REVIEW

Evaluation of coronary flow with computed tomography derived FFR: Advantages and pitfalls

Koroner akımın bilgisayarlı tomografiden türetilmiş FFR ile değerlendirilmesi: Avantajlar ve tuzaklar

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Summary– Coronary computed tomographic angiography (CCTA) is an excellent noninvasive, anatomic imaging modality for direct visualization of coronary arteries and for the assessment of coronary artery disease (CAD). CCTA has high sensitivity and high negative-predictive value for the identification of obstructive CAD; however, its specificity and positive-predictive value are low. After more than a decade of using CCTA to assess the anatomic severity of CAD, novel modalities of obtaining functional information from CCTA have been developed to increase its specificity and accuracy. These modalities use computational fluid dynamics to calculate fractional flow reserve (FFR) from CCTA datasets. Computed tomography-derived FFR (FFR_{CT}) predicts virtual hyperemia for computation. Therefore, no additional image acquisition, medication, radiation exposure, or pharmacologic stress agent during CCTA examination are necessary for the calculation of FFR_{CT}. Multiple, prospective single or multicenter studies have shown that FFR_{CT} is poised to become a gate-keeper for catheterization laboratory. In this article, we aim to review the principles, diagnostic accuracy, advantages, limitations, and pitfalls of FFR_{CT}.

Özet– Koroner bilgisayarlı tomografik anjiyografi (KBTA), koroner arterlerin doğrudan görüntülenmesi ve koroner arter hastalığının (KAH) değerlendirilmesi için kullanılan mükemmel bir girişimsel olmayan anatomik görüntüleme yöntemidir. KBTA, tıkayıcı KAH'ın tanımlanması için yüksek bir duyarlılığa ve negatif tahmin değerine sahiptir, ancak özgüllüğü ve pozitif öngörü değeri düşüktür. KAH'ın anatomik şiddetini değerlendirmek için kullanıldığı on yıldan uzun bir sürenin ardından, KBTA'nın özgüllüğünü ve doğruluğunu artırmak için KBTA'dan işlevsel bilgi elde etmenin yeni modaliteleri geliştirilmiştir. Bu modaliteler, KBTA veri setlerinden fraksiyone akım rezervini (FAR) hesaplamak için hesaplamalı akışkanlar dinamiğini kullanır. Bilgisayarlı tomografiden türetilen FAR (FAR_{BT}), hesaplama için sanal hiperemiyi tahmin eder. Bu nedenle, FAR'ın hesaplanması için KBTA incelemesi sırasında ek görüntü elde edilmesi veya ilaç verilmesi, radyasyona maruz kalma veya farmasötik bir stres maddesinin kullanılması gerekli değildir. Çok sayıda, ileriye dönük tek veya çok merkezli çalışmalar, FAR_{BT}'nin kateter laboratuvarı için bir kapı bekçisi olmaya hazır olduğunu göstermiştir. Bu makalede, FAR_{BT}'nin ilkelerini, tanısal doğruluğunu, avantajlarını, sınırlamalarını ve tuzaklarını gözden geçirmeyi amaçladık.

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality worldwide and it accounts for approximately 2 million deaths each year in Europe.[1,2] Therefore, timely and accurate diagnosis and treatment of CAD is crucial. For the assessment of CAD, noninvasive diagnostic modalities with high diagnostic accuracy have always been necessary to avoid unnecessary, costly, and potentially hazardous invasive tests. Indeed, in a large-scale retrospective study conducted by Patel et al.[3] which included 398978 patients, it was demonstrated that almost 62% of the patients who underwent elective invasive coronary angiography (ICA) had no significant CAD. Among the available noninvasive diagnostic modalities for diagnosing of CAD, only coronary computed tomographic angiography (CCTA) depicts coronary artery anatomy (the arterial lumen and the wall) as well as characterizes and quantifies the atherosclerotic plaques—a function which is not possible with other modalities. Furthermore, CCTA has excellent diagnostic sensitivity (94%) and negative-predictive value (99%) which help reduce unnecessary diagnostic ICA.[4,5] The European Society of Cardiology guidelines on the diagnosis and

