Original Article

Analysis of coronary computed tomography angiography-derived pericoronary fat attenuation index characteristics in the diagnostic assessment of patients with Takayasu arteritis

Wenjing Zhao[1]^, Nan Zhang[1], Shiyu Yang[2], Lili Pan[2], Jiayi Liu[1], Dongting Liu[1], Lei Xu[1], Guicheng Zhang[3], Zhonghua Sun[4]^, Zhaoying Wen[1]

[1]Department of Radiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; [2]Department of Rheumatology and Immunology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; [3]School of Population Health, Curtin University, Perth, Australia; [4]Discipline of Medical Radiation Science, Curtin Medical School, Curtin University, Perth, Australia

Contributions: (I) Conception and design: N Zhang, J Liu, Z Sun, W Zhao; (II) Administrative support: Z Wen, J Liu, L Xu; (III) Provision of study materials or patients: L Pan, S Yang, G Zhang; (IV) Collection and assembly of data: W Zhao, S Yang, G Zhang; (V) Data analysis and interpretation: S Yang, G Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jiayi Liu, MD. Department of Radiology, Beijing Anzhen Hospital, No. 2, Anzhen Road, Chaoyang District, Beijing 100029, China. Email: ljy76519@163.com; Zhonghua Sun, PhD. Discipline of Medical Radiation Science, Curtin Medical School, Curtin University, Perth, Western Australia 6102, Australia. Email: z.sun@curtin.edu.au.

Background: The clinical value of pericoronary adipose tissue in assessing Takayasu arteritis (TAK) with coronary artery involvement (CAI) is yet to be determined. The purpose of this study was to investigate the characteristics of pericoronary fat attenuation index (FAI) derived from coronary computed tomography angiography (CTA) in patients with TAK.

Methods: This is a retrospective study involving enrollment of 111 consecutive patients (mean age, 33.92±12.48 years) who were diagnosed as TAK, of which 52 patients had coronary artery involvement (TAK-CAI) and 59 patients without coronary artery involvement (TAK-nonCAI). Based on the extent of coronary artery lesion, the TAK-CAI group was further classified into localized group (n=25) and diffused group (n=27). Furthermore, patients with TAK were divided into active group (n=33) and inactive group (n=78). Meanwhile, 51 gender-matched individuals with normal appearance in coronary CTA examination were enrolled as the control group. The pericoronary FAI was quantitatively evaluated on each coronary CTA examination groups. The diagnostic value of pericoronary FAI was determined using the area under the curve (AUC) of the receiver operating characteristic.

Results: A higher pericoronary FAI was found in TAK-nonCAI group than control group with normal coronary arteries (P<0.001). Multivariate analysis showed that the FAI is an independent risk factor for coronary involvement in TAK patients [odds ratio (OR): 1.23, 95% confidence interval (CI): 1.13–1.35, P<0.001]. With the best cut-off value of –86.50, the pericoronary FAI identified coronary involvement with 67.8% sensitivity and 74.5% specificity (AUC: 0.794, 95% CI: 0.713–0.875, P<0.001). Multivariate analysis showed that the pericoronary FAI is an independent risk factor for determination of active TAK patients (OR: 1.57, 95% CI: 1.25–1.97, P<0.001). With the best cut-off value of –79.50, the pericoronary FAI identified active inflammation with 93.9% sensitivity and 74.4% specificity (AUC: 0.911, 95% CI: 0.860–0.962, P<0.001).

Conclusions: Coronary CTA-derived FAI is significantly increased in patients with TAK and can be used as a reliable biomarker to distinguish TAK patients from those with normal coronary arteries, and determine

^ ORCID: Wenjing Zhao, 0000-0001-6507-4594; Zhonghua Sun, 0000-0002-7538-4761.

the extent of TAK inflammation.

Keywords: Takayasu arteritis (TAK); pericoronary adipose tissue density; coronary artery disease; coronary computed tomography angiography (coronary CTA)

Submitted Mar 30, 2023. Accepted for publication Aug 17, 2023. Published online Sep 05, 2023.
doi: 10.21037/qims-23-419
View this article at: https://dx.doi.org/10.21037/qims-23-419

Introduction

Although Takayasu arteritis (TAK) is a rare vasculitis, TAK with coronary artery involvement (TAK-CAI) is not uncommon and is associated with poor prognosis and increased mortality. According to the literature, approximately 10–30% of patients with TAK exhibit coronary artery involvement (1,2). Another study reported that 17% of patients with TAK have cardiac manifestations, of which 7–35% die of congestive heart failure and 14% die of acute myocardial infarction (3). Early diagnosis of CAI has a significant clinical impact on improving the prognosis and clinical outcomes, but patients with TAK-nonCAI often face a significant diagnostic delay owing to nonspecific signs, such as normal coronary arteries.

In recent years, analysis of pericoronary adipose tissue (PCAT) has proven to be a promising imaging biomarker in the diagnostic assessment of coronary artery disease (4-8). PCAT is considered a good indicator in evaluating the development of coronary atherosclerosis. PCAT wrapped around coronary arteries secretes inflammatory cytokines that may affect the adjacent vessel wall, and the resulting vascular inflammation leads to the formation and progression of coronary atherosclerosis (9). The assessment of PCAT attenuation on coronary computed tomography angiography (CTA) has emerged as a noninvasive and widely accessible surrogate marker of coronary inflammation, which is capable of mapping inflammatory changes associated with coronary artery disease (CAD) in both stable and vulnerable populations (7,10-12). The identification of a bidirectional interplay between the vascular wall and the PCAT has revealed new pathways with key implications in cardiovascular diagnostics and therapeutics.

