Running Head: Scleroderma myocardial flow reserve

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

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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 primary and secondary RP patients and controls.

Methods: RP patients, 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: 49 RP patients (80% female, 65 ± 11 years): 11 primary RP, 18 systemic sclerosis (SSc) and 20 other autoimmune diseases (AID) (n=6 systemic lupus erythematosus, n=6 rheumatoid arthritis, n=4 overlap syndrome, n=2 Sjogren's syndrome, n=2 inflammatory arthritis), 49 matched patients without RP or AID (78% female, 64 ± 13 years) and 14 healthy participants (50% female, 35 ± 5 years) were studied. Primary RP patients, matched patient controls and healthy participants had comparable MFR. SSc-RP patients 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 AID diagnosis and MFR (r= -0.37; 95% CI: -0.61 to -0.09; p=0.01).

Conclusion: Our findings suggest that only secondary, not primary, RP is associated with reduced MFR, and that SSc-RP patients have reduced MFR compared to primary RP and other

autoimmune disease patients. Larger prospective studies are warranted to fully elucidate the prognostic value of MFR in patients with secondary RP.

Abbreviations

CV=cardiovascular

RP=Raynaud phenomenon

AID=autoimmune disease

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=myocardial flow reserve

CMVD=coronary 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

MRI=magnetic resonance imaging

MPRI=myocardial perfusion reserve index

BMI=body mass index

Introduction:

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 diseases (AIDs) [*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. Primary RP usually presents in women who demonstrate normal nailfold capillaries and lack ischemic complications, whereas secondary RP develops later, and abnormal nailfold capillaries and concomitant ischemia-induced injury (*e.g.,* digital pitting, digital ulcers and acro-osteolysis) may be present.

Cardiovascular disease (CVD) lifetime risk is significantly higher in patients with AIDs including RA (1-3), SLE (4, 5), SSc (6, 7) and SS (8) compared to the general population. Increased CVD risk is likely due to the synergy of traditional risk factors accentuated by AID-associated cardiac involvement, systemic inflammation, side effects of medications used to treat AID such as glucocorticoids and cyclophosphamide, and the sedentary lifestyle adopted by many patients with AID due to arthritis, pain and/or depression. Therefore, better techniques to determine which AID patients have subclinical CVD 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 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 (Fig. 1) and has robust prognostic literature (10).

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 myocardial blood flow (MBF) during pharmacological stress compared to rest, thus the measurement is unitless. Normal MFR values greatly depend on age and gender, but most investigators consider MFR<2.0 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.

Patient and Methods:

Research participants and PET Imaging Protocol

Patients with a RP diagnosis (ICD9=443.0 and/or ICD10=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 (New Haven, CT) 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 AID 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 co-existing medical conditions that underwent ^{82}Rb PET/CT myocardial perfusion study with regadenoson stress between years 2013 and 2016 were also included (HIC# 1305012105). In addition, a matched group of 49 Yale New Haven Hospital patients without RP or AID (adjudicated by EHR review), but with risk factors similar to the RP patients and who had also undergone ^{82}Rb PET from 05/2017 – 11/2019 were identified. Using a nearest neighbor matching method (Environment Software (R version 3.4 and R Studio version 1.1.453, MatchIt package version 3.0.4) patients matched for age, gender, body mass index (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, 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; 0.4mg bolus over 40 seconds); 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 PET images attenuation correction. 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). On the study day, one of six 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 1-2, 3-4 or more than 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 one-compartment tracer kinetic model as described (12). 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 mmHg x beats/min). MFR was calculated as the ratio of stress to rest MBF (Fig. 1).

Statistical Analyses

Chi-square tests assessed differences between categorical variables. Analysis of variance (ANOVA) with multiple comparisons (Dunnett's test) or Kruskal-Wallis test with multiple comparisons (Dunn's test) assessed difference among groups for normally and non-normally distributed variables, respectively. Pearson correlation [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] or Spearman correlation coefficient (RP diagnosis date) with 95% confidence interval (CI) was 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 RP patients (primary and secondary). Age and gender were included in the multivariate regression model irrespective of significance. In order to control for coronary artery disease, analyses were repeated excluding patients with medium to large perfusion defects and patients with severe coronary calcifications. Statistical analyses were performed using SPSS (Microsoft Inc, College Station, TX), and statistical significance was defined as $p <0.05$ or as noted.

