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THE PRESENT AND FUTURE

JACC REVIEW TOPIC OF THE WEEK

Pericoronary Adipose Tissue as a Marker of Cardiovascular Risk

JACC Review Topic of the Week

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ABSTRACT

Vascular inflammation is a key driver in atherosclerotic progression and plaque rupture. Recent evidence has shown that coronary computed tomography provides a noninvasive method of quantifying coronary inflammation by mapping changes in pericoronary adipose tissue (PCAT) radiodensity, which are associated with cardiovascular diseases. However, there are significant knowledge gaps in the performance and measurement of PCAT that complicate its interpretation. In this review the authors aim to summarize the role of PCAT in cardiac imaging and explore the clinical implications and applicability as a novel biomarker of cardiovascular risk, as well as to discuss its limitations and potential pitfalls.
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Inflammation is a component of the pathophysiological mechanisms underpinning atherosclerosis.[1] In the past decade, trials have shown that anti-inflammatory drugs and novel anti-inflammatory monoclonal antibodies reduce cardiovascular events.[2] However, anti-inflammatory medications have potential risks, so it would be desirable to have a process for identifying patients with coronary inflammation who are likely to benefit.

Adipose tissue is associated with systemic inflammation, contributing to the development and progression of atherogenesis mediated by inflammatory cytokines. However, systemic inflammatory biomarkers do not accurately reflect local vascular processes. Consequently, there has been interest in a radiologic biomarker to represent local cardiac inflammation.[3,4] Advances in coronary computed tomographic angiography (CTA) have shown the feasibility of measuring the epicardial adipose tissue (EAT) that intimately overlays the coronary arteries, known as pericoronary adipose tissue (PCAT). This fat depot is in immediate apposition to the coronary arteries, and its density, a surrogate of adipocyte cell size, may reflect underlying inflammatory activity of either the surrounding EAT or the underlying vascular wall. The appeal of PCAT as a validated radio-biomarker of inflammation is its capacity for noninvasive measurement. Several important histologic and clinical studies have demonstrated the association of PCAT with adverse plaque

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CAD = coronary artery disease

CT = computed tomography

CTA = computed tomographic angiography

EAT = epicardial adipose tissue

HRP = high-risk plaque

LAD = left anterior descending coronary artery

LCx = left circumflex coronary artery

PCAT = pericoronary adipose tissue

PVAT = perivascular adipose tissue

RAS = renin-angiotensin system

RCA = right coronary artery

characteristics and prognosis.[5] It may account for "residual" cardiovascular risk and provide a tool to measure the response to anti-inflammatory agents.

In this review we seek to summarize the pathophysiology of PCAT and its contemporary use in cardiac imaging and to explore its clinical implications and applicability as a novel marker of cardiovascular risk, as well as to discuss its limitations and potential pitfalls.

PATHOPHYSIOLOGY OF PCAT

Adipose tissue produces and stores a large variety of bioactive molecules, including adipokines, inflammatory cytokines, and inorganic molecules.[6] Several of these markers from both subcutaneous and visceral sources diffuse into and circulate within the bloodstream. PCAT is of particular importance given its direct contact with the coronary circulation, proximity to arterial smooth muscle cells, and potential to influence vessel homeostasis and atherosclerosis.[4]

Visceral adipose tissue lies predominantly in the abdominal and thoracic cavities. It shares arterial and venous blood supply with adjacent anatomical structures and organs and confers a unique ability to regulate metabolism in a paracrine manner. "EAT" is a general term for the fat between the myocardium and the visceral layer of the pericardium (**Table 1**).[7] It is easily evaluable on cardiac computed tomography (CT) and has been shown to associate with coronary artery disease (CAD), specifically high-risk plaque (HRP).[8] At the cellular level, EAT is composed of smaller and more numerous adipocytes compared with other visceral adipose tissue.[9] Perivascular adipose tissue (PVAT; the general term for adipose tissue surrounding blood vessels) secretes vasoprotective adipokines that exert anti-inflammatory and antioxidant effects and promote vasodilation.[10] PCAT shares a blood supply with the vasa vasorum of coronary arteries and thus has a distinct role in regulating cardiometabolic function. PCAT was originally considered to surround only the coronary artery, but recent studies have found some adipocytes embedded within the vessel wall of smaller caliber vessels, particularly within the coronary microcirculation.[11,12] Importantly, EAT and PCAT are anatomically contiguous, with no anatomical barrier or fascial separation. This poses challenges in delineating these layers on cardiac imaging.

HIGHLIGHTS

- Pericoronary adipose tissue responds to vascular inflammation, and through chemokine pathways may promote progression of atherosclerosis and plaque instability.
- PCAT measured by CTA is a marker of cardiovascular disease.
- Pitfalls in assessment of the pericoronary adipose tissue by CTA involve heterogeneity in image acquisition and measurement that must be addressed to ensure accurate translation into clinical practice.

