The Journal of Rheumatology 2021;xx:xxxx
doi:10.3899/jrheum.210040
First Release September 1 2021

The Journal of Rheumatology

Impaired Myocardial Flow Reserve on ^{82}Rubidium Positron Emission Tomography/Computed Tomography in Patients With Systemic Sclerosis

Attila Feher[1], Nabil E. Boutagy[2], Evangelos K. Oikonomou[1], Stephanie Thorn[1], Yi-Hwa Liu[1], Edward J. Miller[1], Albert J. Sinusas[3], and Monique Hinchcliff[4]

ABSTRACT. ***Objective.*** To investigate the association between Raynaud phenomenon (RP) and coronary microvascular dysfunction, we measured myocardial flow reserve (MFR) using positron emission tomography/computed tomography (PET/CT) in patients with primary and secondary RP and controls.

Methods. Patients with RP, patient controls, and healthy participants who underwent dynamic rest-stress 82-rubidium PET/CT were studied. Differences in heart rate–blood pressure product-corrected MFR and clinical predictors of reduced MFR (< 2.0) were determined.

Results. Forty-nine patients with RP (80% female; aged 65 ± 11 yrs; 11 with primary RP, 18 with systemic sclerosis [SSc], and 20 with other autoimmune rheumatic diseases [AIRDs] including 6 with systemic lupus erythematosus, 6 with rheumatoid arthritis, 4 with overlap syndrome, 2 with Sjögren syndrome, and 2 with inflammatory arthritis), 49 matched patients without RP or AIRD (78% female; 64 ± 13 yrs), and 14 healthy participants (50% female; 35 ± 5 yrs) were studied. Patients with primary RP, matched patient controls, and healthy participants had comparable MFR. Patients with SSc-RP had significantly reduced MFR (1.62 ± 0.32) compared to matched patient controls (P = 0.03, 2.06 ± 0.61) and to healthy participants (P = 0.01, 2.22 ± 0.44). In multivariable logistic regression, SSc was an independent predictor of reduced MFR. We identified a correlation between time since AIRD diagnosis and MFR (r = –0.30, 95% CI –0.63 to –0.02, P = 0.04).

Conclusion. Our findings suggest that only secondary, not primary, RP is associated with reduced MFR, and that patients with SSc-RP have reduced MFR compared to those with primary RP and patients with other AIRDs. Larger prospective studies are warranted to fully elucidate the prognostic value of MFR in patients with secondary RP.

Key Indexing Terms: cardiovascular disease, radionuclide imaging, Raynaud phenomenon, scleroderma, systemic sclerosis

Raynaud phenomenon (RP) is a vasoactive condition that occurs in response to cold temperature exposure or stress. The currently used classification distinguishes between primary (idiopathic) and secondary RP that is associated with a variety of autoimmune rheumatic diseases (AIRDs; e.g., systemic sclerosis [SSc], systemic lupus erythematosus [SLE], rheumatoid arthritis [RA] and Sjögren syndrome [SS]), hematologic and vascular disorders, vibration exposure, hypothyroidism, and carpal tunnel syndrome. Primary RP usually presents in women who demonstrate normal nailfold capillaries and lacks ischemic complications, whereas secondary RP develops later, and abnormal nailfold capillaries and concomitant ischemia-induced injury (e.g., digital pitting, digital ulcers, and acroosteolysis) may be present.

Cardiovascular (CV) disease lifetime risk is significantly higher in patients with AIRDs including RA,[1,2,3] SLE,[4,5] SSc,[6,7] and SS[8] compared to the general population. Increased CV

This research was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (NIH) under Award Numbers R01 AR073270 (MH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

[1]A. Feher, MD, PhD, E.K. Oikonomou, MD, PhD, S. Thorn, PhD, Y.H. Liu, PhD, E.J. Miller, MD, PhD, Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine; [2]N.E. Boutagy, PhD, Section of Cardiovascular Medicine, Department of Internal Medicine, and Vascular Biology and Therapeutics Program, and Department of Pharmacology, Yale School of Medicine; [3]A.J. Sinusas, MD, BSc, Section of Cardiovascular Medicine, Department of Internal Medicine, and Department of Radiology and Biomedical Imaging, Yale School of Medicine, and Department of Biomedical Engineering, Yale University; [4]M. Hinchcliff, MD, Section of Rheumatology, Department of Internal Medicine, and Department of Internal Medicine, Clinical and Translational Research Accelerator, Yale School of Medicine, New Haven, Connecticut, USA.

The authors declare no conflicts of interest relevant to this article.

Address correspondence to Dr. M. Hinchcliff, Director, Yale Scleroderma Program, Yale School of Medicine, Section of Allergy, Rheumatology, and Immunology, The Anlyan Center, 300 Cedar Street, PO BOX 208031, New Haven, CT 06520, USA. Email: monique.hinchcliff@yale.edu.

Accepted for publication July 5, 2021.

disease risk is likely a result of the synergy of traditional risk factors accentuated by AIRD-associated cardiac involvement, systemic inflammation, side effects of medications used to treat AIRDs such as glucocorticoids and cyclophosphamide, and the sedentary lifestyle adopted by many patients with AIRDs because of arthritis, pain, and/or depression. Therefore, better techniques to determine which patients with AIRD have subclinical CV disease are needed to provide early diagnosis and potentially improved outcomes through targeted therapies.