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management of chronic coronary syndromes classify CCTA as a Class 1 recommendation for diagnosing of CAD in symptomatic patients wherein obstructive CAD cannot be excluded by clinical evaluation.[6] Since 2016, the National Institute for Health and Care Excellence (NICE) guidelines have recommended CCTA as the first-line investigation for all patients presenting with new onsets of chest pain in the United Kingdom.[7]

Fractional flow reserve (FFR) is a reliable physiological index to identify the hemodynamic significance of CAD. This method is based on the pressure differential across the stenosis. FFR (roughly a measure of lesion-level ischemia; it can be easily measured by a guiding catheter and pressure wire on ICA) is described as the ratio of the myocardial blood flow in the presence of coronary artery stenosis to the myocardial blood flow in the absence of coronary artery stenosis.[8,9] The FFR Versus Angiography for Multivessel Evaluation (FAME),[10] FFR Versus Angiography for Multivessel Evaluation 2 (FAME-2),[11] and Deferral Versus Performance of Percutaneous Transluminal Coronary Angioplasty in Patients Without Documented Ischemia (DEFER)[12] randomized, prospective trials have demonstrated that an FFR-guided management to perform or defer percutaneous coronary intervention in patients with stable CAD is safe and reduces the long-term, major adverse cardiac events. Over the past decade, because of technological advancements, it has become possible to calculate FFR from standard CCTA datasets (Figures 1 and 2) without additional imaging and medications or any invasive intervention; this meth-

Abbreviations:

CAD	*Coronary artery disease*
CCTA	*Coronary computed tomographic angiography*
CFD	*Computational fluid dynamics*
FDA	*Food and Drug Administration*
FFR	*Fractional flow reserve*
ICA	*Invasive coronary angiography*
NICE	*National Institute for Health and Care Excellence*
PET	*Positron emission tomography*