Initial considerations of EAT associated with coronary inflammation and subsequent atherogenesis stemmed from the theory of an "outside-to-inside" gradient of inflammatory cytokines from the EAT to the coronary wall. Further understanding of PVAT's response to inflammation has led to a "bidirectional signaling" theory, whereby not only can PCAT secrete inflammatory cytokines into the vessel wall, but it may receive signals from the vessel wall as well, the so-called inside-out gradient (**Central Illustration**).

PCAT plays an important modulatory role in vascular homeostasis by local secretion of anti-inflammatory and antioxidant chemokines. In a histologic study,[13] adiponectin was shown to act as a means of communication between local vasculature and surrounding PCAT. The production of circulating vascular superoxide is associated with lower levels of circulating adiponectin, thus leading to dysfunctional endothelial nitric oxide synthase.[14] Markers of oxidative stress cause increased adiponectin gene expression in local PCAT, contrary to previous studies in which oxidative stress led to a degradation in adiponectin. This highlights a unique physiology of PCAT, which is regulated by mechanisms independent of other adipose tissue depots, in that it may receive "inside-out" signaling in response to vascular inflammatory markers in the coronary circulation.[15] Further support for this theory was demonstrated in a study of PCAT attenuation and inflammatory cytokine expression in patients with left anterior descending coronary artery (LAD) myocardial bridging. This allowed examination of the effect exerted on PCAT in the proximal nonbridging segment (with overlying adipose tissue), compared with the separate, tunneled segment (without

TABLE 1 Types of Adipose Tissue

Fat Type	Anatomical Location	Role and Function
Subcutaneous fat	Commonly known as body fat Located all over the body, under the skin	Energy reserve comprising fatty molecules, predominantly triglycerides Under hormonal control, regulated by insulin, glucagon, catecholamines, and cortisol[7] Can stimulate adipose tissue metabolism (lipolysis) or storage (lipogenesis) depending on the body's requirements
Visceral adipose tissue	Internal organs (visceral fat), between muscles, inside bone marrow, and breast tissue	Produces bioactive adipokines (adiponectin, leptin, and apelin), inflammatory cytokines, and inorganic molecules[6]
EAT	Fat depot on the surface of myocardium and contained beneath the pericardium	Aggregate EAT volume increases the risk for CAD, ischemia, high-risk plaque, and cardiovascular events[8] Contains a subset closer to arterial vessels (see PVAT and PCAT) that is uniquely biologically active, acting in a paracrine fashion[4]
PVAT	Specific type of adipose tissue that surrounds blood vessels	Modulate signaling pathways in vascular wall through paracrine and vasocrine routes[13] Under normal physiological conditions, produces antioxidant, anti-inflammatory components[10]
PCAT	Specific form of PVAT surrounding the coronary arteries Embedded inside vessel, increasing in degree with smaller vessel calibers and microcirculation[11]	Despite being anatomically contiguous with EAT is functionally different Adipocytes have an increased paracrine role on coronary arterial vessels; because of shared blood supply (via vasa vasorum), inflammatory molecules from plaque rupture can modify the phenotype of adipocytes[12]

CAD = coronary artery disease; EAT = epicardial adipose tissue; PCAT = pericoronary adipose tissue; PVAT = perivascular adipose tissue.

overlying adipose tissue).[16] Inflammatory cytokines were at their highest concentration in PCAT overlying atherosclerotic plaque (proximal to the bridge), indicating that inflammation may be caused by atherogenic molecular signaling from the vascular endothelium into the surrounding PCAT. In a seminal histologic study of coronary inflammation, PCAT adipocytes decreased in size in response to the release of the inflammatory markers tumor necrosis factor-α, interleukin-6, and interferon-γ.[17,18] This "cachexia-type" effect on adipocytes adjacent to an inflamed artery wall results in lipid-poor adipocytes with greater water content in a proximal to distal pattern. This consequent change in fat density is detectable on CT because of altered radiodensity.

Although PCAT has been shown to be associated with increased cardiovascular risk and atherosclerosis, a key question yet to be definitively answered is whether it acts as a "barometer" of existing inflammation or plays a more directly causative role in the atherogenic cascade, possibly triggering plaque instability through an "outside-to-inside" pathway. In the contemporary "inside-out theory" of atherosclerosis, the inflammatory cascade begins with an injury to the endothelial intima, followed by accumulation and proliferation of inflammatory cells in the subendothelial space, smooth muscle proliferation, fibrous cap growth, and established plaque formation,[19] with enlargement of plaque in the immediate period of weeks to months prior to acute coronary syndrome.[20] These insights have provided additional impetus on identifying plaques at higher risk for instability. Consequently, the utility of an imaging biomarker such as PCAT in quantifying inflammatory activity is of significant interest, particularly with its potential association with plaque instability.

