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

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Abstract

Introduction: Cardiovascular (CV) disease including coronary microvascular dysfunction is the leading cause of morbidity and mortality in patients with autoimmune conditions and may be linked with Raynaud phenomenon (RP). Positron emission tomography/computed tomography (PET/CT) has emerged as the noninvasive gold standard for the evaluation of coronary microvascular function. As such, we sought to determine the prevalence of coronary microvascular dysfunction as assessed by PET/CT-derived coronary flow reserve (MFR) in patients with primary and secondary RP evaluated for dyspnea or chest pain.

Materials and methods: Patients with a diagnosis of RP in the electronic health record who underwent dynamic rest-stress 82-Rubidium PET/CT from 09/2012-09/2019 for evaluation of chest pain or dyspnea were studied. Heart rate-blood pressure product corrected MFR was calculated (Corridor 4DM, INVIA). Patients were grouped based on their comorbid autoimmune condition, and differences in MFR and clinical predictors of reduced MFR (< 2.0) were compared between patients and healthy controls (n=17, 35% female, age: 35 ± 5 years, BMI 27 ± 4kg/m^2).

Results: 49 patients with RP (84% female, age: 65 ± 11 years, BMI: 33 ± 11 kg/m^2) were studied. Of these, 11 had primary RP, 18 had systemic sclerosis (SSc) and 20 had other autoimmune diagnosis (n=6 systemic lupus erythematosus, n=6 rheumatoid arthritis, n=4 overlap syndrome, n=2 Sjogren's syndrome, n=2 inflammatory arthritis). Patients with primary RP had MFR comparable to healthy participants. In patients with

secondary RP, only those with underlying SSc had significantly reduced MFR compared to healthy participants (p=0.002, 1.62 ± 0.32 vs 2.22 ± 0.44). In multivariable logistic regression, SSc was an independent predictor of reduced MFR. In addition, there was a modest significant correlation between time since autoimmune disease diagnosis and MFR (r= -0.37; 95% CI: -0.61 to -0.09; p=0.01). Inflammatory markers (sedimentation rate: r= -0.19, C-reactive protein: r= -0.31) were not significantly associated with MFR (p>0.05).

Conclusions: Our findings suggest that there is reduced PET/CT MFR compared to healthy participants in patients with SSC and secondary RP, and that SSc may be an independent predictor of reduced MFR. Patients with primary RP had MFR values that were comparable to healthy participants. Larger prospective studies are warranted to fully elucidate the prognostic value of MFR in patients with secondary RP.

Key words: myocardial flow reserve, myocardial blood flow, autoimmune disease, positron emission tomography, prognosis, Raynaud phenomenon, microvascular cardiac disease, cardiovascular disease

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Ethics approval and consent to participate: The Yale University Institutional Review Board approved the study (HIC# 2000025019 and 1305012105).

Availability of Data and Material: The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Consent for Publication: Not Applicable.

Authors' Contributions: AF designed the study, collected demographic and outcome data, analyzed the PET studies and participated in writing the manuscript, NB helped with study design, data analysis and writing the manuscript, EKO helped with study design, statistical analysis and writing the manuscript, ST helped with data collection for the healthy individuals and writing the manuscript, YHL helped with data collection and with writing the manuscript, EJM helped with study design and was a major contributor in writing the manuscript, AJS helped with data collection for the healthy individuals and with writing the manuscript, MH designed the study with AF and was the main contributor in writing the manuscript.

Abbreviations

CV=cardiovascular

RP=Raynaud phenomenon

SSc=systemic sclerosis

SLE=systemic lupus erythematosus

RA=rheumatoid arthritis

SS=Sjögren's syndrome

CVD=cardiovascular disease

^{82}Rb=rubidium-82

PET=positron emission tomography

CT=computed tomography

MFR=coronary flow reserve

MVD=microvascular dysfunction

IV=intravenous

miC=millicurie

ECG=electrocardiogram

MBF=myocardial blood flow

LAD=left anterior descending

LCX=left circumflex

RCA=right coronary artery

ANOVA=analysis of variance

CI=confidence interval

AID=autoimmune disease

MRI=magnetic resonance imaging

MPRI=myocardial perfusion reserve index

BMI=body mass index

Introduction:

Raynaud phenomenon (RP) is a vasoactive condition that most commonly occurs in response to cold temperature exposure or stress. During a typical RP attack, the finger color shifts between blue/purple (cyanosis), white (ischemia) and red (hyperemia) (1,2). The currently used classification distinguishes between primary (idiopathic) RP and secondary RP. Primary RP is diagnosed in the absence of underlying associated disease, while secondary RP is diagnosed when RP is associated with a variety of predisposing conditions including rheumatologic conditions [e.g., systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjögren's syndrome (SS)], hematologic and vascular disorders, vibration exposure, hypothyroidism and carpal tunnel syndrome, among others. Primary RP usually presents in adolescent women who demonstrate normal nailfold capillaries and lack ischemic complications, whereas secondary RP develops later, and patients may manifest abnormal nailfold capillaries and concomitant ischemia-induced injury (e.g., digital pitting, digital ulcers and acroosteolysis).

Many rheumatic diseases are independent risk factors for cardiovascular disease (CVD). In fact, CVD lifetime risk is significantly higher in patients with RA (3-5), SLE (6,7), SSc (8,9) and SS (10) compared to the general population. This increased CVD risk is likely due to the synergy of traditional risk factors accentuated by autoimmune disease (AID)-associated cardiac involvement, systemic inflammation, side effects of

medications used to treat rheumatic diseases such as glucocorticoids and cyclophosphamide, and the sedentary lifestyle adopted by many patients with arthritis due to pain and/or depression. Therefore, better techniques to determine which patients with rheumatic disease have subclinical CVD either alone or with concomitant AID cardiac involvement, are needed to provide early diagnosis and potentially improved outcomes through targeted therapies.

Positron emission tomography/computed tomography (PET/CT) with the perfusion tracer rubidium-82 (^{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 to be the noninvasive gold standard for the evaluation of coronary microvascular function (11). This technique uses kinetic modeling to generate estimates of absolute global and regional myocardial blood flow **(Fig. 1).** This quantitative methodology has been extensively validated and has robust prognostic literature (12).