Results:

Research participants

Forty-nine RP patients, 49 matched patient controls and 14 healthy participants underwent rest and stress ^{82}Rb PET between November 2012 and November 2019. Table 1 presents clinical characteristics. The majority of AID patients 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 (other AID-RP), and 18 patients had RP secondary to SSc (SSc-RP). The RP duration was longer in SSc versus patients with primary RP and other AIDs. Primary RP patients were more likely to have a history of prior coronary artery revascularization and less likely to be on hydroxychloroquine, the groups were otherwise not significantly different. Patients with RP (primary and secondary) were more likely taking hydroxychloroquine and clopidogrel compared to the matched patient controls, but other medication use was otherwise similar. Age, gender, BMI, race and co-morbidities (including prior revascularization) were comparable between the combined RP and the matched patient control groups.

Positron emission tomography/computed tomography

Table 2 presents imaging characteristic 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 [peri-operative risk stratification (n=3), syncope (n=2) or unexplained cardiomyopathy work-up (n=1)]. Regadenoson use was most common (88%) and no participants developed ischemic resultant ECG changes. Perfusion defects and coronary calcifications were found in 27% (similar prevalence in primary RP, SSc-RP, and other AID-RP patients) and 59% of RP patients, 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 AID. Stress systolic blood pressure and rest 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 hemoglobin levels were similar (Table 1). 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 ESR (Fig. 2B and C, data available for 35 and 29 secondary RP patients, 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 body mass index (BMI), (r= 0.19, 95% CI: -0.10 to 0.44, p= 0.20).

Global stress MBF was significantly lower in AID-RP, but not primary RP, patients compared to healthy participants but similar to the matched patient controls (Fig. 3A). Matched patient controls had significantly reduced rest MBF compared to healthy participants (Fig. 3B), but SSc-RP and other AID-RP patients 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) (Fig. 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 that received the stressor regadenoson (Supplementary Fig. 1A). Regional MFR was reduced in the left anterior descending (LAD) and left circumflex (LCX) territories in SSc-RP patients compared to matched patient controls, and in the LAD and right coronary artery (RCA) territories compared to healthy participants (Supplementary Fig. 2). MFR was not significantly different in any of the vascular

territories in primary RP patients or other AID-RP patients compared to healthy participants or matched patient controls. In the binary logistic regression model, SSc diagnosis was the only independent predictor of reduced MFR (Fig. 4). Lower MFR in SSc patients 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 (n=6 RP patients, Supplementary Fig. 1), or excluding patients with medium to large perfusion defects (n=4 RP patients, Supplementary Fig. 3) or excluding patients with severe coronary calcifications (n=10 RP patients, Supplementary Fig. 4).

Out of 49 RP patients, five patients underwent left heart catheterization within 100 days of PET/CT perfusion imaging. Among these, two RP patients had obstructive coronary artery disease, one underwent percutaneous coronary intervention (global MFR: 1.14), whereas the other RP person's coronary anatomy was not amenable for revascularization (global MFR: 1.43). The remaining three RP patients had no evidence of coronary artery disease (global MFR values for patients: 1.31, 1.52 and 1.53). Out of 49 matched patient controls, five patients underwent left heart catheterization within 100 days of PET/CT perfusion imaging. Among these, four matched patient controls had obstructive coronary artery disease, all underwent percutaneous coronary intervention (global MFR values for patients: 1.20, 2.06, 2.13 and 3.03). The remaining one matched patient control had no evidence of obstructive coronary artery disease (global MFR: 1.68).

Discussion

We identified patients in our electronic health record with a diagnosis of RP, a group of patients without RP or AID matched for age, gender, BMI and co-morbidities 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 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.

Prior studies – cardiovascular risk in Raynaud phenomenon

Although increased CVD risk is 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 (3.3%) reported RP (primary or secondary was not delineated), 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) (14). Other population-based studies indicate that RP may be associated with increased CVD risk especially in Caucasians (15, 16); 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 demonstrate 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 (17). 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 (18).

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 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 two mechanisms including 1) increased baseline coronary flow and associated reduced coronary microvascular resistance, or 2) reduced stress MBF due to high microvascular resistance under maximum hyperemia attributed to impaired vasodilation (9). Recent evidence suggests, that decreased MFR in CMVD is often associated with high resting MBF, rather than reduced stress MBF (19, 20), and reduced MFR due to increased rest MBF can be associated with adverse cardiovascular outcomes in patients undergoing myocardial perfusion imaging (19). Similarly, our results indicate that SSc patients 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 via positive chronotropic and positive inotropic effects. This may be supported by the observed higher rest left ventricular ejection fraction in the combined RP patients, when compared to the matched patient control group. On the other hand, anemia and heart failure are unlikely to be responsible for the increased rest MBF in SSc patients, as hemoglobin levels and heart failure diagnosis rates were comparable between the four groups.