PCAT can now be quantitatively evaluated with a novel CT-derived metric, namely perivascular fat attenuation index (FAI), with no extra cost or radiation exposure (11-13). However, to the best of our knowledge, no such studies have been performed in the Asian population with TAK. Therefore, in this work, the imaging characteristics of PCAT in patients with TAK and those with normal coronary arteries were analyzed for comparison, and the differences of these imaging features among various groups were examined. Furthermore, the diagnostic value of coronary CTA-derived FAI in differentiating TAK patients from normal coronary artery individuals was investigated and the involvement of coronary artery, activity of TAK was also identified. The purpose of this study is to quantitatively evaluate the activity of patients with TAK using FAI and ability to distinguish patients with TAK in the normal coronary artery group. We hypothesized that FAI derived from CTA could serve as a reliable biomarker to distinguish patients with TAK from those with normal coronary arteries, and also assist determining the extent of TAK inflammation whether it is at active or inactive stage. We present this article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-419/rc).

Methods

Patient population

This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Beijing Anzhen Hospital, Beijing, China (No. 2022023X), and the requirement for written informed consent was waived due to the retrospective nature of the study.

A total of 236 consecutive patients were diagnosed as TAK according to the American College of Rheumatology criteria (1990) (14) from September 2015 to March 2022 in Beijing Anzhen Hospital. Of these, 146 patients underwent coronary CTA examination because of chest tightness, chest pain, palpitation, and other symptoms. Thirty-five patients were excluded from the study owing to the following reasons: unqualified coronary CTA images (n=3); anomalous

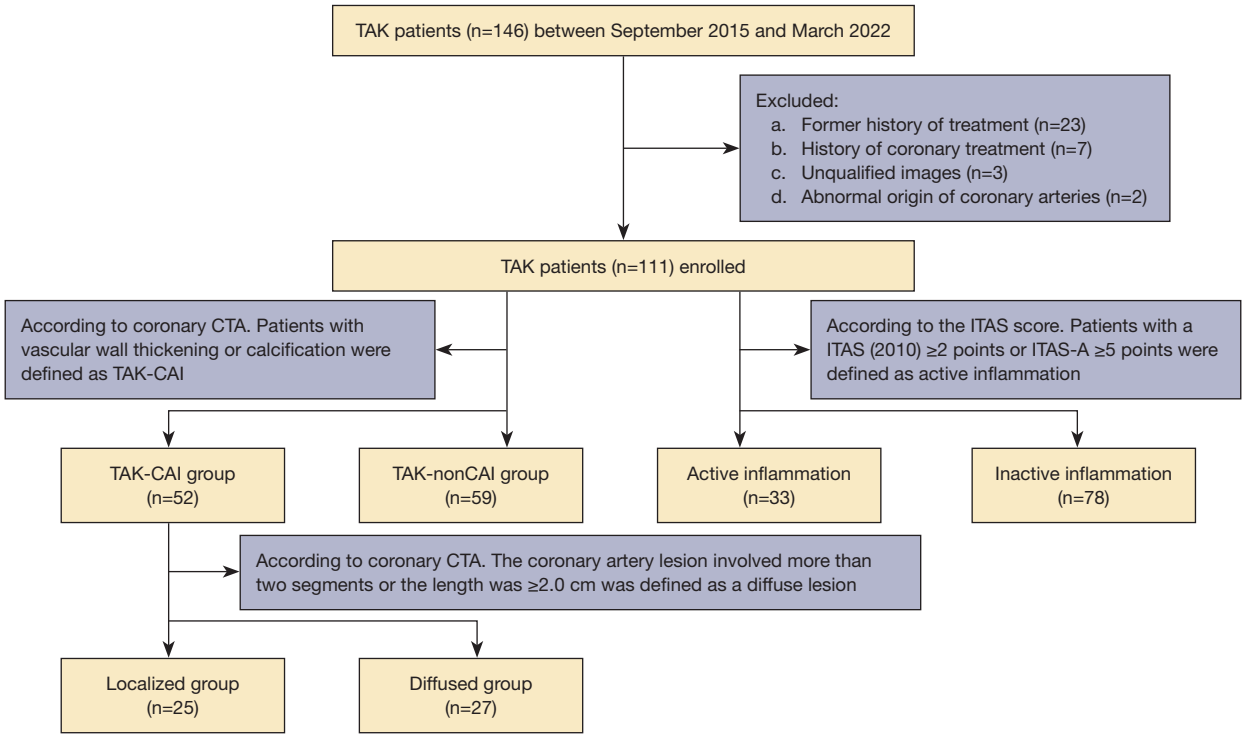

Figure 1 The flowchart of patient recruitment and study design. TAK, Takayasu arteritis; CTA, computed tomography angiography; CAI, coronary artery involvement.

origin of the coronary artery (n=2); former history of medical treatment (n=23); and history of revascularization of the coronary artery (n=7) with bypass surgery or coronary stenting. Finally, 111 patients were enrolled in the study.

Meanwhile, we also reviewed patients who underwent coronary CTA examination due to chest pain, dyspnea, palpitation or other related cardiac symptoms or electrocardiogram abnormalities in the same site during the same period. A total of 51 age- and gender-matched patients with normal coronary arteries were included as the control group. *Figure 1* is the flowchart of patient recruitment and study design.

