JACC: CARDIOVASCULAR IMAGING VOL. ■, NO. ■, 2021
© 2021 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

CLINICAL RESEARCH

Impaired Coronary Vasodilator Reserve and Adverse Prognosis in Patients With Systemic Inflammatory Disorders

Brittany N. Weber, MD, PhD,[a,c] Emma Stevens, BS,[b] Lourdes M. Perez-Chada, MD, MMSc,[e] Jenifer M. Brown, MD,[a,c] Sanjay Divakaran, MD,[a,c] Camden Bay, PhD,[d] Courtney Bibbo, MSc,[c] Jon Hainer, BS,[c] Sharmila Dorbala, MD, MPH,[c] Ron Blankstein, MD,[a,c] Viviany R. Taqueti, MD, MPH,[a,c] Joseph F. Merola, MD, MMSc,[b,e] Elena Massarotti, MD,[b] Karen Costenbader, MD, MPH,[b] Katherine Liao, MD, MPH,[b] Marcelo F. Di Carli, MD[a,c]

ABSTRACT

OBJECTIVES The purpose of this study was to evaluate the prognostic value of quantitative myocardial blood flow (MBF) and myocardial flow reserve (MFR), reflecting the integrated effects of diffuse atherosclerosis and microvascular dysfunction in patients with systemic inflammatory disorders.

BACKGROUND Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriasis (PsO) are common inflammatory conditions with excess cardiovascular (CV) risk compared to the general population. Systemic inflammation perturbs endothelial function and has been linked to coronary vasomotor dysfunction. However, the prognostic significance of this vascular dysfunction is not known.

METHODS This was a retrospective study of patients with RA, SLE, and PsO undergoing clinically indicated rest and stress myocardial perfusion positron emission tomography (PET). Patients with an abnormal myocardial perfusion study or left ventricular dysfunction were excluded. MFR was calculated as the ratio of myocardial blood flow (MBF, ml/min/g) at peak stress compared to that at rest.

RESULTS Among the 198 patients (median age: 65 years; 80% female), 20.7% had SLE, 31.8% had PsO, and 47.5% had RA. There were no differences in mean MFR between these conditions. Over a median follow-up of 7.8 years, there were 51 deaths and 63 major adverse cardiovascular events (MACE). Patients in the lowest tertile (MFR <1.65) had higher all-cause mortality than the highest tertile, which remained significant after adjusting for age, sex, and the pre-test clinical risk score (hazard ratio [HR]: 2.4; 95% confidence interval [CI]: 1.05 to 5.4; $p = 0.038$). Similarly, compared to the highest MFR tertile, those in the lowest tertile had a lower MACE-free survival after adjusting for age, sex, and the pre-test clinical risk score (HR: 3.6; 95% CI: 1.7 to 7.6; $p = 0.001$).

CONCLUSIONS In patients with systemic inflammatory disorders, impaired coronary vasodilator reserve was associated with worse cardiovascular outcomes and all-cause mortality. (J Am Coll Cardiol Img 2021;■:■-■) © 2021 by the American College of Cardiology Foundation.

From the [a]Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [b]Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [c]Cardiovascular Imaging Program, Departments of Medicine and Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [d]Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; and the [e]Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. James Udelson, MD, served as Guest Editor for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received August 5, 2020; revised manuscript received December 11, 2020, accepted December 23, 2020.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2020.12.031

ABBREVIATIONS AND ACRONYMS

ACR = American College Rheumatology

CRP = C-reactive protein

CVA = cerebral vascular accident

MACE = major adverse cardiovascular event(s)

MBF = myocardial blood flow

MFR = myocardial flow reserve

PET = positron emission tomography

PsO = psoriasis

RA = rheumatoid arthritis

SLE = systemic lupus erythematosus

Autoimmune systemic inflammatory diseases are associated with increased cardiovascular risk, including atherosclerosis and myocardial infarction (1-5). Although an increased prevalence of cardiovascular (CV) risk factors has been implicated in systemic inflammatory diseases, these pathophysiologic features provide only a partial explanation for the excess risk of myocardial infarction, heart failure, and death (6-9). Prior work identified the fact that the presence of impaired myocardial flow reserve (MFR) in patients without overt obstructive coronary artery disease (CAD) identified patients at increased risk of adverse cardiac events and improves the ability of models to discriminate patients with elevated CV risk, independent of conventional CV risk factors and stress test scores (10,11). This suggests that diffuse atherosclerosis and coronary microvascular dysfunction play a more important role in the pathophysiologic abnormalities leading to increased risk than previously thought. There is ample laboratory evidence showing that inflammation plays a major role in all stages of atherothrombosis, including the early functional abnormalities in vascular endothelial and smooth muscle cell function (12). There is also increasing in vivo human evidence that increased systemic inflammation is associated with coronary vascular dysfunction (13).