The lower resting MBF in the matched patient control group compared to healthy participants could be attributable to prior myocardial infarcts; however, the percentage of patients with any perfusion defects was not significantly different between groups. However, clopidogrel use was significantly higher and prior percutaneous coronary interventions (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 cardiovascular co-morbidities 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 due to concurrent rest MBF reduction.

Previously, limited reports have evaluated PET MFR in small AID 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 AID duration, and no

significant correlation between inflammatory markers and MFR was 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. Both studies did not identify an association between inflammatory markers and MFR that could be due to small sample sizes, co-morbidities, medication regimens, other uncaptured confounders (*e.g*. lipid profile) or relatively more advanced stages of vasculopathy without active inflammation.

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 healthy controls (28). 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, which is essential for adequate MBF quantification (29). In addition, the patient population studied by Mavrogeni et al. was asymptomatic, 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 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.

Study limitations

Despite being one of the larger studies reporting PET MFR in patients with RP, our single center, nonrandomized, retrospective study design and within group small sample sizes carries inherent limitations. Despite carefully controlling for numerous co-variables reported to be associated with reduced MFR in the general population (e.g. hypertension, hyperlipidemia and diabetes mellitus), we cannot exclude the possibility of measured or unmeasured confounders impacting 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 due to better sensitivity and specificity for perfusion defects). The average RP duration was ~9 years in our population, thus our findings may not be applicable to patients with shorter RP duration. In the SSc-RP group, significantly reduced MFR may indicate higher prevalence of CMVD despite the relatively lower incidence of perfusion defects though subclinical epicardial disease may be a factor.

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 AID with similar age, gender, BMI and co-morbidities. 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.

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

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

Figure 4. Forest plot of odds ratios (OR) of clinical predictors of reduced myocardial flow reserve (MFR <2.0) in univariate (A) and multivariate (B) regression models. BMI: body mass index, RP: Raynaud phenomenon, CT: computed tomography, PET: positron emission tomography, CI: confidence interval.

Supplementary Figure 1. Myocardial flow reserve (A) and Forest plot of odds ratios (OR) of clinical predictors of reduced myocardial flow reserve (MFR <2.0) in multivariate models (B) including patients with regadenoson as stressor agent (n=42). Abbreviations as in Figures 3 and 4.

Supplementary Figure 2. Regional myocardial flow reserves in the LAD (left anterior descending), LCx (left circumflex) and RCA (right coronary) arteries. Abbreviations as in Figure 3.

Supplementary Figure 3. Myocardial flow reserve (A) and Forest plot of odds ratios (OR) of clinical predictors of reduced myocardial flow reserve (MFR <2.0) in multivariate models (B) including RP patients without medium to large perfusion defect (n=45). Abbreviations as in Figures 3 and 4.

Supplementary Figure 4. Myocardial flow reserve (A) and Forest plot of odds ratios (OR) of clinical predictors of reduced myocardial flow reserve (MFR <2.0) in multivariate models (B) including patients without severe coronary calcifications (n=39). Abbreviations as in Figures 3 and 4.

Baseline characteristics	Primary RP n=11	Other AID-RP n=20	SSc-RP n=18	P value	All RP n=49	Matched patient controls n=49	P value	Healthy Participants n=14
Age, y	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/m2	30 (25-36)	35 (29-41)	32 (28 – 37)	0.43	30 (25-41)	29 (24-35)	0.25	27 (25-29)
Duration of RP, years	2.8 (0.41-4.0)	2.5 (1.1 – 4.0)	6.0 (3.4-32.8)	0.003		N/A		
Race				0.15			0.09	
Caucasian	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%)	1.00	
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	
Deep vein thrombosis	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								
Hydroxychloroquine	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	
ACE-I / ARB	7 (4%)	6 (14%)	6 (12%)	0.17	19 (39%)	20 (41%)	1.00	
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%)	1.00	
Clopidogrel	2 (18%)	3 (15%)	3 (17%)	1.00	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

Table 2. Imaging Characteristics

Baseline characteristics	Primary RP n=11	Other AID-RP n=20	SSc-RP n=18	P value	All RP n=49	Matched patient controls n=49	P value	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 (interquartile ranges), categorical variables are expressed as absolute frequencies (percentages). Abbreviations: RP: Raynaud phenomenon, SSc: systemic sclerosis, AID: autoimmune disease, SOB: shortness of breath, SBP: systolic blood pressure, HR: heart rate, LVEF: left ventricular ejection fraction.