CT acquisition protocols

CTA was performed on a 128-slice dual-source CT scanner (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). Contrast-enhanced scan was performed in the craniocaudal direction with a standard prospectively electrocardiogram-gated protocol (15). The exposure interval was selected depending on the heart rate, as follows: 30–40% RR interval for patients with heart rate of ≥70 beats per minute and 70–80% RR interval for patients with heart rate of <70 beats per minute. The acquisition range covered the region 1 cm below the carina to the cardiac apex. Scanning parameters were as follows: detector beam collimation of 2 mm × 64 mm × 0.6 mm, field of view of 220 mm × 220 mm and gantry rotation time of 280 ms. Respiration training was performed to reduce the respiratory motion artifact. Body mass index was calculated to select the appropriate kilovoltage (80–140 kV) with the use of automatic tube current modulation. There were no adverse events that occurred during the CTA examination. Reconstruction was completed using a high-spatial-frequency algorithm. The CT images were transferred to a separate workstation using the Skviewer software program (Coronary System; Shukun Technology, Beijing, China) for image processing and analysis. First, each image was processed for image consistency to eliminate the impact of different window widths and window levels on the quality of the reconstructed image. Then, the coronary system was used for longitudinal and axial multiplanar reconstruction of the coronary artery. Finally, an experienced radiologist (with 11 years of experience in interpreting cardiac CT

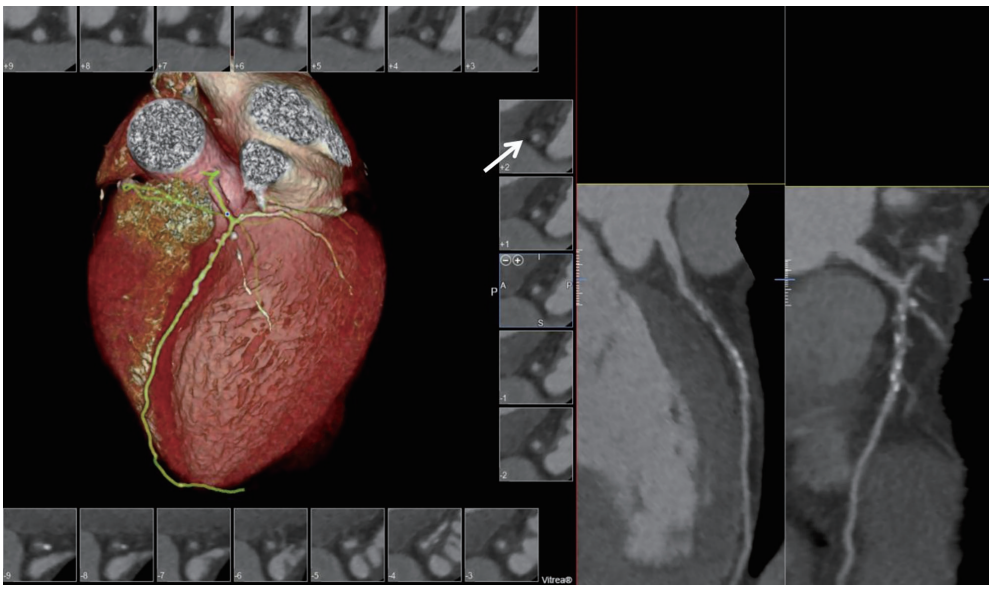

Figure 2 A 28-year-old female TAK patient underwent coronary CTA examination due to chest tightness and pain. MPR of the coronary artery showed diffuse thickening of the left main artery and left anterior descending branch, narrowing of the lumen, and concentric signs of blood vessels, namely, TAK-CAI. The white arrow indicates a concentric circle sign of the left main artery vascular wall thickening in the transverse section image. TAK, Takayasu arteritis; CTA, computed tomography angiography; MPR, multiplanar reformation; CAI, coronary artery involvement.

images) evaluated the image quality of coronary artery reconstruction.

Definition of TAK-CAI

TAK-CAI was defined as coronary arterial wall thickening or calcification noticed in coronary CTA, regardless of lumen stenosis and dilation. TAK-CAI should be visible in at least one of the following vessels: left anterior descending (LAD), left circumflex branch (LCX), and right coronary artery (RCA). Example figures of TAK-CAI and TAK-nonCAI are presented in *Figures 2*,*3*. According to the length of the coronary artery lesion, patients with TAK-CAI were classified into diffused and localized subgroups. At coronary CTA, diffuse disease is defined as a long coronary segment (≥20 mm) with angiographic irregularities. Localized disease, as well as focal lesion, was characterized as a lesion length <20 mm (16).

Definition of TAK disease activity

Clinical assessment of disease activity in TAK relies on a composite assessment of clinical features, inflammatory markers, and serial imaging. Disease activity was assessed using ITAS (2010) and ITAS-A (17). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were obtained from the patient's laboratory examination details in the electronic medical record system. If the patient scores a ITAS (2010) ≥2 points or ITAS-A ≥5 it was classified as having active disease. ESR 21–39 mm/h (1 point), ESR 40–59 mm/h (2 points), ESR >60 mm/h (3 points) or CRP 6–10 mg/dL (1 point), CRP 11–20 mg/dL (2 points), CRP >20 mg/dL (3 points). Patients with TAK were categorized into two groups: active disease (n=33) and inactive disease (n=78). Acute phase reactants such as erythrocyte sedimentation rate and C-reactive protein were also collected. All enrolled patients underwent coronary CTA examination within one week before and after diagnosis of TAK, and did not receive clinical medication adjustments.

Coronary CTA-derived FAI quantification

The scanned images were transferred to a workstation with the Skviewer software program (Coronary System; Shukun Technology, Beijing, China). PCAT was extracted automatically by using the Skviewer software FAI intelligent analysis system (Skviewer FAI; Shukun Technology,

