Journal of the American Heart Association

ORIGINAL RESEARCH

Association Among Noncalcified Coronary Burden, Fractional Flow Reserve, and Myocardial Injury in Psoriasis

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BACKGROUND: Myocardial infarction and premature death have been observed in patients with psoriasis. Although inflammation-driven accelerated atherosclerosis has been proposed as a mechanism, the relationship between subclinical noncalcified coronary burden (NCB), functional coronary flow impairment, and myocardial injury is unclear.

METHODS AND RESULTS: In an ongoing longitudinal cohort study, 202 consecutive patients with psoriasis (168 at 1 year) underwent coronary computed tomography angiography to identify coronary plaque, quantify NCB, and calculate coronary fractional flow reserve by computed tomography. Serum high-sensitivity troponin-T (hs-cTn-T) was measured using a fifth-generation assay. Overall, patients were middle-aged, predominantly male, and low cardiovascular risk. A higher than median NCB associated with a positive hs-cTn-T (fully adjusted model [odds ratio (OR), 1.72; 95% CI, 1.10–2.69, P=0.018]) at baseline. Additionally, patients with a higher than median baseline NCB had higher odds of positive hs-cTn-T at 1 year in fully adjusted analyses (adjusted OR, 2.36; 95% CI, 1.47–3.79, P<0.001). Higher NCB was associated with a higher frequency of fractional flow reserve by computed tomography ≤0.80 (36.11% versus 25.11%, Pearson χ^2=6.84, P=0.009, unadjusted OR, 2.09; 95% CI, 1.36–3.22, P<0.001) and higher frequency of a positive hs-cTn-T (54.36% versus 27.54%, Pearson χ^2=32.23, P<0.001) in adjusted models (OR, 2.63; 95% CI, 1.56–4.42, P<0.001).

CONCLUSIONS: NCB was associated with hs-cTn-T at baseline as well as at 1 year. Furthermore, patients with high NCB had higher prevalence of fractional flow reserve by computed tomography ≤0.80 and a >2- fold higher odds of positive hs-cTn-T. These findings underscore the importance of early vascular disease in driving myocardial injury, and support conduct of myocardial perfusion studies to better understand these findings.

Key Words: fractional flow reserve ■ myocardial injury ■ noncalcified coronary burden ■ psoriasis

Atherosclerosis and its progression to myocardial infarction involve evolution and rupture of coronary plaque in patients with nonobstructive coronary artery disease (CAD). Serial angiographic studies before and immediately after myocardial infarction have shown that plaque with elevated early noncalcified component and rapid progression are most likely to rupture.[1-3] Advancements in noninvasive coronary computed tomography angiography (CCTA) have allowed measurement of not only plaque stenosis but also quantitative plaque composition in the form of early noncalcified coronary burden (NCB).[4,5] Additionally, computed tomography (CT)-derived fractional flow reserve (FFR_{CT}) has emerged as a reliable noninvasive technique to estimate potential hemodynamic significance of coronary plaque to improve

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For Sources of Funding and Disclosures, see page 9.

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CLINICAL PERSPECTIVE

What Is New?

- In patients with psoriasis and who did not have cardiovascular symptoms, subclinical noncalcified coronary burden was associated with impaired fractional flow reserve and positive high-sensitivity troponin-T.

What Are the Clinical Implications?

- Early vascular changes may drive myocardial injury in chronic inflammation, and future studies are needed to delineate the exact mechanism and assess downstream myocardial changes.

Nonstandard Abbreviations and Acronyms

NCB	noncalcified coronary burden
FFRCT	fractional flow reserve by computed tomography

diagnostic accuracy of CCTA,[6] modify treatment pathway, and predict revascularization.[7,8] Thus, studies using CCTA have led to deeper understanding of the natural history of atherosclerosis and how this process may be altered by lifestyle changes and statins to provide more refined prognostic risk stratification among patients across a variety of settings.[4,9-11]

High-sensitivity troponin permits ultrasensitive detection of myocardial injury, defined as elevated troponin concentrations without overt myocardial ischemia.[12] Regardless of the cause, patients with myocardial injury in the absence of myocardial infarction experience a high long-term overall mortality rate of 72% and major adverse cardiovascular events of 31% at 5-year follow-up,[13] underscoring the importance of identification of these high-risk individuals.

Small prior studies in chronic inflammatory states have revealed that visually assessed early atherosclerotic plaque was associated with positive troponins.[14-16] However, the relationship between quantitative NCB by CCTA and troponin have not been performed. Psoriasis is a chronic inflammatory skin disease associated with accelerated NCB,[17] premature myocardial infarction,[18] and early cardiovascular death.[19] Therefore, in a well-characterized cohort of patients with psoriasis, the aims of the present study were to examine the association between quantitative NCB and positive high-sensitivity troponin independent of traditional risk factors, prevalent coronary plaque, and left ventricular hypertrophy at baseline and 1-year follow-up. Moreover, we sought to determine whether coronary flow impairment as assessed by FFR_{CT} (≤0.8) was associated with myocardial injury in this sample.