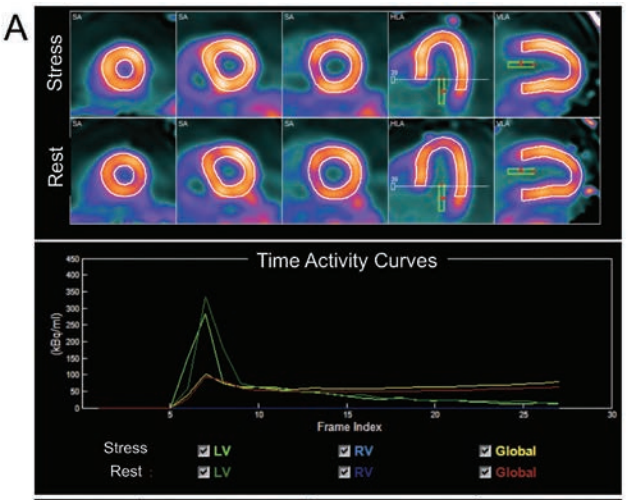
Positron emission tomography/computed tomography (PET/CT) with the perfusion tracer 82-rubidium (^{82}Rb), is an established technique for evaluating myocardial perfusion. Dynamic ^{82}Rb PET/CT performed at rest followed by imaging after administration of a pharmacologic stressor such as the vasodilator regadenoson is considered the noninvasive gold standard for coronary microvascular function evaluation.[9] This validated quantitative methodology uses kinetic modeling to generate estimates of absolute global and regional myocardial blood flow (MBF; Figure 1) and has robust prognostic literature.[10]

The coronary microvasculature consists of intramural vessels derived from the epicardial vasculature with an intraluminal diameter < 500 μm. In the absence of epicardial coronary artery disease (CAD), myocardial flow reserve (MFR) is an indirect measure of cardiac microvascular health and is defined as the ratio of MBF during pharmacological stress compared to rest; thus, the measurement is unitless. Normal MFR values greatly depend on age and sex, but most investigators consider MFR< 2.0 to be sufficiently abnormal to result in ischemia[9] and < 1.5 to be associated with poor outcomes.[11]

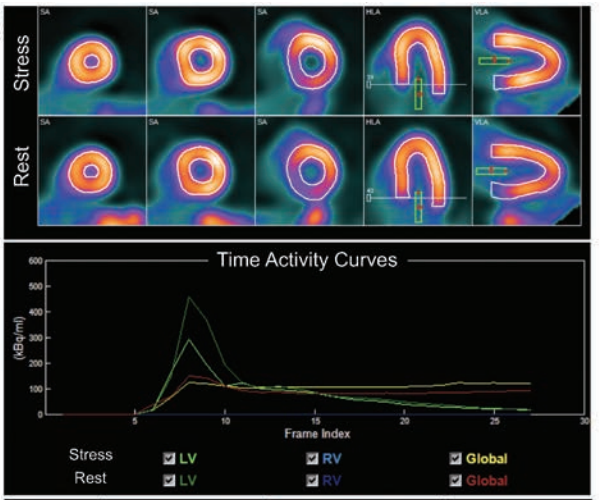
Little is known about the association between RP and coronary microvascular dysfunction (CMVD). To date, no studies have investigated the relationship between RP and CMVD using PET/CT MFR. We hypothesized that secondary RP may be associated with reduced PET/CT MFR.

METHODS

Research participants and PET/CT imaging protocol. Patients with an RP diagnosis (International Classification of Diseases, 9th revision [ICD-9] 443.0 and/or ICD-10 I73.0) in the electronic health record (EHR), who underwent ^{82}Rb PET/CT myocardial perfusion evaluation from November 2012 to November 2019 at Yale New Haven Hospital were studied. Because of the retrospective study design, informed consent from patients and healthy participants was not obtained. A manual EHR review (e.g., office notes, antinuclear antibody testing, and diagnosis codes) was conducted to scrutinize whether patients had received an AIRD diagnosis prior to or following PET/CT testing. The study complied with the Declaration of Helsinki, and the Yale Institutional Research Ethics board approved this single-center, retrospective study (HIC# 2000025019). Healthy volunteers without coexisting medical conditions who underwent ^{82}Rb PET/CT myocardial perfusion study with regadenoson stress between the years 2013 and 2016 were also included (HIC# 1305012105). In addition, a matched group of 49 Yale New Haven Hospital patients without RP or AIRD (adjudicated by EHR review), but with risk factors similar to the patients with RP and who had also undergone ^{82}Rb PET from May 2017 to November 2019 were identified. Using a nearest neighbor matching method (Environment Software R version 3.4 and R Studio version



Region	Stress MBF (mL/min/g)	Rest MBF (mL/min/g)	MFR
LAD	1.37	1.06	1.28
LCx	1.37	1.24	1.10
RCA	1.22	1.02	1.19
Global	1.32	1.08	1.22



Region	Stress MBF (mL/min/g)	Rest MBF (mL/min/g)	MFR
LAD	2.77	1.11	2.50
LCx	2.58	1.15	2.24
RCA	2.78	0.87	3.20
Global	2.71	1.04	2.60

Figure 1. Representative relative perfusion images, time-activity curves, and MBF values obtained at stress and rest (A) for a patient with SSc and (B) for a healthy control subject. Perfusion imaging showed no perfusion defects; however, for the patient with SSc, blood flow quantification revealed global reduction in stress MBF and MFR (< 2.0), whereas the healthy control subject had normal MBF values. HLA: horizontal long axis; kBq/mL: kilobecquerel/milliliter; LAD: left anterior descending artery; LCx: left circumflex artery; LV: left ventricle; MBF: myocardial blood flow; MFR: myocardial flow reserve; RCA: right coronary artery; RV: right ventricle; SA: short axis; SSc: systemic sclerosis; VLA: vertical long axis.

1.1.453 and MatchIt package version 3.0.4; R Foundation for Statistical Computing), patients matched for age, sex, BMI, smoking history, and clinical diagnosis of hypertension, hyperlipidemia, diabetes mellitus, heart failure (HF), transient ischemic attack or stroke, peripheral artery disease, history of myocardial infarction (MI), coronary bypass surgery, percutaneous coronary intervention (PCI), chronic kidney disease, and obstructive sleep apnea were identified.

Dynamic rest-stress ^{82}Rb PET myocardial perfusion imaging was performed on a hybrid PET 64-slice CT scanner (Discovery 690, GE Healthcare) as described.[12] Briefly, dynamic rest PET/CT images were acquired after intravenous (IV) injection of 23 ± 4 millicuries (mCi) of ^{82}Rb. Then pharmacological stress with regadenoson (n = 42, 0.4 mg bolus over 40 s), or adenosine (n = 5, 140 μg/kg/min) or dobutamine (n = 1, maximum rate 40 μg/kg/min) as continuous infusions, based on clinical indication, was induced. At peak stress, 23 ± 4 mCi of ^{82}Rb was administered IV and dynamic PET images were acquired. A low-dose CT scan was acquired for attenuation correction of PET images. Heart rate and rhythm (12-lead electrocardiogram [ECG]) and noninvasive blood pressure were recorded at rest, peak stress, and in recovery.