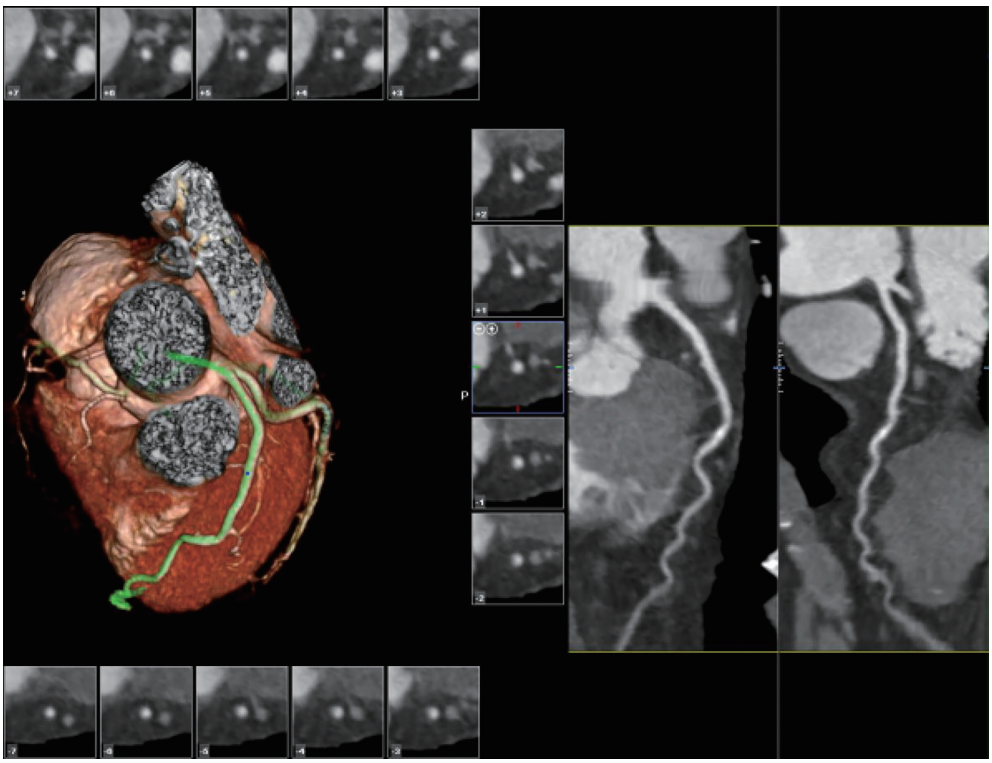

Figure 3 A 28-year-old female TAK patient underwent coronary artery CTA examination due to chest tightness and pain. The coronary CTA image and MPR of the coronary artery showed no thickening of the left main artery and left anterior descending branch walls, no stenosis of the lumen, and unobstructed artery lumen, indicating a healthy coronary artery. TAK, Takayasu arteritis; CTA, computed tomography angiography; MPR, multiplanar reformation.

Beijing, China) (10). The volume and FAI of PCAT were measured using the method described by Oikonomou *et al.* (8). Regarding PCAT analysis strategy, the same measurements and calculations strategy applied to TAK analysis. To measure the perivascular FAI, the software automatically traced the proximal 40 mm segments of all three major epicardial coronary vessels (RCA, LAD and LCX). The software defined the respective perivascular fat as the adipose tissue within a radial distance from the outer vessel wall equal to the diameter of the vessel (8). To avoid the effects of the aortic wall, the most proximal 10 mm of the RCA was excluded. The proximal 10–50 mm of the vessel was measured. The calculation range of fat density was from –190 to –30 HU (10) (*Figures 4,5*). In the LAD and LCX, the proximal 40 mm of each vessel was measured without the left main coronary artery. The perivascular FAI was determined by quantifying the weighted perivascular fat attenuation after adjusting the technical parameters based on the attenuation histogram of perivascular fat in the range from –190 to –30 HU. Pericoronary fat attenuation index was measured in three coronary arteries (RCA, LAD and LCX) of each patient and those with normal coronary arteries. For each measurement, the artery with the highest FAI value was selected for comparison. The radiologist was blinded to clinical findings. According to the measured adipose tissue around the coronary artery, we semi-automatically extract the value of each pixel, selected the CT value of each pixel to measure and record, and calculated the value of all pixel points for statistical selection and analysis. The pixel value of each point is more accurate. Five parameters of the PCAT values, namely, FAI, 10^{th} percentile, 90^{th} percentile, MEAN and MEDIAN were obtained using the software semiautomatic measurement.

All measurements were performed by a radiologist with 2 years of experience in interpreting cardiac CT images. To ensure consistency, 20 patients were randomly selected 1 month after the first series of measurements. The second measurements were conducted by two radiologists with 2 years of experience in interpreting cardiac CT images. The results of the same measurements by each observer

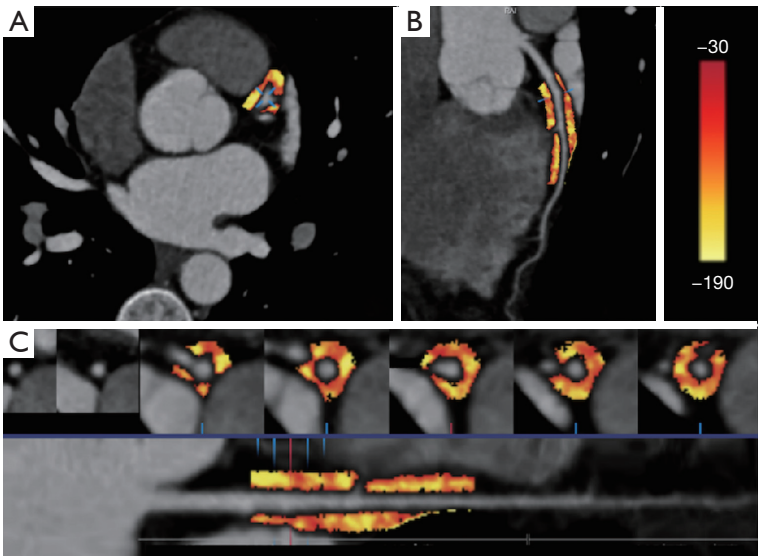

Figure 4 Perivascular FAI analysis around epicardial coronary vessels of the LAD coronary artery in an age- and gender-matched normal coronary control individual. (A) Axial view and range of HU to detect pericoronary fat [PCAT colour map ranging from bright yellow (–190 HU) to dark red (–30 HU)]. (B) Curved multiplane review of PCAT measurement. (C) Cross-sectional and longitudinal view of PCAT measurement. The software automatically tracked the ROI within the set fat threshold (from –190 to –30 HU), ROI: the length of FAI measurement was 0–40 mm to the proximal LAD, and the radial distance was equal to the diameter of the vessel. FAI of LAD was measured as –109 HU. Perivascular fat was defined as fat within a radial distance equal to the diameter (d) of the vessel. FAI, fat attenuation index; LAD, left anterior descending artery; HU, Hounsfield unit; PCAT, pericoronary adipose tissue; ROI, region of interest.