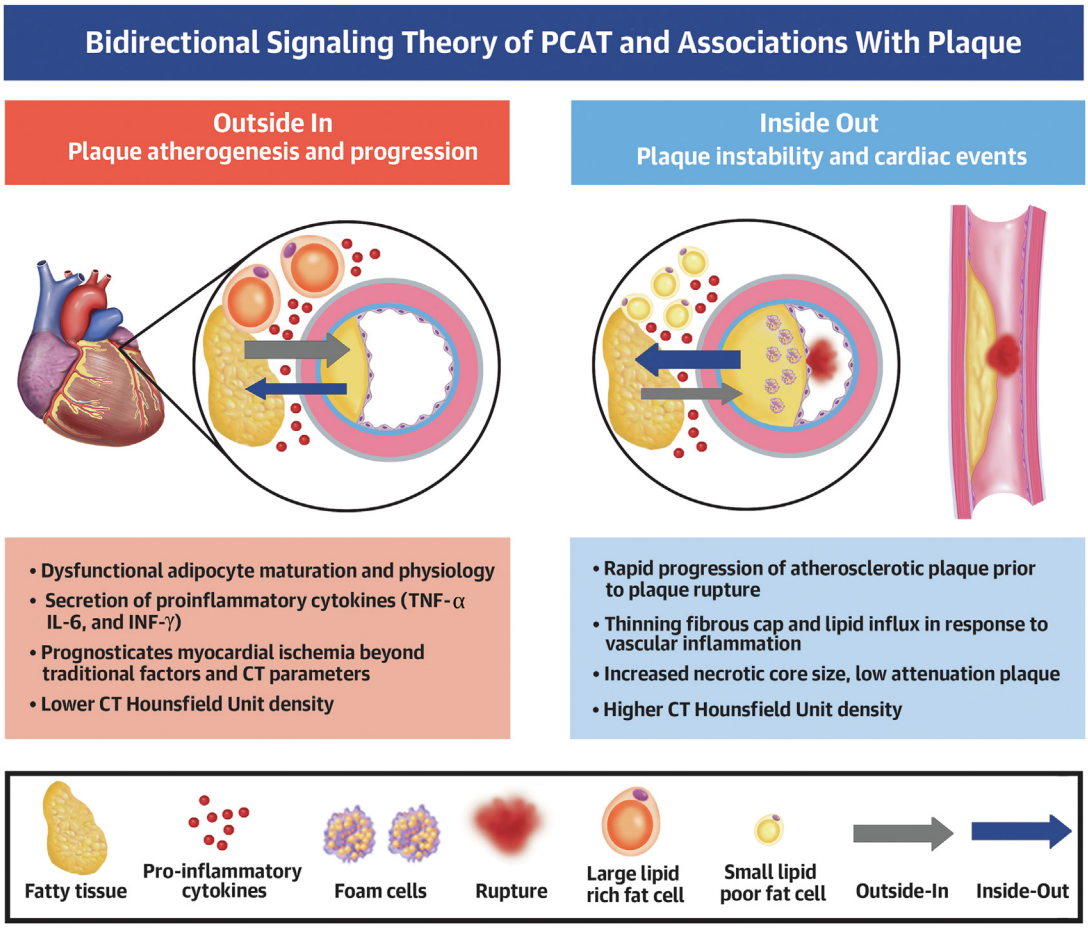
PCAT AND CAD

Several studies have demonstrated the association of coronary disease with PCAT (Supplemental Tables 1a and 1b). In the seminal proof-of-concept study by Antonopoulos et al,[21] changes in PCAT attenuation on coronary CTA were shown to correlate with histologic inflammatory changes in epicardial arteries, biopsied from patients undergoing cardiac surgery. Numerous subsequent studies have further characterized the utility of PCAT in detecting atherosclerotic progression and its prognostic value in predicting various clinical and angiographic outcomes.

The distinct physiological phenotype and paracrine signaling ability of PCAT relative to EAT and other visceral fat was highlighted using positron emission tomography.[22] Patients with non-ST-segment elevation myocardial infarction demonstrated selectively increased ^{18}F-fluorodeoxyglucose uptake in PCAT overlying the ischemic segments relative to surrounding visceral fat.

PCAT attenuation around the right coronary artery (RCA) (the most commonly cited measurement location) has shown differences across different stages of CAD severity, with patients with myocardial infarction having elevated PCAT attenuation compared with patients with stable CAD and patients with no discernible CAD having the least attenuation.[23]

CENTRAL ILLUSTRATION **Pericoronary Adipose Tissue as an Atherosclerotic Biomarker vs the Proposed "Bidirectional" Signaling Relationship**



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Pericoronary adipose tissue's (PCAT) secretome includes proinflammatory cytokines that are closely associated with coronary plaque. PCAT is hypothesized to exert a causative role in atherosclerotic progression through an "outside-to-inside" signaling pathway **(gray arrow)**. PCAT adipocytes adjacent to an inflamed arterial wall undergo dysfunctional cachexia-type maturation into a lipid-poor phenotype, and this "inside-to-outside" signaling pathway **(blue arrow)** results in detectable attenuation changes on coronary computed tomographic angiography. The overall signaling direction is likely to be a function of the underlying inflammatory milieu. As represented in the side-by-side examples, noninflamed endothelium with minimal plaque (case 1) encased by dysfunctional PCAT tissue is receiving predominantly outside-inward signaling, in contrast to potential inward-outward signaling from coronary artery with an unstable plaque (case 2) with evolving necrotic core features, macrophages, and foam cells. Figure partially created using Servier Medical Art templates, licensed under a Creative Commons Attribution 3.0 Unported License. CT = computed tomography; IL = interleukin; INF = interferon; TNF = tumor necrosis factor.