PET/CT data analysis. PET images were reconstructed with attenuation correction on system software creating a dynamic series of PET images that were reoriented and processed using Invia Corridor 4DM v2017 (Invia). On the study day, 1 of 6 expert readers reviewed perfusion imaging and attenuation CT scans to assess for perfusion defects that are associated with epicardial disease and coronary calcification. Small, medium, and large perfusion defects were reported with involvement of 1 to 2, 3 to 4, or > 4 cardiac segments, respectively, based on the 17-segment model.[13] Presence of coronary calcifications was graded qualitatively (mild, moderate, and severe).

Regional and global rest and peak stress MBF were calculated by fitting the ^{82}Rb time-activity curves to a 1-compartment tracer kinetic model as described.[12] Rest and stress flows were corrected for the rate pressure product (heart rate × systolic blood pressure) as follows: rest and stress flows were multiplied by the respective rest or peak stress rate pressure products and then divided by the reference rate pressure product (9000 mmHg × beats/min). MFR was calculated as the ratio of stress to rest MBF (Figure 1).

Statistical analyses. Chi-square tests assessed differences between categorical variables. ANOVA with multiple comparisons (Dunnett test) or Kruskal-Wallis test with multiple comparisons (Dunn test) assessed the difference among groups for normally and nonnormally distributed variables, respectively. Pearson correlation (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]) or Spearman correlation coefficient (RP diagnosis date) with 95% CI were used to evaluate the correlation between dependent variables of interest and MFR. Including variables known to affect MBF,[12] a stepwise binary logistic regression analysis was performed with backward selection ($P < 0.10$) to identify independent predictors of reduced MFR (MFR < 2.0) in patients with RP (primary and secondary). Age and sex were included in the multivariate regression model regardless of significance. In order to control for CAD, analyses were repeated excluding patients with medium to large perfusion defects and patients with severe coronary calcifications. Statistical analyses were performed using SPSS (IBM Corp.), and statistical significance was defined as $P < 0.05$ or as noted.

RESULTS

Research participants. Forty-nine patients with RP, 49 matched patient controls, and 14 healthy participants underwent rest and stress ^{82}Rb PET/CT between November 2012 and November 2019. Table 1 presents the clinical characteristics of the participants. The majority of patients with AIRD were women, whereas patients with primary RP were approximately equally likely to be men. Approximately half of the study patients were obese (BMI > 30). Eleven patients had primary RP, 20 had secondary RP as a result of an AIRD distinct from SSc (other AIRD-RP), and 18 patients had RP secondary to SSc (SSc-RP). The RP duration was longer in SSc vs patients with primary RP and other AIRDs. Patients with primary RP were more likely to have a history of prior coronary artery revascularization and less likely to be on hydroxychloroquine (HCQ); the groups were otherwise not significantly different. Patients with RP (primary and secondary) were more likely taking HCQ and clopidogrel compared to the matched patient controls, but other medication use was otherwise similar. Age, sex, BMI, race, and comorbidities (including prior revascularization) were comparable between the combined RP and the matched patient control group.

PET/CT. Table 2 presents imaging characteristics for research participants. The PET/CT indication in the combined RP patient group was chest pain in 59%, shortness of breath in 41%, and other indications in 12% of patients (perioperative risk stratification [n = 3], syncope [n = 2], or unexplained cardiomyopathy investigations [n = 1]), with some patients having multiple indications. Regadenoson use was most common (88%) and no participants developed resultant ischemic ECG changes. Perfusion defects and coronary calcifications were found in 27% (similar prevalence in patients with primary RP, SSc-RP, and other AIRD-RP) and 59% of patients with RP, respectively. There was no significant difference in the stressor used or in the prevalence of perfusion defects and coronary calcifications between the combined RP group and matched patient controls without RP and AIRD. Stress systolic blood pressure and rest left ventricular ejection fraction (LVEF) were significantly higher in the combined RP group when compared to matched patient controls, whereas rest systolic blood pressure, rest and stress heart rates, and stress LVEF were comparable along with similar hemoglobin levels (Table 1). There was a weak but significant inverse correlation between MFR values and the time interval between RP diagnosis and PET/CT (Figure 2A), whereas there was no significant correlation between MFR and ESR or CRP (Figures 2B,C; data available for 35 and 29 patients with secondary RP, respectively). There was no significant correlation between MFR and age at PET/CT (r = 0.06, 95% CI −0.22 to 0.34, $P = 0.66$) or BMI (r = 0.19, 95% CI −0.10 to 0.44, $P = 0.20$).

Global stress MBF was significantly lower in patients with AIRD-RP, but not primary RP, compared to healthy participants but similar to the matched patient controls (Figure 3A). Matched patient controls had significantly reduced rest MBF compared to healthy participants (Figure 3B), but patients with SSc-RP and other patients with AIRD-RP had significantly higher rest MBF compared to matched patient controls. Global MFR was significantly lower in patients with SSc-RP (1.62 ± 0.32) when compared to healthy participants (2.22 ± 0.44) and matched patient controls (2.06 ± 0.61; Figure 3C). Global MFR was reduced (< 2.0) in 89% of patients with SSc-RP. Global MFR was significantly lower in patients with SSc-RP (1.63 ± 0.33) when compared to healthy participants and matched patient controls after restricting the analyses to those who received the stressor regadenoson (Supplementary Figure 1A, available with the online version of this article). Regional MFR was reduced in

Table 1. Study cohort clinical characteristics.

