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Editorial

No contrast? No problem! Value in assessing pericoronary fat in non-contrast studies

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In this issue of *Atherosclerosis*, Takahashi et al. present a novel method for quantifying pericoronary adipose tissue (PCAT) attenuation on non-contrast chest computed tomography (NC-PCAT) scans performed for coronary artery calcium score (CACS) assessment. They also assessed its efficacy and utility as a prognostic tool [1]. The authors divided the study population into two cohorts. Cohort 1 (N = 300 consecutive patients with previous CCTA) was used to assess the correlation between PCAT on non-contrast chest CT and coronary CT angiography (CCTA) and then the association between NC-PCAT and high-risk plaques (HRP). This analysis showed a moderate positive correlation between PCAT and NC-PCAT (R = 0.67, $p < 0.0001$). NC-PCAT was a significant indicator of presence of HRP on multivariable models (OR = 1.063, 95% CI: 1.030–1.097, $p = 0.0001$). A similar trend was observed among patients with CACS >0, as NC-PCAT remained significantly associated with presence of HRP in multivariable models (OR = 1.064, 95% CI: 1.029–1.100, $p = 0.0002$). Cohort 2 (N = 333) was used to examine the association between NC-PCAT (dichotomized by the median value) and risk of all-cause death and non-fatal major adverse cardiovascular events. Cumulative incident cardiac events were higher in the NC-PCAT group above the median (93.55 HU) as compared to the NC-PCAT group below the median (log-rank $p = 0.014$). In Cox regression NC-PCAT above the median was significantly associated with MACE in multivariable models (HR = 4.3; 95%CI: 1.2–15.2; $p = 0.012$).

Pericoronary adipose tissue (PCAT), which is the fat surrounding the coronary arteries, can be assessed on CCTA scans using the pericoronary fat attenuation index (pFAI). This marker has recently been recognized as a marker of arterial wall inflammation [2]. Evidence suggests that the vascular walls of diseased vessels interact with the fatty tissue around it through secretion of pro-inflammatory molecules, which inhibit differentiation of pre-adipocytes and the accumulation of lipids inside these cells [3]. Hence, PCAT of inflamed vessels is less rich in lipid content compared to healthy vessels, which leads to a higher pFAI. Inflammation is a crucial step in the pathogenesis of atherosclerosis and plays a key role in both development and progression of atherosclerotic plaques [4]. Previous studies have shown an association between pFAI and presence of high-risk plaques (HRP) [5,6] as well as incidence of major adverse cardiovascular events (MACE) [3,7]. However, the assessment of pFAI has been limited to only contrast enhanced studies. This is needed to allow for vessel segmentation and accurate delineation of pericoronary fat. Assessment of pFAI from non-contrast enhanced CT has always been a sought-out goal, as it would expand the availability of this important index to additional studies that are performed more frequently (such as calcium scores).

Several groups have attempted to measure NC-PCAT. One study found an increase in NC-PCAT volume, but not attenuation, around coronary segments containing atherosclerotic plaques compared to normal segments [8]. Another one showed that PCAT attenuation was correlated with presence of coronary plaque as well as total burden of non-calcified plaque, low-density non calcified plaque, and calcified plaque. However, compared to these previous studies, Takahashi et al. used a different technique to measure NC-PCAT. Therefore, one of the limitations of this study seems to be the lack of clear consensus or guidance on how to measure pFAI on non-contrast studies. Another limitation of this study is the lack of ethnic diversity which limits generalizability to the general population.

The novel methodology proposed by the authors offers the possibility of employing PCAT in two important domains within the clinical sphere. Firstly, an important consideration in patients undergoing CCTA is the risk of contrast allergy and nephropathy. Because of growing aging populations living with more comorbidities that are often undergoing contrast cardiac imaging, nephropathy is of particular concern [9]. Thus, the novel approach presented in this study would allow for the utilization of PCAT even in patients with a potential risk of contrast-induced nephropathy.

More importantly, the proposed methodology would provide the

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capability to utilize NC-PCAT as a supplementary risk assessment tool to established prognostic imaging modalities. An important example would be in the use of CACS for primary prevention. Although CACS has been guideline-endorsed in tailoring the management of a primary prevention population, studies have demonstrated the presence of subgroups of patients within risk categories of CACS that would benefit from additional risk assessment – even those with CACS of zero [10]. With the proliferation of hybrid imaging, another opportunity for add-on risk stratification is in patients who undergo cardiac SPECT or PET with CACS assessment [11,12]. In both settings, NC-PCAT can potentially be used to identify patients who would benefit from more aggressive management and enhanced risk prediction.

However, for NC- PCAT to have any meaningful use – particularly at a time when the role of plaque burden in predicting the risk has been firmly established - it would need to have a distinct independent and incremental prognostic role beyond CACS. In the present study, CACS≥400 was not significantly associated with outcomes in maximally adjusted multivariable models with NC-PCAT. This could potentially be explained by the small number of events in the prognostic cohort. Two prior studies had explored the prognostic role of pCAT *vs* CACS/plaque burden. Oikonomou et al. studied 1575 patients from the Scottish COmputed Tomography of the HEART (SCOT-HEART) trial study and showed that fat radiomic profile (FRP) – a composite measure of inflammation, vascularity and fibrosis - was a significant predictor of incident cardiovascular events in multivariable models adjusted for CACS [13]. More recently, Van Diemen et al. showed that RCA pCAT was significantly associated with incident death/non-fatal MI after adjusting for clinical and imaging variables (including CACS and plaque volume) in 539 patients who underwent CCTA and [^{15}O]H_2O PET perfusion imaging for suspected CAD [14]. Considering the established association between inflammation and plaque progression, it is conceivable to surmise how measures of plaque burden and coronary inflammation could potentially have complementary and synergistic role. Further studies are needed in this regard.

An important challenge that needs to be addressed is the lack of standardization in the methodology to assess NC-PCAT. There is significant heterogeneity in the methodology of PCAT assessment, especially with regards to segment tracing and analysis [15]. Deep learning may play an important role in this domain by allowing for automated assessment, and hence, considerably shortening the processing time.

In summary, this study is an important step forward in making PCAT utilization more widely available. Nevertheless, in order for the novel imaging biomarker to be more readily adopted, future studies need to address the issues regarding standardization, automation, and - most importantly - its incremental prognostic value compared to plaque burden assessment.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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