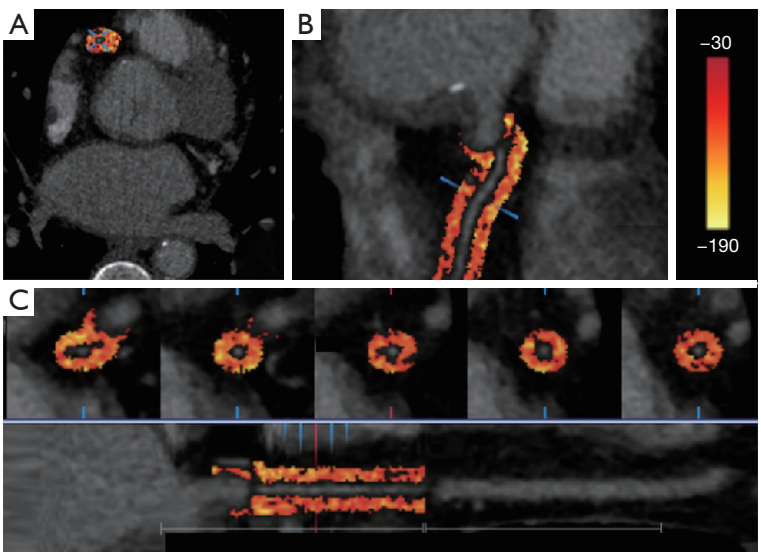

Figure 5 Perivascular FAI analysis around epicardial coronary vessels of the RCA in a TAK-CAI patient. (A) Axial view and range of HU to detect pericoronary fat [PCAT colour map ranging from bright yellow (–190 HU) to dark red (–30 HU)]. (B) Curved multiplane review of PCAT measurement. (C) Cross-sectional and longitudinal view of PCAT measurement. The software automatically tracked the ROI within the set fat threshold (from –190 to –30 HU), ROI: the length of FAI measurement was 10–50 mm to the proximal RCA, and the radial distance was equal to the diameter of the vessel. FAI of RCA was measured as –59 HU. FAI, fat attenuation index; RCA, right coronary artery; TAK, Takayasu arteritis; CAI, coronary artery involvement; HU, Hounsfield unit; PCAT, pericoronary adipose tissue; ROI, region of interest.

Table 1 Clinical characteristics of the study population

Parameters	Control group (n=51)	Total study patients (n=111)	P value	TAK-CAI (n=52)	TAK-nonCAI (n=59)	P value
Age (years)	47.98±10.98	33.92±12.48	<0.001	37.69 ±13.45	30.59±10.61	0.002
Duration of disease (months)	0	52 [12, 180]	<0.001	138 [27, 240]	18 [5, 108]	<0.001
Body mass index (kg/m^2)	22.82±2.86	22.80±3.06	0.965	23.49±3.11	22.37±2.98	0.083
Female patients	46 (90.20)	96 (86.49)	0.505	44 (84.62)	52 (88.14)	0.588
Hypertension	0	16 (14.41)	<0.001	10 (19.23)	6 (10.17)	0.175
Hyperlipidemia	0	44 (39.64)	<0.001	24 (46.15)	20 (33.90)	0.188
Diabetes	0	13 (11.71)	<0.001	7 (13.46)	6 (10.17)	0.590
ESR (mm/h)	–	26.75 [7.35, 36.54]	–	16 [6, 30]	19.50 [9.75, 43.50]	0.164
CRP (mg/L)	–	4.62 [0.66, 21.24]	–	2.31 [0.40, 18.14]	6.16 [0.93, 25.00]	0.234
ITAS (2010)	–	6 [3.0, 9.0]	–	–	–	–
ITAS-A	–	8 [3.5, 12.0]	–	–	–	–

Data are presented as mean ± SD or median [25%, 75%] or n (%). Diabetes mellitus was defined as blood glucose levels ≥7.0 mmol/L based on fasting conditions, ≥11.1 mmol/L at 2 h post-meal or at a random time, and/or levels of glycosylated hemoglobin A1C ≥6.5%. TAK, Takayasu arteritis; CAI, coronary artery involvement; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SD, standard deviation.

were checked for intra-reader consistency, and those of two different physicians were checked for inter-reader consistency.

Statistical analysis

The data were analysed using SPSS 25.0 (SPSS, Inc, Chicago, IL, USA). Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), and data with non-normal distribution were expressed as median with 25% and 75% interquartile range. Categorical variables are presented as cases (n) and percentages [count (%)]. Distribution of the normality of continuous variables was examined using the Kolmogorov-Smirnov test. Normally distributed variables were compared using the independent samples *t*-test. Non-normally distributed variables were compared using the Mann-Whitney *U* test between two groups. Univariate and multivariate logistic regression models were built to explore the relationship between FAI parameters and diagnosis of TAK patients among subjects who underwent coronary CTA examination and displayed normal coronary arteries, as well as disease activity of TAK. The diagnostic value of FAI in TAK patients was determined using the AUC of the ROC curve. A 2-tailed probability (P) value <0.05 was considered statistically significant. GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA) was used to generate the line art.

Results

Demographics and clinical features of the study population

Demographic data and CT parameters of the 111 patients with TAK are presented in *Table 1*. There was no gender difference between patients with TAK-CAI and TAK-nonCAI Patients with TAK-CAI were older than those with TAK-nonCAI (mean ± SD: 37.69±13.45 *vs.* 30.59±10.61 years, P=0.002). The duration of the disease was longer in TAK-CAI group than that in patients with TAK-nonCAI {138 [27, 240] *vs.* 18 [5, 108] months, P<0.001}.