An increased prevalence of coronary vasomotor dysfunction has been identified in patients with autoimmune systemic inflammatory conditions, including psoriasis (PsO), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) (14-19). However, whether impaired coronary vasomotor dysfunction is also associated with adverse cardiac events or mortality in this patient population has not been studied. The objective of this study was to determine the prognostic value of impaired coronary vasodilator reserve in patients with common autoimmune systemic inflammatory diseases (PsO, RA, and SLE).

METHODS

STUDY POPULATION. This retrospective study population included consecutive patients with a diagnosis of PsO, RA, or SLE prior to the date of cardiovascular assessment who underwent cardiac positive emission tomography (PET) for evaluation of CV symptoms (e.g., chest pain or dyspnea, or both) between 2006 and 2019 at the authors' institution. Patient demographics, clinical history, medications, and indications for testing were collected prospectively at the time of PET. The cohort consisted of patients enrolled in the authors' CV PET database using an International Classification of Diseases, ninth or 10th revision, with codes for PsO, RA, or SLE prior to the date of PET (Supplemental Figure 1). All electronic medical records were then independently reviewed by a physician to confirm a diagnosis of PsO, RA, or SLE. Diagnosis of SLE was confirmed based on 1997 updated American College Rheumatology (ACR) criteria (20,21) and further validated by cross-reference with the Brigham and Women's Hospital Rheumatology SLE Registry. Likewise, RA was further confirmed by cross-reference to a validated RA cohort at Brigham and Women's Hospital Rheumatology (22). Patients with left ventricular ejection fraction <50%, an abnormal myocardial perfusion study (summed stress score ≥3), prior coronary artery bypass surgery, or prior heart transplantation were excluded. The study was approved by the Partners Healthcare Institutional Review Board and conducted in accordance with institutional guidelines.

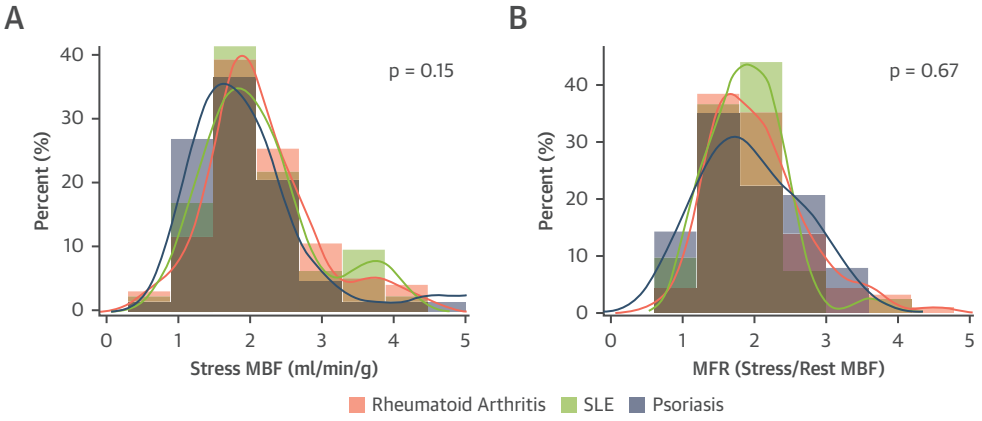
TABLE 1 Baseline Demographics of the Study Cohort

	Total Cohort (N = 198)
Systemic inflammatory disease type	
Systemic lupus erythematosus	41 (20.7)
Psoriasis	63 (31.8)
Rheumatoid arthritis	94 (47.5)
Age at PET, yrs	65.3 ± 11.8
Females	158 (80)
Diabetes	60 (30.3)
Previously known CAD	24 (12.1)
Dyslipidemia	112 (56.6)
Hypertension	149 (75.3)
Family history of CAD	56 (28.3)
Obesity	79 (39.9)
Current tobacco use	9 (4.6)

Values are n (%) or mean ± SD.
CAD = coronary artery disease; PET = positron emission tomography.