METHODS

Study Design and Population

A total of 202 consecutive patients with psoriasis (168 followed up at 1 year) were examined from our ongoing longitudinal cohort study of psoriasis recruited between January 1, 2013 and November 1, 2019 (The Psoriasis Atherosclerosis Cardiometabolic Initiative). The recruitment scheme for this study is summarized in Figure 1 and study methodology is summarized in Figure 2. Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed for reporting of our findings.[20] Study protocols were approved by the institutional review board at the National Institutes of Health. Research was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent after a full explanation of the procedures. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Inclusion/Exclusion Criteria

This cohort is an asymptomatic, community-dwelling sample without any history of cardiovascular disease (CVD) or active cardiac disease at time of recruitment. Participants were >18 years of age and underwent blood draw and CCTA imaging at baseline and 1-year follow-up. Participants with psoriasis were required to have a formal diagnosis of plaque psoriasis by a dermatologist and were examined by a certified healthcare provider to confirm the onset, duration, and severity of skin disease as assessed by Psoriasis Area Severity Index (PASI) score. Participants were excluded if they had an estimated glomerular filtration rate <30 mL/min per 1.73 m^2, existing CVD, any comorbid condition known to promote CVD or systemic inflammation, such as uncontrolled hypertension, internal malignancy within 5 years, HIV, active infection within the past 72 hours of baseline, major surgery within the past 3 months, and pregnancy or lactation.

Coronary Artery Characterization

Acquisition

Guidelines implemented by the National Institutes of Health Radiation Exposure Committee were followed. CCTA scans were performed with prospective ECG gating, 100 or 120 kV tube potential, tube current of 100 to 850 mA adjusted to the patient's body size, with a gantry rotation time of 275 ms. All CCTA scans were performed using similar settings. Images were acquired at a slice thickness of 0.5 mm

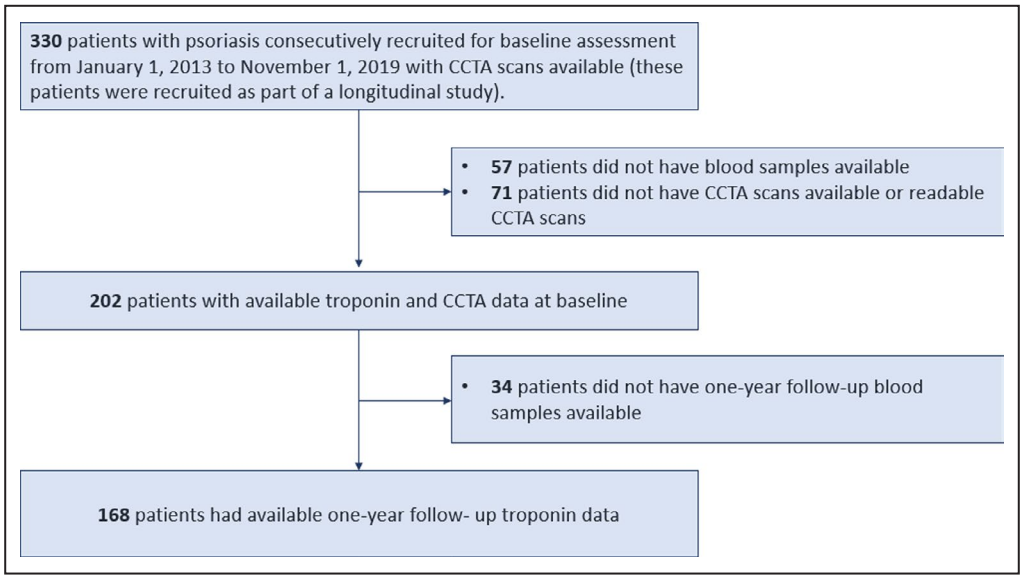

Figure 1. Recruitment scheme of the study
CCTA indicates coronary computed tomography angiography.

with a slice increment of 0.25 mm.[17,21,22] Patients with psoriasis underwent CCTA on the same day as blood draw, using the same CT scanner (320-detector row Aquilion ONE ViSION, Toshiba, Japan). The scans were then read by a cardiologist to adjudicate presence or absence of coronary plaque based on visual assessment, and blinded readers (blinded to demographics, treatment, and time of scan) evaluated coronary artery characteristics across each of the main coronary arteries >2 mm using dedicated