Baseline Characteristics	Primary RP, n = 11	Other AIRD-RP, n = 20	SSc-RP, n = 18	*P*	All RP, n = 49	Matched Patient Controls, n = 49	*P*	Healthy Participants, n = 14
Age, yrs	68 (61–77)	62 (57–67)	65 (61–70)	0.24	64 (58–70)	64 (54–71)	0.78	34 (32–37)
Female sex	5 (45)	18 (100)	16 (89)	< 0.001*	39 (80)	38 (78)	0.61	7 (50)
BMI, kg/m^2	30 (25–36)	35 (29–41)	32 (28–37)	0.43	30 (25–41)	29 (24–35)	0.25	27 (25–29)
RP duration, yrs	2.8 (0.41–4.0)	2.5 (1.1–4.0)	6.0 (3.4–32.8)	0.003*	–	NA		
Race				0.15			0.09	
White	11 (100)	13 (65)	15 (83)		39 (80)	35 (71)		
African American	0 (0)	6 (30)	2 (11)		8 (16)	8 (16)		
Other	0 (0)	1 (5)	1 (6)		2 (4)	6 (12)		
Comorbidities								
Prior PCI/CABG	5 (45)	3 (15)	0 (0)	0.004*	8 (16)	2 (4)	0.09	
Prior MI	2 (18)	1 (5)	2 (11)	0.43	5 (10)	1 (2)	0.21	
CHF	1 (9)	4 (20)	1 (6)	0.55	6 (12)	8 (16)	0.78	
Hypertension	9 (82)	14 (70)	11 (61)	0.57	34 (69)	31 (63)	0.67	
Hyperlipidemia	8 (73)	9 (45)	9 (50)	0.39	26 (53)	30 (61)	0.84	
Diabetes mellitus	3 (27)	3 (15)	4 (22)	0.74	10 (20)	8 (16)	0.79	
Smoking	1 (9)	7 (35)	1 (6)	0.05	9 (18)	10 (20)	> 0.99	
PAD	2 (18)	1 (5)	4 (22)	0.26	7 (14)	5 (10)	0.76	
CKD	0 (0)	4 (20)	2 (11)	0.35	6 (12)	3 (6)	0.48	
DVT	1 (9)	1 (5)	3 (17)	0.49	5 (10)	1 (2)	0.20	
Atrial fibrillation	2 (18)	1 (5)	3 (17)	0.44	6 (12)	9 (18)	0.58	
Medications								
HCQ	0 (0)	12 (60)	7 (39)	0.003*	19 (39)	0 (0)	0.001*	
Beta blockers	7 (64)	10 (50)	5 (28)	0.15	22 (45)	16 (31)	0.30	
CCB	2 (18)	8 (40)	9 (50)	0.27	19 (39)	12 (24)	0.19	
PDE5 inhibitor	0 (0)	0 (0)	3 (17)	0.053	3 (6)	1 (2)	0.62	
ACEi/ARB	7 (4)	6 (14)	6 (12)	0.17	19 (39)	20 (41)	> 0.99	
Diuretic	5 (45)	12 (60)	8 (44)	0.62	25 (51)	15 (31)	0.06	
Nitrate	1 (9)	4 (20)	0 (0)	0.12	5 (10)	2 (4)	0.44	
Aspirin	7 (64)	6 (30)	6 (33)	0.18	19 (39)	19 (39)	> 0.99	
Clopidogrel	2 (18)	3 (15)	3 (17)	> 0.99	8 (16)	1 (2)	0.03*	
Statin	7 (64)	8 (40)	9 (50)	0.51	24 (49)	20 (41)	0.54	
Anticoagulation	1 (9)	1 (5)	6 (33)	0.06	8 (16)	7 (14)	1.00	
Laboratory values								
Hemoglobin, mg/dL	13.3 (12.1–15.3)	12.5 (9.4–13.7)	11.5 (10.7–12.5)	0.17	12.1 (10.9–13.5)	13.1 (11.4–14.0)	0.46	

Continuous variables are expressed as medians (IQRs) and categorical variables are expressed as n (%). * Statistically significant values. ACEi: angiotensin-converting enzyme inhibitor; AIRD: autoimmune rheumatic disease; ARB: angiotensin receptor blocker; CABG: coronary artery bypass graft; CCB: calcium channel blocker; CHF: congestive heart failure; CKD: chronic kidney disease; DVT: deep vein thrombosis; HCQ: hydroxychloroquine; MI: myocardial infarction; NA: not applicable; PAD: peripheral artery disease; PCI: percutaneous intervention; PDE5: phosphodiesterase 5; RP: Raynaud phenomenon; SSc: systemic sclerosis.

the left anterior descending (LAD) and left circumflex territories in patients with SSc-RP compared to matched patient controls, and in the LAD and right coronary artery territories compared to healthy participants (Supplementary Figure 2). MFR was not significantly different in any of the vascular territories in patients with primary RP or patients with other AIRD-RP compared to healthy participants or matched patient controls. In the binary logistic regression model, SSc diagnosis was the only independent predictor of reduced MFR (Figure 4). Lower MFR in patients with SSc compared to both healthy participants and to matched patient controls was observed, and SSc remained an independent predictor of low MFR even after excluding patients with adenosine or dobutamine stress (patients with RP [n = 6]; Supplementary Figure 1), or excluding patients with medium to large perfusion defects (patients with RP [n = 4]; Supplementary Figure 3), or excluding patients with severe coronary calcifications (patients with RP [n = 10];Supplementary Figure 4).

Of 49 patients with RP, 5 patients underwent left heart catheterization within 100 days of PET/CT perfusion imaging. Among these, 2 patients with RP had obstructive CAD and 1 underwent PCI (global MFR = 1.14), whereas the other's coronary anatomy was not amenable to revascularization (global MFR = 1.43). The remaining 3 patients with RP had no evidence of CAD (global MFR values = 1.31, 1.52, and 1.53, respectively). Of 49 matched patient controls, 5 patients underwent left heart catheterization within 100 days of PET/CT perfusion imaging.

Table 2. Imaging characteristics.

