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Radiology: Cardiothoracic Imaging

ORIGINAL RESEARCH

Impact of Smoking on Coronary Volume–to–Myocardial Mass Ratio: An ADVANCE Registry Substudy

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The ADVANCE registry was funded by HeartFlow via individual clinical study agreements with each enrolling institution and with the Duke Clinical Research Institute Core Laboratory and Clinical Event Committee.

Conflicts of interest are listed at the end of this article.

See also commentary by van Assen and Onnis in this issue.

Radiology: Cardiothoracic Imaging 2024; 6(2):e220197 • https://doi.org/10.1148/ryct.220197 • Content codes: CA CT

Purpose: To examine the relationship between smoking status and coronary volume–to–myocardial mass ratio (V/M) among individuals with coronary artery disease (CAD) undergoing CT fractional flow reserve (CT-FFR) analysis.

Materials and Methods: In this secondary analysis, participants from the ADVANCE registry evaluated for suspected CAD from July 15, 2015, to October 20, 2017, who were found to have coronary stenosis of 30% or greater at coronary CT angiography (CCTA) were included if they had known smoking status and underwent CT-FFR and V/M analysis. CCTA images were segmented to calculate coronary volume and myocardial mass. V/M was compared between smoking groups, and predictors of low V/M were determined.

Results: The sample for analysis included 503 current smokers, 1060 former smokers, and 1311 never-smokers (2874 participants; 1906 male participants). After adjustment for demographic and clinical factors, former smokers had greater coronary volume than never-smokers (former smokers, 3021.7 mm^3 ± 934.0 [SD]; never-smokers, 2967.6 mm^3 ± 978.0; P = .002), while current smokers had increased myocardial mass compared with never-smokers (current smokers, 127.8 g ± 32.9; never-smokers, 118.0 g ± 32.5; P = .02). However, both current and former smokers had lower V/M than never-smokers (current smokers, 24.1 mm^3/g ± 7.9; former smokers, 24.9 mm^3/g ± 7.1; never-smokers, 25.8 mm^3/g ± 7.4; P < .001 [unadjusted] and P = .002 [unadjusted], respectively). Current smoking status (odds ratio [OR], 0.74 [95% CI: 0.59, 0.93]; P = .009), former smoking status (OR, 0.81 [95% CI: 0.68, 0.97]; P = .02), stenosis of 50% or greater (OR, 0.62 [95% CI: 0.52, 0.74]; P < .001), and diabetes (OR, 0.67 [95% CI: 0.56, 0.82]; P < .001) were independent predictors of low V/M.

Conclusion: Both current and former smoking status were independently associated with low V/M.

Clinical trial registration no. NCT02499679

Supplemental material is available for this article.

Epidemiologic data have identified smoking as an important risk factor for coronary artery disease (CAD), atherosclerotic progression, myocardial infarction, and cardiac death and demonstrate that smoking cessation reduces cardiac risk and mortality (1–3). Furthermore, much of the risk reduction associated with smoking cessation appears to occur in the initial years after quitting (3). A report from the CONFIRM Registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) found that although current and former smokers had a similar extent and severity of CAD, only current smokers had significantly increased rates of major adverse cardiac events compared with never-smokers after 2.8 years of follow-up; this effect could not be explained by age, sex, or other cardiovascular risk factors (4). These findings suggest that the increased cardiovascular risk associated with smoking may not be entirely explained by atherosclerotic burden and may reflect pathology not apparent at standard anatomic imaging, involving endothelial dysfunction, plaque composition, or coronary and myocardial remodeling. This situation highlights the need for a more integrated tool capable of a combined assessment of anatomic

Abbreviations

ADVANCE = Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care, CAD = coronary artery disease, CCTA = coronary CT angiography, CT-FFR = CT fractional flow reserve, LV = left ventricle, OR = odds ratio, V/M = coronary volume–to–myocardial mass ratio

Summary

Both current and former smoking status were independently associated with lower coronary volume–to–myocardial mass ratio in participants from the ADVANCE registry.

Key Points

- Both current and former smoking were independently associated with lower coronary volume–to–myocardial mass ratio (V/M) in participants with coronary artery disease (ADVANCE registry).
- When stratified by stenosis severity, the relationship between smoking and low V/M remained significant only in participants with stenosis of 50% or greater.
- Lower V/M among smokers appeared to be driven by an increase in myocardial mass.

Keywords

CT Angiography, Cardiac, Heart, Ischemia/Infarction

CAD, physiologic characteristics, and the myocardium.

CT fractional flow reserve (CT-FFR) analysis has emerged as an accurate noninvasive alternative to invasive fractional flow reserve measurement for the determination of lesion-specific pressure loss and is useful in guiding clinical decision-making (5,6). Through the CT-FFR computational modeling process, an additional measure known as coronary volume–to–myocardial mass ratio (V/M) can be determined and is proposed as a quantitative measure of myocardial supply and demand (7). Based on allometric scaling laws, coronary luminal volume typically exhibits a strong linear relationship with myocardial mass, a relationship that has been confirmed in human studies (8). In turn, V/M is believed to provide insight into cardiovascular characteristics related to coronary and myocardial remodeling. Previous reports found V/M to be reduced in multiple disease states, including microvascular angina and hypertrophic cardiomyopathy; in CAD, low V/M is associated with greater stenosis (9). However, to date, the effect of smoking status on V/M has not been well established in the literature. Therefore, this study examined the relationship between smoking status and V/M among individuals with CAD from the Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care (ADVANCE) registry.

Materials and Methods

Participants

This study was a retrospective analysis of the ADVANCE registry (ClinicalTrials.gov: NCT02499679), a prospective, multicenter registry of participants who underwent coronary CT angiography (CCTA) for suspected CAD at 38 sites across North America, Europe, and Japan from July 15, 2015, to October 20, 2017. Registry design and data management have been previously described (10). All participating sites required institutional review board approval, and all participants provided written informed consent. Participants within the ADVANCE registry were symptomatic but clinically stable at the time of enrollment, with CAD identified at CCTA as stenosis of 30% or greater in one or more vessels. Additional inclusion criteria included being aged 18 years or older, having the ability to provide informed consent, and meeting eligibility criteria for CT-FFR analysis on the basis of CAD severity. Smoking status within the ADVANCE registry was classified as current smoker (individuals who smoked at the time of CCTA or quit <90 days before CCTA), former smoker (individuals who quit smoking ≥90 days before CCTA), or never-smoker.

