Computed tomography quantification of coronary plaque volume may provide further perspective on intermediate severity stenoses

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Abstract: Coronary computed tomography angiography (CCTA) is an emerging modality for comprehensive non-invasive assessment of coronary artery disease (CAD). CCTA was traditionally used for anatomical assessment of coronary plaque, including luminal narrowing, plaque burden, location, and composition. Preliminary studies have also demonstrated CCTA's capabilities for functional assessment of coronary plaque, including fractional flow reserve (FFR) and myocardial perfusion—albeit they are not routinely available at all centers and are focus of research. Although the identification and development of treatment strategies of severely stenotic lesions has advanced tremendously over the past years, the evaluation, prognostication, and treatment of patients with intermediate severity stenosis in whom there is equipoise between invasive versus medical management is only now receiving attention. Intermediate severity stenosis is the most likely to benefit from additional measures of disease beyond traditional clinical risk profiling and CCTA visual examination. Nakazato *et al.* studied 58 patients with intermediate severity stenosis and quantified the percent aggregate plaque volume (%APV), a novel measure of total arterial plaque disease. %APV had the highest correlation with ischemic lesions on FFR, outperforming luminal diameter, luminal area, minimal lumen diameter, and minimal lumen area. This study extracts additional information from pre-existing CT data-sets and suggest novel concept that might improve classification of moderate severity coronary stenoses.

Keywords: Aggregate plaque volume (APV); coronary artery disease (CAD); coronary computed tomography angiography (CTCA); coronary plaque

Progression of coronary atherosclerosis leads to obstructive coronary artery disease (CAD) which eventually culminates in myocardial ischemia and patient symptoms. However our ability to extrapolate the severity of ischemia and patient symptoms based on visual examination of luminal stenosis often proves limited. Invasive coronary angiogram (ICA) remains the gold standard for identifying coronary stenosis, especially when used in conjunction with intravascular ultrasound (IVUS) to assess lesion area and composition and fractional flow reserve (FFR) to assess for lesion-specific hemodynamic significance.

Since it is less desirable to image all patients invasively, alternative non-invasive modalities have been developed. Coronary computed tomography angiography (CCTA) has been shown to be a relatively reliable measure of luminal stenosis as compared to ICA (1,2). In addition to describing single point degree of luminal narrowing, CCTA is also capable of directly visualizing and characterizing plaque burden, location, and composition, which are all independent predictors of adverse coronary events (3,4). For instance, total plaque score on CT obtained by summing the number of assessable coronary segments with calcified, non-calcified, or mixed plaque seems to provide incremental prognostic value over routine clinical

72

Liu et al. Moderate coronary stenosis plaque volume on CT

predictors such as CAD severity and left ventricular ejection fraction for all-cause mortality and nonfatal myocardial infarction although the effect is small (5,6). In addition to anatomical appraisal of CAD, promising preliminary trials have shown potential for cardiac CT to be used for non-invasive functional appraisal which can help clarify which patients should undergo invasive angiography and potential revascularization versus optimal medical therapy. First, FFR can be derived from CCTA (FFRCT) through complex algorithms to determine the physiologic importance of coronary lesions (6,7). This method has a high sensitivity and negative predictive value as compared to the gold standard of invasive FFR, enabling FFRCT to effectively exclude coronary lesions causing ischemia. Second, studies have shown that CCTA is capable of visualizing the myocardium not only at rest but also during stress for the detection of ischaemic myocardium in an intermediate risk population, but in order to establish myocardial CT perfusion as a viable modality, further research is still needed to develop a standardized protocol and provide robust evidence (8-10).

Although the identification and development of treatment strategies for severely stenotic lesions has advanced tremendously over the past years, the evaluation, prognostication, and management of intermediate anatomical stenosis has been slower to evolve. The population with intermediate lesions is the most likely to benefit from additional measures of disease (beyond traditional clinical risk profiling and CCTA visual examination), as they represent a potentially lower risk cohort where there is often equipoise between optimal medical therapy and revascularization. Just as luminal area in 2-dimensions as demonstrated by IVUS has surpassed luminal stenosis in 1-dimension on ICA, in their recent study, Nakazato *et al.* attempted to determine the prognostic value of quantifying plaque volume in 3-dimensions in the evaluation of cardiac ischemia (11). They examined 58 patients with intermediate severity stenosis (30% to 69%) detected on CCTA. The patients also underwent invasive ICA with FFR within 3 months of CCTA (mean inter-test duration of 21 days). The investigators analyzed a novel quantitative measure of total arterial plaque disease: percent aggregate plaque volume (%APV)—a parameter obtained by dividing the sum of the plaque area in the vessel wall by the sum of the total vessel area in each CCTA slice from the ostium to the distal point of the pre-identified stenosis. In their study, 22 of the 58 lesions (38%) were presumed to be causative of ischemia based on the established criteria

of FFR <0.80 (12). These intermediate severity lesions were most frequent in the left anterior descending artery, followed by the right coronary artery, and then the left circumflex artery. In differentiating between ischemic and non-ischemic lesions by FFR, the traditional 1- and 2-dimensional CCTA measures of diameter stenosis and area stenosis were not found to be significant. Patients with ischemic lesions exhibited smaller minimal lumen diameter (1.3±0.5 *vs.* 1.7±0.5 mm, P=0.01), smaller minimal lumen area (2.5±1.6 *vs.* 3.8±1.9 mm^2, P=0.01) and larger %APV (48.9%±7.4% *vs.* 39.3%±5.8%, P<0.0001) with %APV strikingly outperforming the two other markers. Only the proximal to mid coronary segments were examined, which appears reasonable both from a biological significance due to a greater dependent cardiac mass and a pragmatic vantage of more accurate visualization of larger caliber proximal vessels given the finite of spatial resolution on CT.

This study identifies a potential new non-invasive surrogate marker of CAD that appears to have incremental discriminatory power. %APV may indeed help refine the risk stratification of patients with equivocal disease severity. It appears to be intuitive that 2-dimensional measure of luminal area may be superior to 1-dimensional characterization of luminal diameter and that the integration of multiple areas along the proximal and mid coronary arteries into a single quantifiable 3-dimentional aggregate could be prognostically advantageous.

Nevertheless, this study is not without its limitations such as a relatively small sample size and time-consuming nature. Processing time will eventually be overcome with automated and semi-automated CCTA software. Notably, all the patients in this study were symptomatic prompting clinically-indicated CCTA, further information regarding the typicality of symptoms and Canadian Cardiovascular Society classification were not available. Lesions in this study were initially identified visually. The authors underscore the importance of objective and quantitative coronary plaque burden assessment over the unreliability of visual examination of degree of stenosis and thus the removal of the 'human variable' through automation of this task may improve lesion discrimination and accuracy. Finally, atherosclerosis in general is a diffuse and slowly progressive disease, with patients likely having multiple atherosclerotic lesions. The authors excluded patients with multiple moderate or high risk lesions within the same vessel which potentially biases the study by underestimating disease burden and underestimating the power of CCTA measures. Automatic detection of total proximal coronary

plaque volume based on predetermined anatomical arterial branches rather than individual lesion location could provide an option to overcome this hurdle.

Overall, despite the aforementioned limitations, this study extracted incremental information from pre-existing datasets and generates new ideas regarding improved classification of moderate severity coronary stenosis. %APV provides promising information in the continued development of CCTA into a reliable imaging modality for thorough non-invasive assessment of CAD.

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