The coronary microvasculature consists of intramural vessels derived from the epicardial vasculature with an intraluminal diameter <500μm. In the absence of epicardial coronary artery disease, myocardial flow reserve (MFR) is an indirect measure of cardiac microvascular health and is defined as the ratio of coronary blood flow during pharmacological stress compared to rest, thus the measurement is unitless. The normal value of MFR greatly depends on age and gender, but most investigators consider MFR<2.0 sufficiently abnormal to result in ischemia (11) and <1.5 to be associated with poor outcomes (13).

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

Patient and Methods:

Research participants and PET Imaging Protocol

Patients with a diagnosis of RP (ICD9=443.0 and/or ICD10=173.0) in the electronic health record, who underwent ^{82}Rb PET/CT myocardial perfusion evaluation from November 2012 to November 2019 at Yale New Haven Hospital (New Haven, CT) were enrolled. The Yale University Institutional Review Board approved the single center, retrospective study (HIC# 2000025019 and 1305012105). In addition, 14 healthy volunteers without co-existing medical conditions that underwent ^{82}Rb PET/CT myocardial perfusion study with regadenoson stress between years 2013 and 2016 were also included for comparison.

Dynamic rest-stress ^{82}Rb PET myocardial perfusion imaging was performed on a hybrid PET 64-slice CT scanner (Discovery 690, GE Healthcare) as previously described (14). Briefly, dynamic rest PET/CT images were acquired after intravenous (IV) injection of 23 ± 4 millicuries (mCi) of ^{82}Rb. After the rest PET scan, patients underwent pharmacological stress with regadenoson (n=42), adenosine (n=5) or dobutamine (n=1) based on clinical indications. Regadenoson was administered as a bolus (0.4mg over 40 seconds), and adenosine (140 μg/kg/min) and dobutamine (maximum rate 40 μg/kg/min) were given as continuous infusions. 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, at 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 (Ann Arbor, MI). Regional and global rest and peak stress myocardial blood flow (MBF) were calculated by fitting the ^{82}Rb time-activity curves to a one-compartment tracer kinetic model as described previously (14). Rest and stress flows were corrected for the rate pressure product (heart rate x 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). MFR was calculated as the ratio of stress to rest MBF (**Fig. 1**).

Statistical Analyses

Differences between dichotomous and categorical variables were assessed using Fisher's exact and Chi-square tests, respectively. Continuous variables were compared using a 2-tailed t-test for normally distributed data. Non-normally distributed continuous variables were compared with Mann-Whitney or Wilcoxon tests for un-matched and matched data, respectively. Analysis of variance (ANOVA) or Kruskal-Wallis test with multiple comparisons was used to compare the difference among more than two groups for normally and non-normally distributed variables, respectively. Pearson correlation (ESR and CRP) or Spearman correlation coefficient (RP diagnosis date) with 95% confidence interval (CI) was used to evaluate the correlation between dependent variables of interest with MFR. In box and whiskers graphs, the boxes represent the 25th to 75th percentiles, the midlines represent the median values, and the whiskers indicate minimal and maximal values. Including variables known to affect myocardial blood flow (14), a binary logistic regression analysis was performed to

identify independent predictors of reduced MFR (MFR < 2.0). All statistical analyses were performed using SPSS (Microsoft Inc, College Station, TX), and statistical significance was defined as $p < 0.05$ for all analyses unless otherwise noted.

Results:

Research participants

Forty-nine RP patients and 14 healthy participants underwent rest and stress ^{82}Rb PET between November 2012 and November 2019. The baseline clinical characteristics are depicted in **Table 1.** The majority of patients with underlying AID were women while 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 due to AID distinct from SSc, and 18 patients had RP secondary to SSc. As for comorbidities and medications, patients with primary RP were more likely to have a history of prior revascularization and less likely to be on hydroxychloroquine, the groups were otherwise not significantly different.

Positron emission tomography/computed tomography

Imaging characteristic for research participants are shown in **Table 2**. The indication for the PET/CT was chest pain in 59%, shortness of breath in 40% and other indications in 12% of the patients [including peri-operative risk stratification (n=3), syncope (n=2) or work-up for unexplained cardiomyopathy (n=1)]. The most frequently used stressor was regadenoson (88%). Perfusion defects were found in less than one third of the patients, whereas coronary calcification was frequent (59%). There was no significant difference in the proportion of patients with perfusion defects or coronary calcification across groups. There was a weak, but significant inverse correlation between MFR values and the time interval between RP diagnosis and PET/CT (**Fig. 2A**), whereas there was no significant correlation between MFR and sedimentation rate (Fig. 2B, data available in n=35 secondary RP patients) or C-reactive protein levels (Fig.

2C, data available in n=29 secondary RP patients). There was no correlation between MFR and the age at the time of PET/CT (r= 0.06, 95% CI: -0.22 to 0.34, p= 0.66) or MFR and body mass index (BMI), (r= 0.19, 95% CI: -0.10 to 0.44, p= 0.20).

There was no difference in global rest MBF among the groups, but global stress MBF was significantly lower in all patient groups when compared to controls (**Fig. 3A**). Global MFR was significantly lower in patients with RP and SSc (1.62 ± 0.32) when compared to healthy controls (2.22 ± 0.44) **(Fig. 3C**). Global MFR was reduced (<2.0) in 89% of patients with RP and SSc. Patients with RP and other autoimmune disease (AID) (1.85 ± 0.67) as well as patients with primary RP (2.14 ± 0.69) showed no significant difference in MFR when compared to controls. Regional MFR was reduced in all three vessel territories [left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA)] in SSc patients (**Supplementary Figure**). Patients with other AID had reduced MFR in the LAD, but not in other vascular territories, whereas MFR was not significantly different in any of the vascular territories in primary RP patients. In the binary logistic regression model, SSc diagnosis was the only independent predictor of reduced MFR (**Fig. 4**).

