

Perivascular Fat Attenuation Index on Non-Contrast-Enhanced Cardiac Computed Tomography: Comparison with Coronary Computed Tomography Angiography

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Abstract

Objective: Perivascular fat attenuation index (FAI) measurement on non-contrast-enhanced cardiac computed tomography (NCCT) has not been rigorously validated in previous studies. Herein, we compared perivascular FAI values between NCCT and coronary computed tomography angiography (CCTA). We also investigated the variability and reproducibility of perivascular FAI measurement. **Methods:** A total of 44 patients who underwent NCCT and CCTA were included in this study. For NCCT, perivascular FAI was measured using three threshold settings: from -30 to -190 Hounsfield Units (HU), -20 to -180 HU, and -10 to -170 HU. For CCTA, perivascular FAI was measured using one threshold setting: from -30 to -190 HU. Perivascular FAI measurements by NCCT were compared with those by CCTA using the paired *t*-test, and correlations were assessed using Pearson's correlation coefficient. The intra- and inter-observer variabilities for the measurements with NCCT and CCTA were evaluated with the intraclass correlation coefficient. **Results:** Perivascular FAI measurements with the threshold setting of -30 to -190 HU were significantly lower on NCCT than on CCTA. There were no significant differences between the perivascular FAI measurements at the remaining thresholds on NCCT and those on CCTA. The perivascular FAI at all thresholds on NCCT correlated significantly with those on CCTA. The intra- and inter-observer agreements were excellent for the measurements on NCCT and CCTA. **Conclusion:** There were significant differences between the perivascular FAI measurements on NCCT and CCTA. However, the differences could be modified by threshold adjustment.

Keywords

Computed Tomography, Coronary Computed Tomography Angiography, Perivascular Fat Attenuation Index, Perivascular Adipose Tissue

1. Introduction

The presence of myocardial ischemia related to hemodynamically significant coronary artery stenosis is important in deciding percutaneous coronary intervention. Reducing myocardial ischemia by revascularization improves a patient's status and outcome [1]. Acute coronary syndrome (ACS) describes the range of myocardial ischemic states such as unstable angina or myocardial infarction. ACS is associated with substantial morbidity and mortality and places a large financial burden on the health care system [2].

Coronary computed tomography angiography (CCTA) is a noninvasive method for the identification of anatomical coronary artery stenosis [3] [4] [5]. Several modifications of CCTA for detecting hemodynamically significant coronary stenosis and assessing anatomical coronary stenosis have been established recently [6] [7]. Among these, noninvasive fractional flow reserve derived from computed tomography (FFRCT) has been demonstrated to have high diagnostic utility for the detection of hemodynamically significant stenosis [8] [9].

In recent years, the perivascular fat attenuation index (FAI) derived from CCTA was developed as a novel technique showing signs of coronary inflammation and edematous perivascular adipose tissue [10]-[15]. Coronary inflammation is associated with coronary atherosclerotic plaque formation and plaque rupture, leading to acute coronary syndrome [16]. Oikonomou *et al.* showed that perivascular FAI measurement significantly improves cardiac risk prediction and risk stratification compared to current assessments using CCTA by providing a quantitative measurement of coronary inflammation [10]. High perivascular FAI values indicate increased mortality and can be utilized for early primary prevention of cardiac events in patients.

However, all studies related to the perivascular FAI were investigated using CCTA images. A previous study revealed that technical parameters, such as lumen attenuation and tube voltage, influence perivascular FAI values measured by CCTA [9]. In addition, adverse reactions to contrast media are most commonly seen after the intravascular administration of contrast agents. These are limitations of the perivascular FAI measurement on CCTA. Along with CCTA, non-contrast-enhanced cardiac computed tomography (NCCT) is often performed for the evaluation of coronary artery calcium scoring [17] [18]. NCCT and CCTA may be employed separately depending on the clinical condition. Perivascular FAI measurement on NCCT has not been rigorously validated, and to the best of our knowledge, no studies have investigated the feasibility of this measurement with NCCT. The characteristic and accuracy of the measurement

with NCCT were unknown. Therefore, we compared the perivascular FAI values measured by NCCT and CCTA and investigated the variability and reproducibility of perivascular FAI measurements with NCCT.