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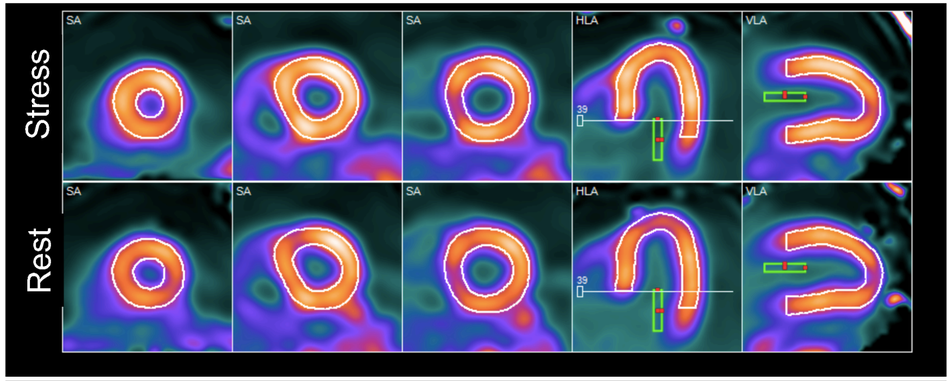
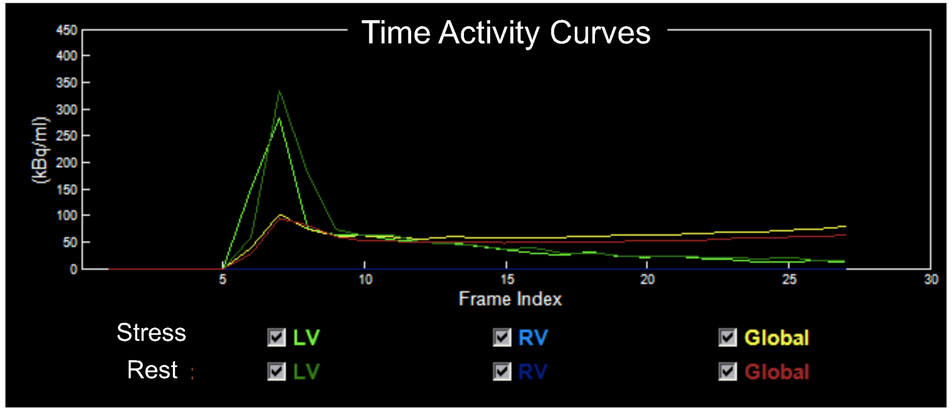
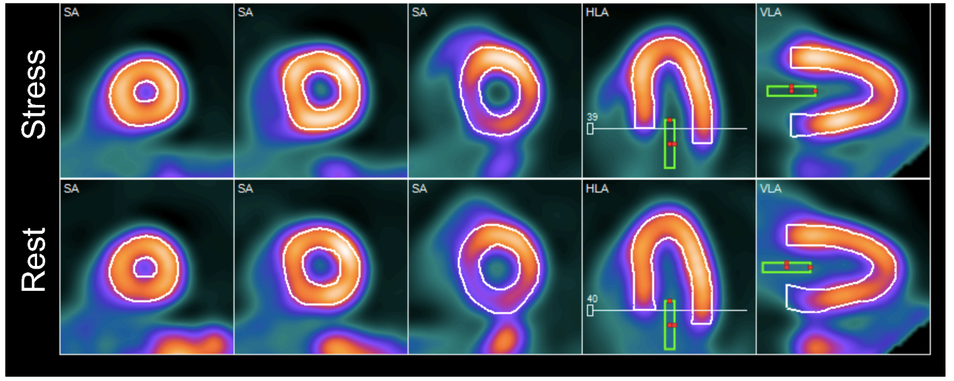
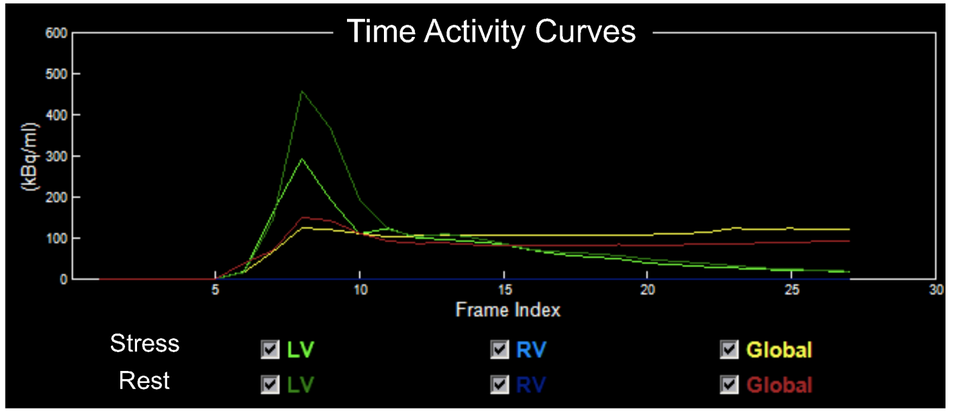