Out of 49 patients, five patients underwent left heart catheterization within 100 days of PET/CT perfusion imaging. Among these, two patients had obstructive coronary artery disease, one underwent percutaneous coronary intervention (global MFR: 1.14), whereas the other person's coronary anatomy was not amenable for revascularization (global MFR: 1.43). The remaining three patients had no evidence of coronary artery disease (global MFR values for patients: 1.31, 1.52 and 1.53).

Discussion

We identified patients in our electronic health record with a diagnosis of RP as well as 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 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. Our study results showed no significant correlation between inflammatory markers and RP, which might be explained by the relatively small sample size.

Prior studies – cardiovascular risk in Raynaud phenomenon

Although increased CVD risk in well known to be higher in patients with AID, it has been incompletely characterized in patients with RP. A study of the Framingham Offspring Cohort with over 3400 participants, of whom 113 reported RP, found a positive association of primary RP and CVD defined as a history of angina, coronary insufficiency, myocardial infarction, congestive heart failure, intermittent claudication, stroke, or transient ischemic attack with an odds ratio of 1.69 (95% confidence interval 1.22 - 2.34) (15). Other population-based studies indicate that RP may be associated with increased CVD risk especially in Caucasians (16,17), however these studies did not distinguish between primary and secondary RP patients. A small prospective Korean cohort 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 via technetium-99m-labeled red blood cell radionuclide angiography. In this study, the 20 patients with

angiographically proven coronary artery spasm did not report more RP nor demonstrated more significant decrease in digital blood flow in response to cold compared with 30 patients with coronary artery disease and 31 hospitalized control participants without heart disease (18). In a small study examining MBF by myocardial contrast echocardiography in 51 SSc patients, the presence of cardiac RP (cold-induced reversible myocardial ischemia) at baseline in 15 patients was an independent predictor for the development of LV systolic dysfunction (defined as LVEF<50%) during a mean follow-up of seven years (19).

PET myocardial blood flow in RP and systemic sclerosis

To our knowledge our 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. Interestingly, primary RP patients in our study had a non-significantly reduced rest MBF and a significantly reduced stress MBF. We speculate that this finding may indicate that primary RP patients to some extent have baseline hypoperfusion but show adequate proportional response to vasodilators. Previously, limited reports have evaluated PET MFR in a handful of AID patients. In line with our findings, PET MFR and PET hyperemic MBF was reported to be reduced in 25 patients with SLE or RA when compared to controls, but there was no mention of the presence or absence of RP (20). Similar to our results, this study demonstrated a weak inverse correlation between global MFR and AID duration and no significant correlation between inflammatory markers and MFR. It has to be noted, that correlation estimates in both studies could be confounded by presence of co-morbidities and medication regimens.

Assessing myocardial blood flow with other imaging modalities in patients with RP

Mavrogeni et al. performed adenosine stress perfusion magnetic resonance imaging (MRI) in 20 secondary RP patients and compared them to 20 primary RP patients and 20 controls (21). The authors used 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 myocardial blood flow 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. First, in head-to-head comparisons, MRI-derived MPRI significantly underestimates coronary blood flow reserve when compared to PET MFR which 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 (22). In addition, the patient population studied by Mavrogeni et al. was significantly younger with shorter RP duration when 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 when compared to age and sex matched controls (23). 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.

Study limitations

Despite the fact that this was one of the larger studies reporting upon PET MFR in patients with RP to date, this study was a single center, nonrandomized, retrospective study, which carries all the inherent limitations of such a study design. Therefore, we cannot exclude the presence of confounders despite carefully controlling for numerous co-variables reported to be associated with reduced MFR in the general population. In addition, as the indication for the PET was chest pain and shortness of breath in the majority of the patients many of whom were obese (PET is often the selected imaging modality for obese patients due to better sensitivity and specificity for perfusion defects), selection bias cannot be excluded. Our population included patients with long standing RP diagnoses (average duration ~9 years), thus our findings may not be applicable to patients with RP of shorter duration. In addition, the frequent presence of regional perfusion defects and coronary artery calcifications suggest that in addition to microvascular disease, epicardial disease might be responsible for the reduced MFR.

Conclusions

Our results indicate that patients with secondary RP, only SSc was associated with reduced global PET MFR compared to healthy controls. Thus, SSc may be an independent predictor of reduced MFR. Patients with primary RP had MFR values that were comparable to healthy controls. Larger prospective studies are warranted to elucidate the prognostic value of MFR in patients with RP.

Table 1. Baseline Patient Characteristics

Baseline characteristics	Primary RP n=11	RP + Other AID n=20	RP + SSc n=18	P value	Healthy Controls n=14
Age, y	68 (61-77)	62 (57-67)	65 (61-70)	0.24	34 (32-37)
Female sex	5 (45%)	18 (100%)	16 (89%)	<0.001	7 (50%)
BMI, kg/m^2	30 (25-36)	35 (29-41)	32 (28 – 37)	0.43	27 (25-29)
Race				0.15	
Caucasian	11 (100%)	13 (65%)	15 (83%)		
African American	0 (0%)	6 (30%)	2 (11%)		
Other	0 (0%)	1 (5%)	1 (6%)		
Comorbidities					
Prior PCI / CABG	5 (45%)	3 (15%)	0 (0%)	**0.004**	
Prior MI	2 (18%)	1 (5%)	2 (11%)	0.43	
CHF	1 (9%)	4 (20%)	1 (6%)	0.55	
Hypertension	9 (82%)	14 (70%)	11 (61%)	0.57	
Hyperlipidemia	8 (73%)	9 (45%)	9 (50%)	0.39	
Diabetes Mellitus	3 (27%)	3 (15%)	4 (22%)	0.74	
Smoking	1 (9%)	7 (35%)	1 (6%)	0.05	
PAD	2 (18%)	1 (5%)	4 (22%)	0.26	
CKD	0 (0%)	4 (20%)	2 (11%)	0.35	
Medications					
Hydroxychloroquine	0 (0%)	12 (60%)	7 (39%)	**0.003**	
Beta blockers	7 (64%)	10 (50%)	5 (28%)	0.15	
CCB	2 (18%)	8 (40%)	9 (50%)	0.27	
ACE-I / ARB	7 (4%)	6 (14%)	6 (12%)	0.17	
Diuretic	5 (45%)	12 (60%)	8 (44%)	0.62	
Nitrate	1 (9%)	4 (20%)	0 (0%)	0.12	
Aspirin	7 (64%)	6 (30%)	6 (33%)	0.18	
Clopidogrel	2 (18%)	3 (15%)	3 (17%)	1.00	
Statin	7 (64%)	8 (40%)	9 (50%)	0.51	
Anticoagulation	1 (9%)	1 (5%)	6 (33%)	0.06	