2. Materials and Methods

2.1. Patients

This retrospective study was approved by the institutional review board, and the need to obtain informed consent from patients was waived. Patients who underwent NCCT and CCTA between January and March 2020 were included in this study. Patients with a history of coronary artery bypass grafting were excluded.

2.2. Acquisition Protocol

NCCT and CCTA were performed using 256-slice CT (Brilliance iCT; Philips Healthcare, Best, The Netherlands). First, sublingual nitrates were administered for coronary vasodilatation. NCCT was performed with a prospectively electrocardiogram-gated step-and-shoot acquisition mode. Scan parameters were as follows: slice thickness, 2.5 mm; slice gap, 2.5 mm; tube voltage, 120 kV; detector collimation, 32×0.625 mm; and gantry rotation time, 270 ms. Tube current was set according to the body mass index (BMI) of patients as follows: 24 mAs (BMI < 23 kg/m²), 30 mAs (23 kg/m² ≤ BMI < 26 kg/m²), 36 mAs (26 kg/m² ≤ BMI < 29 kg/m²), or 42 mAs (29 kg/m² ≤ BMI). Subsequently, CCTA was performed with the prospectively electrocardiogram-gated axial mode based on the tube current modulation technique. Intravenous β -blockers were administered before scanning if the resting heart rate exceeded 65 beats/min. The scan was acquired during injection of 23.5 mgI/kg/s of 100% iomeprol (Iomeron 350; Eisai, Bunkyo-ku, Japan), followed by 30 mL of saline at the same rate. The injection duration of the contrast agent varied from 13 to 15 s depending on the heart rate. Scans were manually triggered using bolus tracking when the contrast attenuation reached 100 HU in the ascending aorta. Scan parameters were as follows: slice thickness, 0.8 mm; slice gap, 0.4 mm; tube voltage, 120 kV; detector collimation, 128×0.625 mm; gantry rotation time, 270 ms; and pitch, 0.14 - 0.16. Tube current was set according to the BMI of patients as follows: 320 mAs (BMI < 23 kg/m²), 450 mAs (23 kg/m² ≤ BMI < 26 kg/m²), 600 mAs (26 kg/m² ≤ BMI < 29 kg/m²), or 840 mAs (29 kg/m² ≤ BMI).

2.3. CT Image Reconstruction

Images were reconstructed using the hybrid iterative reconstruction algorithm (iDose4; Philips Healthcare). Reconstruction parameters of NCCT were as follows: field of view (FOV), 25 cm; matrix, 512×512 pixels; and filter, cardiac standard. Reconstruction parameters of CCTA were as follows: FOV, 19 cm; matrix, 512×512 pixels; and filter, cardiac standard. **Figure 1** shows samples of reconstruction images.

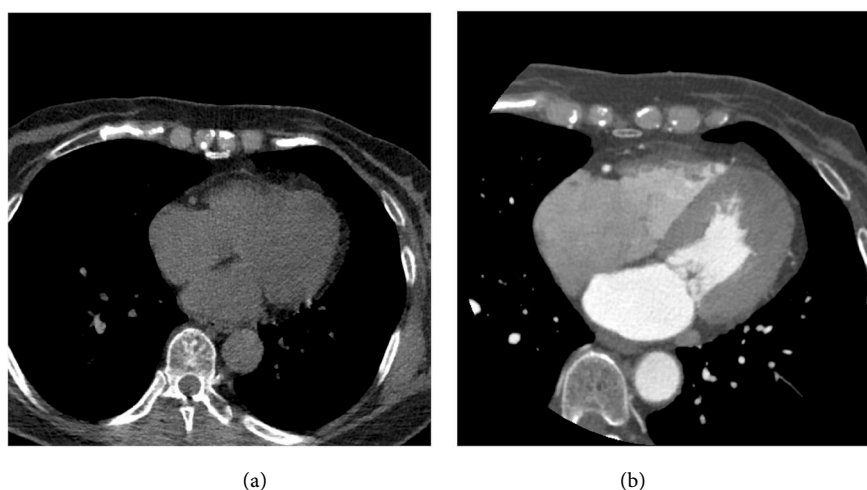


Figure 1. Reconstruction images on non-contrast-enhanced cardiac computed tomography (a) and coronary computed tomography angiography (b). Both images were reconstructed using the hybrid iterative reconstruction algorithm.