The control group with normal coronary arteries was older than the total study population (mean ± SD: 47.98±10.98 *vs.* 33.92±12.48 years, P<0.001). In the control group there were no hypertension, hyperlipidemia, or diabetes. In addition, the LAD artery is the most commonly involved coronary artery in patients with TAK, with mild stenosis and varying lengths of involvement. The location of coronary artery involvement, the degree of stenosis and the lesion length of disease in TAK-CAI patients are shown in *Table 2* (18).

Table 2 Vascular involvement of coronary arteries in TAK-CAI patients

TAK-CAI (n=52)	Location of lesion involvement			
	LAD (n=50)	LCX (n=15)	RCA (n=23)	Total (n=88)
Vascular stenosis rate, n (%)				
1–24% minimal stenosis	22 (44.0)	4 (26.7)	9 (39.1)	35 (39.8)
25–49% mild stenosis	23 (46.0)	10 (66.7)	10 (43.5)	43 (48.9)
50–69% moderate stenosis	5 (10.0)	1 (6.7)	3 (13.0)	9 (10.2)
≥70% severe stenosis	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.1)
Lesion length (mm), mean ± SD	16.43±10.82	5.86±2.86	9.32±3.81	–

TAK, Takayasu arteritis; CAI, coronary artery involvement; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; SD, standard deviation.

Comparison of perivascular FAI parameters between different groups

PCAT parameters, including FAI, 10th percentile, 90th percentile, MEAN and MEDIAN were significantly higher in the TAK group than in the normal coronary artery control group (P<0.001 for all comparisons) as shown in *Table 3*. The levels of MEAN, FAI/HU, 10th and 90th percentile in the TAK-nonCAI group were significantly higher than those in the control group (P<0.001 for all comparisons) (*Figure 6*, *Table 3*). The levels of MEAN, MEDIAN, FAI/HU, 10th and 90th percentile in the TAK-CAI group were significantly higher than in the TAK-nonCAI group (P<0.05 for all comparisons) (*Table 3*). The levels of FAI/HU, 10th and 90th percentile, MEAN and MEDIAN levels in the diffuse group were significantly higher than those in the group with localized lesions (P<0.05 for all comparisons) (*Table 3*). FAI/HU, 10th and 90th percentile, MEAN and MEDIAN levels in the active inflammation group were significantly higher than those in the inactive inflammation group (P<0.001 for all comparisons) (*Figure 7*, *Table 3*).

Univariate and multivariate analysis of FAI

Univariate and multivariate analysis showed that the FAI is an independent risk factor to distinguish TAK patients from those with normal coronary arteries [odds ratio (OR): 1.23, 95% confidence interval (CI): 1.13–1.35, P<0.001] (*Table 4*). For every 1 HU increase in FAI, the risk of active TAK patients is increased by 57% (P<0.001). Univariate and multivariate analysis showed that the FAI is an independent risk factor for determining active inflammation in TAK (OR: 1.57, 95% CI: 1.25–1.97, P<0.001) (*Table 5*). For every 1 HU increase in FAI, the risk of developing TAK-nonCAI in healthy coronary arteries is increased by 23% (P<0.001).

Diagnostic performance of FAI

The FAI showed the best diagnostic performance in differentiating the TAK groups (AUC: 0.865, 95% CI: 0.789–0.927) from the normal coronary artery group (*Table 6*). With the best cut-off value of –86.50, the FAI identified TAK patients with 67.8% sensitivity and 74.5% specificity (AUC: 0.794, 95% CI: 0.713–0.875, P<0.001) (*Table 6*). With the best cut-off value of –79.50, the FAI identified active inflammation with 93.9% sensitivity and 74.4% specificity (AUC: 0.911, 95% CI: 0.860–0.962, P<0.001) (*Table 6*).

ICCs to check consistency of the measurements

Intra-observer correlation and inter-observer reliability ICC coefficient evaluation FAI measurement value showed consistency good readership (P<0.001) (*Table 7*).

Discussion

In this study, quantitative assessment of pericoronary FAI was performed based on the analysis of coronary CTA images of 52 patients with TAK-CAI, 59 patients with TAK-nonCAI and 51 normal coronary artery controls to determine the clinical value of using FAI for differentiating among these groups. The following were the important findings. Compared with the control group, FAI was

Table 3 Comparison of perivascular FAI parameters with different study groups (TAK *vs.* control group, TAK-CAI *vs.* TAK-nonCAI, localised *vs.* diffuse groups, active *vs.* inactive inflammation groups)

Parameters (HU)	Control group[1] (n=51)	TAK group[2] (n=111)	TAK-nonCAI group[3] (n=59)	TAK-CAI group[4] (n=52)	Diffused group[5] (n=27)	Localized group[6] (n=25)	Active inflammation group[7] (n=33)	Inactive inflammation group[8] (n=78)	P value				
									(1 *vs.* 2)	(1 *vs.* 3)	(4 *vs.* 3)	(5 *vs.* 6)	(7 *vs.* 8)
FAI	−90 [−94, −86]	−81 [−76, −74]	−84 [−88, −77]	−78 [−82.75, −69.75]	−74.00 [−80.00, −66.00]	−81 [−85.50, −75]	−77.50 [−72, −66]	−84 [−87, −79]	<0.001	<0.001	<0.001	0.005	<0.001
10th percentile	−138 [−144, −131]	−128 [−135, −115]	−132 [−142, −119]	−121 [−130, −106]	−111.00 [−123.00, −100.00]	−128 [−134, −116.50]	−109 [−120.50, −100]	−131.50 [−139.25, −123]	<0.001	0.005	<0.001	0.003	<0.001
90th percentile	−43 [−47, −42]	−39 [−41, −38]	−40 [−41.10, −38]	−39 [−41, −37]	−38.00 [−40.00, −37.00]	−39 [−42, −38]	−38 [−38.50, −36.50]	−40 [−42, −39]	<0.001	<0.001	0.020	0.023	<0.001
MEAN	−89.57 [−94.33, −86.09]	−80.75 [−85.76, −74.25]	−84.31 [−87.72, −77.39]	−78.04 [−82.49, −69.70]	−73.77 [−79.98, −65.59]	−80.75 [−85.56, −75.16]	−72.05 [−77.50, −66]	−84.15 [−86.99, −79.28]	<0.001	<0.001	<0.001	0.004	<0.001
MEDIAN	−88.07±5.95	−76.04±8.28	−78.83±7.33	−72.88±8.23	−69.88±7.96	−76.12±7.36	−67.66±6.17	−79.58±6.27	<0.001	<0.001	<0.001	0.004	<0.001