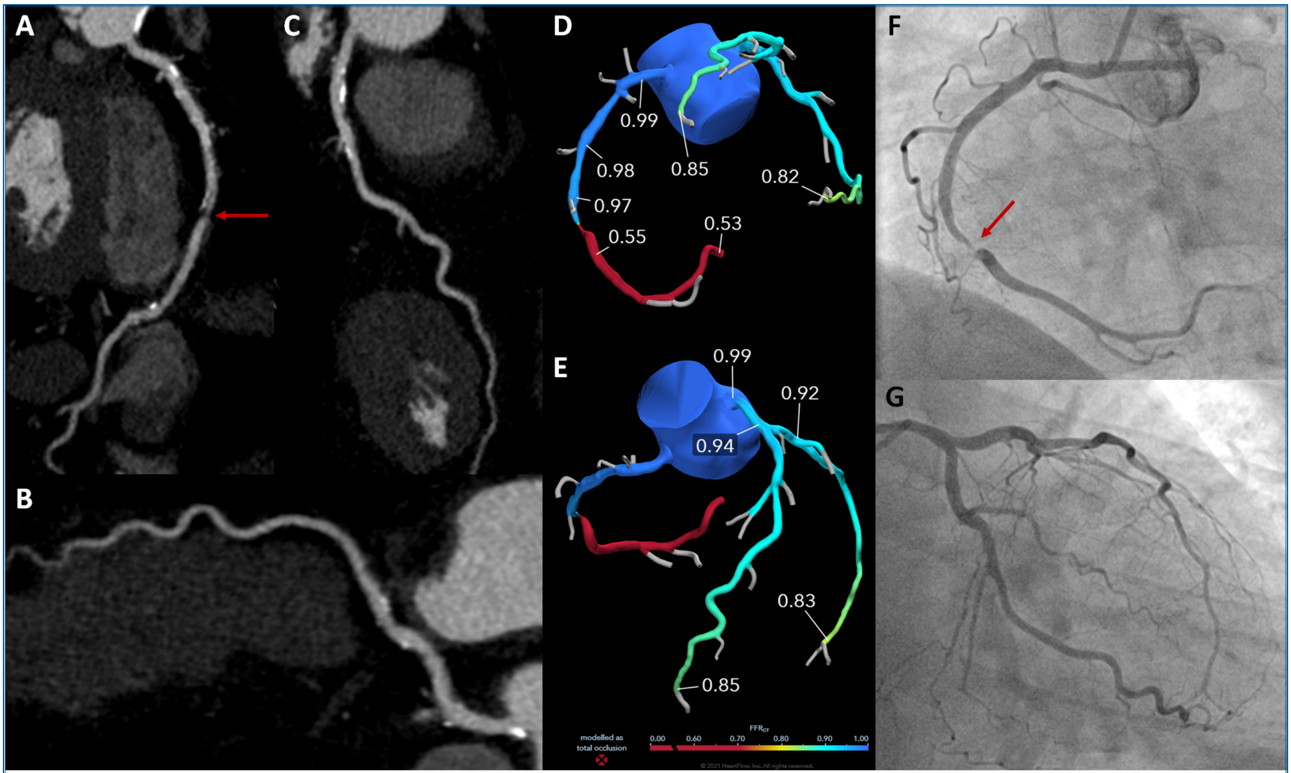

Figure 1. A 60-year-old man, former smoker, known for dyslipidemia, and has a family history of coronary artery disease, developed chest pain on exertion and a coronary computed tomographic angiography was performed, with **(A)** the evidence of critical stenosis at midright coronary artery (RCA) (red arrow), and **(B)** mild stenosis at left main coronary artery (LM), **(B)** mid-left circumflex (LCx) and **(C)** proximal left anterior descending artery (LAD). FFR_{CT} analysis provided by HeartFlow showed **(D)** marked FFR_{CT} value drop at the level of mid-RCA stenosis, **(E)** while normal values in LAD and LCx; **(F)** at invasive coronary angiography, critical stenosis at mid- RCA (red arrow) and **(G)** mild stenoses at LM, LCx and LAD were confirmed.
Images courtesy of Professor Gianluca Pontone, Monzino Cardiology Center, University of Milan, Milan, Italy