2.4. Perivascular FAI Analysis

Data were analyzed in a workstation (AZE Virtualplace; AZE, Tokyo, Japan) by two independent experienced observers (with 11 and 13 years of experience, respectively, in the analysis of CCTA). The analysis was repeated by an observer (11 years of experience in the analysis of CCTA) after a 2-week interval for the evaluation of the intra-observer variability. **Figure 2** shows the overview of the perivascular FAI analysis. We accessed only the right coronary artery because of the significance of perivascular FAI measured around the proximal right coronary artery. In CCTA datasets, the centerlines of the vessels were automatically determined and manually corrected, if necessary. In NCCT datasets, the centerlines of all vessels were manually determined. Cross-sectional images perpendicular to the vessel centerline and 10 - 50 mm proximal to the right coronary artery were reconstructed. The most proximal 10-mm portion of the vessel was excluded from analysis to avoid the effects of the aortic wall. Perivascular FAI is defined as the mean CT attenuation of adipose tissue, which is within a radial distance from the outer vessel wall equal to the diameter of the target vessel [10]. To measure the perivascular FAI, perivascular adipose tissue was masked with a circular region of interest (ROI) from the center of the vessel. The diameter of ROI was three times longer than that of the vessel. For masking, an upper threshold of -30 HU and a lower threshold of -190 HU was applied, as previously demonstrated [10]. In the case of NCCT, additional combinations of upper and lower thresholds were applied as follows: from -10 to -170 HU and from -20 HU to -180 HU. To avoid the effects of non-adipose tissues, the areas masking the coronary arteries or veins were manually excluded. Mean attenuation values of masked voxels at each threshold combination (from -10 to -170 HU, from -20 to -180 HU, and from -30 to -190 HU for NCCT; from -30 to -190 HU for CCTA) were calculated.