Baseline Characteristics	Primary RP, n = 11	Other AIRD-RP, n = 20	SSc-RP, n = 18	*P*	All RP, n = 49	Matched Patient Controls, n = 49	*P*	Healthy Participants, n = 14
Study indication								
Chest pain	7 (64)	13 (65)	9 (50)	0.70	29 (59)	24 (49)	0.42	
SOB	2 (18)	7 (35)	11 (61)	0.07	20 (41)	12 (24)	0.13	
Hemodynamics								
Rest SBP, mmHg	139 (129–155)	137 (130–146)	125 (112–141)	0.32	134 (124–145)	137 (129–155)	0.15	108 (102–122)
Rest HR, bpm	68 (63–73)	68 (64–80)	77 (65–85)	0.24	71 (64–80)	75 (62–83)	0.65	73 (61–83)
Stress SBP, mmHg	122 (117–146)	124 (117–135)	119 (112–138)	0.86	122 (114–138)	115 (104–131)	0.04*	112 (101–124)
Stress HR, bpm	95 (85–98)	88 (79–107)	91 (83–106)	0.98	91 (80–105)	96 (83–107)	0.41	106 (99–115)
Stressor agent				0.14			0.06	
Regadenoson	10 (91)	16 (80)	17 (94)		43 (88)	49 (100)		14 (100)
Adenosine	1 (9)	4 (20)	0 (0)		5 (10)	0 (0)		
Dobutamine	0 (0)	0 (0)	1 (6)		1 (2)	0 (0)		
Study results								
Perfusion defects	4 (36)	6 (30)	3 (17)	0.49	13 (27)	13 (27)	1.00	
Coronary calcium	7 (64)	10 (50)	12 (67)	0.57	29 (59)	25 (51)	0.54	
Rest LVEF	64 (58–71)	64 (53–69)	66 (54–70)	0.84	64 (56–70)	60 (48–67)	0.04*	
Stress LVEF	69 (62–76)	68 (57–74)	70 (61–74)	0.69	68 (61–74)	64 (54–72)	0.125	

Continuous variables are expressed as medians (IQRs) and categorical variables are expressed as absolute frequencies (%). * Statistically significant values. AIRD: autoimmune rheumatic disease; bpm: beats per minute; HR: heart rate; LVEF: left ventricular ejection fraction; RP: Raynaud phenomenon; SBP: systolic blood pressure; SOB: shortness of breath; SSc: systemic sclerosis.

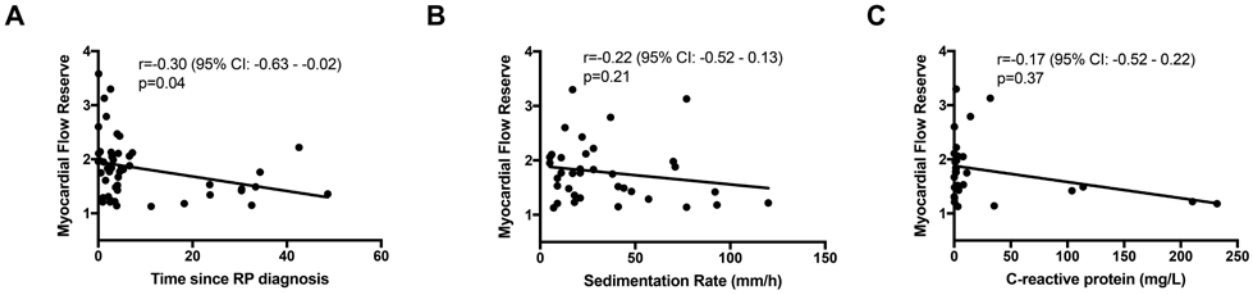


Figure 2. Correlation between myocardial flow reserve and (A) time since RP diagnosis, (B) sedimentation rate, and (C) C-reactive protein levels. RP: Raynaud phenomenon.

Among these, 4 matched patient controls had obstructive CAD, and all underwent PCI (global MFR values = 1.20, 2.06, 2.13, and 3.03, respectively). The remaining 1 matched patient control had no evidence of obstructive CAD (global MFR = 1.68; data not shown).

DISCUSSION

We identified patients in our EHR with a diagnosis of RP; a group of patients without RP or AIRD matched for age, sex, BMI, and comorbidities; and a group of healthy control participants who had undergone dynamic rest-stress ^{82}Rb PET/CT myocardial perfusion imaging. We showed that patients with secondary RP had significantly reduced MFR compared to both healthy participants and matched patient controls, whereas patients with primary RP had preserved MFR. Additionally, an SSc diagnosis was an independent predictor of reduced MFR when controlling for other variables known to be associated with reduced MFR such as hypertension, hyperlipidemia, diabetes, and prior revascularization. Our study results showed no significant correlation between inflammatory markers and RP, which might be explained by the relatively small sample size.

Although increased CV disease risk is well known to be higher in patients with AIRD, it has been incompletely characterized in patients with RP. A study of the Framingham Heart Study Offspring Cohort, with over 3400 participants of whom 113 (3.3%) reported RP (primary or secondary was not delineated), found a positive association of primary RP and CV disease defined as a history of angina, coronary insufficiency, MI, congestive HF, intermittent claudication, stroke, or transient ischemic attack with an OR of 1.69 (95% CI 1.22–2.34).[14] Other population-based studies indicate that RP may be associated with increased CV disease risk, especially in White patients[15,16]; however, these studies did not distinguish between patients with primary and secondary RP. A small prospective Korean cohort

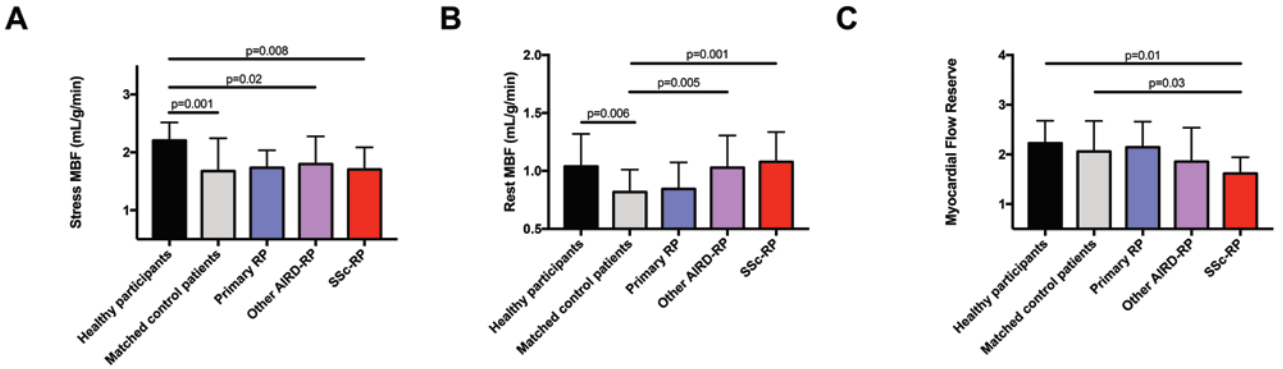


Figure 3. (A) Stress and (B) rest MBF and (C) myocardial flow reserve in healthy participants, in matched patient controls without RP, and in patients with primary RP, secondary RP with AIRD-RP other than SSc, and in patients with SSc-RP. AIRD: autoimmune rheumatic disease; MBF: myocardial blood flow; RP: Raynaud phenomenon; SSc: systemic sclerosis.