Continuous variables are expressed as medians (interquartile ranges), categorical variables are expressed as absolute frequencies (percentages). Abbreviations: RP: Raynaud phenomenon, AID: autoimmune disease, SSc: systemic sclerosis, BMI: body mass index, CAD: coronary artery, PCI: percutaneous coronary intervention, CABG: coronary artery

bypass graft, MI: myocardial infarction, CHF: congestive heart failure, PAD: peripheral arterial disease, CKD: chronic kidney disease, CCB: calcium channel blocker, ACE I/ARB: angiotensin converting enzyme inhibitor/ angiotensin II receptor blocker

Table 2. Imaging Characteristics

Baseline characteristics	Primary RP n=11	RP + Other autoimmune n=20	RP +SSc n=18	P value
Study Indication				
Chest Pain	7 (64%)	13 (65%)	9 (50%)	0.70
SOB	2 (18%)	7 (35%)	11 (61%)	0.07
Hemodynamics				
Rest SBP (mmHg)	139 (129-155)	137 (130-146)	125 (112-141)	0.32
Rest HR (bpm)	68 (63-73)	68 (64-80)	77 (65-85)	0.24
Stress SBP (mmHg)	122 (117-146)	124 (117-135)	119 (112-138)	0.86
Stress HR (bpm)	95 (85-98)	88 (79-107)	91 (83-106)	0.98
Stressor agent				0.14
Regadenoson	10 (91%)	16 (80%)	17 (94%)	
Adenosine	1 (9%)	4 (20%)	0 (0%)	
Dobutamine	0 (0%)	0 (0%)	1 (6%)	
Study results				
Perfusion defects	4 (36%)	6 (30%)	3 (17%)	0.49
Coronary calcium	7 (64%)	10 (50%)	12 (67%)	0.57
Rest LVEF	64 (58-71)	64 (53-69)	66 (54-70)	0.84

Stress LVEF	69 (62-76)	68 (57-74)	70 (61-74)	0.69

Continuous variables are expressed as medians (interquartile ranges), categorical variables are expressed as absolute frequencies (percentages). Abbreviations: RP: Raynaud phenomenon, SSc: systemic sclerosis, SOB: shortness of breath, SBP: systolic blood pressure, HR: heart rate, LVEF: left ventricular ejection fraction

Figure Legends:

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

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

Figure 3. Rest (A) and stress (B) myocardial blood flow (MBF) and coronary flow reserve (MFR, C) in healthy controls, patients with primary Raynaud phenomenon (RP), secondary RP with autoimmune disease (AID) other than systemic sclerosis (SSc) and in patients with SSc.

Figure 4. Forest plot of odds ratios (OR) of clinical predictors of reduced coronary flow reserve (MFR <2.0). BMI: body mass index, RP: Raynaud phenomenon, CT: computed tomography, PET: positron emission tomography, CI: confidence interval.

Supplementary Figure. Regional coronary flow reserves in the LAD (left anterior descending), LCx (left circumflex) and RCA (right coronary) arteries. BMI: body mass index, RP: Raynaud phenomenon, CT: computed tomography, PET: positron emission tomography, CI: confidence interval.

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Figures:

Figure 1

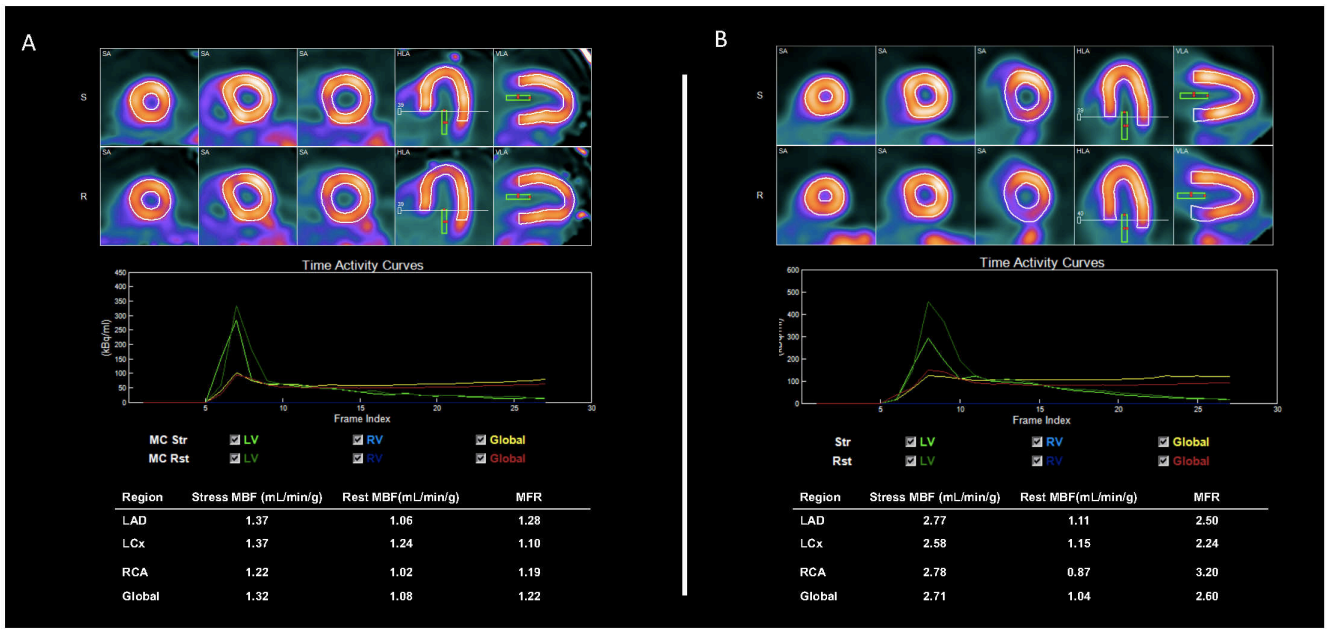


Figure 2

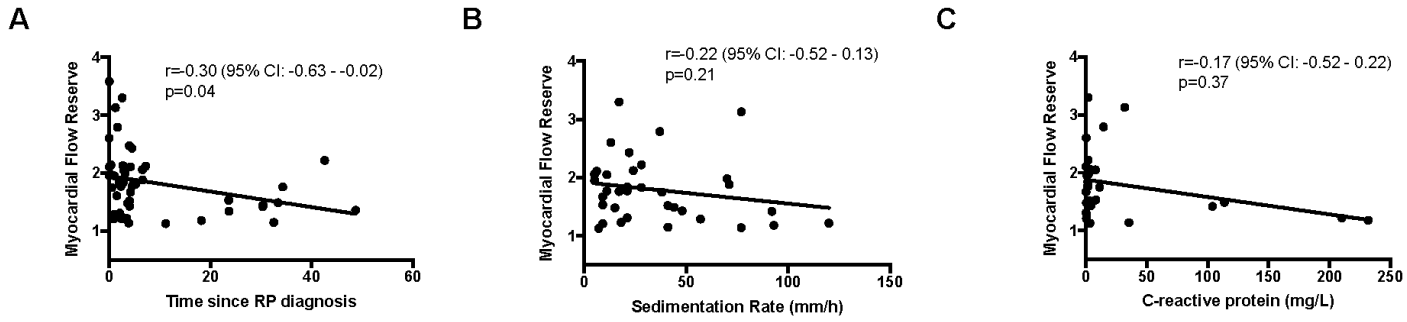

A
r=-0.30 (95% CI: -0.63 - -0.02)
p=0.04
Myocardial Flow Reserve
Time since RP diagnosis
B
r=-0.22 (95% CI: -0.52 - 0.13)
p=0.21
Myocardial Flow Reserve
Sedimentation Rate (mm/h)
C
r=-0.17 (95% CI: -0.52 - 0.22)
p=0.37
Myocardial Flow Reserve
C-reactive protein (mg/L)