QUANTIFICATION OF MYOCARDIAL BLOOD FLOW AND VASODILATOR RESERVE. Myocardial blood flow (MBF) and vasodilator reserve were assessed with quantitative PET imaging using a hybrid whole-body PET-computed tomography (CT) scanner (Discovery RX or STE LightSpeed 64 model; GE Healthcare, Milwaukee, Wisconsin) with nitrogen-13-labeled ammonia or rubidium-82 as flow tracers. Myocardial perfusion images were obtained with the patient at rest and in response to vasodilator stress, as previously described (23,24). Summed

FIGURE 1 Distribution of MFR and Stress MBF in Systemic Inflammatory Disease Within Study Cohort



(A) Overlay histogram demonstrates that the distribution of stress MBF was similar in SLE, RA, and psoriasis patients (p = 0.15). **(B)** Overlay histogram demonstrates that the distribution of MFR was similar in SLE, RA, and psoriasis patients (p = 0.67). MBF = myocardial blood flow; MFR = myocardial flow reserve; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

rest, stress, and differences in scores were computed. Rest and stress left ventricular ejection fraction were calculated from gated myocardial perfusion images with commercially available software (Corridor4DM; Invia Medical Imaging Solutions, Ann Arbor, Michigan). Regional and global rest and stress MBF (ml/min/g) was quantified using a validated tracer kinetic model as previously described (23,24). Regional and global MFR was calculated as the ratio of stress to rest MBF. In the authors' laboratory, the intraclass correlation coefficient for MFR among 4 readers was 0.94 (95% confidence interval [CI]: 0.88 to 0.98) (25), reflecting high reproducibility.

OUTCOMES

For the outcomes of all-cause mortality and first major adverse cardiovascular event (MACE), patients were followed from the time of PET imaging until death, first MACE event, or censoring. Censoring was defined by the time at which medical records were adjudicated if the patient was still actively seen within the Partner's Health Care System or by the last date of follow-up available. MACE was defined as a composite of CV death or hospitalization for nonfatal myocardial infarction, late coronary revascularization, cerebral vascular accident (CVA), or heart failure. All adverse CV events were ascertained >28 days

TABLE 2 Cardiac Stress PET/CT Hemodynamics and Characteristics of the Study Cohort

	All (N = 198)	SLE (n = 41)	Psoriasis (n = 63)	RA (n = 94)	p Value
Resting HR, beats/min	69 (61-78)	70 (63-76)	68 (60-76)	70 (61-80)	0.38
Peak HR, beats/min	86 (78-96)	83 (80-93)	87 (78-93)	87 (77-98)	0.76
Stress SBP, mm Hg	133 (118-155)	133 (117-155)	134 (117-154)	133 (122-156)	0.78
Resting MAP, mm Hg	95.7 (88-107)	91.7 (87-109)	98.0 (87-107)	95.8 (89-107)	0.68
Stress MAP, mm Hg	89.0 (80-100)	90.3 (81-103)	88.3 (80-100)	89.0 (81-100)	0.62
Rest LVEF, %*	62 (55-68)	57 (53-64)	64 (55-72)	62.5 (57-69)	0.005
Stress LVEF, %†	67 (61-74)	65 (56-74)	68 (62-76)	69 (62-72)	0.13
Stress MBF, (ml/min/g)	1.96 (1.6-2.4)	2.01 (1.6-2.4)	1.83 (1.4-2.3)	2.04 (1.7-2.5)	0.15
Rest MBF, (ml/min/g)	1.01 (0.82-1.30)	1.01 (0.88-1.40)	0.99 (0.80-1.30)	1.03 (0.82-1.30)	0.66
MFR	1.87 (1.5-2.3)	1.83 (1.6-2.2)	1.80 (1.4-2.5)	1.93 (1.5-2.3)	0.67

Values are median with interquartile range (25th-75th percentiles). The p values refer to the comparison across the 3 groups of systemic inflammatory disease. *Resting LVEF (%) n = 193. †Stress LVEF (%) n = 190.