Individuals were excluded from the ADVANCE registry if they had no evidence of CAD at CCTA, CCTA findings that were uninterpretable or rejected from CT-FFR analysis, life expectancy less than 1 year, or inability to adhere to follow-up requirements. Individuals were also excluded from the current analysis if their smoking history was unknown or if V/M analysis was unavailable; V/M was determined in only a subset of the participants in the ADVANCE registry because of software development during the study period. Analysis was completed using data within the locked 1-year ADVANCE database. All participants from this study have been previously reported on, with the parent study evaluating the relationship between CT-FFR and downstream clinical care and outcomes (11–17).

Demographic and clinical factors were recorded for each participant in accordance with the values reported within the registry. The presence of hypertension requiring treatment, dyslipidemia, and diabetes was recorded. Angina status was categorized as typical angina, atypical angina, dyspnea, noncardiac chest pain, no chest pain, and unknown. Among those with typical angina, severity was graded by Canadian Cardiovascular Society class.

CCTA and CT-FFR

CCTA was recommended to be performed according to Society of Cardiovascular Computed Tomography guidelines (18). Across all participating sites, CCTA was performed using scanners with at least 64 detector rows after administration of sublingual nitroglycerin (3–5 minutes before scanning); the target heart rate was below 60 beats per minute, with β-blockers given at the discretion of the supervising physician. The presence of coronary stenosis was then visually assessed in all vessels measuring at least 2 mm in diameter. The location of highest-grade stenosis was recorded, and stenosis severity was categorized as 0% (no stenosis), less than 50%, 50% or greater, and 70% or greater. The number of epicardial vessels affected by at least 50% stenosis was also recorded.

CT-FFR analysis of CCTA images was performed using HeartFlow, version 2 (HeartFlow), as previously described (19). Minimum CT-FFR was recorded with both nadir and poststenosis CT-FFR values. Nadir CT-FFR values represent the lowest CT-FFR value in each of the epicardial systems for the left anterior descending, left circumflex, and right coronary arteries, as well as the overall lowest CT-FFR value across all territories. The poststenosis CT-FFR value represents the value 2 cm distal

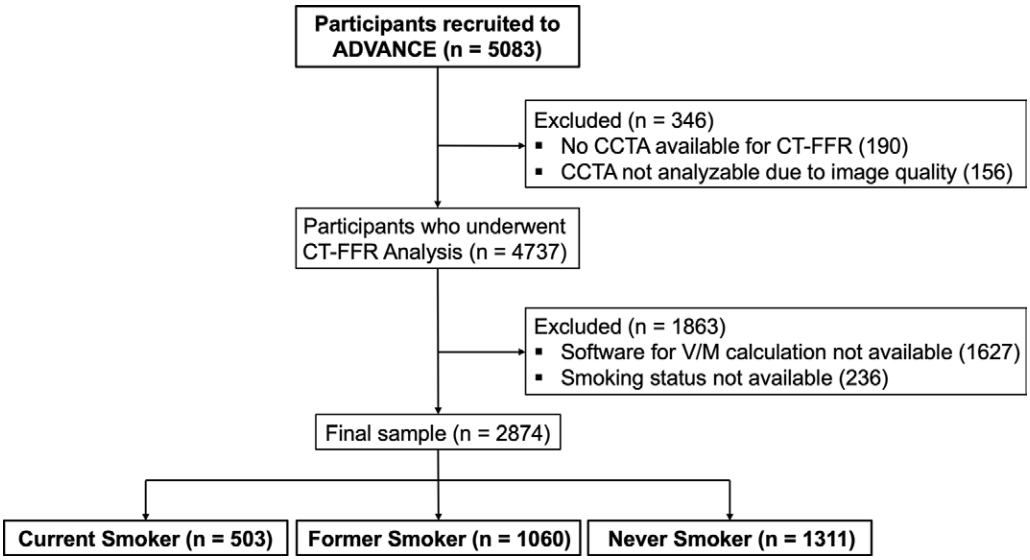

Figure 1: Flow diagram outlines participant inclusion in the study. ADVANCE = Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care, CCTA = coronary CT angiography, CT-FFR = CT fractional flow reserve, V/M = coronary volume–to–myocardial mass ratio.

to the greatest stenosis across all epicardial vessels. In the event of stenoses of equal severity, poststenosis CT-FFR value was preferentially selected from the left anterior descending artery, followed by the left circumflex artery. The Duke Clinical Research Institute (Durham, North Carolina) acted as the core laboratory analyzing all CCTA and CT-FFR data in a blinded fashion.

Computation of V/M

V/M derived from CT-FFR analysis represents the ratio between total coronary luminal volume (in cubic millimeters) and left ventricular (LV) mass (in grams) and is proposed as a quantitative metric of myocardial supply relative to demand (7). V/M was calculated as previously described (15). In brief, epicardial coronary arteries (>1 mm) were segmented from the three-dimensional anatomic model generated from the imaging data and used to calculate total coronary volume. The volume of the LV myocardium was calculated using semiautomated image segmentation during the cardiac phase that best visualized the ventricular lumen. This value was then multiplied by a value estimating myocardial tissue density (1.05 g/mL) to determine LV myocardial mass. Finally, V/M was computed as the ratio of total coronary luminal volume to LV myocardial mass.