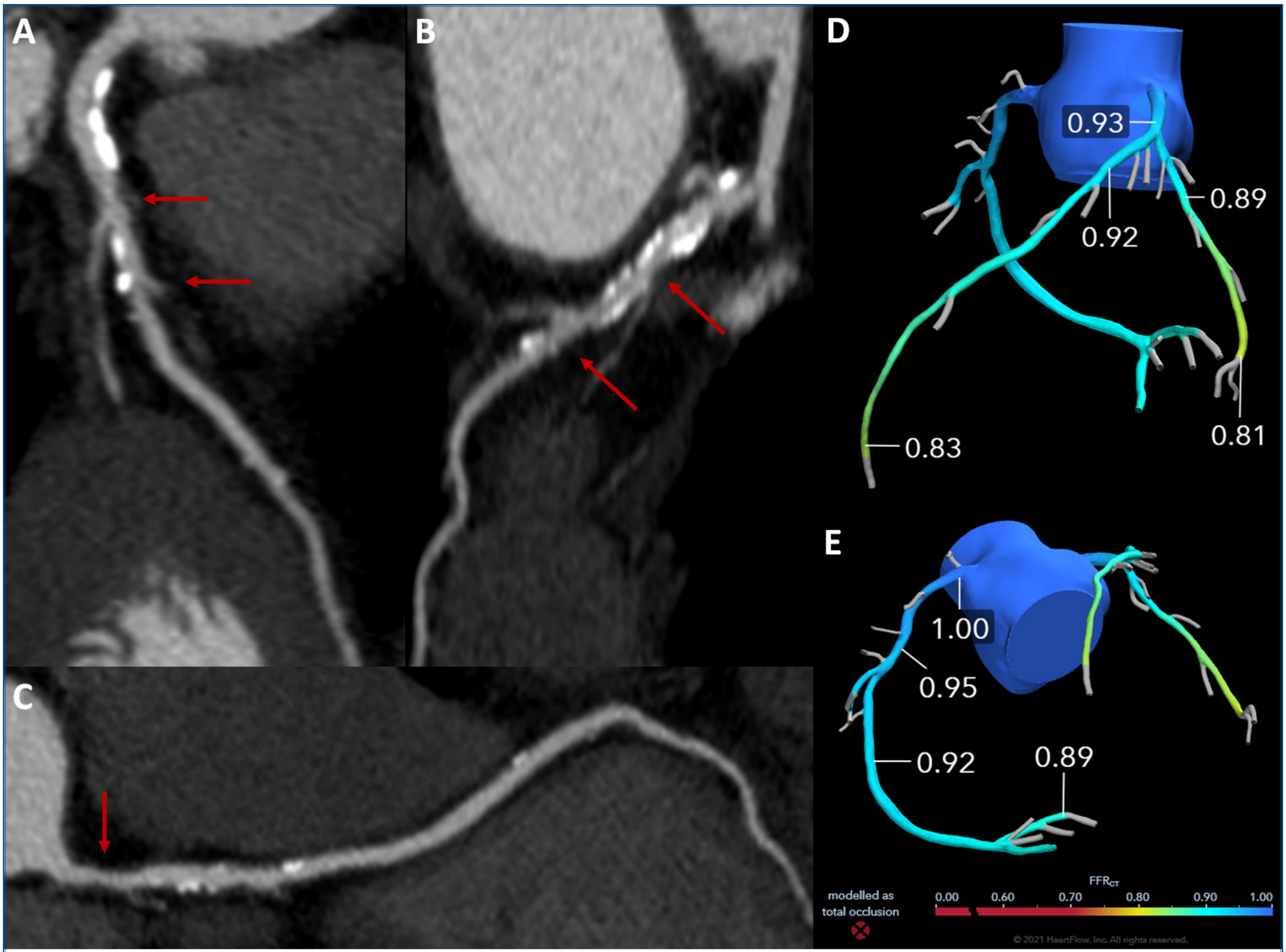

Figure 2. A 73-year-old man, former smoker, known for hypertension, developed atypical chest pain and effort dyspnea and a coronary computed tomographic angiography was performed, with the evidence of **(A)** moderate stenoses at proximal and mid-left anterior descending artery (LAD) (red arrows), **(B)** proximal and mid-left circumflex artery (LCx) (red arrows) and **(C)** proximal right coronary artery (RCA) (red arrow); **(D)** FFR_{CT} analysis provided by HeartFlow showed normal values at left coronary artery (LAD and LCx) and **(E)** RCA and at the 2-year follow-up, no major acute cardiovascular event occurred.
Images courtesy of Professor Gianluca Pontone, Monzino Cardiology Center, University of Milan, Milan, Italy

odology is known as computed tomography-derived FFR (FFR_{CT}, HeartFlow; cFFR, Siemens; CT-FFR, Canon).[13] Although, at the moment, Heartflow FFR_{CT} (Redwood city, California, USA) is the only Food and Drug Administration (FDA) and NICE approved method, there are several other vendors. For instance, Siemens (Siemens Healthineers; Erlangen, Germany) and Canon Medical Systems (Formerly Toshiba Medical, Otawara, Tochigi, Japan) use similar techniques known as computational fluid dynamics (CFD) to compute FFR from CCTA datasets. Moreover, artificial intelligence–based deep machine learning algorithms can derive FFR values from CCTA datasets.[14] The FFR_{CT} aims to combine anatomical and physiological data in a noninvasive modality to help the physician in guiding the best treatment and management of CAD.