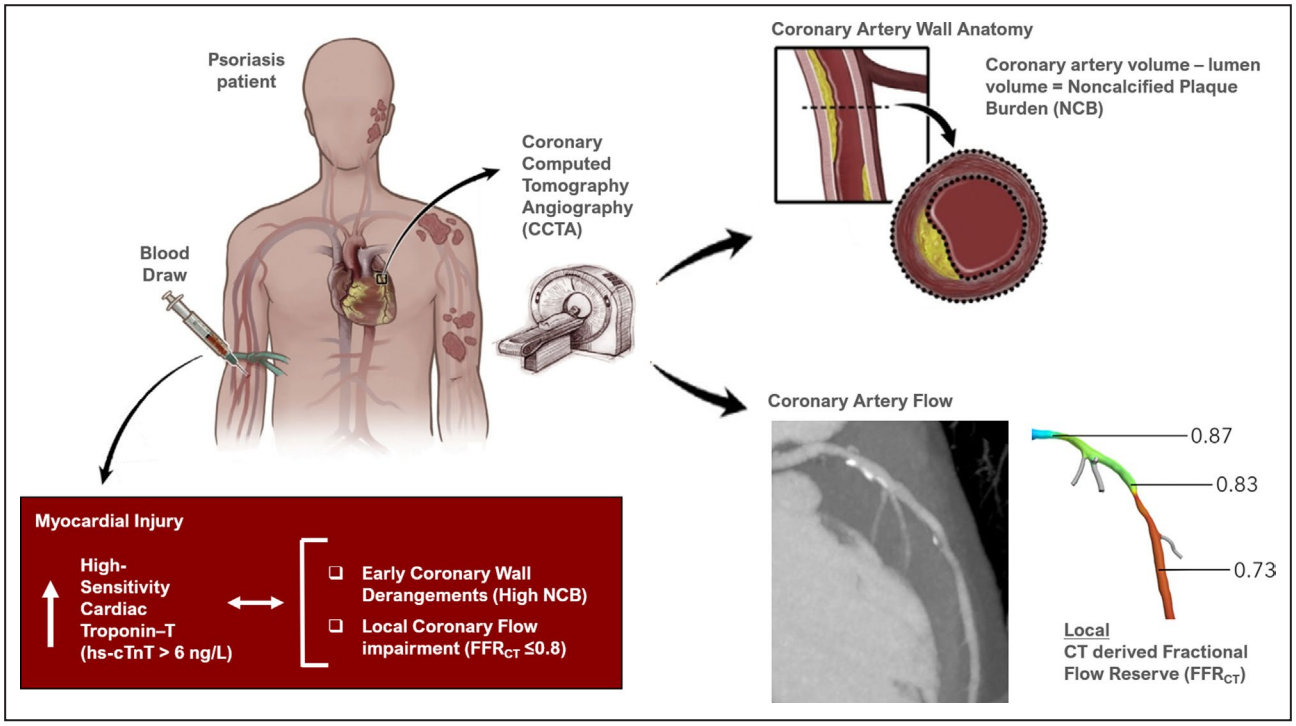

Figure 2. Subjects with psoriasis were prospectively enrolled to undergo CCTA assessment and measurement of serum hs-cTn-T using a fifth-generation assay
The CCTA data were used to quantify NCB and calculate FFR_{CT}. CCTA indicates coronary computed tomography angiography; CT, computed tomography; FFR_{CT}, fractional flow reserve by computed tomography; NCB, noncalcified coronary burden; and hs-cTn-T, high-sensitivity troponin-T.

software (QAngio CT; Medis, The Netherlands).[17] Automated longitudinal contouring of the inner lumen and outer wall was performed, and results were manually adjusted when clear deviations were present. Results of the automated contouring were also reviewed on transverse reconstructed cross-sections of the artery on a section-by-section basis at 0.5-mm increments. Quantitative CT coronary angiographic analysis was performed in the National Heart, Lung and Blood Institute core lab fashion using QAngio software (Medis, The Netherlands). Plaque characterization was performed using QAngio in the "adaptive" threshold mode, which considers varying Hounsfield unit intensities throughout the entire vessel, whereas the fixed method allows setting thresholds for the plaque characterization as previously described[23] and more recently reported to be more independent of lumen contrast intensity when compared with fixed threshold methods.[24] The primary outcome of the study—coronary burden per unit length—was calculated to account for variable coronary artery lengths between patients. Segmental coronary artery volume (in cubic millimeters) was divided by the corresponding segment length (in millimeters), and was subsequently attenuated for luminal intensity, which yielded noncalcified coronary artery burden and dense calcified coronary artery burden. Global NCB was defined as the average NCB from the left anterior descending coronary artery, left circumflex artery, and right coronary artery. Quantitative as well as qualitative coronary artery burden evaluation was performed in 98% of the available coronary segments. The inter- and intraread variations from our analysis were <10%. Coronary artery characterization included the following: prevalence of obstructive CAD, defined as ≥50% stenosis in any major coronary artery; prevalence of positive remodeling (remodeling index >1.10); prevalence of low attenuation plaque (<30 Hounsfield units); and prevalence of high-risk plaque, defined as presence of either positive remodeling or low-attenuation plaque.

Analysis of FFR_{CT}

Deidentified CCTA data sets were sent to HeartFlow (HeartFlow Inc., Redwood City, CA), which performed FFR_{CT} in a blinded fashion. In short, segmentation of a patient's epicardial coronary artery lumen down to 1 mm in diameter was extracted from CCTA data and the total coronary arterial lumen volume calculated. The lowest FFR_{CT} value within a vessel of interest, nadir FFR_{CT} values, were determined for each patient in the major epicardial vessels (left anterior descending coronary artery, left circumflex artery, and right coronary artery) as previously described.[25] Segmentation of the patient's aortic root and epicardial coronary lumen diameter were extracted from CCTA data in early diastole. Blood flow was simulated as a Newtonian fluid and modeled under conditions of adenosine-mediated vasodilation. FFR_{CT} values were calculated as the ratio of the mean coronary pressure at the point of interest to the mean aortic root pressure. FFR_{CT} ≤0.8 was defined as a positive value according to prior published literature validated against invasive FFR, which is the criterion standard.[25]