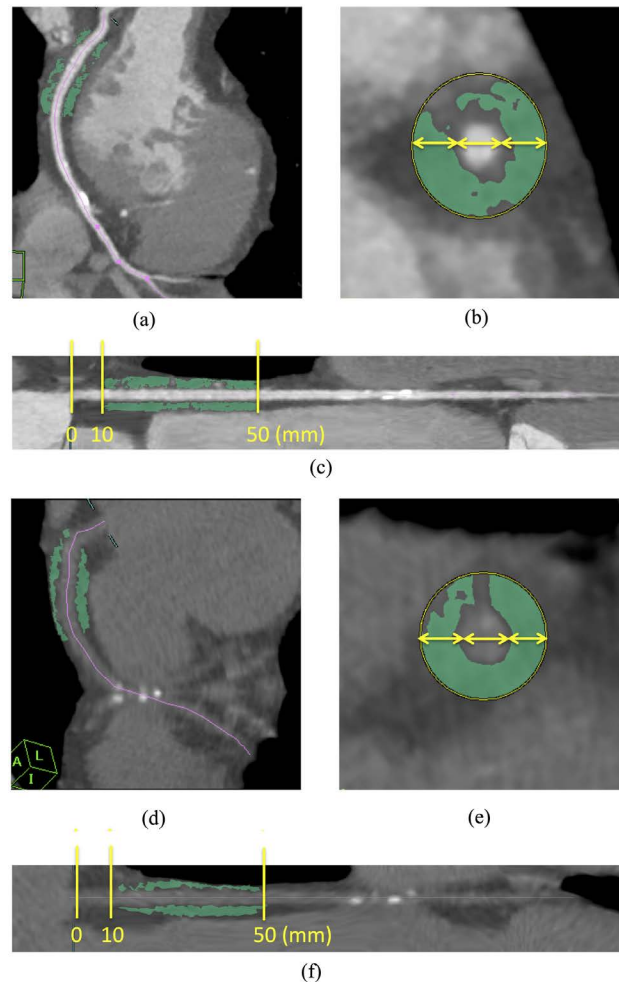


Figure 2. Overview of the perivascular fat attenuation index analysis of the right coronary artery on coronary computed tomography angiography (CCTA) ((a)-(c)) and non-contrast-enhanced cardiac computed tomography (NCCT) ((d)-(f)). Coronary luminal attenuation on CCTA images was higher than that on NCCT images. Cross-sectional images perpendicular to the vessel centerline ((b) and (e)) from the proximal 10 - 50-mm portion of the vessel were reconstructed. To measure perivascular fat attenuation index (FAI), perivascular adipose tissue was masked with a circular region of interest (ROI) from the center of the vessel. The diameter of ROI was three times longer than that of the vessel. The masking range was from the proximal 10 - 50-mm portion ((c) and (f)).

2.5. Statistical Analysis

Continuous variables are expressed as mean \pm standard deviation. Categorical variables are expressed as percentages. Perivascular FAI values from NCCT were compared with those from CCTA using the paired t-test. Correlation was assessed using Pearson's correlation coefficient. The intra-observer and inter-observer variabilities for perivascular FAI measurement at the threshold setting from -30 to -190 HU on NCCT and CCTA were evaluated with the intraclass correlation coefficient (ICC). Statistical analysis was performed with statistical software R, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). A p -value < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Patient Characteristics

Table 1 shows the patient characteristics. A total of 48 patients were considered for this study, four of whom were excluded because of their history of coronary artery bypass grafting. Finally, a total of 44 patients were included.

3.2. Perivascular FAI Measurements

Table 2 shows the results of perivascular FAI measurements at each threshold setting on NCCT and CCTA. At the threshold setting from -30 to -190 HU, perivascular FAI values were significantly lower on NCCT than on CCTA (-77.3 ± 9.7 HU vs. -70.0 ± 9.5 HU, $p < 0.001$). There were no significant differences between the perivascular FAI values at the threshold setting from -20 to -180 HU on NCCT and those at the threshold setting from -30 to -190 HU on CCTA (-73.5 ± 10.8 HU vs. -70.0 ± 9.5 HU, $p = 0.11$). Likewise, there were no significant differences between the perivascular FAI values at the threshold setting from -10 to -170 HU on NCCT and those at the threshold setting from -30 to -190 HU on CCTA (-70.4 ± 12.0 HU vs. -70.0 ± 9.5 HU, $p = 0.87$).

Table 1. Patient characteristics (n = 44).

Characteristic	Value
Age (years)	69.5 \pm 10.2
Male	37 (84.1%)
Body Mass Index (kg/m ²)	23.7 \pm 3.5
Cardiovascular risk factors	
Diabetes	19 (43.2%)
Hypertension	28 (63.6%)
Hypercholesterolemia	18 (40.9%)
Hyperlipidemia	24 (54.5%)

Values are expressed as mean \pm standard deviation or n (%).

Table 2. Perivascular fat attenuation index measurement on coronary computed tomography angiography and non-contrast-enhanced cardiac computed tomography.

	Perivascular FAI (HU)	p-value	Pearson correlation coefficient	p-value for Pearson correlation coefficient
CCTA				
from -30 to -190 HU	-70.0 ± 9.5			
NCCT				
from -30 to -190 HU	-77.3 ± 9.7	<0.001	0.76	<0.001
from -20 to -180 HU	-73.5 ± 10.8	0.11	0.76	<0.001
from -10 to -170 HU	-70.4 ± 12.0	0.87	0.75	<0.001

FAI: fat attenuation index, CCTA: coronary computed tomography angiography, NCCT: non-contrast-enhanced cardiac computed tomography.

The perivascular FAI values at all threshold settings for NCCT correlated significantly with those for CCTA ($r = 0.76$ and $p < 0.001$, $r = 0.76$ and $p < 0.001$, and $r = 0.75$ and $p < 0.001$ at the threshold settings from -30 to -190 HU, -20 to -180 HU, and -10 to -170 HU, respectively).