study investigated the association between RP and vasospastic angina by assessing coronary vasospasm response to ergonovine maleate provocation and by assessing digital blood flow response to cold stimulation with technetium-99m-labeled red blood cell radionuclide angiography. In this study, the 20 patients with angiographically proven coronary artery spasm neither reported more RP nor demonstrated more significant decrease in digital blood flow in response to cold compared with 30 patients with CAD and 31 hospitalized control participants without heart disease.[17] In a small study examining MBF by myocardial contrast echocardiography in 51 patients with SSc, the presence of cardiac RP (cold-induced reversible myocardial ischemia) at baseline in 15 patients was an independent predictor for the development of left ventricular systolic dysfunction (defined as LVEF < 50%) during a mean follow-up of 7 years.[18]

To our knowledge, this study is the first to report results of dynamic rest-stress ^{82}Rb PET/CT myocardial perfusion imaging in patients with RP compared with healthy control participants and with a matched patient control cohort. Our results suggest that patients with SSc show impairment in MFR, which can potentially indicate microvascular dysfunction. CMVD can result from 2 mechanisms, including (1) increased baseline coronary flow and associated reduced coronary microvascular resistance, or (2) reduced stress MBF as a result of high microvascular resistance under maximum hyperemia attributed to impaired vasodilation.[9] Previous evidence suggests that decreased MFR in CMVD is often associated with high resting MBF, rather than reduced stress MBF,[19,20] and reduced MFR as a result of increased rest MBF can be associated with adverse CV outcomes in patients undergoing myocardial perfusion imaging.[19] Similarly, our results indicate that patients with SSc have higher resting MBF when compared to the matched patient control group. A potential explanation for this phenomenon is that resting MBF is elevated to account for the ischemia related to the increased microvascular resistance in the setting of CMVD.[20] The increased resting MBF may also be explained by the frequently observed autonomic dysfunction in patients with SSc with associated sympathetic overactivity and impaired parasympathetic activity.[21,22] These autonomic changes may lead to increased resting MBF by increasing cardiac metabolism through positive chronotropic and positive inotropic effects. This may be supported by the observed higher rest LVEF in the combined RP patient cohort, when compared to the matched patient control group. On the other hand, anemia and HF are unlikely to be responsible for the increased rest MBF in patients with SSc, as hemoglobin levels and HF diagnosis rates were comparable between the 4 groups.

The lower resting MBF in the matched patient control group compared to healthy participants could be attributable to prior MI; however, the percentage of patients with any perfusion defects was not significantly different between groups. However, clopidogrel use was significantly higher and prior PCIs (mostly present in the primary RP population) were more common in the combined RP patient cohort as opposed to the matched patient control cohort. The observed reduced stress MBF in the matched patient control group in comparison to healthy participants might be related to age-dependent decreases in stress MBF,[23] or related to the presence of CV comorbidities known to be associated with reduced stress MBF including hypertension,[24] diabetes mellitus,[25] and obesity.[26] Importantly, MFR was preserved in our matched patient control cohort despite reduced stress MBF as a result of concurrent rest MBF reduction.

Previously, limited reports have evaluated PET MFR in small AIRD patient cohorts. In line with our findings, ^{15}O-water PET MFR and PET hyperemic MBF was reported to be reduced in 25 patients with SLE or RA compared to controls, but concomitant RP was not mentioned.[27] Similar to our results, a weak inverse correlation between global MFR and AIRD duration, and no significant correlation between inflammatory markers and MFR were reported. Importantly, despite the presence of longer RP diagnosis in our SSc group, RP duration was not associated with reduced MFR in univariate analysis, and only SSc diagnosis remained a predictor of low MFR in multivariate models. Neither study identified an association between inflammatory markers and MFR; this could be because of small sample sizes, comorbidities, medication regimens, other uncaptured confounders (e.g., lipid profile), or relatively more advanced stages of vasculopathy without active inflammation.

Mavrogeni, *et al* performed adenosine stress perfusion magnetic resonance imaging (MRI) in 20 patients with secondary RP and compared them to 20 patients with primary