These observations were independent of age, sex, traditional risk factors, EAT volume, and coronary plaque volume. Notably, this relationship was not influenced by the anatomical location of culprit lesions. The similarity in PCAT between the RCA and non-RCA subgroups suggests that PCAT undergoes systemic changes in response to plaque rupture and inflammatory activity, even if plaque rupture occurs in a different coronary artery. This is consistent with previous studies that have demonstrated a pan-coronary inflammatory state after myocardial infarction.[24]

In a post hoc analysis from the landmark CRISP-CT (Cardiovascular Risk Prediction Using Computed Tomography) study, 3,912 patients who underwent coronary CTA had PCAT attenuation assessed using a weighted perivascular fat attenuation technique, the fat attenuation index. A significant association was

demonstrated for cardiac mortality at a threshold of >−70.1 HU[25] and was incremental beyond typical risk prediction algorithms.[26]

Noncalcified and low-attenuation plaque and HRP presence is associated with a high risk for future myocardial infarction and is considered a marker of plaque vulnerability. Calcified plaques tend to represent a more stable phenotype.[27] Elevated PCAT attenuation is an independent predictor of the presence of noncalcified, but not calcified, plaque[28] as well as HRP,[29] independent of other cardiovascular risk factors, and therefore may suggest a surrogate marker of active inflammation. A recent post hoc analysis of the SCOT-HEART (Scottish Computed Tomography of the Heart) trial demonstrated a marked and complementary predictive value for the risk for future myocardial infarction with the combination of low-attenuation plaque burden and RCA PCAT in patients with stable chest pain.[30]

PCAT may potentially demonstrate effects of plaque change with anti-inflammatory agents. Changes have been seen with use of statin therapies,[28] but responses to other agents, including targeted therapies, have yet to be reported.

ASSOCIATIONS OF PCAT WITH NONCORONARY DISEASES

There is limited evidence regarding the associations of noncoronary cardiovascular disease and noncardiac disease with PCAT. Adiposity is an important risk factor for atrial fibrillation (AF), but the pathophysiological mechanisms by which obesity causes AF are complex and incompletely understood. Studies focusing on the EAT secretome indicate that inflammatory cytokines interleukin-1β and tumor necrosis factor-α may lead to atrial fibrosis via paracrine effects.[31] Subsequent micro-re-entry circuits can also be created via fatty infiltration, interrupting wave fronts in the conduction pathway.[32] EAT volume may be a much stronger predictor of AF than is overall general or abdominal adiposity. In 364 patients with AF undergoing pulmonary vein catheter ablation, higher PCAT attenuation (averaged across 3 vessels) was a predictor of AF recurrence following cryoablation of the pulmonary vein.[33] This was independent of EAT volume, which was inversely correlated with PCAT attenuation.

EAT has also been shown to have an association with heart failure syndromes, specifically in patients with preserved ejection fraction.[34] Obesity is strongly associated with heart failure with preserved ejection fraction, and EAT possibly exerts its effect by limiting left ventricular filling, partly from mechanical restriction.[35] However, EAT (especially PCAT), can also exert neurohormonal effects via adrenergic and cholinergic pathways. Overactivation of the renin-angiotensin system (RAS) is an important pathophysiological mechanism in heart failure. In vivo studies have demonstrated systemic RAS activation in response to the diminished cardiac output state in heart failure, and this sustained RAS activation over a long period induces tissue changes such as vascular inflammation, oxidative stress, and endothelial dysfunction.[36] In a rat-based model, PVAT was shown to regulate vascular contractility by modulating the responsiveness of aortic smooth muscle to norepinephrine, and it exerted an overall anticontractile effect.[37] However, this effect was impaired in the presence of "PVAT dysfunction." Additionally, in a subsequent rodent study, the presence of heart failure–induced endothelial dysfunction substantially diminished the anticontractile effect of PVAT,[38] although it could be restored by angiotensin-converting enzyme inhibitors or angiotensin I receptor blockers. No specific studies of PCAT have been performed in heart failure subgroups.

ASSESSMENT OF PCAT

Cardiac CT remains the only accurate, validated noninvasive method for PCAT assessment. It has high spatial resolution and the ability to volumetrically quantify total fat as well as differentiate tissue characteristics on the basis of density thresholds. In addition to these benefits, CT allows the assessment of coronary artery anatomy and the identification of coronary plaque.

HUs are a quantitative measure of relative radiodensity in the interpretation of computed tomographic images.[39] A difference in radioabsorptive properties among various types of tissue generate different attenuation coefficients. The density of the tissue is proportional to a higher attenuation, thus producing a grayscale image. By convention, low-density tissues are darker (gray or black), and higher density tissues are lighter (white). The HU scale is calculated on the basis of a linear transformation of baseline linear attenuation coefficient. Distilled water is arbitrarily defined as 0 HU, air as −1,000 HU, blood as +30 to 45 HU, adipose tissue as −30 HU, and bone as +1,000 HU. Adipose tissue is typically defined to range from −190 to −30 HU, although different upper and lower boundaries have also been considered. Lower radiodensity (a more negative value) is associated with greater lipid volume. Dysfunctional

adipose tissue due to inflammatory stimuli may result in arrest of lipid maturation and subsequently smaller adipocytes, resulting in a less negative HU value.