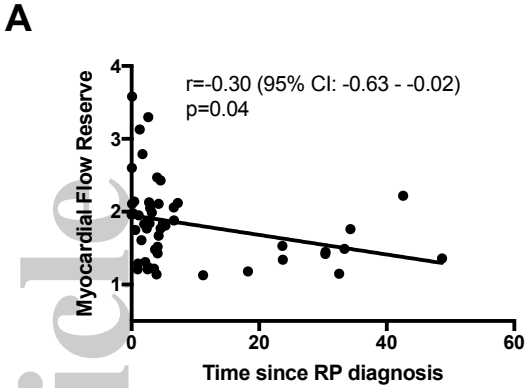
Region	Stress MBF (mL/min/g)	Rest MBF (mL/min/g)	MFR
LAD	1.37	1.06	1.28
LCx	1.37	1.24	1.10
RCA	1.22	1.02	1.19
Global	1.32	1.08	1.22

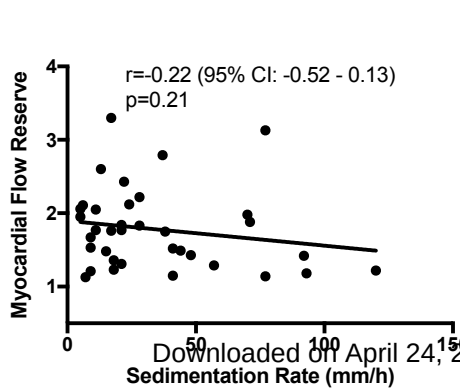
B

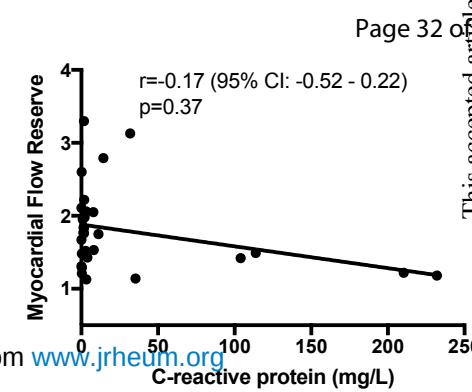


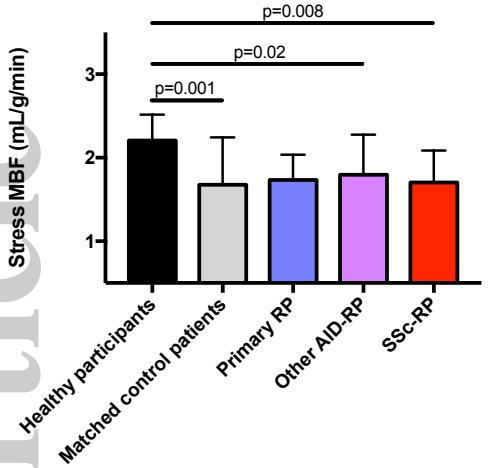


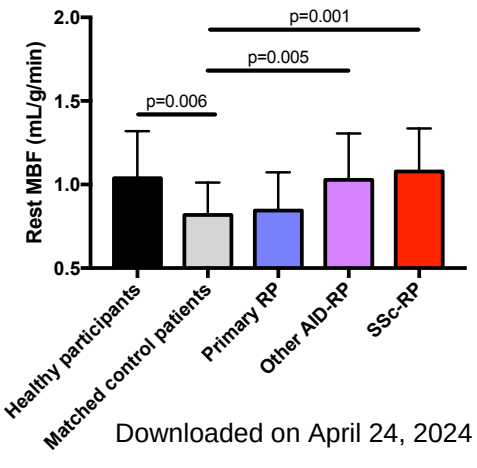
Region	Stress MBF (mL/min/g)	Rest MBF (mL/min/g)	MFR
LAD	2.77	1.11	2.50
LCx	2.58	1.15	2.24
RCA	2.78	0.87	3.20
Global	2.71	1.04	2.60