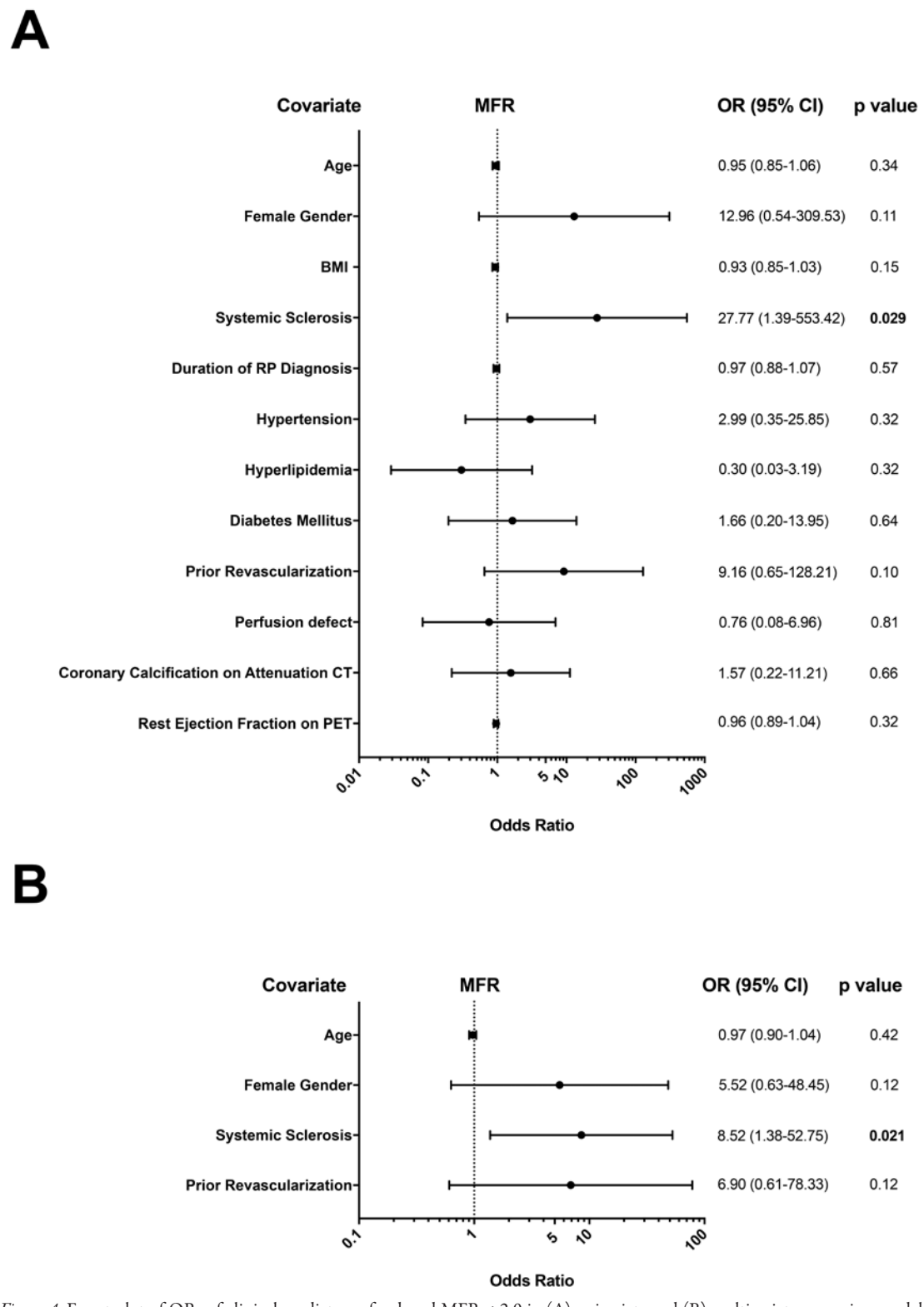


Figure 4. Forest plot of ORs of clinical predictors of reduced MFR < 2.0 in (A) univariate and (B) multivariate regression models. Values in bold are statistically significant. CT: computed tomography; MFR: myocardial flow reserve; PET: positron emission tomography; RP: Raynaud phenomenon.

RP and 20 healthy controls.[28] The authors used the myocardial perfusion reserve index (MPRI) as a marker of myocardial perfusion obtained from first pass contrast-enhanced MRI studies. This marker is similar to ^{82}Rb PET MFR, as it provides an assessment of myocardial perfusion based on kinetic modeling and is calculated as a ratio of stress and rest perfusion metrics. However,

unlike ^{82}Rb PET, it does not provide an absolute MBF estimate. Interestingly, MPRI was significantly reduced in both primary RP (1.7 ± 0.65) and secondary RP (0.7 ± 0.2) when compared to controls (3.5 ± 0.4). A few details can provide explanation for the difference between our findings and those from Mavrogeni, *et al*.[28] First, in head-to-head comparisons, MRI-derived MPRI significantly underestimates MFR when compared to PET MFR. This has been speculated to be related to the low extraction fraction of gadolinium-containing contrast agents and to errors in the estimation of the arterial input function, which is essential for adequate MBF quantification.[29] In addition, the patient population studied by Mavrogeni, *et al*[28] was asymptomatic and significantly younger with shorter RP duration compared to our patient population. By assessing coronary Doppler flow velocities at rest and following adenosine infusion, a small Italian study investigated 27 patients with SSc (22 patients with RP) and found reduced coronary flow velocity reserve when compared to age- and sex-matched healthy controls.[30] This study did not report whether there was any difference in the flow velocity reserves in patients with or without RP, and also did not include patients with primary RP.

Despite being one of the larger studies reporting PET/CT MFR in patients with RP, our single-center, nonrandomized, retrospective study design and within-group small sample sizes carry inherent limitations. Even with controlling for numerous covariables reported to be associated with reduced MFR in the general population (e.g., hypertension, hyperlipidemia, diabetes mellitus), we cannot exclude the possibility of measured or unmeasured confounders affecting our results. Notably, selection bias cannot be excluded because the PET indication was chest pain and shortness of breath in the majority of the patients, many of whom were obese (PET is often used to image obese patients because of better sensitivity and specificity for perfusion defects). The average RP duration was approximately 9 years in our population; thus, our findings may not be applicable to patients with shorter RP duration. In the SSc-RP group, a significantly reduced MFR may indicate higher prevalence of CMVD despite the relatively lower incidence of perfusion defects, although subclinical epicardial disease may be a factor.