Statistical Analysis

Clinical, CCTA, CT-FFR, and V/M data are presented as counts and percentages for categorical variables and means and SDs for continuous variables. Categorical variables were compared using the χ^2 test, and continuous variables were compared using an analysis of variance model followed by a *t* test in a pairwise fashion. Additionally, an analysis of covariance model was used to assess differences in total coronary volume and myocardial mass between smoking groups while correcting for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), and presence of other cardiovascular risk factors. Predictors of low V/M were determined using a multivariable logistic regression analysis. High and low V/M were defined using the sample median V/M as the threshold. Data were analyzed by combining all variables of interest, including age, sex, symptoms, stenosis severity, and cardiovascular risk factors, in a single multivariable logistic model to determine independent predictors of V/M. $P < .05$ was considered to indicate a statistically significant difference. All study data were controlled and verified by two study authors (K.R.H. and S.L.S.) and an independent study statistician (Nicholas Ng), with statistical analyses completed using SAS software, version 9.2 (SAS Institute).

Results

Participant Characteristics

Of the 5083 participants recruited into the ADVANCE trial, 4737 participants (93.2%) had diagnostic CCTA examinations eligible for CT-FFR analysis (Fig 1). Of these, 3110 participants (65.7%) underwent assessment of V/M; 1627 participants (34.3%) were excluded because their CT-FFR analysis was completed before the development of the V/M software plug-in and reprocessing was not feasible. Among those with calculated V/M, 2874 (92.4%) participants had known smoking status and made up the final study sample for analysis. The study sample consisted of 503 current smokers (17.5%), 1060 former smokers (36.9%), and 1311 never-smokers (45.6%).

Participant demographic characteristics by smoking group are outlined in Table 1. Among the total 2874 participants, 1906 (66.3%) were male and 968 (33.7%) were female, with the current smoker and former smoker groups having a higher proportion of male participants compared with the never-smoker group (current smokers, 364 of 503 [72.4%];

Table 1: Participant Demographic Characteristics by Smoking Status

Characteristic	Current Smoker (*n* = 503)	Former Smoker (*n* = 1060)	Never-Smoker (*n* = 1311)
Age (y)	62 ± 10	68 ± 10	67 ± 11
Sex			
Male	364 (72.4)	818 (77.2)	724 (55.2)
Female	139 (27.6)	242 (22.8)	587 (44.8)
Body mass index*	26.1 ± 4.9	26.7 ± 4.8	26.2 ± 4.9
Dyslipidemia	292 (58.1)	665 (62.7)	790 (60.3)
Diabetes	134 (26.6)	235 (22.2)	269 (20.5)
Hypertension	292 (58.1)	665 (62.7)	790 (60.3)
Angina status			
Typical angina	105 (20.9)	215 (20.3)	236 (18.0)
Atypical angina	177 (35.2)	370 (34.9)	488 (37.2)
Noncardiac pain	47 (9.3)	63 (5.9)	66 (5.0)
Dyspnea	38 (7.6)	146 (13.8)	145 (11.1)
No chest pain	130 (25.8)	263 (24.8)	365 (27.8)
Unknown	6 (1.2)	3 (0.3)	11 (0.8)
CCS class (typical angina)			
CCS I	28 (26.7)	36 (16.7)	65 (27.5)
CCS II	56 (53.3)	134 (62.3)	124 (52.5)
CCS III	14 (13.3)	18 (8.4)	26 (11.0)
CCS IV	2 (1.9)	5 (2.3)	3 (1.3)
Unknown	5 (4.8)	22 (10.2)	18 (7.6)

Note.—Total study sample was 2874 participants. Categorical values are expressed as numbers of participants, with percentages in parentheses. Continuous values are expressed as means ± SDs. CCS = Canadian Cardiovascular Society.
* Body mass index calculated as weight in kilograms divided by height in meters squared.

former smokers, 818 of 1060 [77.2%]; never-smokers, 724 of 1311 [55.2%]). Current smokers were younger than former and never-smokers (mean age: current smokers, 62 years ± 10 [SD]; former smokers, 68 years ± 10; never-smokers, 67 years ± 11). Former smokers had higher mean body mass index than current and never-smokers (current smokers, 26.1 ± 4.9; former smokers, 26.7 ± 4.8; never-smokers, 26.2 ± 4.9). Former smokers had a higher rate of dyslipidemia than never-smokers (former smokers, 665 of 1060 [62.7%]; never-smokers, 790 of 1311 [60.3%]), and current smokers had a higher rate of diabetes than never-smokers (current smokers, 134 of 503 [26.6%]; never-smokers, 269 of 1311 [20.5%]). Angina status also differed between groups, with both current and former smokers more frequently exhibiting typical angina (current smokers, 105 of 503 [20.9%]; former smokers, 215 of 1060 [20.3%]; never-smokers, 236 of 1311 [18.0%]). Among participants with typical angina, there was no evidence of a difference in Canadian Cardiovascular Society class between groups.

At CCTA, current but not former smokers were more likely than never-smokers to have stenosis of 50% or greater (current smokers, 391 of 503 [77.7%]; never-smokers, 909 of 1311 [69.3%]) and stenosis of 70% or greater (current smokers, 193 of 503 [38.4%]; never-smokers, 390 of 1311 [29.7%]) (Table S1). Similarly, current smokers had a higher prevalence of stenosis of 50% or greater affecting multiple vessels than did never-smokers. When stratified by epicardial vessel, never-smokers were more likely than current smokers to have their highest-grade stenosis involve the left anterior descending artery (current smokers, 302 of 503 [60.0%]; never-smokers, 967 of 1311 [73.8%]), while both current and former smokers showed higher rates of their highest-grade stenosis affecting the right coronary artery than did never-smokers (current smokers, 171 of 503 [34.0%]; former smokers, 350 of 1060 [33.0%]; never-smokers, 321 of 1311 [24.5%]).

Evaluation of coronary stenosis with CT-FFR demonstrated that current but not former smokers had lower mean nadir CT-FFR value (current smokers, 0.71 ± 0.12; never-smokers, 0.73 ± 0.11) and lower mean poststenotic CT-FFR value (current smokers, 0.74 ± 0.12; never-smokers, 0.76 ± 0.12) compared with never-smokers. Table S1 shows a detailed analysis of coronary stenosis and CT-FFR by smoking status.