In a study that measured both PCAT and EAT attenuation and volume, only PCAT was found to be a significant correlate of plaque burden, despite attenuation and volume parameters of PCAT and EAT being correlated.[28] This substantiates the hypothesis that PCAT holds a distinct and more physiologically significant phenotype because of its closer proximity to the vessel wall than more remote adipose tissue. The lack of anatomical demarcation between EAT and PCAT and lack of a universal definition of PCAT are challenging when attempting to interpret associations with disease processes. Most recent studies define PCAT as the adipose tissue located within a radial distance from the outer vessel wall equal to the diameter of the coronary vessel and measured around the RCA, 10 mm away from the RCA ostium and along a 40-mm segment length. However, there is marked heterogeneity in measurement approaches, and a standardized approach to measuring and quantifying PCAT is yet to be determined.

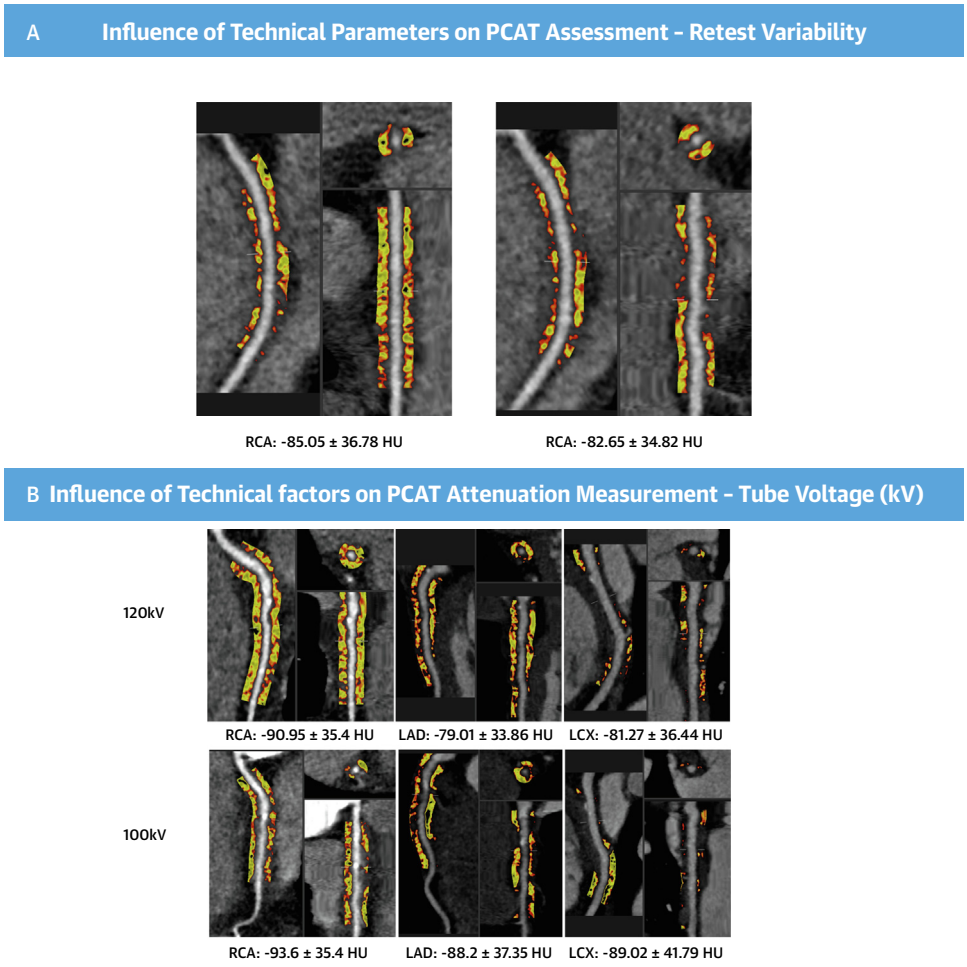
FACTORS INFLUENCING PCAT ATTENUATION MEASUREMENT