Data are presented as median [25%, 75%] or mean ± SD. FAI, fat attenuation index; TAK, Takayasu arteritis; CAI, coronary artery involvement.

Figure 6 Comparison of perivascular FAI parameters between TAK-nonCAI and coronary healthy controls. FAI/HU levels in the TAK-nonCAI group were significantly higher than those in the healthy control group. P<0.001 for all comparisons. TAK, Takayasu arteritis; CAI, coronary artery involvement; FAI, fat attenuation index; HU, Hounsfield unit.

Figure 7 Comparison of perivascular FAI parameters between active and inactive inflammation. Five parameters were used for evaluating the attenuation of PCAT values, including FAI/HU, 10th percentile, 90th percentile, MEAN and MEDIAN, which were significantly higher in the active inflammation group than those in the inflammation control group (P<0.001 for all comparisons). FAI, fat attenuation index; HU, Hounsfield unit; PCAT, pericoronary adipose tissue.

increased in all patients with TAK, including those with TAK-nonCAI. The mean and FAI/HU levels in the TAK-nonCAI group were significantly higher than those in the control group. Five parameters were used for evaluating the attenuation of PCAT values, including FAI/HU, 10th percentile, 90th percentile, MEAN and MEDIAN, which were significantly higher in the active inflammation group than those in the inactive inflammation control group. For every 1 HU increase in FAI, the risk of active TAK patients is increased by 57% (P<0.001). For every 1 HU increase in FAI, the risk of developing TAK-nonCAI in healthy coronary arteries is increased by 23% (P<0.001).

Table 4 Univariate and multivariate analysis of FAI predicting TAK patients from those with normal coronary arteries

Parameters	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
FAI	1.15	0.64–2.05	<0.001	1.23	1.13–1.35	<0.001
10th percentile	1.05	1.02–1.09	<0.001	1.27	0.54–2.88	0.63
90th percentile	1.50	1.27–1.77	<0.001	0.53	0.03–8.00	0.55
MEAN	1.23	1.12–1.34	<0.001	1.60	0.53–4.85	0.93
MEDIAN	1.22	1.13–1.33	<0.001	0.71	0.17–2.87	0.64

FAI, fat attenuation index; TAK, Takayasu arteritis; OR, odds ratio; CI, confidence interval.

Table 5 Univariate and multivariate analysis of FAI predicting active stage of TAK patients

Parameters	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
FAI	1.37	1.21–1.55	<0.001	1.57	1.25–1.97	<0.001
10th percentile	1.13	1.08–1.19	<0.001	0.4	0.04–3.83	0.98
90th percentile	2.31	1.62–3.29	<0.001	2.29	0.84–6.21	0.16
MEAN	1.37	1.21–1.56	<0.001	4.12	0.14–11.90	0.40
MEDIAN	1.39	1.22–1.58	<0.001	0.71	0.17–2.87	0.64

FAI, fat attenuation index; TAK, Takayasu arteritis; OR, odds ratio; CI, confidence interval.

Table 6 Receiver operating characteristic curve analysis for TAK patients and the control group

Diagnostic value[†]	All TAK versus control	TAK active versus inactive	TAK-CAI versus TAK-nonCAI	Control versus TAK-nonCAI
FAI				
AUC (95% CI)	0.865 (0.789–0.927)	0.911 (0.860–0.962)	0.719 (0.665–0.783)	0.794 (0.713–0.875)
Cut off value/HU	–86.50	–79.50	–83.50	–86.50
Sensitivity	0.811	0.939	0.788	0.678
Specificity	0.745	0.744	0.559	0.745
P value	<0.001	<0.001	<0.001	<0.001

[†], the maximum value of Youden's J statistic also corresponds to the best diagnostic critical value of the method, that is, cut off value/HU. TAK, Takayasu arteritis; CAI, coronary artery involvement; FAI, fat attenuation index; AUC, area under the curve; CI, confidence interval; HU, Hounsfield unit.

Furthermore, these parameters had a high diagnostic value in distinguishing patients with TAK from controls when their coronary arteries were normal.

Studies have reported the occurrence of CAD in 44–53% of patients with TAK undergoing coronary CTA, including atherosclerotic-type lesions, ostial stenoses and aneurysms (19,20). Characteristics and distribution of coronary artery lesions revealed that TAK most commonly involved coronary artery openings and the proximal coronary artery. Previous studies have suggested that the main mechanism of TAK involvement in coronary artery stenosis is the extension of aortic inflammation to the coronary artery, which leads to intimal hyperplasia and fibrosis contracture of the external membrane (21-23). In patients with TAK-nonCAI, although there was no obvious morphological change in the tubular wall, PCAT values were elevated,

Table 7 ICCs checking the consistency of the measurements

Variables	Intra-observer reliability ICC	Inter-observer reliability ICC
FAI	0.945	0.951
10^{th} percentile	0.922	0.936
90^{th} percentile	0.953	0.962
MEAN	0.985	0.974
MEDIAN	0.972	0.963

ICC, intraclass correlation coefficient; FAI, fat attenuation index.

which could be attributed to the early stage of the disease, insufficient spatial resolution of coronary CTA or very early coronary atherosclerosis. Significant difference was noted between the healthy control group and the TAK-nonCAI group. Although the inflammation was invisible and difficult to observe with the naked eye, the vascular wall was inflamed. Patients with TAK whose coronary arteries are not involved can also develop early coronary lesions. Our grouping of patients with TAK according to morphological differences only indicates that the pathological changes in the coronary artery had not progressed to macroscopic changes that may not be detected via visual assessment of the healthy coronary arteries. In our study, although there was no obvious morphological change in the coronary artery in patients with TAK-nonCAI, the increase in the FAI value implies the possible inflammatory reaction of the vessel wall to some extent. Therefore, it may be beneficial for patients with chronic vascular disease to receive timely intervention for the inflammation in the vascular wall of the coronary artery before morphological changes occur (23).