Analysis of V/M

Analysis of total coronary volume, myocardial mass, and V/M is outlined in Tables 2 and 3. In the unadjusted analysis, there

Table 2: Coronary Volume and Myocardial Mass according to Smoking Status

Variable	Current Smoker (n = 503)		Former Smoker (n = 1060)		Never-Smoker (n = 1311)
	Variable Value	*P* Value*	Variable Value	*P* Value*	Variable Value
Total coronary volume (mm^3)	2997.9 ± 1005.8	.55 (unadjusted) .15 (adjusted)	3021.7 ± 934.0	.18 (unadjusted) .002 (adjusted)	2967.6 ± 978.0
Myocardial mass (g)	127.8 ± 32.9	<.001 (unadjusted) .02 (adjusted)	124.6 ± 31.4	<.001 (unadjusted) .36 (adjusted)	118.0 ± 32.5
V/M (mm^3/g)	24.1 ± 7.9	<.001 (unadjusted) .005 (adjusted)	24.9 ± 7.1	.002 (unadjusted) .005 (adjusted)	25.8 ± 7.4
V/M > 24.70 mm^3/g (sample median)	212 (42.1)	<.001 (unadjusted)	507 (47.8)	.004 (unadjusted)	705 (53.8)

Note.—Total study sample was 2874 participants. Categorical values are expressed as numbers of participants, with percentages in parentheses. Continuous values are expressed as means ± SDs. V/M = coronary volume–to–myocardial mass ratio.
* *P* value for comparison with never-smoker group. Adjusted *P* values adjusted for age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), dyslipidemia, diabetes, and hypertension.

Table 3: Coronary Volume–to–Myocardial Mass Ratio according to Smoking Status, Stratified by Stenosis Severity

Variable	Current Smoker	Former Smoker	Never-Smoker	*P* Value*
Maximum stenosis < 50%				
No. of participants	111	291	400	
V/M (mm^3/g)	25.4 ± 8.6	26.9 ± 7.1	27.2 ± 7.6	.09
Maximum stenosis ≥ 50%				
No. of participants	391	767	909	
V/M (mm^3/g)	23.8 ± 7.6	24.1 ± 6.9	25.2 ± 7.2	<.001

Note.—Continuous values are expressed as means ± SDs.
* *P* value for groupwise comparison of current smokers, former smokers, and never-smokers.

was no evidence of a difference in total coronary volume between groups, but both former and current smokers had higher myocardial mass than never-smokers (current smokers, 127.8 g ± 32.9; former smokers, 124.6 g ± 31.4; never-smokers, 118.0 g ± 32.5; $P < .001$ for both comparisons). After adjustment for participant factors, former but not current smokers had greater total coronary volume than never-smokers (former smokers, 3021.7 mm^3 ± 934.0; current smokers, 2997.9 mm^3 ± 1005.8; never-smokers; 2967.6 mm^3 ± 978.0; $P = .002$ and .15, respectively), while current but not former smokers had increased myocardial mass compared with never-smokers ($P = .02$ and .36, respectively). Both current and former smokers had a lower V/M than never-smokers (current smokers, 24.1 mm^3/g ± 7.9; former smokers, 24.9 mm^3/g ± 7.1; never-smokers, 25.8 mm^3/g ± 7.4; unadjusted $P < .001$ and $P = .002$, respectively; adjusted $P = .005$ for both). Current and former smoking status were also associated with a decreased likelihood of having a V/M value above the sample median of 24.70 mm^3/g compared with never-smoker status (current smokers, 212 of 503 [42.1%]; former smokers, 507 of 1060 [47.8%]; never-smokers, 705 of 1311 [53.8%]; $P < .001$ and $P = .004$, respectively).

In a two-way groupwise analysis, both smoking status and the presence of stenosis of 50% or greater were associated with significant between-group differences in V/M ($P < .001$ for both); however, there was no interaction between smoking status and stenosis severity with respect to V/M ($P > .99$). Nonetheless, after stratification by stenosis severity, V/M differed between smoking groups among participants with stenosis of 50% or greater, with a graded reduction in V/M observed from never- to former to current smokers (current smokers, 23.8 mm^3/g ± 7.6; former smokers, 24.1 mm^3/g ± 6.9; never-smokers, 25.2 mm^3/g ± 7.2 ; $P = .001$), while V/M did not appear to differ between groups among participants with maximum stenosis less than 50% (current smokers, 25.4 mm^3/g ± 8.6; former smokers, 26.9 mm^3/g ± 7.1; never-smokers, 27.2 mm^3/g ± 7.6; $P = .09$) (Table 3). Representative images of CT-FFR–derived V/M models are shown in Figure 2, and the relationship between smoking status and V/M is shown in Figure 3.

Predictors of V/M

Multiple regression analysis demonstrated both current and former smoking status to be independent predictors of a V/M value below the sample median (current smokers, odds ratio [OR] = 0.74 [95% CI: 0.59, 0.93], $P = .009$; former smokers, OR = 0.81 [95% CI: 0.68, 0.97], $P = .02$). Presence of stenosis of 50% or greater (OR = 0.62 [95% CI: 0.52, 0.74]; $P < .001$), diabetes

