Commentary

Association of coronary plaque burden with fractional flow reserve: should we keep attempting to derive physiology from anatomy?

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Abstract: Coronary computed tomography angiography (CTA) has been used increasingly for the diagnosis of coronary artery disease over the past decade. Compared to invasive coronary angiography (ICA), coronary CTA has the ability to visualize and quantify atherosclerotic plaque both calcified and non-calcified. Traditional measures of evaluating a coronary stenosis such as diameter stenosis, area stenosis, minimal lumen diameter and minimal luminal area are limited in their ability to predict its functional significance especially when diameter stenosis ranges between 30-69% (intermediate range). Measurement of invasive fractional flow reserve (FFR) is considered the gold standard for assessment of the hemodynamic significance of a stenosis. The current study by Nakazato *et al*. evaluates the performance of an emerging coronary CTA-derived anatomical measure "percent aggregate plaque volume" to improve the detection of hemodynamic significant stenosis as compared with invasive FFR.

Keywords: Coronary computer tomography angiography (coronary CTA); invasive coronary angiography (ICA); fractional flow reserve (FFR); plaque burden; intermediate coronary stenosis

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The association between coronary stenosis (anatomy) and coronary flow (physiology) has been recognized for more than 40 years (1). However, the degree of coronary stenosis that can cause a significant reduction in coronary flow (ischemia) is variable. This is especially true for lesions of intermediate severity with 30-70% luminal diameter reduction. In a study of 1,000 patients, Park *et al*. evaluated the relationship between coronary stenosis as measured by percent diameter stenosis (%DS) by quantitative invasive coronary angiography (ICA) and its physiological significance as measured by fractional flow reserve (FFR) and found they were mismatched 57% of the time (2). Additionally, in the FAME trial, 40% of the angiographically significant lesions by ICA were deemed to be non-ischemic by FFR (3).

Coronary computed tomography angiography (CTA) correlates very well with ICA and intravascular ultrasound (IVUS) in assessing the anatomical severity of coronary stenoses and overall plaque volume (4-6). However, coronary CTA has lower spatial resolution that ICA, therefore, this discrepancy between the severity of an anatomical coronary stenosis and its functional severity can only be expected to be more relevant when stenoses are assessed with coronary CTA than with ICA. Assessing the functional severity of a coronary stenosis is a critical step to guide the management strategy where percutaneous coronary intervention is indicated for ischemia-producing stenosis while medical therapy is preferred for hemodynamically non-significant stenosis (7).

Different strategies are used to evaluate the functional status of coronary lesions. The most widely used is stress testing with single photon emission computed tomography (SPECT) myocardial perfusion imaging. However, recently the accuracy of this test has been brought into question with several studies demonstrating lower sensitivity and specificity than previously thought (8,9). In the past, the

identification of an intermediate stenosis on coronary CTA is often followed by a non-invasive stress test requiring an additional time and financial costs.

Therefore, evaluating coronary anatomy and physiology at the same time with one non-invasive imaging modality has become the Holy Grail of coronary atherosclerosis imaging. Using cardiac CT imaging alone, several strategies have been evaluated with promising results. Although it has not yet gained widespread implementation, myocardial CT perfusion (CTP) imaging is rapidly gaining momentum after the results of the CORE320 study demonstrated that the combination of coronary CTA and myocardial CTP imaging can accurately predict the presence of a stenosis on ICA causing a perfusion deficit on SPECT (10). In addition, myocardial CTP imaging has demonstrated excellent diagnostic accuracy in predicting FFR and the presence of in-stent restenosis (11,12). Another approach, which does not require additional contrast or a stress examination, is to estimate invasive, pressure-derived FFR from pure anatomical data obtained from coronary CTA using computation fluid dynamic modeling. CT-derived FFR, commonly referred to as (FFR-CT) has gained wide publicity (13). Initially, this promising technology missed demonstrating non-inferiority with invasive FFR (13). However, a more recent trial demonstrated high accuracy in predicting invasive FFR when used in carefully selected patients with acceptable image quality (14). FFR-CT demonstrates the concept that physiology can be predicted from anatomy when computational fluid dynamic modeling is employed.