HR = heart rate; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; MBF = myocardial blood flow; MFR = myocardial flow reserve; RA = rheumatoid arthritis; SBP = systolic blood pressure; SLE = systemic lupus erythematosus.

TABLE 3 Characteristics of All Autoimmune Systemic Inflammation Disease Patients (SLE, RA, and Psoriasis) by MFR Tertile

	MFR <1.65(n = 66)	1.65 ≤ MFR ≤ 2.19 (n = 66)	MFR >2.19 (n = 66)	p Value
Systemic inflammatory disease type				0.98
SLE	13 (19.7)	15 (22.7)	13 (19.7)	
Psoriasis	20 (30.3)	21 (31.8)	22 (33.3)	
RA	33 (50)	30 (45.5)	30 (47)	
Age at PET, yrs	67.2 ± 12.2	67.1 ± 11.7	60.6 ± 11.5	0.002
Females	55 (83.3)	54 (81.8)	49 (74.2)	0.38
Obesity	25 (37.9)	27 (40.9)	27 (40.9)	0.92
Hypertension	57 (86.4)	50 (75.8)	42 (63.6)	0.01
Dyslipidemia	44 (66.7)	38 (57.6)	30 (45.5)	0.05
Diabetes	26 (39.4)	20 (30.3)	14 (21.2)	0.08
Previously known CAD	9 (13.6)	6 (9.1)	9 (13.6)	0.65
Any tobacco use	3 (4.6)	2 (3)	4 (6)	0.71
Family history of CAD	21 (31.8)	25 (37.8)	10 (15.2)	0.01

Values are n (%) or mean ± SD.

CAD = coronary artery disease; MBF = myocardial blood flow; MFR = myocardial flow reserve; PET = positron emission tomography; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

after the time of cardiac PET scan. Of the 198 patients, 146 had records of clinical follow-up through 2019 in the electronic medical records. The remaining 52 patients had a last clinical record between 2007 and 2018 and were censored at the last date of follow-up within the electronic medical record. Ascertainment of nonfatal myocardial infarction, CVA, or heart failure required a discharge note with a primary hospitalization diagnosis of myocardial infarction, CVA, or heart failure. In addition, only events were included that met the 2018 Fourth Universal Definition of Myocardial Infarction or defined clinical criteria for the presence of symptoms, signs, and escalation of therapy for heart failure, were classified as such (26). Ascertainment of clinical endpoints, including cause of death, was determined by blinded adjudication of the electronic health medical records, Partners HealthCare Research Patient Data Registry, and the National Death Index (27).

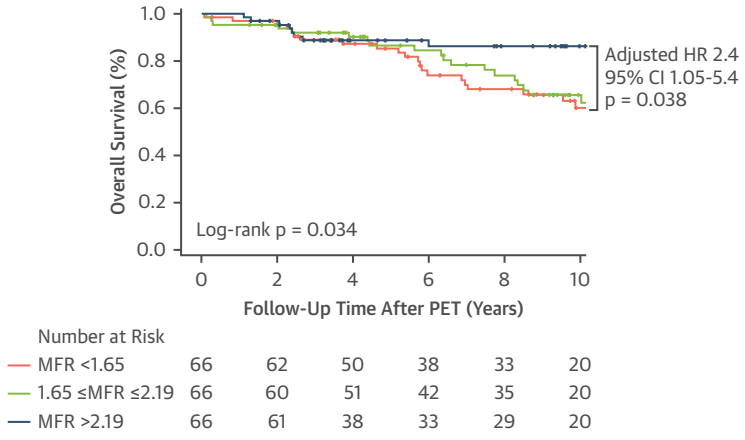
STATISTICAL ANALYSIS. Pearson's chi-squared and 1-way analysis of variance or Kruskal-Wallis was used to evaluate differences in categorical and continuous baseline characteristics, respectively, across the different systemic inflammatory disease and MFR tertiles. The Kruskal-Wallis test, which can be interpreted as an assessment of whether at least 1 distribution in a set of distributions is more likely to produce larger values than the others or not was used when the normality of the observed data was questionable. Categorical variables were reported as frequencies with percentages (%). Continuous variables were expressed as mean ± SD) or median (interquartile range [IQR]). C-reactive protein (CRP) concentration was log transformed, and Pearson's correlation was used to compare the relationship between CRP and MFR. To study the baseline effect of MFR and stress MBF on all-cause mortality and on CV events, univariate Cox proportional hazards modeling was performed for overall survival and survival free from CV events using available covariates. Multivariate adjustment was performed using covariates with known clinical significance or that had significant univariate association with the outcome in question. To avoid overfitting, demographic and medical history variables (age, sex, symptoms, hypertension, diabetes, hyperlipidemia, smoking history, family history of premature CAD, body mass index, and estrogen status) were incorporated into the validated Morise pretest clinical risk score for diagnosing significant CAD (with values 0-8, 9-15, and 16-24, indicating low, intermediate, and high pre-test risk, respectively), as previously described (28,29). Kaplan-Meier curves were constructed by MFR tertiles or stress MBF tertiles to illustrate overall and CV event-free survival. Differences were tested with the log-rank test. Cox proportional hazards models with multivariate adjustment using the previously identified covariates were used to examine the association between events and MFR or stress MBF tertiles. Cox proportional hazards assumptions tests were assessed using graphic methods to verify that proportional hazards assumptions were met. All tests were 2-sided, and a p value of <0.05 was considered statistically significant. Statistical analysis was performed using SAS University Edition 9.4 (SAS, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS OF THE STUDY COHORT. There were 198 patients in this cohort: 41 with SLE (20.7%), 63 with PsO (31.8%), and 94 with RA (47.5%) (Table 1). The mean age was 65.3 years ± 11.8 years, and 80% were female. There was a high prevalence of coronary risk factors including hypertension (75.3%), dyslipidemia (56.6%), diabetes mellitus (30.3%), and obesity (39.9%). Comparison of demographics and coronary risk factor burden among the 3 systemic inflammatory diseases showed that patients with SLE were younger, more likely to be female, and less likely to have diabetes and dyslipidemia than patients with RA or PsO (Supplemental Table 1).