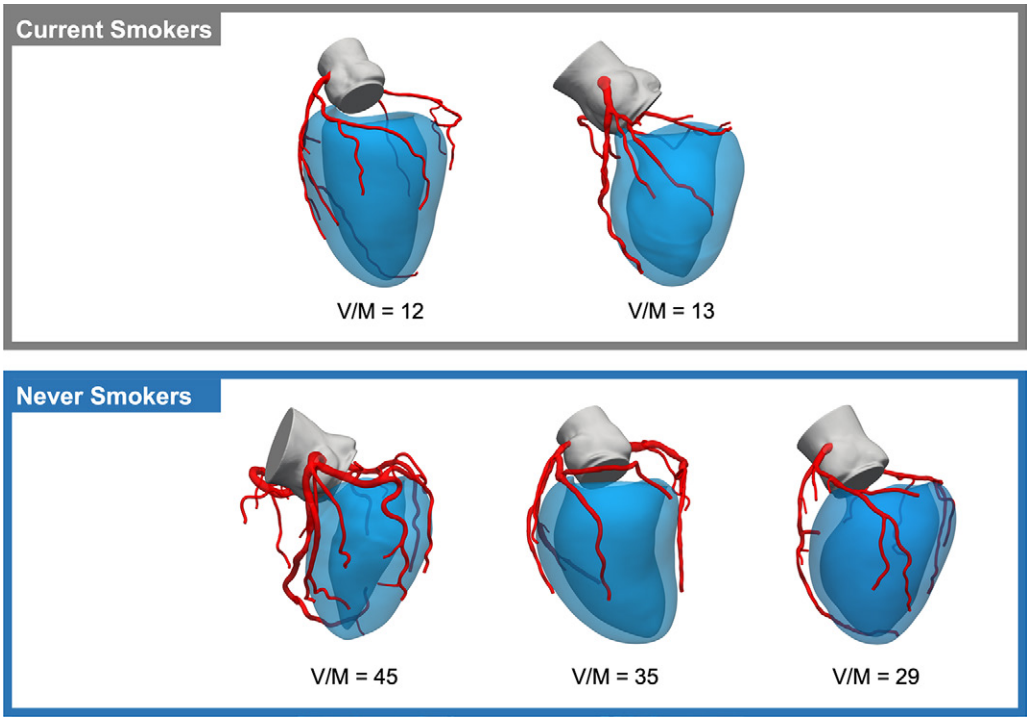

Figure 2: Sample CT fractional flow reserve models and calculated coronary volume–to–myocardial mass ratio (V/M, in cubic millimeters per gram) in current smokers and never-smokers demonstrate low and high V/M, respectively.

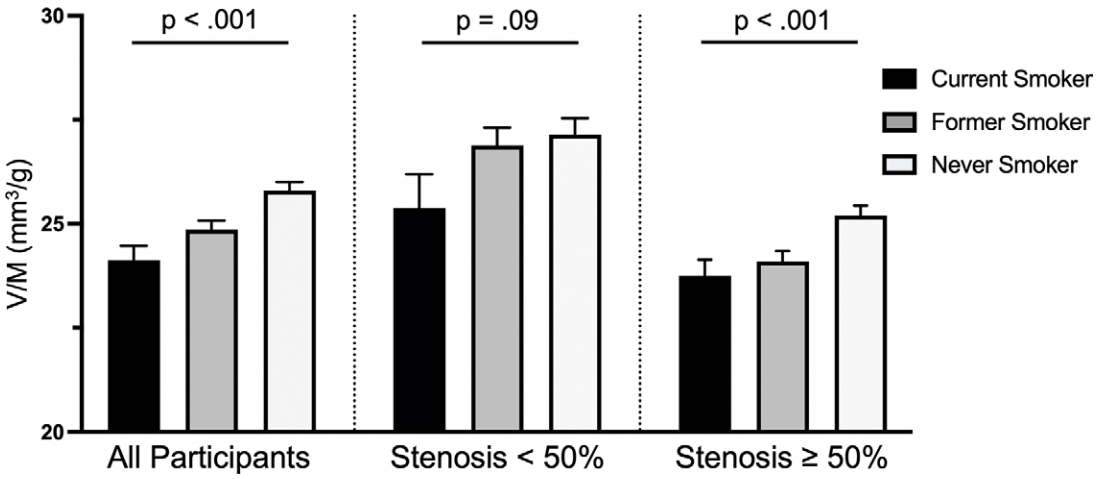

Figure 3: Graph shows mean (± SD) coronary volume–to–myocardial mass ratio (V/M) according to smoking status across all participants and stratified by stenosis severity.

(OR = 0.67 [95% CI: 0.56, 0.82]; $P < .001$), typical angina (OR = 0.65 [95% CI: 0.51, 0.81]; $P < .001$), and dyspnea (OR = 0.63 [95% CI: 0.48, 0.84]; $P = .001$) were also independent predictors of low V/M, while age 65 years or older (OR = 1.60 [95% CI: 1.35, 1.88]; $P < .001$) and female sex (OR = 1.39 [95% CI: 1.17, 1.66]; $P < .001$) predicted higher V/M (Fig 4).

Discussion

In this large, multicenter, international sample of individuals with stable CAD who underwent CT-FFR analysis, current and former smoking status were associated with reduced V/M compared with never-smoking status (current smokers, 24.1 mm^3/g ± 7.9; former smokers, 24.9 mm^3/g ± 7.1; never-smokers, 25.8 mm^3/g ± 7.4) and were independent predictors of having lower V/M in a multivariable analysis (current smoking, OR = 0.74 [95% CI: 0.59, 0.93]; former smoking, OR = 0.81 [95% CI: 0.68, 0.96]). Of note, when participants were stratified by stenosis severity, differences in V/M between smoking groups remained significant only among participants with stenosis of 50% or greater, suggesting that a deleterious effect of smoking on coronary supply-demand balance may be more prominent in persons with more advanced luminal narrowing.