Figure 3

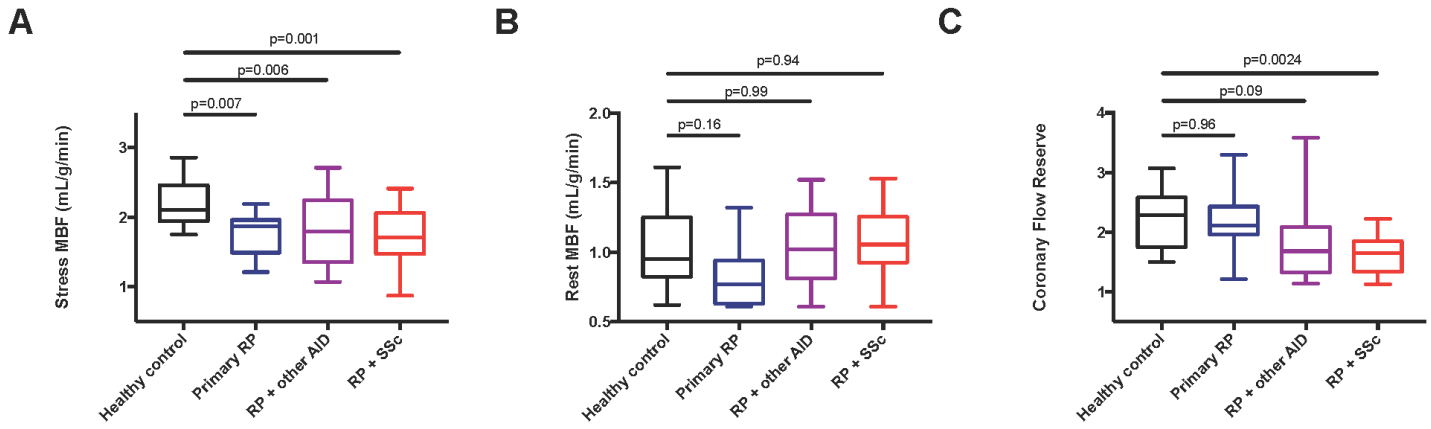
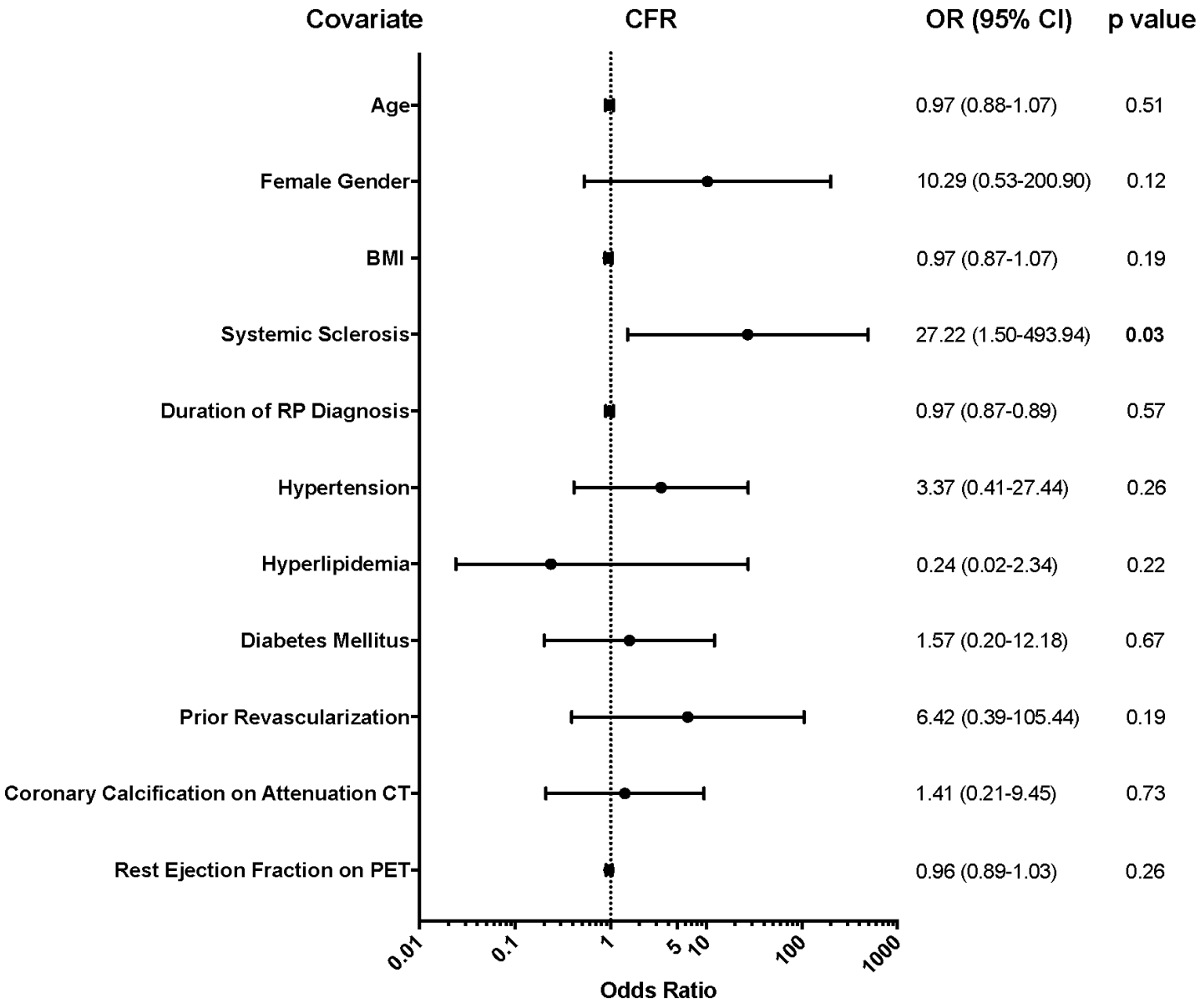
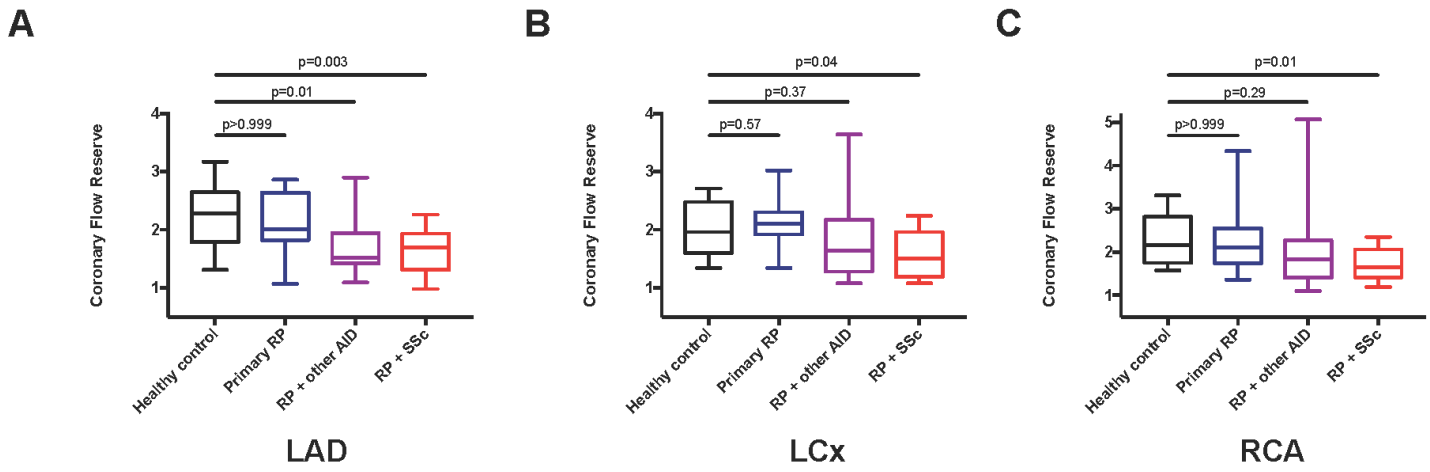

A
p=0.001
p=0.006
p=0.007
Stress MBF (mL/g/min)
3
2
1
Healthy control
Primary RP
RP + other AID
RP + SSc
B
p=0.94
p=0.99
p=0.16
Rest MBF (mL/g/min)
2.0
1.5
1.0
0.5
Healthy control
Primary RP
RP + other AID
RP + SSc
C
p=0.0024
p=0.09
p=0.96
Coronary Flow Reserve
4
3
2
1
Healthy control
Primary RP
RP + other AID
RP + SSc

Figure 4


Covariate
CFR
OR (95% CI)
p value
Age
0.97 (0.88-1.07)
0.51
Female Gender
10.29 (0.53-200.90)
0.12
BMI
0.97 (0.87-1.07)
0.19
Systemic Sclerosis
27.22 (1.50-493.94)
0.03
Duration of RP Diagnosis
0.97 (0.87-0.89)
0.57
Hypertension
3.37 (0.41-27.44)
0.26
Hyperlipidemia
0.24 (0.02-2.34)
0.22
Diabetes Mellitus
1.57 (0.20-12.18)
0.67
Prior Revascularization
6.42 (0.39-105.44)
0.19
Coronary Calcification on Attenuation CT
1.41 (0.21-9.45)
0.73
Rest Ejection Fraction on PET
0.96 (0.89-1.03)
0.26
0.01
0.1
1
5
10
100
1000
Odds Ratio