The study by Nakazato *et al*. is another example of deriving a correlate of physiology from anatomy (15). It evaluates the performance of several easily derived anatomical measures: percent diameter stenosis, area stenosis, minimal lumen diameter, and minimal lumen area; and a more difficult to derive anatomical measure: percent aggregate plaque volume; in an effort to better estimate the hemodynamic effect of coronary artery stenosis and atherosclerosis compared to invasive FFR, the current reference standard.

The study included 58 patients from two centers with isolated intermediate coronary diameter stenoses (30-69%) diagnosed by coronary CTA. The role of percent aggregate plaque volume in evaluating ischemia was assessed in isolation and as an additive parameter to other four traditional measures of coronary stenosis including diameter stenosis, area stenosis, and minimum lumen diameter (MLD) and minimum lumen area (MLA). Plaque volume was assessed as "percent aggregate plaque volume" (%APV) which was defined as the sum of plaque volume divided by the sum of vessel volume from the ostium to the distal portion of the lesion. All patients had ICA and pressure-derived, invasive FFR measured for the stenosis in question. An FFR value of <0.8 was used to define a hemodynamically significant stenosis.

Ischemia (FFR <0.8) was diagnosed in 22 (37%) patients. Diameter stenosis and area stenosis did not differ between ischemic and non-ischemic lesions. However, ischemic stenoses have significantly lower MLD and MLA. Even more importantly, %APV outperformed the other four traditional measures. %APV showed good diagnostic accuracy for ischemia with area under curve (AUC) of 0.85 compared to 0.68, 0.66, 0.75 and 0.78 for diameter stenosis, area stenosis, MLD and MLA; respectively. The use of %APV and MLD together improved discrimination from 0.75 to 0.90. Moreover, %APV improved reclassification with net reclassification index (NRI) of 77% compared to diameter stenosis. Less improvement in reclassification was seen when %APV is compared to MLA with a NRI of 43%. This is expected given that MLA outperformed diameter stenosis in predicting ischemia.

These findings support the notion that atherosclerotic burden proximal to a focal coronary stenosis plays an important role in determining the functional significance of that stenosis. The sole reliance on percent diameter stenosis to judge its hemodynamic significance has showed to be unreliable in many studies (16,17). One explanation is that diameter stenosis is often underestimated by comparing the stenotic area to a nearby, seemingly normal coronary segment that nevertheless is still affected by atherosclerosis (18). Additionally, diameter stenosis ignores the fact that other anatomical factors, like lesion length, lesion geometry and proximal atherosclerotic disease are very important in determining the blood flow reduction past a coronary stenosis. De Bruyne *et al*. showed that even mild, diffuse coronary atherosclerosis can increase coronary resistance and reduce coronary blood flow (19). Measuring the plaque burden proximal to a focal coronary stenosis of interest is a way of incorporating more additional data in the determination of hemodynamic significance of the focal stenosis and adjacent atherosclerosis.

The study is limited by its small sample size (58 patients) and its possible selection bias of including only patients with intermediate stenoses and who had a clinical indication for invasive FFR measurements. Additionally, measuring plaque volume is still a time and labor consuming process

and there is not a standard, automated, well-validated and widely-accepted method of measuring plaque volume or %APV. Despite those limitations, this study adds more to our understanding of the relationship between coronary anatomy and physiology. It provides a new way to incorporate more anatomical data to predict physiological status. Although it is unlikely that we will ever be able to perfectly predict the functional status of a coronary stenosis from anatomical data alone (20), there is a definite opportunity to incorporate more anatomical information into our prediction methods to reduce the occurrence of indeterminate coronary lesions when direct functional measurement with stress tests or FFR is needed. This may ultimately reduce patients' exposure to further unnecessary invasive and noninvasive tests.

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