generation technique. NXT is a study designed to assess the diagnostic ability of FFRCT in detecting flow-limiting obstructive coronary lesions, compared to the reference standard, which is invasively measured by FFR. Two hundred fifty-four patients from 10 sites underwent ICA with FFR, CCTA and FFRCT computation. Compared with previous studies, NXT integrated technological improvements in physiologic modeling and focused on the quality of the CCTA images that were used. The primary end-point of the study was to determine the diagnostic performance of noninvasive FFRCT compared with coronary CCTA alone, and to determine the presence of hemodynamically significant coronary lesions. The second objective was to assess the diagnostic precision, sensitivity, specificity, PPV and NPV of FFRCT. The NXT trial demonstrated a good correlation between invasive and noninvasive FFR.[31] A substudy of the NXT trial revealed that there were no differences in FFRCT diagnostic accuracy, sensitivity, specificity, PPV and NPV in patients with high Agatston scores that indicate coronary calcifications.[32]

The latest published trial, PLATFORM, was performed in 11 centers from Europe and evaluated 584 patients with stable CAD, in order to determine the effect on cost and quality of life by using FFRCT compared to usually used methods. The study concluded that an evaluation strategy based on FFRCT was associated with lower costs within 90 days and less resource use than evaluation with ICA. Also, patients who underwent FFRCT showed a greater improvement in their quality of life compared to those with usual noninvasive assessment.[33]

Currently, there are no guidelines to provide recommendations about FFRCT in clinical settings. FFRCT testing should be used for intermediate stenosis, where studies demonstrated higher diagnostic performance and CAD guidelines recommend additional ischemia testing. FFRCT interpretation is referred to the same value as invasive FFR: stenoses with an FFRCT lower than 0.75 in general cause ischemia, while lesions with FFRCT higher than 0.80 rarely present hemodynamic significance. For a FFRCT value between 0.75 and 0.80 therapeutic decisions should take into account all available information, especially symptom severity.[2]

CONCLUSION

FFRCT is a promising novel procedure that provides both anatomic and functional assessment of CAD, using data obtained from standard CCTA as a single noninvasive test, without additional radiation or contrast. Interdisciplinary research including cardiology, radiology, physiology, physics, mathematics and computational science allowed the development of FFRCT. Studies revealed that FFRCT has an improved diagnostic accuracy in identifying hemodynamically significant CAD compared to CCTA alone, mostly by reducing the false positive rate. This new technology may play an important role in the therapeutic decision process, in selecting patients who will benefit from medical treatment or further invasive evaluation and revascularization. FFRCT can identify intermediate stenoses in order to avoid unnecessary invasive procedures. In the future, this method could be adjusted and applied for cardiovascular disease involving other regions, including: cerebrovascular, peripheral or renal.

CONFLICT OF INTEREST

Nothing to declare.

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