Covariates

Patients were asked to complete survey-based questionnaires regarding smoking, previous CVD, family history of CVD, and previously established diagnoses of hypertension and diabetes mellitus. Patient responses were then confirmed during history and physical examination by the study provider. CVD included acute coronary syndrome comprising both myocardial infarction and unstable angina pectoris, angina pectoris, cerebrovascular event, transient ischemic attack, peripheral vascular disease, and revascularization procedures including coronary artery bypass grafting and percutaneous interventional procedures. Diabetes mellitus was defined as fasting glucose ≥6.99 mmol/L, glycated hemoglobin >6.5%, or use of diabetic medication. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication. Hyperlipidemia was defined as total cholesterol >5.18 mmol/L, low-density lipoprotein ≥4.14 mmol/L, or high-density lipoprotein ≤1.04 mmol/L. However, hypertriglyceridemia was not included.

Clinical Data and Laboratory Measurements

At the time of recruitment, our healthcare provider collected data on patient demographics, clinical history, physical examination, and anthropometric measurements. Blood samples were collected after an overnight fast and analyzed for basic chemistry, complete lipid profile, insulin, and hs-CRP (high-sensitivity C-reactive protein) at the National Institutes of Health Clinical Center. Baseline psoriasis treatment was patient-reported and defined by use of any of the following in the 3 months before their baseline visit: systemic therapy (steroids or methotrexate), biologic therapy (adalimumab, etanercept, ustekinumab, secukinumab, and ixekizumab), statins, and light therapy (psoralen plus ultraviolet or ultraviolet B), and topical treatments were recorded. A majority of the cohort underwent intensification of psoriasis treatment at 1 year and the same variables were recorded again at 1-year post-treatment. Clinical

parameters including blood pressure, height, weight, and waist and hip circumferences were measured. Laboratory parameters including fasting blood glucose, fasting lipid panel, complete blood count, and systemic inflammatory markers, including hs-CRP, were evaluated in a clinical laboratory. Circulating high-sensitivity cardiac troponin-T (hs-cTn-T) was measured blindly at the National Institutes of Health laboratory by field scientists running undiluted serum using an immunoassay (Roche, Gen 5 STAT, Switzerland). hs-cTn-T value >6 ng/L, the lower limit of detection for this assay, were considered positive. The inter- and intra-assay variations from our analysis were <10%.

Statistical Analysis

Data were reported as mean with SD for parametric variables, median with interquartile range for nonparametric variables, and percentages for categorical variables. Variables that did not meet criteria for normality were log-transformed. In baseline analyses, parametric and nonparametric variables were compared between the 2 groups using Student's *t* test and Mann-Whitney *U* test, respectively. In longitudinal analyses, parametric variables were analyzed using paired *t* test and nonparametric variables using Wilcoxon signed-rank test. Dichotomous variables were analyzed using Pearson's χ^2 test. Linear regression was used to assess the association between NCB (independent variable) and hs-cTn-T (dependent variable) as a continuous variable. Logistic regression was used to assess the impact of NCB (independent variable) on positive hs-cTn-T (dependent variable) as a binary variable. Potential confounding variables were determined and added to the base model by a combination of a priori knowledge of biological, clinical, or statistical significance on univariable analyses. Fully adjusted models included age, sex, hypertension, hyperlipidemia, waist:hip ratio, lipid-lowering therapy, left ventricular hypertrophy, and prevalent coronary plaque. Standardized beta values from these analyses were reported, which indicate number of SDs change in the outcome variable per SD change in the predicting variable. *P* value <0.05 was deemed significant. All statistical analyses were performed using STATA 15 (Stata Corp., College Station, TX) by National Institutes of Health staff, blinded to clinical demographics and imaging characteristics.

RESULTS

Baseline Characteristics of Study Group

The demographic and clinical characteristics of 202 study participants are summarized in Table 1. Compared with patients with below median global NCB (n=102), patients with above median global NBC (n=100) were predominantly male, had increased prevalence of hypertension, higher waist:hip ratio, and higher Framingham cardiovascular risk score. Importantly, psoriasis severity, as measured by the PASI score, was similar between the high and low NCB groups. Furthermore, although the total cholesterol level was lower in the high NCB group, the low-density lipoprotein cholesterol level was similar between the 2 groups, with high-density lipoprotein cholesterol being lower in the high NCB group. Additionally, patients with higher NCB had higher prevalence of taking antihypertensive medications and lipid-lowering medications. Finally, hs-cTn-T values were higher in patients with high NCB compared with their counterparts.

Association Between Noncalcified Coronary Burden and Positive hs-cTn-T

A higher than median total coronary burden value was associated with positive hs-cTn-T in both the unadjusted model (unadjusted odds ratio [OR], 3.26; 95% CI, 2.29–4.63, *P*<0.001) as well as the fully adjusted model for age, sex, hypertension, hyperlipidemia, waist:hip ratio, lipid-lowering therapy, left ventricular hypertrophy, and coronary plaque (fully adjusted model OR, 1.88; 95% CI, 1.20–2.96, *P*=0.006) (Table 2). There was a similar association between NCB and hs-cTn-T (unadjusted OR, 2.78; 95% CI, 1.97–3.93, *P*<0.001; fully adjusted model [OR], 1.72; 95% CI, 1.10–2.69, *P*=0.018). Finally, in patients who had a positive hs-cTn-T, we found a linear relationship between NCB and log hs-cTn-T in fully adjusted analyses (standardized β=0.35, *P*<0.001) (Figure 3).