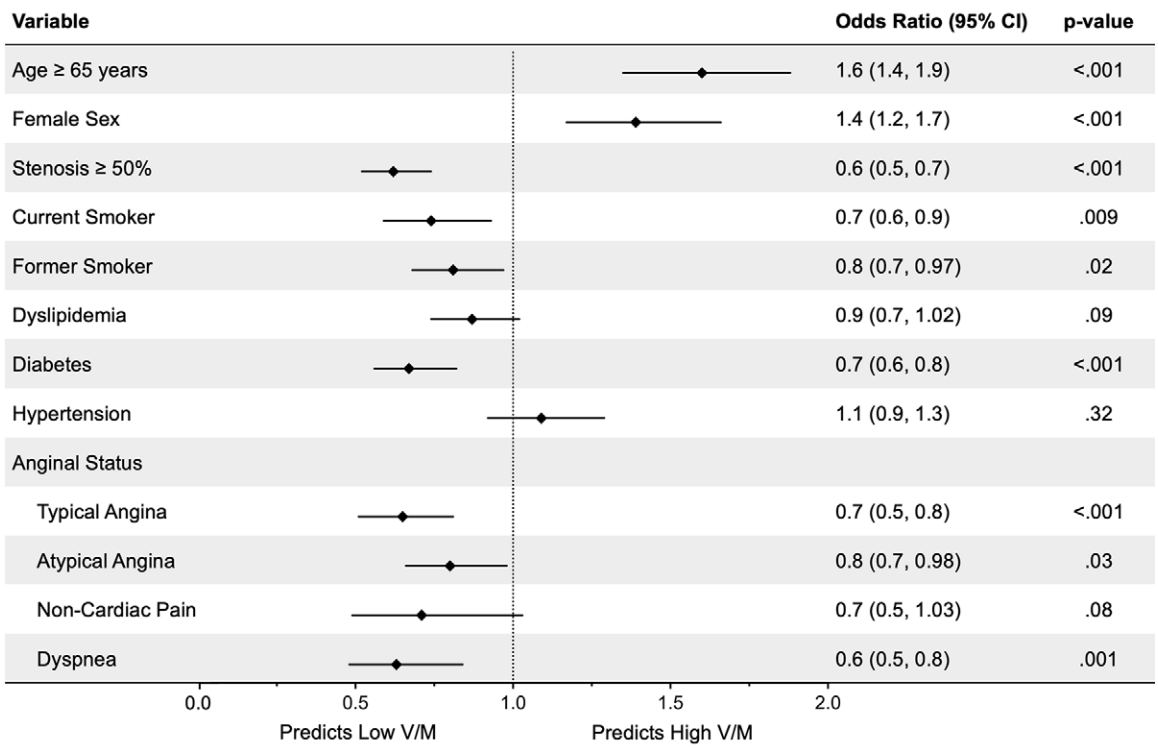

Figure 4: Forest plot shows multivariable analysis for the prediction of coronary volume–to–myocardial mass ratio (V/M) above or below the sample median.

The reduction in V/M observed in current and former smokers appeared to be driven by greater myocardial mass among current and former smokers. However, after adjustment for participant and clinical factors, only current smokers demonstrated increased myocardial mass compared with never-smokers. Although experience with V/M in patients with elevated myocardial mass is limited, a previous analysis demonstrated reduced V/M despite preserved coronary volume among patients with hypertrophic cardiomyopathy (20). Remodeling of the LV may be a similarly important contributor to myocardial supply-demand mismatch and potentially elevated cardiovascular risk in those who smoke. Alternatively, the relatively similar coronary volume between smoking groups may reflect a failure to compensate for increased myocardial mass in smoking, suggesting that impaired vasomotor function or vascular remodeling may also underpin reduced V/M among current and former smokers.

Smoking is a recognized risk factor for CAD, myocardial infarction, and death. The mechanism of action is multifaceted, including oxidative stress, inflammation, lipid modification, prothrombosis, and vasomotor dysfunction (21–23). Smoking-associated hypertension is a proposed mechanism that could explain our observations; however, there was no evidence of a difference in hypertension requiring treatment between current or former smokers and never-smokers, and hypertension itself was not an independent predictor of lower V/M.

Other studies have shown smoking to be independently associated with LV mass; the LARGE Heart study (24) found smoking to be an independent predictor of increased LV mass during exercise training in young people, and this finding is consistent with studies showing an association of increased LV mass and smoking in older populations (25–28). Although these studies relied on clinical imaging and patient history to document changes in LV mass associated with smoking, mechanisms associated with smoking not appreciable in our study may explain increased myocardial mass with a history of smoking. Smoking causes oxidative stress owing to the generation and inhalation of reactive oxygen species as well as expression of inflammatory and fibrotic signaling markers and may contribute to myocardial hypertrophy, based on translational studies (29,30). Nicotine has been shown to activate similar proteins as angiotensin II (including extracellular signal–regulated kinase, mitogen-activated protein kinase, and AMPa2), leading to tissue remodeling, including activation of mitogen responses in vascular smooth muscle cells and fibroblasts (31,32). Moreover, both nicotine and reactive oxygen species are associated with insulin resistance in cardiomyocytes, and insulin resistance molecular pathways are linked to cardiomyocyte growth and cardiac hypertrophy (33,34).

Smoking-induced endothelial dysfunction and reduced coronary vasomotion reduce coronary hyperemic response during cold pressor testing among smokers with normal resting coronary flow (35). This phenomenon may also be appreciable in our study as a relative reduction in coronary volume at CCTA. Although total coronary volume did not significantly differ between groups in our study, calculation of V/M may allow interrogation of coronary vascular reserve in smokers through quantification of the supply-demand balance. In addition, the ability to achieve adequate hyperemic response among smokers when acquiring CCTA data suggests that alterations in V/M may represent a fixed supply-demand mismatch.

Aside from smoking, the presence of diabetes was also an independent predictor of low V/M in our sample. Previous studies have demonstrated reduced coronary vascular reserve in patients with diabetes and marked coronary microvascular dysfunction in response to both endothelium-dependent and -independent vasodilatory stimuli (36). In addition, coronary microvascular dysfunction has been independently linked to increased cardiac mortality in this population (37), warranting further investigation into the potential use of V/M to assess microvascular function among patients with diabetes. Conversely, age 65 years or older and female sex were predictors of higher V/M, with the observed relationship between sex and V/M consistent with previous reports from the ADVANCE registry (15).

Our study had important limitations. It was a post hoc analysis of participants enrolled in the ADVANCE registry, which was designed to assess the real-world utility of CT-FFR in the evaluation of stable, symptomatic CAD; therefore, we cannot rule out the possibility that referral bias affected our study sample. The analysis was also limited to participants with greater than 30% stenosis at CCTA, limiting generalizability to populations without CAD. Among former smokers, information on time since last smoking was not collected, resulting in potentially inappreciable differences between current and former smokers if mean time elapsed since quitting was inadequate to allow sufficient cardiovascular remodeling. Similarly, information on duration and intensity of smoking was not available; this prevented comparison of total smoking exposure between groups. Participant groups also differed with respect to baseline demographic characteristics and severity of atherosclerotic disease. This was addressed by including these variables as covariates in our statistical analysis; however, the potential for residual confounding remains. Some potentially important clinical factors were also not available for analysis, including lifestyle factors (such as alcohol use), use of cardiovascular medication, presence of dilated or hypertrophic cardiomyopathy, and quantified atherosclerotic burden. Because of the relatively low event rates in the ADVANCE cohort, it was also not statistically feasible to evaluate the relationship between V/M and clinical outcomes across smoking groups, representing a notable limitation and an important avenue of future investigation.