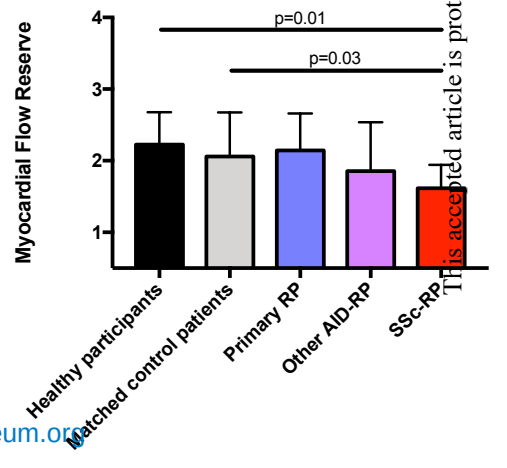












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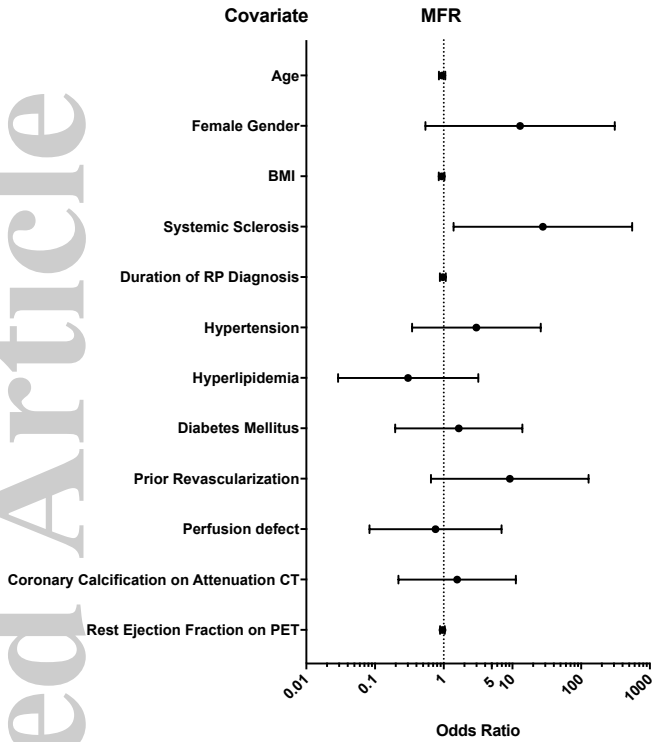

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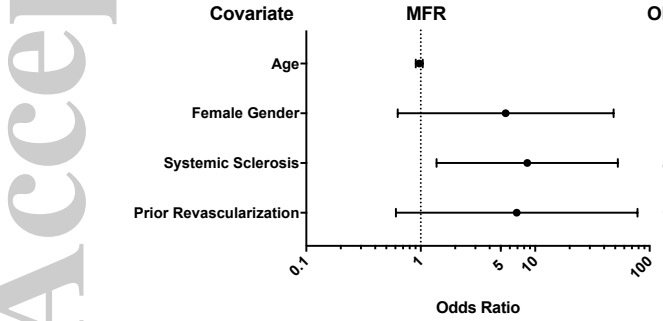


Table 1. Study Cohort Clinical Characteristics

Baseline characteristics	Primary RP n=11	Other AID-RP n=20	SSc-RP n=18	P value	All RP n=49	Matched patient controls n=49	P value	Healthy Participants n=14
Age, y	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/m2	30 (25-36)	35 (29-41)	32 (28 – 37)	0.43	30 (25-41)	29 (24-35)	0.25	27 (25-29)
Duration of RP, years	2.8 (0.41-4.0)	2.5 (1.1 – 4.0)	6.0 (3.4-32.8)	0.003		N/A		
Race				0.15			0.09	
Caucasian	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%)	1.00	
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	
Deep vein thrombosis	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								
Hydroxychloroquine	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	
ACE-I / ARB	7 (4%)	6 (14%)	6 (12%)	0.17	19 (39%)	20 (41%)	1.00	
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%)	1.00	
Clopidogrel	2 (18%)	3 (15%)	3 (17%)	1.00	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