High Baseline NCB Is Associated with Myocardial Injury at 1 Year

Next, we sought to understand the relationship of baseline NCB in 168 patients with psoriasis and myocardial injury at 1 year. Compared with patients with low NCB (less than median NCB at baseline), patients with high NCB were male [69 (78.4%) versus 55 (48.2%) *P*<0.001], tended to have higher PASI score (6.15 [3.1-10.25] versus 4.9 [2.8-7.7], *P*=0.14), lower total cholesterol (178.10 [±39.06] versus 190.11 [±40.06], *P*=0.052], lower high-density lipoprotein cholesterol (49.57 [±11.78] versus 63.11 [±22.74] *P*=<0.001] and higher hs-CRP (4.70 [±8.17] versus 3.24 [±5.40], *P*=0.13). As expected, total coronary burden was higher in patients with high NCB compared with those with low NCB (1.60 [± 0.53] versus 0.82 [±0.17], *P*<0.001). At baseline, 46.86% of patients with high NCB had positive hs-cTn-T compared with 24.09% of patients with low NCB (Pearson

Table 1. Baseline Characteristics of the Study Cohort by NCB

	Total Cohort (n=202)	Low NCB (n=102)	High NCB (n=100)	*P* Value
Demographics and clinical characteristics				
Age, y	50.3 (±12.6)	49.60 (±12.87)	51.07 (±12.39)	0.41
Male, n (%)	124 (61)	46 (45.1)	78 (78)	<0.001
Hypertension, n (%)	56 (28)	19 (18.6)	37 (37.8)	0.003
Dyslipidemia, n (%)	85 (42)	39 (38.2)	46 (46)	0.32
Diabetes mellitus, n (%)	19 (9)	8 (7.8)	11 (11)	0.48
Current smoker, n (%)	25 (12)	15 (14.7)	10 (10)	0.39
Framingham risk score	1.90 (0.57–5.25)	1.13 (0.41– 3.93)	3.17 (1.15–7.39)	<0.001
Waist:hip ratio	0.95 (±0.08)	0.93 (±0.08)	0.97 (±0.07)	<0.001
Psoriasis characterization				
Psoriasis area severity index score	5.5 (3.0–8.9)	5 (2.8–8.9)	6.1 (3–9.1)	0.44
Medications				
Cardiovascular				
Anti-hypertensives, n (%)	45 (22)	16 (15.7)	29 (29)	0.028
Lipid-lowering medications, n (%)	60 (30)	23 (22.5)	37 (37)	0.031
Diabetes mellitus medications, n (%)	15 (8)	6 (5.9)	9 (9)	0.44
Psoriasis				
Biologic therapy, n (%)	69 (34)	36 (35.3)	33 (33)	0.87
Topical therapy, n (%)	122 (61)	62 (61.4)	60 (60.6)	1
Light therapy, n (%)	23 (12)	11 (10.9)	12 (12)	0.91
Laboratory values				
Total cholesterol, mg/dL	185.32 (±39.91)	192.81 (±40.48)	177.67 (±38.01)	0.007
HDL cholesterol, mg/dL	57.21 (±19.90)	64.25 (±23.20)	50.03 (±12.32)	<0.001
LDL cholesterol, mg/dL	104.35 (±32.66)	106.85 (±33.32)	101.80 (±31.93)	0.27
Triglycerides, mg/dL	120.89 (±74.13)	110.25 (±67.98)	131.73 (±78.78)	0.039
hs-CRP, mg/L	3.88 (±6.77)	3.05 (±5.15)	4.72 (±8.04)	0.08
Log hs-cTn-T	1.92 (±0.24)	1.86 (±0.16)	1.99 (±0.28)	<0.001
Positive hs-cTn-T, n (%)	72 (36)	21 (20.6)	51 (51)	<0.001
Coronary artery characterization				
Obstructive CAD, n (%)	4 (2)	1 (1)	3 (3)	1.00
Total coronary burden (mm^2 ×100)	1.20 (±0.52)	1.07 (±0.47)	1.33 (±0.54)	<0.001
Noncalcified coronary burden (mm^2 ×100)	1.14 (±0.51)	1.04 (±0.48)	1.25 (±0.51)	<0.001
Dense calcified coronary burden (mm^2 ×100)	0.06 (±0.11)	0.04 (±0.07)	0.08 (±0.15)	<0.001
Presence of high-risk plaque, n (%)	26 (14.4)	6 (7)	20 (22)	0.003
Positive remodeling, n (%)	22 (12.2)	5 (5)	17 (19)	0.006
Low attenuation, n (%)	17 (9.4)	5 (5)	12 (13)	0.080
Abnormal FFR_{CT}≤0.80, n (%)	61 (61)	25 (25)	36 (36)	0.009

Values are mean (± SD), median (Q1, Q3), or number (%).