In conclusion, history of smoking (current or former smoking status) was an independent predictor of low V/M derived from CT-FFR. Mechanisms driving low V/M in smokers and the potential use of V/M as a surrogate marker of vascular health and predictor of downstream clinical outcomes require further study.

Acknowledgments: We would like to thank Nicholas Ng, BS, of HeartFlow for his assistance with the statistical analysis of this study. Requests for data should be directed to ssellers@providencehealth.bc.ca.

Author contributions: Guarantors of integrity of entire study, **K.R.H., J.J.B., S.L.S.**; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agree to ensure any questions related to the work are appropriately resolved, all authors; literature research, **K.R.H., G.S.G., B.L.N., K.N., J.J.B., G.P., M.G.R., T.K., C.R., M.R.P., G.W.P., J.A.L., S.L.S.**; clinical studies, **T.A.F., H.M., B.L.N., J.M.J., K.N., G.P., T. Amano, T.K., T. Akasaka, H.K., C.R., M.R.P., J.A.L., S.L.S.**; statistical analysis, **K.R.H., G.S.G., T.K., G.W.P.**; and manuscript editing, **K.R.H., G.S.G., T.A.F., L.H.K., B.L.N., J.M.J., N.P.R.S., K.N., J.J.B., G.P., K.M.C., M.G.R., T.K., H.K., C.R., M.R.P., G.W.P., J.A.L., S.L.S.**

Data sharing: Requests for data should be directed to the provider indicated in the Acknowledgments.

Disclosures of conflicts of interest: **K.R.H.** No relevant relationships. **G.S.G.** Member of *Radiology: Cardiothoracic Imaging* Trainee Editorial Board. **T.A.F.** Served on speakers bureau for HeartFlow. **L.H.K.** Grant funding to department from HeartFlow, research support and speaking fees from HeartFlow and Siemens Healthineers, and member of *Radiology: Cardiothoracic Imaging* Editorial Board. **H.M.** Honoraria for lectures from HeartFlow. **B.L.N.** Unrestricted institutional research grants from Siemens Healthineers and HeartFlow. **J.M.J.** No relevant relationships. **N.P.R.S.** No relevant relationships. **K.N.** Grants or contracts from Siemens Healthineers, Bayer, HeartFlow, and Novartis; consulting fees from Siemens Healthineers, Elucid, and Novartis; member of the board of directors of the Society of Cardiovascular Computed Tomography; and stock or stock options from Lumen Therapeutics. **J.J.B.** No relevant relationships. **G.P.** Institutional research grant and/or honorarium as consultant or speaker from GE HealthCare, Bracco, Medtronic, Bayer, and HeartFlow. **K.M.C.** Institutional grant and consulting fees from HeartFlow; support for attending meetings and/or travel from Elucid and BioImaging; participation on a data and safety monitoring board or advisory board for HeartFlow; and member of the executive committee and board of directors for the Society of Cardiovascular Computed Tomography. **M.G.R.** Consulting fees from HeartFlow. **T. Amano** No relevant relationships. **T.K.** No relevant relationships. **T. Akasaka** No relevant relationships. **H.K.** No relevant relationships. **C.R.** Employee salary and stock or stock options from HeartFlow. **M.R.P.** Grants or contracts from Bayer, Janssen, Novartis, and the National Heart, Lung, and Blood Institute; consulting fees from Bayer, Janssen, and Novartis; and served on advisory boards for HeartFlow, Bayer, and Janssen. **G.W.P.** No relevant relationships. **J.A.L.** Consulting fees and stock options from Circle Cardiovascular Imaging and HeartFlow, modest speaking fees from Philips and GE HealthCare, support for attending meetings and/or travel from HeartFlow, and deputy editor for *Radiology: Cardiothoracic Imaging*. **S.L.S.** Grants or contracts from Edwards Lifesciences, Medtronic, HeartFlow, and ViVitro Labs and consulting fees from Edwards Lifesciences, Medtronic, and Anteris Technologies.

References

1. Thun MJ, Carter BD, Feskanich D, et al. 50-year trends in smoking-related mortality in the United States. N Engl J Med 2013;368(4):351–364.
2. Howard G, Wagenknecht LE, Burke GL, et al. Cigarette smoking and progression of atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. JAMA 1998;279(2):119–12.
3. Duncan MS, Freiberg MS, Greevy RA Jr, Kundu S, Vasan RS, Tindle HA. Association of smoking cessation with subsequent risk of cardiovascular disease. JAMA 2019;322(7):642–650.
4. Nakanishi R, Berman DS, Budoff MJ, et al. Current but not past smoking increases the risk of cardiac events: insights from coronary computed tomographic angiography. Eur Heart J 2015;36(17):1031–1040.
5. Douglas PS, De Bruyne B, Pontone G, et al. 1-year outcomes of FFRCT-guided care in patients with suspected coronary disease: the PLATFORM Study. J Am Coll Cardiol 2016;68(5):435–445.
6. Fairbairn TA, Nieman K, Akasaka T, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: lessons from the ADVANCE Registry. Eur Heart J 2018;39(41):3701–3711.
7. Taylor CA, Gaur S, Leipsic J, et al. Effect of the ratio of coronary arterial lumen volume to left ventricle myocardial mass derived from coronary CT angiography on fractional flow reserve. J Cardiovasc Comput Tomogr 2017;11(6):429–436.
8. Keulards DCJ, Fournier S, van 't Veer M, et al. Computed tomographic myocardial mass compared with invasive myocardial perfusion measurement. Heart 2020;106(19):1489–1494.
9. Kuneman JH, El Mahdiui M, van Rosendael AR, et al. Coronary volume to left ventricular mass ratio in patients with diabetes mellitus. J Cardiovasc Comput Tomogr 2022;16(4):319–326.
10. Chinnaiyan KM, Akasaka T, Amano T, et al. Rationale, design and goals of the HeartFlow assessing diagnostic value of non-invasive FFRCT in Coronary Care (ADVANCE) registry. J Cardiovasc Comput Tomogr 2017;11(1):62–67.
11. Patel MR, Nørgaard BL, Fairbairn TA, et al. 1-year impact on medical practice and clinical outcomes of FFRCT: the ADVANCE Registry. JACC Cardiovasc Imaging 2020;13(1 Pt 1):97–105.
12. Anastasius M, Maggiore P, Huang A, et al. The clinical utility of FFRCT stratified by age. J Cardiovasc Comput Tomogr 2021;15(2):121–128.
13. Matsuo H, Kawasaki T, Amano T, et al. Effect of coronary computed tomography angiography-derived fractional flow reserve on physicians' clinical behavior—differences between sites with and without appropriate