IMPAIRED CORONARY VASODILATOR RESERVE IN SYSTEMIC INFLAMMATORY DISEASE. At rest, MBF was regionally homogeneous and similar across the 3 groups of systemic inflammatory disease conditions.

FIGURE 2 Kaplan-Meier Estimate of Overall Survival



Overall survival for the cohort is presented stratified by MFR tertile. Multivariate analysis adjusted for age, sex and Morise pre-test clinical risk score, which incorporates cardiovascular risk factors (obesity, hypertension, hyperlipidemia, tobacco use, diabetes mellitus), and age, sex, and symptoms. The lowest tertile is compared to the highest tertile (hazard ratio, 2.4; 95% confidence interval: 1.05 to 5.4; p = 0.038).
MFR = myocardial flow reserve; PET = positron emission tomography.

During maximal hyperemia, there was a similar magnitude of flow augmentation (Figure 1A) and resulting MFR (Figure 1B) in RA, SLE, and patients with PsO (Table 2).

The entire cohort was then grouped into tertiles of increasing MFR as follows: low <1.65; intermediate >1.65 and <2.19; and high >2.19 (Table 3). Patients in the lowest MFR tertile were older and more likely to have a history of hypertension. There were no differences in the distribution of RA, SLE, and patients with PsO across the MFR tertiles (Table 3). Disease-specific severity at the time of cardiac PET was not available for the cohort.

However, the authors examined the relationship between serum CRP, a surrogate measurement of systemic inflammation, and MFR in a subgroup of patients with CRP measurements taken within 30 days of the PET scan (n = 33). Although the sample size was small, CRP was negatively correlated with MFR in this subgroup analysis (r = −0.39; p = 0.02) (Supplemental Figure 2), and this remained significant after adjusting for systemic inflammatory disease conditions.

PATIENT OUTCOMES. Over a median follow-up of 7.8 years (IQR: 3.6 to 10.4) after PET, there were 51 deaths from any cause including 14 CV deaths. Compared with the highest tertile, the adjusted HR for all-cause death in the lowest tertile of MFR was 2.4 (95% CI: 1.05 to 5.4; p = 0.038) (Figure 2), whereas the corresponding adjusted HR for stress MBF was 1.4 (CI: 0.7 to 2.9; p = 0.31) (Supplemental Figure 3A). In univariate analysis, MFR but not stress MBF was associated with all-cause death. Similar results were observed in separate multivariate models adjusted for age, sex, and pretest clinical score (Table 4).