TECHNICAL PARAMETERS, TEST-RETEST VARIABILITY, AND ARTIFACTS. Normal PCAT has a significant range, driven by a number of variables (Supplemental Table 2). The Hounsfield scale has several limitations. First, different x-ray beam energies result in different tissue absorption and hence different HUs. As such, HU measurements are dependent on computed tomographic parameters. The specific reconstruction algorithm, computed tomography model, and tube voltage are all factors that can directly influence HU measurement.[18,40,41] Simply adjusting tube voltage from 70 to 120 kV can lead to a change of 11 HU.[42] Although good intraobserver and interobserver variability has been reported (**Table 2**), there has been no study to assess the test-retest variability of PCAT. This is critical to elucidate if PCAT is to be used in serial assessment with an intervention. **Figure 1A** demonstrates discordance in RCA PCAT attenuation values in a patient who underwent repeat coronary CTA within 24 hours with matched technical parameters. Similarly, **Figure 1B** demonstrates significantly different PCAT attenuation in a patient who underwent repeat coronary CTA at 2 different commonly used tube voltages (100 and 120 kV) 1 month apart. Variation may also be influenced by software type. Interobserver validity is yet to be fully established but appears promising from available data (**Table 2**).[26,41,43-51] Notably, there is a conversion factor that can be applied to account for differences in tube voltage, but this has been established only with certain software.[30]

As coronary CTA scans are acquired at different tube voltages depending on patient characteristics and computed tomography system, threshold values for PCAT may need adjustment by tube voltage setting. Additionally, PCAT computed tomography attenuation is itself directly influenced by body habitus, as obese individuals tend to have large adipocyte size (which alters radiodensity toward the upper boundary of −190 HU)[52] and may misclassify inflammation in this group. Furthermore, poor image quality and computed tomographic artifacts are often seen in obese patients, or those with elevated heart rates or extensive atheroma burden, which may also influence measurement. Partial volume artifact is an important potential source of error in PCAT attenuation measurement. Each voxel (3-dimensional pixel) in a computed tomographic image slice represents a specific radiodensity. However, that calculation is derived from beam attenuation proportional to the average value of immediately adjacent tissues.[53] Thus, confluences of tissues with widely different radioabsorption will lead to an inaccurate result, such as a misdiagnosis of apparent contrast filling defects as pulmonary embolism on computed tomographic angiography; influence from adjacent, dense calcific plaques; or high contrast density within the lumen. This has influenced approaches to measuring PCAT attenuation, given the potential to skew attenuation values. Most studies suggest measurement of the RCA beyond the first proximal 10 mm to avoid blooming due to adjacent aortic contrast. The use of thin-section reconstructions (1-1.5 mm) is recommended to reduce the occurrence of this artifact. Scanner type and technical parameters such as individual voxel volume are important variables to account for when assessing PCAT results. Finally, image quality, which affects plaque interpretation as well, also needs to be accounted for and is also of significance in scans with motion artifacts that commonly affect RCA interpretation.

MEASUREMENT LOCATION. Anatomical site selection for PCAT analysis also significantly influences the values of computed tomographic attenuation, because of differences in anatomy and surrounding tissues.[49,54] Early studies that examined PCAT attenuation focused on the proximal RCA, because of fewer anatomical variations, a lack of side branches, and an abundance of adipose tissue compared with

FIGURE 1 Potential Sources of Variability in PCAT Assessment



(A) Test-retest variability; pericoronary adipose tissue (PCAT) was assessed in a patient who underwent repeat coronary computed tomographic angiography within 24 hours with matched technical parameters. PCAT of the 40-mm segment of the proximal right coronary artery (RCA) demonstrates significant difference in mean attenuation. **(B)** Imaging settings. These coronary computed tomographic angiographic images were obtained from the same patient 1 month apart, at 2 different commonly used tube voltages (100 and 120 kV). Notable variation in mean PCAT attenuation was measured in all epicardial arteries (RCA, left anterior descending coronary artery [LAD], and left circumflex coronary artery [LCX]). A conversion factor can be applied with certain validated software.

LAD and left circumflex coronary artery (LCx).[55,56] Typically, a 40-mm segment is suggested for measurement. Notably, studies by Tzolos et al[46] and van Diemen et al[57] showed that RCA PCAT, but not LCx PCAT and LAD PCAT, is a significant predictor of myocardial infarction and mortality risk, possibly mediated by the increased fat volume surrounding the RCA relative to the other vessels. This is different from the results of CRISP-CT, which showed correlated LAD and RCA PCAT and may be representative of different software algorithms; no head-to-head software comparison has been performed. Although PCAT has been shown in certain studies to change systemically, even away from the culprit lesion,[58] a potential shortcoming of single-vessel measurement is that it will not capture uneven changes among vessels and thus may not be truly representative of global inflammation in the coronary circulation. In particular, it can omit major areas of interest, such as significantly stenosed segment in different vessels.

WITHIN-PATIENT DIFFERENCES. Recent studies have espoused measurement of PCAT in the proximal RCA, LAD, and LCx. One study examining the association between PCAT attenuation and mortality in patients

TABLE 2 Interobserver and Intraobserver Variability in Pericoronary Adipose Tissue Attenuation Studies