CAD indicates coronary artery disease; $FFR_{CT,}$ fractional flow reserve by computed tomography; HDL, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C- reactive protein; hs-cTn-T, high-sensitivity troponin-T; and LDL, low-density lipoprotein cholesterol.

χ^2=34.32, *P*<0.001). At 1-year follow-up, 60.69% of patients with high NCB had positive hs-cTn-T compared with 35.95% of patients with low NCB (Pearson χ^2=30.81, *P*<0.001) (Figure 4). At 1 year, the average PASI score decreased (7.17 ± 6.84 to 4.06 ± 3.48, *P*<0.001). Importantly, patients with high NCB had higher odds of positive hs-cTn-T at 1 year compared with in fully adjusted analyses at baseline (adjusted OR, 2.36; 95% CI, 1.47–3.79, *P*<0.001). To account for the change in psoriasis disease severity in the association between NCB and percent positive hs-cTn-T at 1-year follow-up, further adjustment for delta PASI score demonstrated similar results (adjusted OR, 1.75; 95% CI, 1.05–2.94, *P*=0.033).

Table 2. Association Among Total Coronary Burden, NCB, and Positive hs-cTn-T

N=202 Patients, N=606 Coronary Vessels	Total Coronary Burden	NCB
	OR (95% CI, *P* Value)	OR (95% CI, *P* Value)
Model 1 (unadjusted)	3.26 (2.29–4.63, *P*<0.001)	2.78 (1.97–3.93, *P*<0.001)
Model 2 (adjusted for age, sex, hypertension, hyperlipidemia)	2.01 (1.31–3.07, *P*=0.001)	1.84 (1.21–2.80, *P*=0.005)
Model 3 (adjusted for age, sex, hypertension, hyperlipidemia, WHR)	1.94 (1.25–3.00, *P*=0.003)	1.78 (1.15–2.75, *P*=0.010)
Model 4 (adjusted for age, sex, hypertension, hyperlipidemia, WHR, lipid therapy)	1.94 (1.25–3.00, *P*=0.003)	1.78 (1.15– 2.75, *P*=0.09)
Model 5 (adjusted for age, sex, hypertension, hyperlipidemia, WHR, lipid therapy, left ventricular hypertrophy)	1.98 (1.28–3.07, *P*=0.002)	1.82 (1.18–2.81, *P*=0.007)
Model 6 (adjusted for age, sex, hypertension, hyperlipidemia, WHR, lipid therapy, left ventricular hypertrophy, coronary plaque)	1.88 (1.20–2.96, *P*=0.006)	1.72 (1.10–2.69, *P*=0.018)

hs-cTn-T indicates high-sensitivity troponin-T; NCB, noncalcified coronary burden; OR, odds ratio; and WHR, waist:hip ratio.

NCB, Coronary Flow Impairment, and Myocardial Injury

Finally, we sought to determine the interrelationship between NCB, coronary flow impairment, reflected as decreased FFR_{CT} (≤ 0.8), and myocardial injury by hs-cTn-T. Compared with patients with low NCB, patients with high NCB were associated with increased prevalence of FFR_{CT} ≤0.80 (36.11% versus 25.11%, Pearson χ^2=6.84, *P*=–0.009; unadjusted OR, 2.09; 95% CI, 1.36-3.22, *P*<0.001). Additionally, in patients who had FFR_{CT} ≤0.80, there was a significantly increased prevalence of positive hs-cTn-T (54.36% versus 27.54%, Pearson χ^2=32.23, *P*<0.001). Finally, FFR_{CT} ≤0.80 was associated with positive hs-cTn-T in both the unadjusted model and fully adjusted model (unadjusted OR, 3.13; 95% CI, 2.10–4.68, *P*<0.001; fully adjusted model OR, 2.63; 95% CI, 1.56–4.42, *P*<0.001).

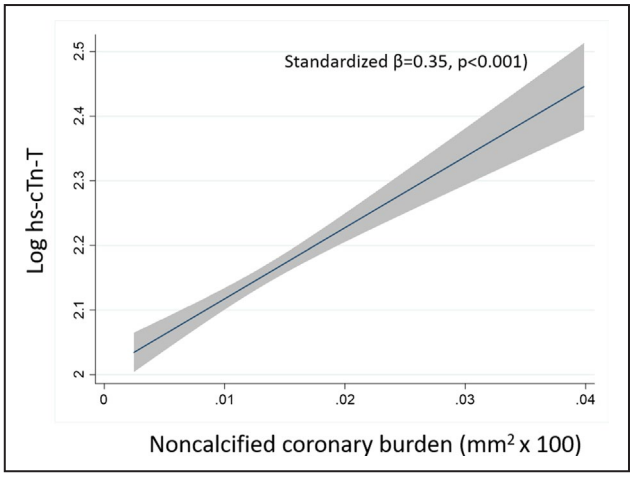

Figure 3. Association between noncalcified coronary burden and log hs-cTn-T in patients with positive hs-cTn-T (adjusted for age, sex, hypertension, hyperlipidemia, waist:hip ratio, lipid therapy, left ventricular hypertrophy, and coronary plaque)
hs-cTn-T indicates high-sensitivity troponin-T.