Table 2. Imaging Characteristics

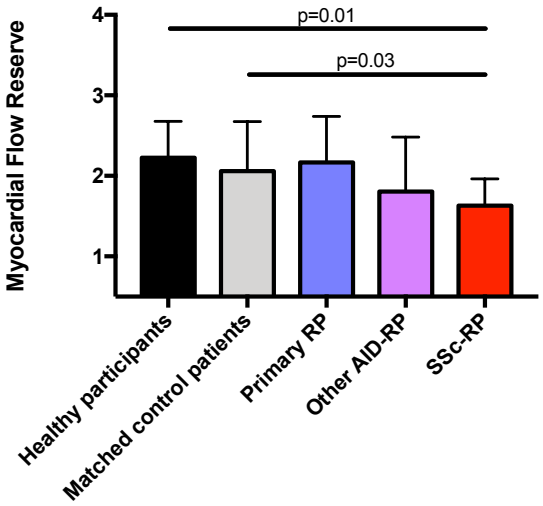
Baseline characteristics	Primary RP n=11	Other AID-RP n=20	SSc-RP n=18	P value	All RP n=49	Matched patient controls n=49	P value	Healthy Participants n=14
Study Indication								
Chest Pain	7 (64%)	13 (65%)	9 (50%)	0.70	29 (59%)	24 (49%)	0.42	
SOB	2 (18%)	7 (35%)	11 (61%)	0.07	20 (41%)	12 (24%)	0.13	
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

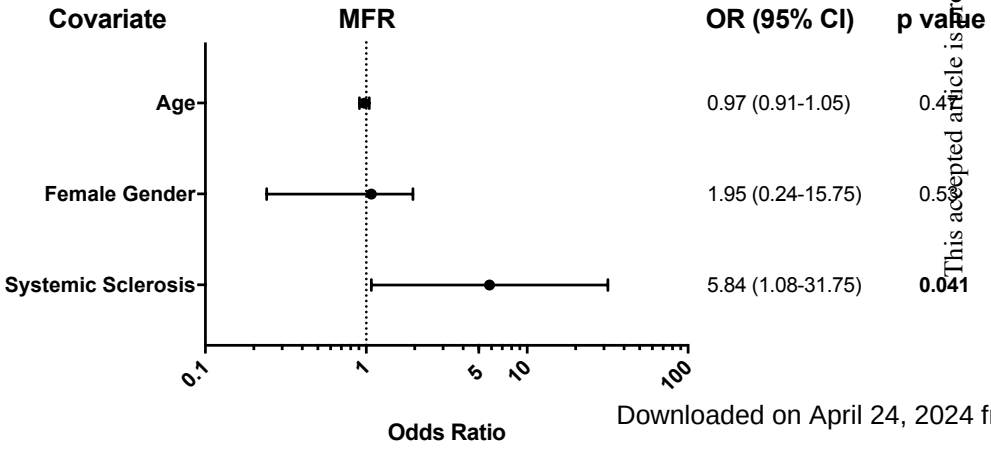
Continuous variables are expressed as medians (interquartile ranges), categorical variables are expressed as absolute frequencies (percentages). Abbreviations: RP: Raynaud phenomenon, SSc: systemic sclerosis, AID: autoimmune disease, SOB: shortness of breath, SBP: systolic blood pressure, HR: heart rate,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

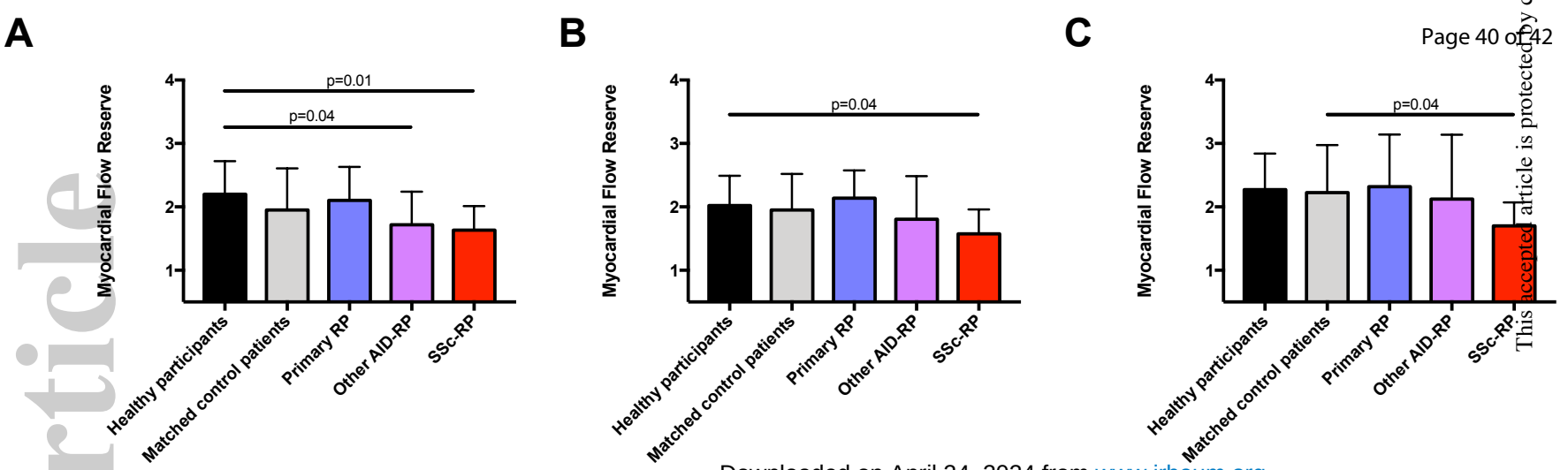
Analysis only including patients with regadenoson as stress agent