Supplementary Figure



Figures

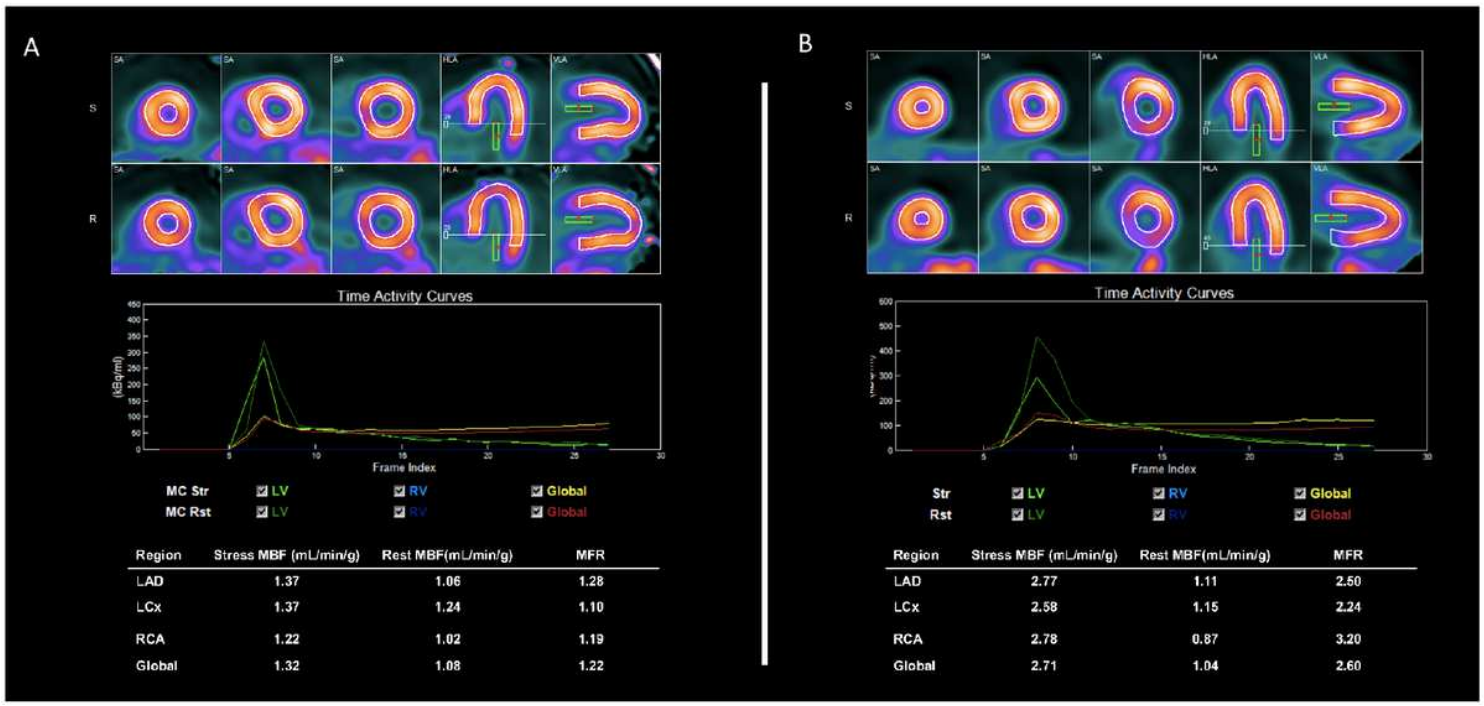


Figure 1

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

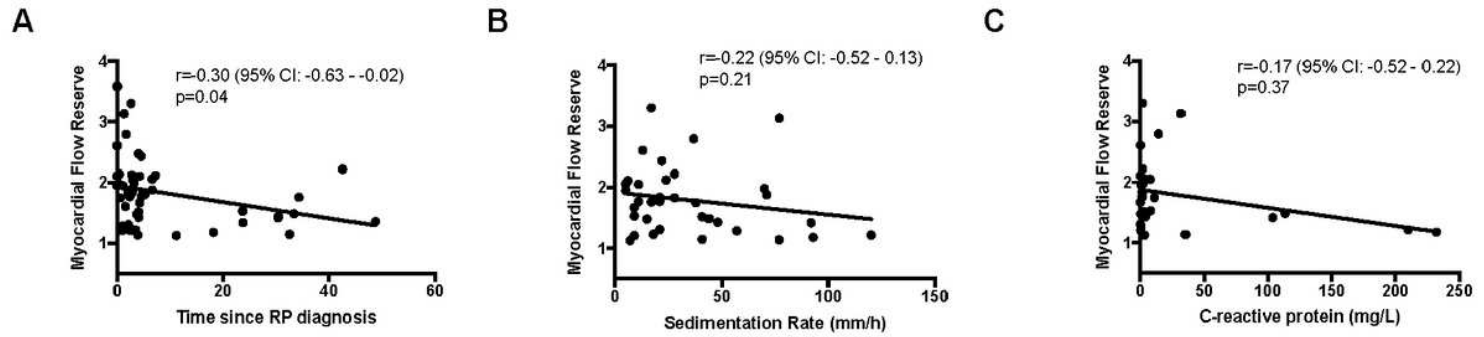


Figure 2

Correlation between coronary flow reserve and time since RP (Raynaud phenomenon) diagnosis (A), sedimentation rate (B) and C-reactive protein levels (C). CI: confidence interval