DISCUSSION

In this study, we demonstrated several important findings: (1) NCB was directly associated with hs-cTn-T and this relationship persisted after adjusting for traditional risk factors, prevalent coronary plaque, and left ventricular hypertrophy; (2) patients with high NCB had a >2-fold increase of positive hs-cTn-T at 1 year in fully adjusted analyses; and (3) high NCB was associated with higher prevalent FFR_{CT} ≤0.80 and patients with FFR_{CT} ≤0.80 had a 2.63-fold higher odds of positive hs-cTn-T in fully adjusted analyses. These findings suggest that having increased NCB is associated with myocardial injury and that early coronary changes, as reflected by high NCB, may identify patients at increased risk of future myocardial injury. Thus, our findings provide important insight into the physiologic consequences of early stages of atherosclerosis.

Psoriasis is a chronic inflammatory disease and an independent risk factor for early coronary artery disease, myocardial infarction, stroke, and cardiovascular mortality.[18,19,26] This elevated cardiovascular risk may be potentially explained by the link between high systemic inflammation, adipose modulation, and lipoprotein dysfunction.[22,27,28] Additionally, traditional cardiovascular risk assessment does not sufficiently capture incremental risk,[29] highlighting the need for refinement in current risk assessment strategies.

Studies using semiautomated quantitative assessment of plaque on CCTA have shown that plaque components correlate with measures of traditional cardiovascular risk[30] and predict cardiovascular events incrementally over traditional clinical risk

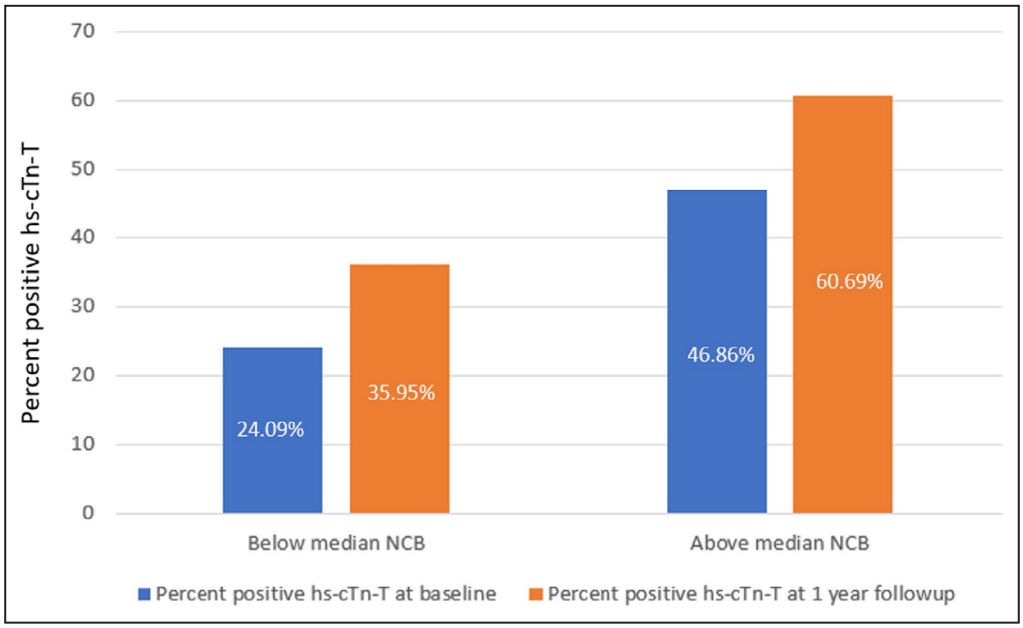

Figure 4. Percent positive hs-cTn-T at baseline and at 1-year follow-up
hs-cTn-T indicates high-sensitivity troponin-T; and NCB, noncalcified coronary burden.

profiles and clinical CCTA reading in asymptomatic patients without inflammatory disease.[30,31] Prior work from our laboratory and others has shown that coronary plaque development and progression, as measured both by coronary artery calcium score[32] and NCB by CCTA,[17] is accelerated in inflammatory-disease states. Additionally, patients with psoriasis have increased total coronary burden and NCB compared with control patients,[17] which may explain the elevated cardiovascular event rate observed in young patients with psoriasis.[19] Prior work has also shown that NCB is associated with high-density lipoprotein function,[22] inflammation, and oxidized lipids[33] in the blood. Because the inflammatory and immunological pathways that drive psoriasis likely also drive atherosclerosis, studies demonstrating modulation of plaque progression by anti-inflammatory biologic therapies[34-36] may offer a targeted treatment approach for reducing CVD in this high-risk population.

Given the excess cardiovascular mortality in inflammatory diseases, the downstream effects of coronary plaque and overall vascular health are important to understand from a therapeutic and prognostic perspective. Studies on other chronic inflammatory conditions have linked early nonobstructive coronary plaque on CCTA with myocardial injury and long-term incident adverse cardiovascular events.[14-16] However, the relationship with quantitative NCB, FFR_{CT}, and hs-cTn-T was not explored. Our findings extend this body of evidence that chronic inflammation-induced CAD is associated with myocardial injury, providing further evidence that chronic inflammation drives early changes in vascular disease. In this study, we found high NCB to be associated with hs-cTn-T positivity irrespective of coronary plaque or left ventricular hypertrophy. Furthermore, in those with a positive hs- cTn-T, there was a linear relationship between NCB and hs-cTn-T, suggesting that NCB has a dose-dependent relationship with markers of myocardial injury. Additionally, when we evaluated whether higher NCB at baseline was associated with myocardial injury at 1 year, we found a >2-fold increase in hs-cTn-T positivity when NCB was higher than baseline. Taken together, these findings suggest that NCB marks adverse coronary characteristics, which are associated with downstream myocardial effects.