3.3. Intra- and Inter-Observer Variabilities

Intra-observer agreements were excellent for measurements with NCCT (ICC: 0.95; 95% CI: 0.91, 0.97) and CCTA (ICC: 0.99; 95% CI: 0.98, 0.99). Likewise, inter-observer agreements were excellent for measurements with NCCT (ICC: 0.93; 95% CI: 0.88, 0.96) and CCTA (ICC: 0.92; 95% CI: 0.85, 0.95).

4. Discussion

The use of perivascular FAI derived from CCTA as a novel imaging biomarker has been reported. However, the feasibility of perivascular FAI measurement on NCCT has not been demonstrated. Moreover, previous studies have not compared perivascular FAI between NCCT and CCTA. The clinically relevant findings of our study are that the differences between perivascular FAI on NCCT and CCTA could be reconciled by modifying the threshold level. In addition, the intra-observer and inter-observer agreements for perivascular FAI on NCCT were excellent.

The mean attenuation of adipose tissue has been reported at -105 HU previously [19]. However, the attenuation of adipose tissue varies between NCCT and CCTA. In our study, perivascular FAI values at the threshold setting from -30 to -190 HU were significantly lower in NCCT than in CCTA. This is mostly due to the partial volume effect and beam hardening [19] [20]. Marwan *et al.* reported that the partial volume effect was pronounced in the pericoronary adipose tissue near the contrast-enhanced coronary artery lumen [21]. Beam hardening occurred because of extracellular distribution of iodinated CT contrast media. The extent of these effects varies according to conditions, such as patient BMI, acquisition protocol, and injection protocol, which may have affected the correlation of measurements between NCCT and CCTA in our study.

The influence of threshold settings on the body fat volume measurements by CT has been reported [21] [22] [23]. Although perivascular FAI is the mean attenuation of adipose tissue rather than of fat volume, the influence of the threshold settings is also substantial, as suggested by our findings. Our results indicated that applying the same threshold levels to NCCT and CCTA for evaluation of perivascular FAI would introduce a significant bias. Moreover, our results showed that perivascular FAI measurements by NCCT at the threshold setting from -10 to -170 HU were approximated most closely by CCTA measurements at the threshold setting from -30 to -190 HU. However, perivascular FAI measurements by NCCT cannot be considered comparable to measurements by CCTA because no standard threshold has been established. Further investigation for optimization of the threshold is necessary.

Quantitative assessments, such as perivascular FAI measurement, require analyses of high accuracy and reliability. In our study, perivascular FAI on NCCT showed excellent intra- and inter-observer agreements despite relatively thicker image slices, non-helical scanning, and manual delineation of the vessel. In addition, the perivascular FAI values obtained using NCCT correlated significantly with those obtained using CCTA. These results indicated the potential utility of NCCT in measuring perivascular FAI.

Various studies have shown the clinical impact of quantitative analyses using NCCT, including coronary calcium scoring and epicardial adipose tissue volume measurement [24] [25]. Together with these analyses, measurement of perivascular FAI using NCCT has potential clinical implications since NCCT and CCTA are not always concurrently obtained. Moreover, NCCT has the advantage over CCTA of no contrast agent requirement. The use of contrast agents can cause adverse reactions [26]. Additional studies are necessary to streamline the measurement of perivascular FAI by NCCT to predict cardiac risk.

Limitation of our study was that it was a retrospective, single-center study that included only 44 patients. It is unclear whether our findings can be generalized to different scanning or injection protocols. Moreover, we did not investigate the diagnostic performance of perivascular FAI measurement by NCCT to predict cardiac events. Further investigations are required before applying perivascular FAI on NCCT in various clinical situations.

5. Conclusion

There were significant differences between perivascular FAI values measured using NCCT and CCTA. However, the differences could be resolved by threshold adjustment. The intra-observer and inter-observer agreements for perivascular FAI measurements with NCCT were excellent.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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