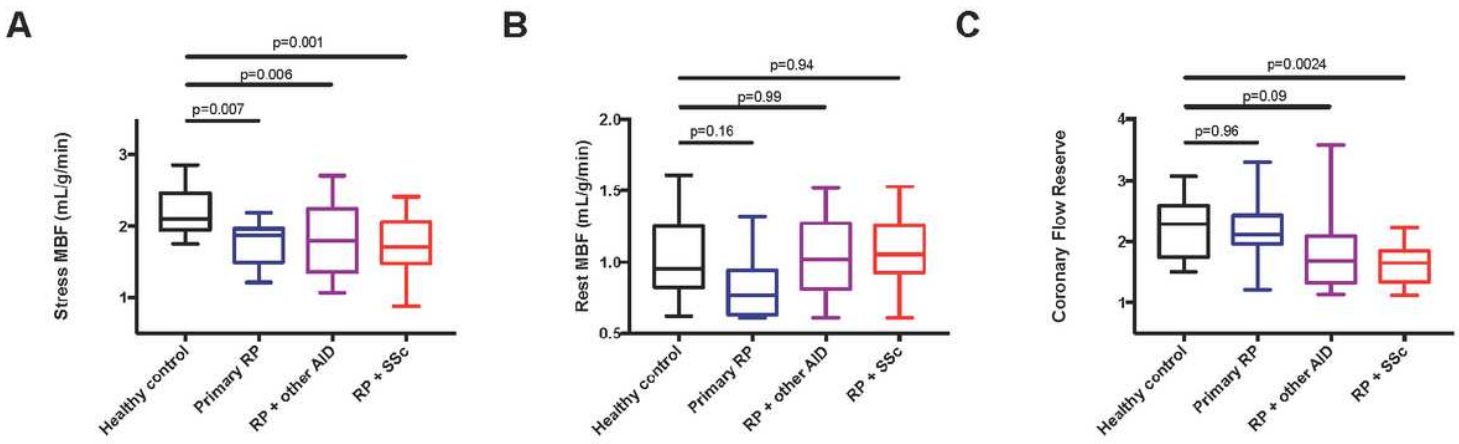


Figure 3

Rest (A) and stress (B) myocardial blood flow (MBF) and coronary flow reserve (MFR, C) in healthy controls, patients with primary Raynaud phenomenon (RP), secondary RP with autoimmune disease (AID) other than systemic sclerosis (SSc) and in patients with SSc.

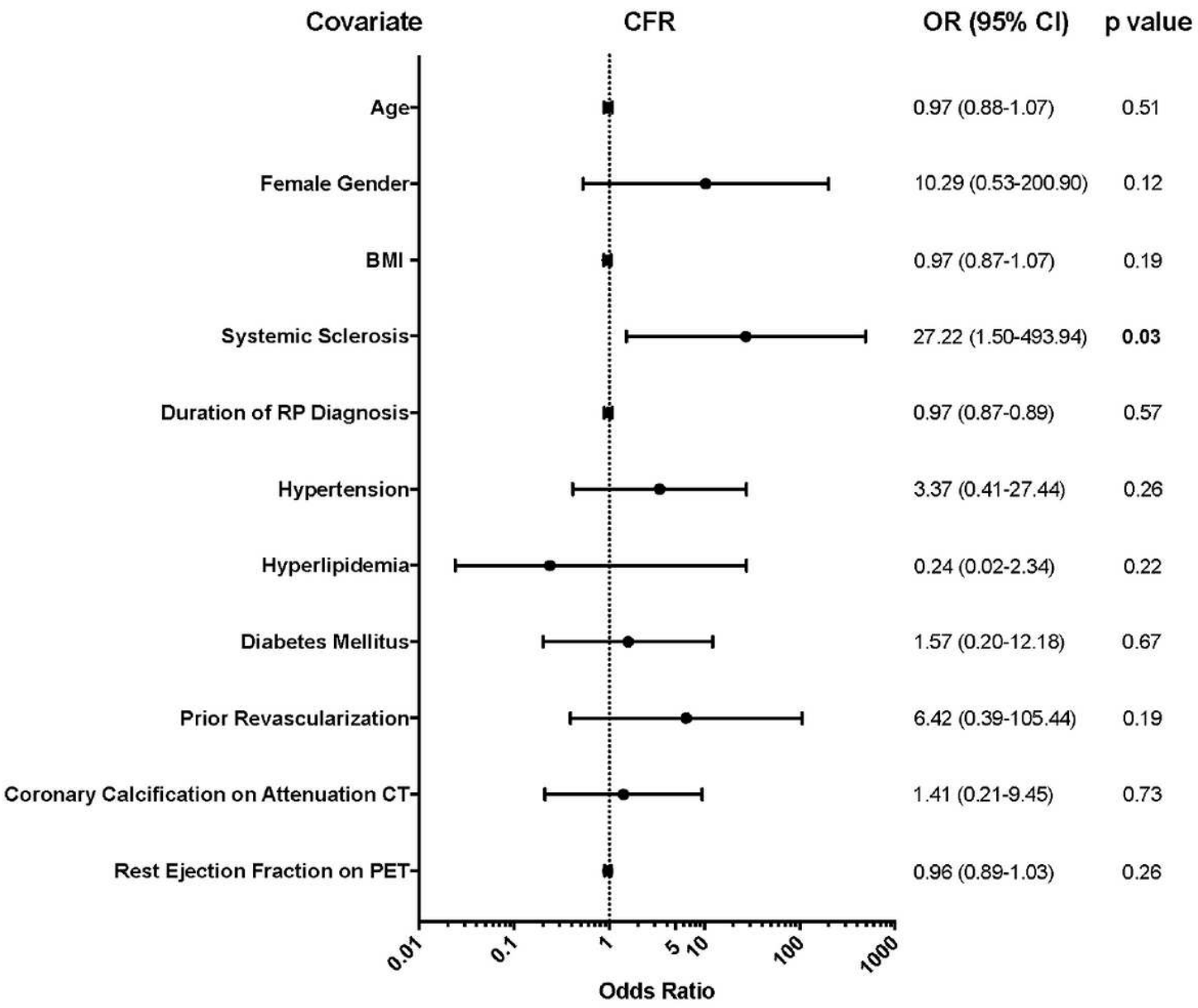


Figure 4

Forest plot of odds ratios (OR) of clinical predictors of reduced coronary flow reserve (MFR <2.0). BMI: body mass index, RP: Raynaud phenomenon, CT: computed tomography, PET: positron emission tomography, CI: confidence interval.

Supplementary Files

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- SupplementalFigure.PNG