How elevated NCB at baseline is associated with a high hs-cTn-T positivity at 1 year is not well understood. We adjusted for left ventricular hypertrophy and also prevalent coronary plaque to account for these factors, which are known to precipitate myocardial injury. Finally, our results showed that high NCB was associated with $FFR_{CT} \leq 0.80$, and patients with $FFR_{CT} \leq 0.80$ had a 2.63-fold higher odds of positive hs-cTn-T in fully adjusted analyses, suggesting that coronary flow impairment is linked to early vascular changes and may partially account for the observed increase of myocardial injury. Recent studies have shown that ischemia in nonobstructive CAD is more common than previously believed, increases with atherosclerotic burden,[37] and increases the risk of future major adverse cardiovascular events.[38] In our cohort of patients with mostly no overt CAD and nonobstructive CAD, our observations associating coronary artery changes and flow impairment with myocardial injury suggest the presence of

vasomotor dysfunction, microvascular dysfunction, endothelial dysfunction, and increased vascular intima media thickness, some of which have been observed in patients with psoriasis and psoriatic arthritis without cardiovascular risk factors or clinical CVD.[39] Prior work from others demonstrated that noncalcified plaque volume in addition to stenosis severity on CCTA was associated with FFR,[40-42] and our results linking NCB with FFR_{CT} support future studies focused on assessing myocardial perfusion and coronary blood flow to better delineate these findings.

Despite these important observations, there are several limitations of our study that need to be discussed. First, this was an observational study and therefore subject to residual confounding. Second, this was a small sample size compared with other studies involving CCTA plaque assessment. However, we performed all studies with the same CT scanner and prospectively under the same conditions and at 1 year, thus providing high-fidelity imaging data with a cardiologist adjudicating all CT results. Third, our study relied on using a serum marker of myocardial injury as a surrogate for hard cardiovascular events. However, our goal was to understand the relationship and natural history between NCB and hs-cTn-T. Future studies should focus on characterization of NCB over longer periods in a larger sample size with adjudication of cardiovascular events. Finally, we were not able to assess specific mechanisms in this study as to how NCB is associated with troponin. However, ongoing studies of myocardial perfusion and coronary flow reserve will better clarify these relationships.

In conclusion, in patients with psoriasis, NCB is directly associated with hs-cTn-T independent of prevalent coronary plaque and left ventricular hypertrophy. In addition, patients with high NCB had >2-fold higher odds of positive hs-cTn-T at 1-year follow-up. Finally, patients with high NCB were associated with increased prevalence of FFR_{CT} ≤0.80, which in turn was associated with >2-fold higher odds of positive hs-cTn-T, suggesting that high NCB is associated with coronary flow impairment and can better identify patients at risk for myocardial injury. Because patients with nonobstructive CAD often have ischemia associated with coronary endothelial and microvascular dysfunction, myocardial perfusion studies with coronary blood flow assessment are needed to ascribe a specific cause to the positive NCB- hs-cTn-T relationship.

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Received May 5, 2020; accepted October 2, 2020.

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Acknowledgments

We would like to acknowledge and thank NIH Clinical Center outpatient clinic-7 nurses for their invaluable contribution to the process of patient recruitment.

Sources of Funding

This study was supported by the National Heart, Lung and Blood Institute Intramural Research Program (HL006193-05). This research was also made possible through the NIH Medical Research Scholars Program, a public–private partnership supported jointly by the NIH and generous contributions to the Foundation for the NIH from the Doris Duke Charitable Foundation (DDCF Grant #2014194), the American Association for Dental Research, the Colgate-Palmolive Company, Genentech, Elsevier, and other private donors.

Disclosures

Dr. Mehta is a full-time US government employee and has served as a consultant for Amgen, Eli Lilly, and Leo Pharma receiving grants/other payments; as a principal investigator and/or investigator for AbbVie, Celgene, Janssen Pharmaceuticals, Inc., and Novartis receiving grants and/or research funding; and as a principal investigator for the National Institutes of Health receiving grants and/or research funding. Dr. Gelfand served as a consultant for BMS, Boehringer Ingelheim, Janssen Biologics, Novartis Corp, UCB (DSMB), Sanofi, and Pfizer Inc., receiving honoraria; and receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Boehringer Ingelheim, Janssen, Novartis Corp, Celgene, Ortho Dermatologics, and Pfizer Inc.; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly, Ortho Dermatologics, and Novartis. Dr. Gelfand is a co-patent holder of resiquimod for treatment of cutaneous T cell lymphoma. Dr. Gelfand is a Deputy Editor for the *Journal of Investigative Dermatology* receiving honoraria from the Society for Investigative Dermatology. The remaining authors have no disclosures to report.

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