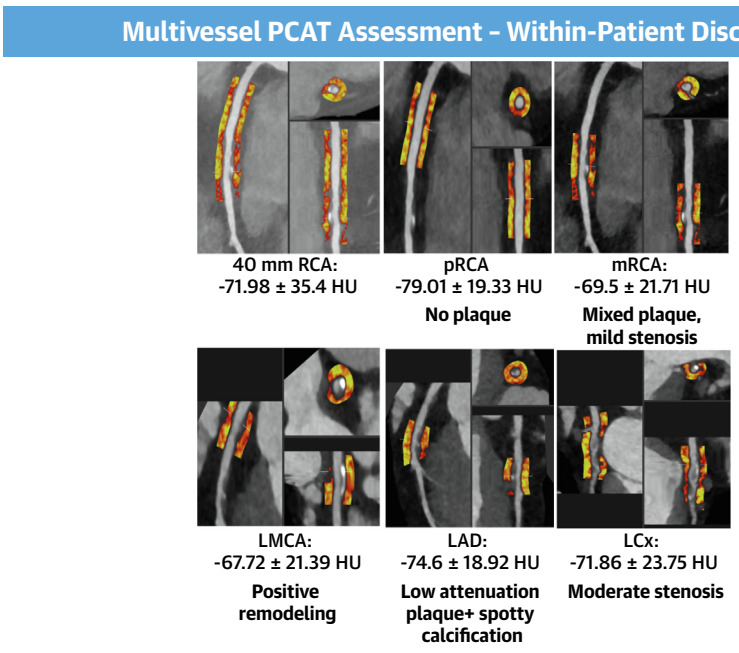
Study	N	Intraobserver Variability	Interobserver Variability
Ichikawa et al[43]	333	0.92	0.95
Bao et al[44]	192	–	0.986 (LMCA), 0.974 (LAD), 0.985 (LCx), 0.995 (RCA)
Wen et al[45]	108	0.984	
Oikonomou et al[26]	3,912	–	0.98 (RCA), 0.99 (LAD), 0.99 (LCx)
Tzolos et al[46]	50	–	0.998
Bittner et al[47]	64	0.998	0.999
Hoshino et al[48]	177	0.92	0.94
Zhu et al[49]	99	0.85	–
Chen et al[41]	104	0.82	
Ma et al[51]	35	–	0.87
Balcer et al[61]	47	0.95	
Maurovich-Horvat et al[50]	51	0.99	0.95

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; RCA = right coronary artery.

with non-ST-segment elevation myocardial infarction prior to coronary angiography revealed differences both along vessels (upstream and downstream of the lesion) and between vessels.[43] In one study of nonatherosclerotic arteries, the average PCAT attenuation varied among the left main coronary artery, LAD, LCx, and RCA, with lower mean attenuation in the LAD compared with the RCA.[42] A further 2 studies in patients with stable CAD also showed a minor difference between PCAT attenuation of the LAD, LCx, and RCA.[43,44] This would seem to indicate that incorporating measuring attenuation across multiple arteries may be necessary, as PCAT attenuation cannot be reliably extrapolated from a single artery. These within patient discrepancies are exemplified in Figure 2, which also demonstrates longitudinal discrepancy within a single artery. The appropriate length of PCAT measurement in a vessel is still uncertain.

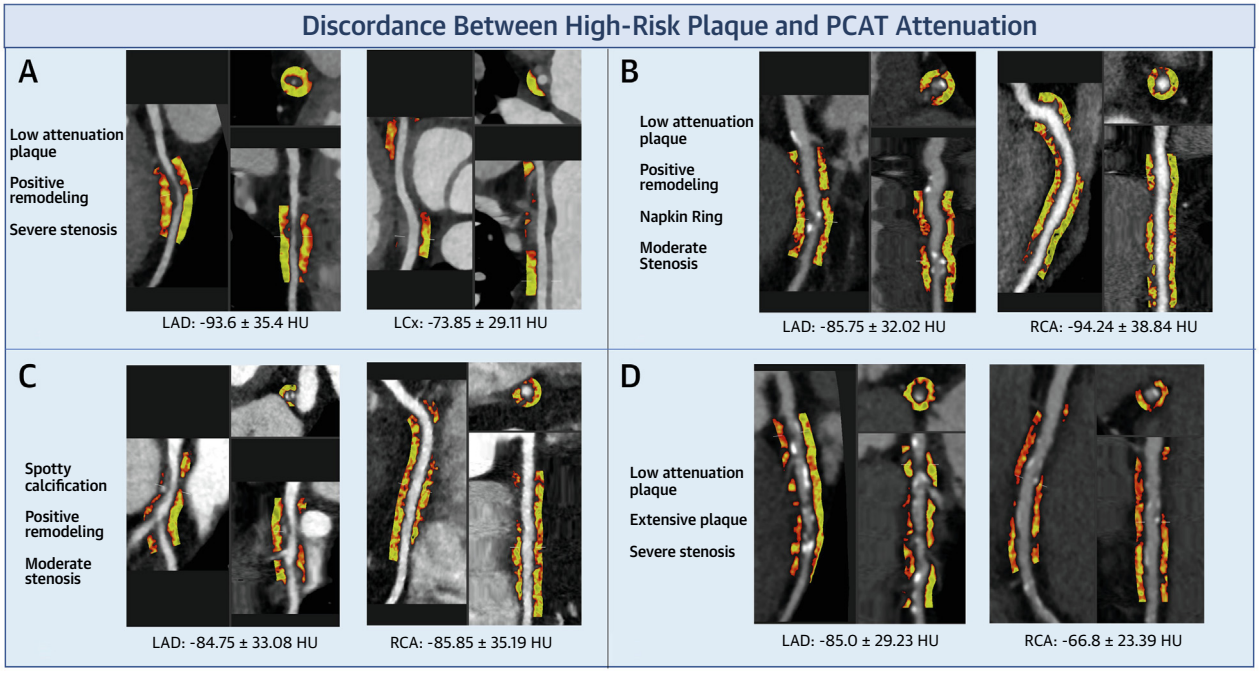
IMPACT OF PLAQUE. Many studies have shown a relationship between coronary computed tomographic angiographic evidence of plaque (and subtype) with mean PCAT attenuation,[59] which was higher in coronary arteries with plaque, compared with vessels without plaque. Where focal lesions were present, PCAT attenuation was higher in noncalcified and mixed plaque compared with calcified plaque, and there was no correlation with calcified plaque