In conclusion, our results indicate that in patients with secondary RP, SSc was associated with reduced global PET MFR compared to healthy participants and to patients without RP and AIRD with similar age, sex, BMI, and comorbidities. Thus, SSc may be an independent predictor of reduced MFR. Patients with primary RP had MFR values that were comparable to healthy participants and matched patient controls. Larger prospective studies are warranted to elucidate the prognostic value of MFR in patients with RP.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum 2005;52:402-11.
2. Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in northern Sweden. J Rheumatol 1997;24:445-51.
3. Myllykangas-Luosujärvi R, Aho K, Kautiainen H, Isomäki H. Cardiovascular mortality in women with rheumatoid arthritis. J Rheumatol 1995;22:1065-7.
4. Roman MJ, Shanker BA, Davis A, Lockshin MD, Sammaritano L, Simantov R, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N Engl J Med 2003;349:2399-406.
5. Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr., Jansen-McWilliams L, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham study. Am J Epidemiol 1997;145:408-15.
6. Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76:1897-905.
7. Shah SJ, Mahmood A, Coghlan JG. Cardiac involvement: evaluation and management. In: Varga J, Denton C, Wigley FM, Allanore Y, Kuwana M, eds. Scleroderma: from pathogenesis to comprehensive management. Springer Science + Business, LLC;2017:331-356.
8. Cai X, Luo J, Wei T, Qin W, Wang X, Li X. Risk of cardiovascular involvement in patients with primary Sjögren's syndrome: a large-scale cross-sectional cohort study. Acta Reumatol Port 2019; 44:71-7.
9. Feher A, Sinusas AJ. Quantitative assessment of coronary microvascular function: dynamic single-photon emission computed tomography, positron emission tomography, ultrasound, computed tomography, and magnetic resonance imaging. Circ Cardiovasc Imaging 2017;10:e006427.
10. Murthy VL, Bateman TM, Beanlands RS, Berman DS, Borges-Neto S, Chareonthaitawee P, et al. Clinical quantification of myocardial blood flow using PET: joint position paper of the SNMMI Cardiovascular Council and the ASNC. J Nucl Cardiol 2018;25:269-97.
11. Murthy VL, Lee BC, Sitek A, Naya M, Moody J, Polavarapu V, et al. Comparison and prognostic validation of multiple methods of quantification of myocardial blood flow with 82Rb PET. J Nucl Med 2014;55:1952-8.
12. Feher A, Srivastava A, Quail MA, Boutagy NE, Khanna P, Wilson L, et al. Serial assessment of coronary flow reserve by rubidium-82 positron emission tomography predicts mortality in heart transplant recipients. JACC Cardiovasc Imaging 2020;13:109-20.
13. Tilkemeier PL, Bourque J, Doukky R, Sanghani R, Weinberg RL. ASNC imaging guidelines for nuclear cardiology procedures: standardized reporting of nuclear cardiology procedures. J Nucl Cardiol 2017;24:2064-128.
14. Suter LG, Murabito JM, Felson DT, Fraenkel L. Smoking, alcohol consumption, and Raynaud's phenomenon in middle age. Am J Med 2007;120:264-71.
15. Gelber AC, Wigley FM, Stallings RY, Bone LR, Barker AV, Baylor I, et al. Symptoms of Raynaud's phenomenon in an inner-city African-American community: prevalence and self-reported cardiovascular comorbidity. J Clin Epidemiol 1999;52:441-6.
16. Nietert PJ, Shaftman SR, Silver RM, Wolf BJ, Egan BM, Hunt KJ, et al. Raynaud phenomenon and mortality: 20+ years of follow-up of the Charleston Heart Study cohort. Clin Epidemiol 2015;7:161-8.
17. Koh KK, Kim SH, Lee KH, Kwon KS, Kim EJ, Baik SH, et al. Does prevalence of migraine and Raynaud's phenomenon also increase in Korean patients with proven variant angina? Int J Cardiol 1995;51:37-46.

18. Mizuno R, Fujimoto S, Saito Y, Nakamura S. Cardiac Raynaud's phenomenon induced by cold provocation as a predictor of long-term left ventricular dysfunction and remodelling in systemic sclerosis: 7-year follow-up study. Eur J Heart Fail 2010;12:268-75.
19. Guerraty MA, Rao HS, Anjan VY, Szapary H, Mankoff DA, Pryma DA, et al. The role of resting myocardial blood flow and myocardial blood flow reserve as a predictor of major adverse cardiovascular outcomes. PLoS One 2020;15:e0228931.
20. Kato S, Saito N, Nakachi T, Fukui K, Iwasawa T, Taguri M, et al. Stress perfusion coronary flow reserve versus cardiac magnetic resonance for known or suspected CAD. J Am Coll Cardiol 2017;70:869-79.
21. Dessein PH, Joffe BI, Metz RM, Millar DL, Lawson M, Stanwix AE. Autonomic dysfunction in systemic sclerosis: sympathetic overactivity and instability. Am J Med 1992;93:143-50.
22. Singh I, Oliveira RKF, Naeije R, Oldham WM, Faria-Urbina M, Waxman AB, et al. Systemic vascular distensibility relates to exercise capacity in connective tissue disease. Rheumatology 2021; 60:1429-34.
23. Uren NG, Camici PG, Melin JA, Bol A, de Bruyne B, Radvan J, et al. Effect of aging on myocardial perfusion reserve. J Nucl Med 1995;36:2032-6.
24. Rimoldi O, Rosen SD, Camici PG. The blunting of coronary flow reserve in hypertension with left ventricular hypertrophy is transmural and correlates with systolic blood pressure. J Hypertens 2014;32:2465-71; discussion 2471.
25. Murthy VL, Naya M, Foster CR, Gaber M, Hainer J, Klein J, et al. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. Circulation 2012;126:1858-68.
26. Schindler TH, Cardenas J, Prior JO, Facta AD, Kreissl MC, Zhang XL, et al. Relationship between increasing body weight, insulin resistance, inflammation, adipocytokine leptin, and coronary circulatory function. J Am Coll Cardiol 2006;47:1188-95.
27. Recio-Mayoral A, Mason JC, Kaski JC, Rubens MB, Harari OA, Camici PG. Chronic inflammation and coronary microvascular dysfunction in patients without risk factors for coronary artery disease. Eur Heart J 2009;30:1837-43.
28. Mavrogeni S, Bratis K, Koutsogeorgopoulou L, Karabela G, Savropoulos E, Katsifis G, et al. Myocardial perfusion in peripheral Raynaud's phenomenon. Evaluation using stress cardiovascular magnetic resonance. Int J Cardiol 2017;228:444-8.
29. Ibrahim T, Nekolla SG, Schreiber K, Odaka K, Volz S, Mehilli J, et al. Assessment of coronary flow reserve: comparison between contrast-enhanced magnetic resonance imaging and positron emission tomography. J Am Coll Cardiol 2002;39:864-70.
30. Montisci R, Vacca A, Garau P, Colonna P, Ruscazio M, Passiu G, et al. Detection of early impairment of coronary flow reserve in patients with systemic sclerosis. Ann Rheum Dis 2003;62:890-3.