Mini-Review

Noninvasive and Invasive Assessments of the Functional Significance of Intermediate Coronary Artery Stenosis: Is This a Matter of Right or Wrong?

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Coronary artery disease · Coronary computed tomographic angiography · Invasive coronary angiography · Intravascular ultrasound · Functional fractional reserve

Abstract

Coronary computed tomographic angiography (cCTA) has emerged in recent years as a non-invasive modality to evaluate coronary artery disease. Many studies have revealed the excellent diagnostic accuracy of cCTA when compared with invasive coronary angiography (ICA) or intravascular ultrasound (IVUS). It is generally accepted that the functional significance of coronary artery stenosis is important to make treatment decisions; however, cCTA, ICA, and IVUS are limited in the ability to determine the physiologic significance of coronary stenosis. The FIGURE-OUT study compared the noninvasive and invasive assessment of the functional significance of intermediate coronary artery stenosis.

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Recent advances in coronary computed tomographic angiography (cCTA) technology have improved its diagnostic performance of identifying anatomically significant coronary artery stenosis when compared with invasive coronary angiography (ICA) or intravascular ultrasound (IVUS) [1, 2]. A meta-analysis of 28 studies involving 1,286 patients that investigated the diagnostic performance of cCTA for the detection of coronary stenosis >50%, using

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Fig. 1. Case example. By invasive angiography (left), two intermediate stenoses at the mid (*) and distal (**) right coronary artery were found. cCTA (middle) shows the plaque as well as the luminal narrowing of those stenoses, and IVUS (upper right) provides precise quantitative and qualitative information. FFR (lower right) reveals that both stenoses are functionally insignificant and revascularization is not necessary.

ICA as the gold standard, showed a per-patient sensitivity of 99%, a specificity of 89%, a positive predictive value of 93%, and a negative predictive value of 100% [3]. As cCTA has become one of the most commonly used noninvasive diagnostic tests for coronary artery disease (CAD), it is important to understand the relationship between cCTA, ICA, and IVUS parameters, as well as the diagnostic accuracy of cCTA compared with that of ICA and IVUS to define the functional significance of coronary stenosis (fig. 1).

Fractional flow reserve (FFR) represents the proportion of reduced myocardial blood flow due to stenosis to the normal maximal myocardial flow. Previous studies have shown the clinical benefits of FFR-guided revascularization. In the DEFER study, FFR was used to determine the need for percutaneous coronary intervention in intermediate stenosis, and it was found that for functionally insignificant lesions ($\text{FFR} \geq 0.75$), percutaneous coronary intervention did not improve the prognosis of the patients [4, 5]. Later, the FAME I and FAME II randomized multicenter studies demonstrated the benefit of the FFR-guided revascularization strategy [6, 7]. As a result, FFR is now regarded as the gold standard invasive method for determining the functional significance of intermediate stenosis in the cardiac catheterization laboratory, and it was classified as a Class IA recommendation in the 2010 European Guidelines on myocardial revascularization [8].

Although it is well known that cCTA can provide excellent anatomical information on obstructive CAD, previous studies have shown the variability in agreement between cCTA and ICA/IVUS parameters. Not only was there a discrepancy in previous results, but the degree of over- or underestimation of lesion severity was different among these studies [9, 10]. Furthermore, previous reports have suggested that the anatomical assessment by cCTA might have limitations in the evaluation of the functional significance of the stenoses, especially in intermediate stenoses [11, 12]. This can precipitate unnecessary ICA and coronary intervention in patients who do not have functionally significant coronary stenosis causing myocardial ischemia.

The prospective multicenter FIGURE-OUT study was performed to determine the diagnostic value of cCTA in the assessment of the functional significance of intermediate stenosis as compared with that of ICA and IVUS [13]. There was a statistically significant but weak correlation between cCTA percent diameter stenosis (%DS) and FFR ($r = -0.271$, $p < 0.001$) and also between cCTA minimal lumen area (MLA) and FFR ($r = 0.547$, $p < 0.001$). The correlations between ICA %DS and FFR and between IVUS MLA and FFR ($r = -0.536$, $p < 0.001$; $r = 0.547$, $p < 0.001$, respectively) were better, but only of moderate degree (fig. 2). These trends were consistent in different lesion subsets. The diagnostic performance of

Fig. 2. Relationship between FFR and MLA by cCTA and IVUS. The correlation between IVUS MLA and FFR (right) was better than that between cCTA MLA and FFR (left).

cCTA to define the functional significance of coronary stenosis by the receiver operating characteristic curve analysis was consequently lower than that of ICA and IVUS (area under the curve, cCTA %DS vs. ICA %DS, 0.657 vs. 0.765; cCTA MLA vs. IVUS MLA, 0.712 vs. 0.801). However, the diagnostic accuracy of these values to predict the presence of ischemia was between 60 and 70%; thus, none of these diagnostic tests showed satisfactory performance in this study [13].