Multiple studies have demonstrated that accelerated atherosclerotic changes are commonly found in patients with TAK (23,24). The role of vessel wall inflammation in TAK-associated atherosclerosis has been well studied (25). Accelerated atherosclerosis is now a well-established complication of multiple systemic autoimmune diseases, notably rheumatoid arthritis, systemic lupus erythematosus and psoriatic arthritis (26-28). The coexistence of arteritis and atherosclerosis has been reported (23). Seyahi *et al.* (29) observed atherosclerotic plaques in 27% of young patients with TAK compared with 2% of healthy individuals (P=0.005). The first hospitalization age of patients with TAK-CAI was 37.69±13.45 years in our study; in contrast, the mean age of patients with TAK-nonCAI was 30.59±10.61 years (P=0.002). The median duration of the disease in patients with TAK-CAI was longer than that in patients with TAK-nonCAI, i.e., 138 (25% and 75%: 27, 240) months *vs.* 18 (25% and 75%: 5, 108) months (P<0.001). This finding indicates that patients with TAK with older age and longer course of the disease are more prone to CAI. Women older than 45–55 years have been reported to be more vulnerable to atherosclerosis (30,31). However, patients with TAK in our study who had coronary artery lesions were younger than 40 years of age, with their median age being 37.69 years. These results demonstrate that the atherosclerotic changes observed in patients with TAK were at least partially due to the disease itself, i.e., inflammatory change, rather than age. This finding indicates that inflammation accelerates atherosclerosis (32). Therefore, treatment of TAK and early diagnosis of atherosclerosis are particularly important.

FAI parameters serve as additional factors for determining the activity of TAK. Presently, the clinical activity of TAK is determined based on systemic symptoms, signs and corresponding laboratory and imaging examinations. However, these findings are not unique to TAK. Furthermore, the patients show elevated ESR and CRP, which are susceptible to the interference of multiple systems and different diseases. In our study, 30% (33/111) of the patients had active inflammation according to the FAI parameter derived from coronary CTA. Although 9 of the 33 patients with aortitis were negative for coronary artery lesions, inflammation was already seen around the tubular wall. Before the wall thickening becomes obvious, the quantitative FAI parameter of perivascular fat may be a sensitive early indicator. This parameter may serve as a new marker to evaluate the activity of TAK. Wall *et al.* (33) proposed that a PCAT density of greater than –74 HU had 100% sensitivity and 95% specificity in differentiating patients with active TAK from controls (AUC =0.99). In our study, ROC analysis showed that the FAI exhibited the best diagnostic performance in differentiating active and inactive inflammation. PCAT density of greater than –79.5 HU had 93.9% sensitivity and 74.4% specificity in differentiating patients with active TAK from controls (AUC =0.911). Therefore, FAI parameters are expected to become one of the additional criteria for evaluating TAK activity scores.

Furthermore, cross-sectional analysis of previous studies showed that the negative correlation between perivascular adipose tissue density and total plaque volume at baseline only existed in the lesions of patients on statins. CAD is a dynamic disease with plaque formation over time, which indicates that patients in different CAD stages should be

examined (24,29). Therefore, our study on the activity of TAK can further observe the characteristics of active pericoronary fat attenuation index in patients with TAK before and after medical treatment. Early detection and diagnosis are crucial to prevent patients with TAK-nonCAI from progressing to typical TAK-CAI.

Limitations

Our study has several limitations. First, we did not analyse the number of vessels involved in the coronary artery of the TAK-CAI group because we only selected the vessels with the highest FAI value. This limitation is expected to be addressed in a future study. Second, the degree of TAK-CAI vascular involvement and plaque type were not classified, which might have affected the result of the attenuation of the FAI value. In addition, ours was a retrospective case–control study conducted in a single center. Also, the sample size was relatively small. Further external validation in an independent cohort is needed to verify our findings. Moreover, our research merely focused on FAI phenotyping at a per-patient level; hence, further research is warranted to extend it to a larger population at a per-lesion level.

Conclusions

The FAI derived from coronary CTA was significantly higher in patients with TAK than in controls with normal coronary arteries. This parameter can be used to distinguish patients with TAK-nonCAI from the control group without obvious CAD. The FAI value was increased in the presence of CAI and inflammatory activity. It can also be used to distinguish whether TAK patients in the active phase.

Acknowledgments

Funding: This study was supported by the National Natural Science Foundation of China (No. 82071880).

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-419/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-419/coif). ZS serves as an unpaid associate editor of Quantitative Imaging in Medicine and Surgery. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics board of Beijing Anzhen Hospital, Beijing, China (No. 2022023X). The requirement for written informed consent was waived due to the retrospective nature of the study.

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Cite this article as: Zhao W, Zhang N, Yang S, Pan L, Liu J, Liu D, Xu L, Zhang G, Sun Z, Wen Z. Analysis of coronary computed tomography angiography-derived pericoronary fat attenuation index characteristics in the diagnostic assessment of patients with Takayasu arteritis. Quant Imaging Med Surg 2023;13(10):7142-7155. doi: 10.21037/qims-23-419