FIGURE 2 Impact of Location



PCAT may be measured at the proximal RCA, at the lesion level, at the stenosis level, or at sites of high-risk plaque (HRP). In this case, all levels of measurement are performed, highlighting the complexities in accurate PCAT interpretation. **(Top row)** Measurement of the typical 40 mm of the RCA demonstrates a different mean attenuation compared with the longitudinal course of the vessel, with lower PCAT in the proximal plaque-free portion and higher PCAT in the distal portion with plaque. The whole RCA value of −71.98 HU is greater than the commonly defined threshold for prognostic significance. **(Bottom row)** Significantly different PCAT values are seen in the other epicardial vessels at lesion and HRP level in the left main coronary artery (LMCA), LAD, and LCx regardless of the presence of HRP. Abbreviations as in Figure 1.

FIGURE 3 **Discordance Between HRP and PCAT Values in the Same Patient**



(A) A patient with severe focal mid-LAD stenosis and 2-feature-positive HRP (low-attenuation plaque [LAP] and positive remodeling [PR]); LAD PCAT is lower than in the corresponding plaque-free LCx (the RCA was nondominant). **(B)** PCAT of another mid-LAD lesion with 3-feature-positive HRP (LAP, PR, and napkin-ring sign); this time PCAT is higher than in the corresponding plaque-free RCA. **(C)** Two-feature-positive HRP (spotty calcification and PR) and moderate stenosis; LAD PCAT is similar to RCA PCAT. **(D)** One-feature-positive HRP, extensive atheroma burden, and severe LAD stenosis, demonstrating lower PCAT attenuation compared with the RCA. Discordances may suggest different pathophysiology; for example, **A** may suggest an outside-in gradient of inflammation and **B** may suggest an inside-out gradient. It may also suggest the dynamic nature of PCAT or be related to different technical parameters used to acquire images. Abbreviations as in **Figures 1 and 2**.

burden.[59,60] This suggests that PCAT attenuation changes are more reflective of plaque development and vulnerability, as opposed to a more established plaque. However, the directional value of PCAT in HRP is unclear. It is expected that more "inflamed" vascular lesions will have higher PCAT values if the "inside-out" theory is to be believed (**Figure 3B**). If the direction of inflammation is "outside-in," then lower values could be seen (**Figure 3A**). Additionally, adipose tissue such as coronary plaque is dynamic, and the timing of capture related to patient physiology may influence the PCAT attenuation, and conceivably a patient may have no significant directional difference in attenuation between segments with and without plaque (**Figure 3C**). This dynamic nature may account for test-retest variability as well. The power of radiomic analysis may enhance the discriminative ability of PCAT in certain outcomes but remains investigational (Supplemental Table 3).

IS PCAT READY FOR PRIME TIME?

PCAT computed tomographic attenuation is a promising imaging biomarker, with potentially significant clinical implications in detecting residual cardiovascular risk and bridging the missing link between clinically undetectable inflammation and atherosclerosis. The identification of a patient group without obstructive coronary disease but elevated PCAT attenuation may enable early commencement of medical therapy and could serve as a "high-risk" subgroup in further trials of anti-inflammatory therapeutic agents such as canakinumab and colchicine.

However, there are still several notable barriers to be overcome before measurement of PCAT can be widely implemented into routine practice. First, standardization of PCAT attenuation measurement is yet to be achieved, and its reproducibility needs validation in larger prospective cohorts. This includes

the performance of coronary CTA to best allow PCAT to be reproducibly measured. Second, the optimal site(s) and extent of measurement of PCAT attenuation to maximize sensitivity are also yet to be fully defined. Additionally, although the hypothesis linking inflammation with PCAT density appears plausible, this is difficult to substantiate without further prospective studies using pathologic or serum analysis.

The widespread use and easy accessibility of coronary CTA make PCAT an alluring prospect as a novel imaging biomarker of coronary inflammation and cardiovascular risk prediction. However, the technical considerations described in this review may lead to misleading results. Further maturation and validation of this technique are needed to unlock the full potential of this exciting tool.

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APPENDIX **For supplemental tables and supplemental references, please see the online version of this paper.**