use criteria as designated by the Japanese Reimbursement System. Circ Rep 2020;2(7):364–37.
14. Nous F, Budde RPJ, Fairbairn TA, et al. Temporal changes in FFRCT-guided management of coronary artery disease—lessons from the ADVANCE registry. J Cardiovasc Comput Tomogr 2021;15(1):48–55.
15. Fairbairn TA, Dobson R, Hurwitz-Koweek L, et al. Sex differences in coronary computed tomography angiography–derived fractional flow reserve: lessons from ADVANCE. JACC Cardiovasc Imaging 2020;13(12):2576–2587.
16. Lowenstern A, Takagi H, Ng N, et al. TCT-303 the influence of obesity on coronary artery disease and clinical outcomes in the ADVANCE Registry. J Am Coll Cardiol 2021;78(19 Suppl):B124–B125.
17. Takagi H, Fairbairn T, Akasaka T, et al. Trans-stenotic pressure gradient as derived from CT improves patient management: ADVANCE registry. Eur Heart J 2021;42(Suppl 1):ehab724.0196.
18. Abbara S, Blanke P, Maroules CD, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee: endorsed by the North American Society for Cardiovascular Imaging (NASCI). J Cardiovasc Comput Tomogr 2016;10(6):435–449.
19. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. J Am Coll Cardiol 2013;61(22):2233–2241.
20. Sellers SL, Fonte TA, Grover R, et al. Hypertrophic cardiomyopathy (HCM): new insights into coronary artery remodelling and ischemia from FFRCT. J Cardiovasc Comput Tomogr 2018;12(6):467–471.
21. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. Arterioscler Thromb Vasc Biol 2014;34(3):509–515.
22. Wannamethee SG, Lowe GDO, Shaper AG, Rumley A, Lennon L, Whincup PH. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. Eur Heart J 2005;26(17):1765–1773.
23. Johnson HM, Gossett LK, Piper ME, et al. Effects of smoking and smoking cessation on endothelial function: 1-year outcomes from a randomized clinical trial. J Am Coll Cardiol 2010;55(18):1988–1995.
24. Payne JR, Eleftheriou KI, James LE, et al. Left ventricular growth response to exercise and cigarette smoking: data from LARGE Heart. Heart 2006;92(12):1784–1788.
25. Heckbert SR, Post W, Pearson GDN, et al. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multiethnic Study of Atherosclerosis. J Am Coll Cardiol 2006;48(11):2285–2292.
26. Lieb W, Xanthakis V, Sullivan LM, et al. Longitudinal tracking of left ventricular mass over the adult life course: clinical correlates of short- and long-term change in the Framingham Offspring Study. Circulation 2009;119(24):3085–3092.
27. Park SK, Ryoo JH, Kang JG, Jung JY. Smoking status, intensity of smoking, and their relation to left ventricular hypertrophy in working aged Korean men. Nicotine Tob Res 2021;23(7):1176–1182.
28. Leigh JA, Kaplan RC, Swett K, et al. Smoking intensity and duration is associated with cardiac structure and function: the ECHOcardiographic Study of Hispanics/Latinos. Open Heart 2017;4(2):e000614.
29. Al Hariri M, Zibara K, Farhat W, et al. Cigarette smoking-induced cardiac hypertrophy, vascular inflammation and injury are attenuated by antioxidant supplementation in an animal model. Front Pharmacol 2016;7:397.
30. Valavanidis A, Vlachogianni T, Fiotakis K. Tobacco smoke: involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects with other respirable particles. Int J Environ Res Public Health 2009;6(2):445–462.
31. Li N, Si B, Ju JF, et al. Nicotine induces cardiomyocyte hypertrophy through TRPC3-mediated Ca2+/NFAT signalling pathway. Can J Cardiol 2016;32(10):1260.e1–1260.e10.
32. Li JM, Cui TX, Shiuchi T, et al. Nicotine enhances angiotensin II-induced mitogenic response in vascular smooth muscle cells and fibroblasts. Arterioscler Thromb Vasc Biol 2004;24(1):80–84.
33. Mellor KM, Ritchie RH, Delbridge LMD. Reactive oxygen species and insulin-resistant cardiomyopathy. Clin Exp Pharmacol Physiol 2010;37(2):222–228.
34. Li Z, Xu W, Su Y, et al. Nicotine induces insulin resistance via downregulation of Nrf2 in cardiomyocyte. Mol Cell Endocrinol 2019;495:110507.
35. Campisi R, Czernin J, Schöder H, et al. Effects of long-term smoking on myocardial blood flow, coronary vasomotion, and vasodilator capacity. Circulation 1998;98(2):119–125.
36. Di Carli MF, Janisse J, Grunberger G, Ager J. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. J Am Coll Cardiol 2003;41(8):1387–1393.
37. Murthy VL, Naya M, Foster CR, et al. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. Circulation 2012;126(15):1858–1868.