In the FIGURE-OUT study, the cCTA minimal lumen diameter (MLD) was smaller than the ICA MLD (1.3 ± 0.5 vs. 1.5 ± 0.4 mm; $p < 0.001$), and the cCTA MLA was also smaller than the IVUS MLA (2.2 ± 1.2 vs. 3.2 ± 1.2 mm²; $p < 0.001$). Compared to %DS, MLA showed a better diagnostic performance (fig. 3). This trend was consistent regardless of lesion location, severity of stenosis, and plaque calcification. Although some studies reported that the degree of coronary artery stenosis had a tendency to be overestimated by calcified plaque, the relationships between cCTA MLD and ICA MLD as well as between cCTA MLA and IVUS MLA were not different in the setting of calcified versus noncalcified plaque in the FIGURE-OUT study. We further analyzed the correlation between cCTA %DS and cCTA MLA in calcified versus noncalcified plaques in lesions of the FIGURE-OUT study, and there was no significant difference in both lesion subsets (correlation coefficient, -0.61 in calcified lesions and -0.63 in noncalcified lesions).

The main purpose of the FIGURE-OUT study was to investigate the functional performance of the various anatomic parameters that are most commonly used in our daily practice. To adequately understand and interpret the results and clinical implications of this study, some issues need to be addressed. First, it is important to understand the limitations and pitfalls of each modality. The study results suggest that cCTA presents higher than actual lesion severity; however, this may not be true. The diameters derived from ICA and cCTA can vary because the metrics to measure the diameter of the reference segments and MLA site are different. While IVUS generally provides accurate diameter and area measurements, the IVUS catheter may not be aligned parallel to the centerline of a lumen in large and tortuous vessels. Therefore, the cross-sectional lumen area may be oblique, thereby overestimating MLA [14]. Furthermore, a recent study comparing IVUS and OCT lumen

Fig. 3. Comparison of the diagnostic performance of %DS and MLA. Comparisons between IVUS MLA versus ICA %DS (left) and cCTA MLA versus cCTA %DS (right) are shown. AUC = Area under the curve; CI = confidence interval.

areas showed that IVUS overestimated the true lumen area [15]. Second, the FIGURE-OUT study did not use the coregistration system for cCTA, ICA, and IVUS images. Systematic coregistration among the modalities might have decreased the difference. A dedicated registration algorithm has been developed to enable the precise matching of different imaging modalities along the longitudinal and transversal axes of coronary arteries [16–18]. Finally, the recent advances in cCTA images and technology may have allowed better diagnostic performance. The study patients were enrolled between 2007 and 2011, and recently introduced CT was applied [19, 20]. Furthermore, recently developed noninvasive FFR from CT (FFR_{CT}), using computational fluid dynamics, consistently provides better diagnostic performance to define the functional significance of a stenosis than anatomical parameters derived from cCTA [21–23]. In the DISCOVER-FLOW study, obstructive CAD by cCTA was defined as >50% diameter stenosis, and a hemodynamically significant lesion was defined as an FFR or FFR_{CT} <0.80 [21]. Compared to cCTA alone, FFR_{CT} demonstrated a similar sensitivity (88 vs. 91%) and negative predictive value (92 vs. 89%), but there was a significantly higher specificity (82 vs. 40%) and positive predictive value (74 vs. 47%) compared to CT alone. The subsequently published DeFACTO study also demonstrated that FFR_{CT} improved the discrimination of ischemia-causing stenoses relative to CT alone [22]. Integrated anatomical parameters such as aggregated plaque volume from cCTA may also be able to improve its diagnostic performance [24].

In conclusion, the key message from the FIGURE-OUT study is not on the matter of what is right and what is wrong. The most important lesson to be learned is that physicians should adequately understand the basic principles, limitations, and pitfalls of each modality to make an appropriate decision for the treatment of patients with CAD.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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