A



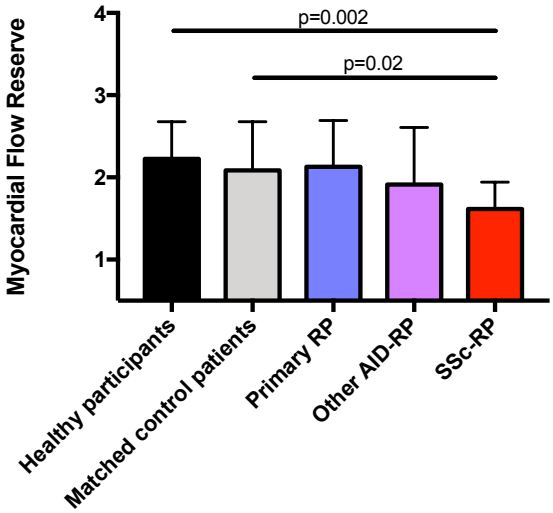
B





Analysis excluding patients with medium to large perfusion defect

A



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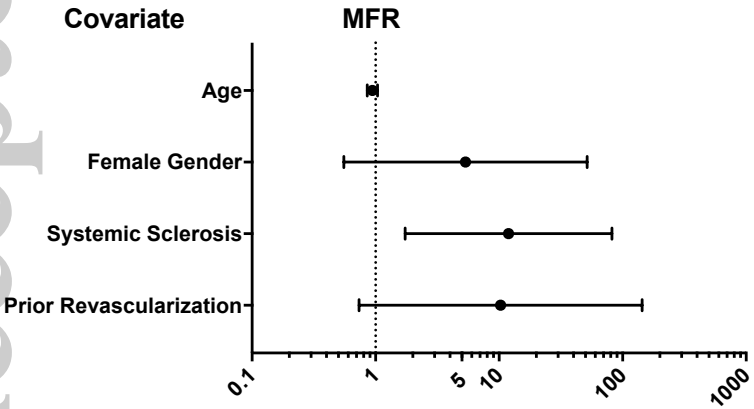
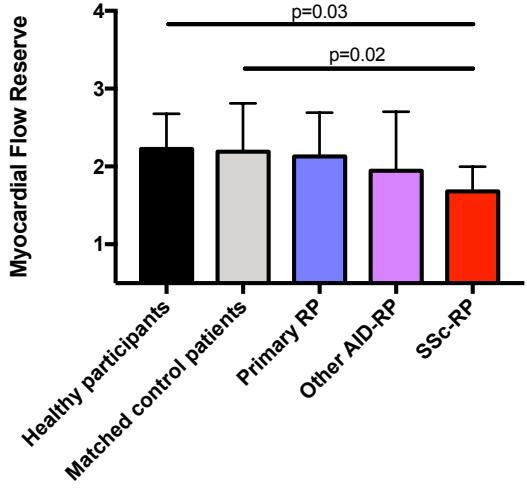


Covariate	OR (95% CI)	p value
Age	0.94 (0.86-1.04)	0.24
Female Gender	5.35 (0.55-51.73)	0.15
Systemic Sclerosis	11.93 (1.74-82.10)	**0.012**
Prior Revascularization	10.29 (0.74-143.90)	0.08

Analysis excluding patients with severe coronary calcification

A



B