Principles of FFR_{CT}

In general, CFD is commonly used in automotive and aircraft industries in testing and design and quantifies fluid velocity and pressure.[15] CFD is not a new technique in medicine; it was used to solve blood flow equations for almost 20-30 years. Perktold et al.[16] first applied CFD to blood flow in the study of carotid bifurcation, this was followed by Taylor et al.[17] who CFD to the study of image-based modeling of the pulsatile blood flow in the abdominal aorta. Similarly, the application of the principles of CFD to coronary blood flow on a standard CCTA

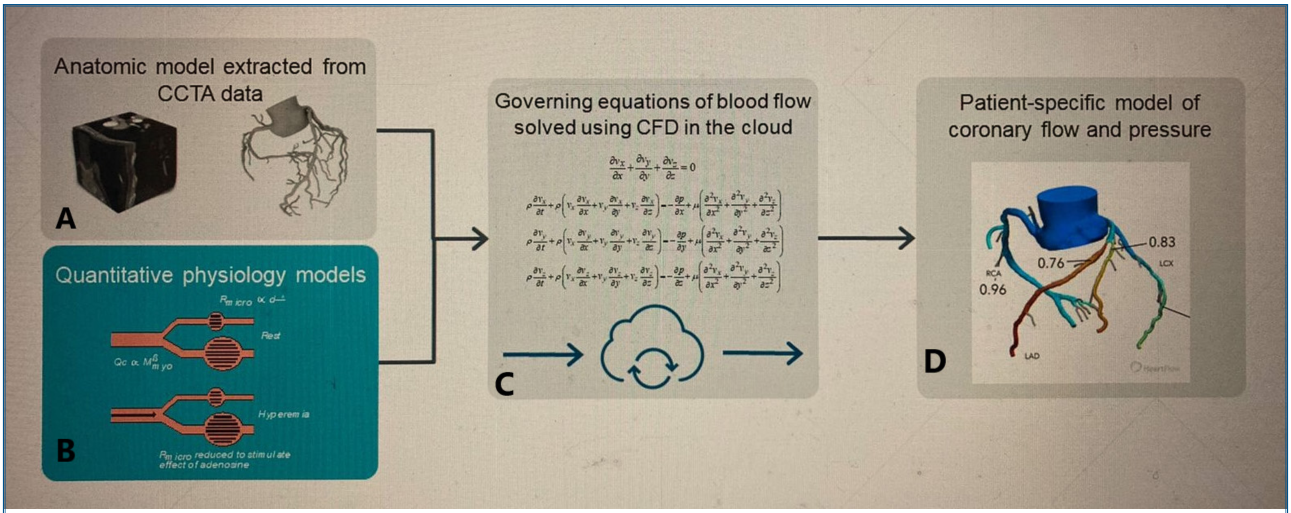

Figure 3. Steps of computation of FFR_{CT}. **(A)** Coronary computed tomographic angiography image dataset acquired using standard imaging protocol without additional medications and a quantitative 3-dimensional anatomic model is generated. **(B)** A physiological model of the coronary microcirculation is derived from patient-specific data. **(C)** Physical laws of fluid dynamics are applied to calculate coronary blood flow. **(D)** FFR_{CT} is computed for each point in the coronary artery tree.
Adapted from Taylor et al.[13] with permission of HeartFlow.

Table 1. Diagnostic performance of FFRCT in different studies

Study	Types	Time	Specificity (%)	Positive prediction (%)	Area under the curve
DISCOVER-FLOW[18]	Multicenter prospective	2011	82	85	0.75
DEFACTO[19]	Multicenter prospective	2012	54	67	0.81
NXT[20]	Multicenter prospective	2014	79	65	0.90
Coenen et al.[22]	Single-center retrospective	2015	65	65	0.83

dataset provides noninvasive quantitation of blood flow velocity and pressure in the major epicardial coronary arteries. Fundamentally, calculation of FFR from CCTA is based on three steps: (1) creating an accurate, patient-specific quantitative three-dimensional anatomic model of the epicardial coronary artery tree which includes the main vessels and side branches; (2) determining inflow and outflow boundary conditions demonstrating patient-specific coronary artery physiology during maximal hyperemia; and (3) performing a numerical solution of the governing equations of blood flow dynamics.[13] The steps for calculating FFR_{CT} are illustrated in Figure 3 FFR_{CT}, an off-site processed full-order model, requires a parallel supercomputer and image transfer to a core laboratory. However, Siemens Healthineers (cFFR), Canon Medical Systems (CT-FFR) and Philips Healthcare (FFR-CT) employ an on-site, reduced-order model on a standard desktop computer to calculate the FFR.

Diagnostic Accuracy of FFR_{CT}

Over the past decade, numerous clinical trials evaluating the diagnostic performance of FFR_{CT} compared with invasive FFR as the gold standard method, have been published. Three major diagnostic trials (DISCOVER-FLOW, DEFACTO, and NXT) compared the diagnostic importance of FFR_{CT} for the diagnosis of significant CAD. Table 1 summarizes the diagnostic performance of FFR_{CT} in different studies. Among these, the Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve (DISCOVER-FLOW) trial was the first prospective multicenter study to assess the accuracy and specificity of FFR_{CT}. In this study, 103 patients underwent CCTA, ICA and invasive FFR. There was a significant improvement in accuracy (per vessel: 84.3 versus 58.5%) and specificity (per vessel: 82.2 versus 39.6%) with the use of FFR_{CT} over CCTA alone.[18] The follow-up Diagnostic Accuracy of FFR from Anatomic CT Angiography (DE FACTO) trial was a prospective multicenter study of 252 patients with known or suspected CAD. Similar to the DISCOVER-FLOW trial, the DEFACTO study demonstrated an improvement in specificity of FFR_{CT} compared with CCTA alone. Furthermore, this trial demonstrated the evidence of improved discriminatory power with an area under the curve value of 0.81 for FFR_{CT} compared with 0.61 for CCTA alone.[19] Finally, in the Analysis of Coronary Blood Flow using CT Angiography: Next Steps (NXT) trial, the largest prospective multicenter study, 254 patients scheduled to undergo clinically indicated ICA for suspected CAD were assessed. The per-patient and per-vessel diagnostic accuracy was 81 and 86%, respectively.[20] After the results of NXT trial, FFR_{CT} was approved by FDA for clinical use. These three trials showed that FFR_{CT} had a high diagnostic accuracy in determining lesion-specific ischemia and a good correlation with invasive FFR. A meta-analysis of these 3 trials, including 609 patients, concluded that FFR_{CT} improved the diagnostic accuracy of CCTA.[21] In addition to these 3 multicenter trials, several single-center studies have validated computed tomography-derived FFR by using an on-site, reduced-order CFD algorithm. For example, Coenen et al.[22] evaluated 106 patients and demonstrated a diagnostic accuracy of 75% for FFR_{CT} and 56% for CCTA alone. Specificity was significantly higher with FFR_{CT} compared with CCTA (65.1 versus 37.6%).[22] There are several meta-analyses and head-to-head comparisons of FFR_{CT} with other noninvasive functional tests. Danad et al.,[23] in a meta-analysis of 23 studies, demonstrated that when using invasive FFR as the gold standard, FFR_{CT} is superior to single-photon emission computerized tomography (SPECT), stress echocardiography, and CCTA alone. The Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CT Coronary Angiography With ICA (PACIFIC) substudy of patients with suspected stable CAD is the first to conduct a head-to-head comparison study between CCTA, SPECT, and positron emission tomography (PET) for the diagnosis of ischemia using invasive FFR as the gold standard. In this study, per-vessel diagnostic performance of FFR_{CT} was superior compared to SPECT, PET, and CCTA alone.[24]

Advantages of FFR_{CT}

There are several advantages of FFR_{CT} over other noninvasive imaging modalities. Assessment of the atherosclerotic plaque burden and its characteristics (positive remodeling, napkin ring sign, low attenuation, and spotty calcification) by CCTA provides excellent diagnostic information about the diagnosis and prognosis of CAD; however, the functional significance of the atherosclerotic lesions remains a challenge with CCTA. FFR_{CT} combines both anatomical and functional data and reduces the need for further downstream testing and also preempts exposure to invasive procedures. Furthermore, FFR_{CT} predicts virtual hyperemia from the computation. Therefore, additional image acquisition or administration of medication, radiation exposure, or using a pharmacologic stress agent during CCTA examination are not necessary for the calculation of FFR. FFR_{CT} has potential for cost saving. A retrospective assessment by Rajani et al.[25] in patients presenting with chest pain to clinics, demonstrated that using FFR_{CT} for lesions between 10%-90% could save 200 pounds per patient.

Limitations of FFR_{CT} and Pitfalls to Avoid

The diagnostic performance of FFR_{CT} can be limited by several factors. The foremost is the extensive, severe coronary calcification and CCTA image quality. There are several factors that can cause impaired image quality, such as misalignment errors, motion artifacts from high heart rate, and increased image noise. In two multicenter trials, DISCOVER-FLOW and NXT, respectively, 11 and 13% of the CCTA datasets were unsuitable for computing FFR_{CT} because of poor image quality. This was mainly because of extensive coronary calcification, misalignment of artifacts, and coronary motion artifacts.[18,20] To obtain a good image quality for FFR_{CT}, heart rate control with beta blockers and breath-hold instructions are mandatory. Secondly, all trials were done with native CAD, therefore no clear information with bypass grafts or stents have yet exist for FFR_{CT} in these situations. Currently, the use of FFR_{CT} should be avoided in coronary artery vein grafts because of competing flow. Patients with chronic total occlusion should be managed with caution and an invasive evaluation should be sought. Further studies are needed to evaluate the impact of collateralization on FFR_{CT}. Thirdly, the utility of FFR_{CT} can be inaccurate in patients with an abnormal response of the microcirculation to vasodilators; FFR_{CT} may overestimate the hemodynamic importance of lesions in the presence of microvascular disease. Other limitations of computed tomography-derived FFR are the turnaround time and cost. FFR_{CT} analysis requires approximately 4-6 hours and this may not be practical for assessing patients with acute chest pain who are in the emergency department. In contrast, using an on-site, reduced-order model can reduce the analysis time and results can be obtained in 1-2 hours; however, the use of this reduced-order model has not been approved by the FDA or other institutions. The cost of FFR_{CT} is a big concern and the price is $1450 per test (Medicare) in the United States. Therefore, FFR_{CT} may not be available or accessible in low-income countries. Finally, based on current trials, FFR_{CT} has extensively been validated against invasive FFR in stable CAD, therefore, the accuracy of FFR_{CT} in patients with acute coronary syndrome still remains unknown.

Conclusion

Computed tomography-derived FFR provides anatomical and physiological evaluation of CAD at the same time and is a modality that employs CFD for determining the hemodynamic significance of coronary artery lesions by using patient-related data that is extracted from CCTA. FFR_{CT} has an important potential in decreasing the necessity for further noninvasive functional tests or invasive angiography and has been shown to be beneficial in determining patients who may benefit from revascularization. FFR_{CT} has the potential to become a gate-keeper for catheterization laboratories, and measurement of FFR from CCTA should be a routine process in the future.

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Keywords: Coronary artery disease; coronary computed tomographic angiography; fractional flow reserve; computed tomography derived FFR; FFR_{CT}

Anahtar Kelimeler: Koroner arter hastalığı; koroner bilgisayarlı tomografik anjiyografi; fraksiyonel akım rezervi; bilgisayarlı tomografiden türetilmiş FFR; FFR_{BT}