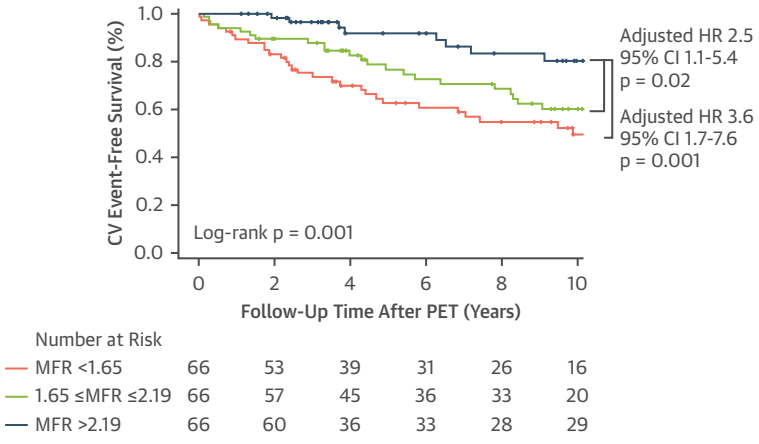
There were 63 MACE events (34 hospitalizations for heart failure, 11 hospitalizations for nonfatal myocardial infarction, 7 hospitalizations for CVA, and 11 CV deaths). Compared with the highest tertile, the adjusted HR for MACE was 3.6 (95% CI: 1.7 to 7.6; p = 0.001) and 2.5 (95% CI: 1.1 to 5.4; p = 0.02) for the lowest and middle tertile of MFR, respectively

TABLE 4 Association Between MFR and Stress MBF and Clinical Outcomes

	Univariate Model HR (95% CI)				Multivariate model HR (95% CI)			
Outcomes	MFR	p Value	Stress MBF	p Value	MFR	p Value	Stress MBF	p Value
All-cause death	1.92 (1.16-3.20)	0.01	1.27 (0.90-1.77)	0.16	1.72 (1.04-2.84)	0.03	1.2 (0.86-1.70)	0.3
MACE	2.3 (1.43-3.70)	<0.001	1.71 (1.20-2.40)	0.002	2.16 (1.40-3.40)	0.001	1.69 (1.20-2.40)	0.002

The multivariate model was adjusted for age, sex, and pre-test clinical score. Myocardial flow reserve (MFR) and stress myocardial blood flow (MBF) were modeled as continuous variables. Hazard ratios (HR) reflect a per unit decrease in MFR or stress MBF.
CI = confidence intervals; MACE = major adverse cardiovascular events.

FIGURE 3 Kaplan-Meier Estimate of CV Event-Free Survival



CV event-free survival for the cohort is stratified by MFR tertile. Multivariate analysis was adjusted for age, sex and the Morise pretest clinical risk score, which incorporates cardiovascular risk factors (obesity, hypertension, hyperlipidemia, tobacco use, and diabetes mellitus), and age, sex and symptoms. Highest tertile is compared with the middle tertile (hazard ratio [HR]: 3.6; 95% confidence interval [CI]: 1.7 to 7.6; p = 0.001), and lowest tertile (HR: 2.5; 95% CI: 1.1 to 5.4; p = 0.02]. CV = cardiovascular; MFR = myocardial flow reserve; PET = positron emission tomography.

(Figure 3). Similar risk stratification in the highest tertile only was observed between tertiles of stress MBF (Supplemental Figure 3B). In univariate analysis, MFR and stress MBF were significantly associated with MACE, and this association persisted in separate multivariate models that similarly included age, sex, and pre-test clinical risk scores (Table 4).

To assess the relative strength of the association between MFR and stress MBF with outcomes, a multivariate model was also tested, including both MFR and stress MBF that was also adjusted for age, sex, and pretest clinical score. In that integrated model, MFR but not stress MBF was associated with MACE (MFR HR: 1.76; 95% CI: 1.03 to 3.01; p = 0.037/U decrease in MFR; stress MBF HR: 1.34; 95% CI: 0.91 to 1.98; p = 0.13/U decrease in stress MBF) and all-cause death (MFR HR: 1.73; 95% CI: 0.98 to 3.1; p = 0.059/U decrease in MFR; and stress MBF HR: 1.0; 95% CI: 0.69 to 1.44; p = 0.99/U decrease in stress MBF).

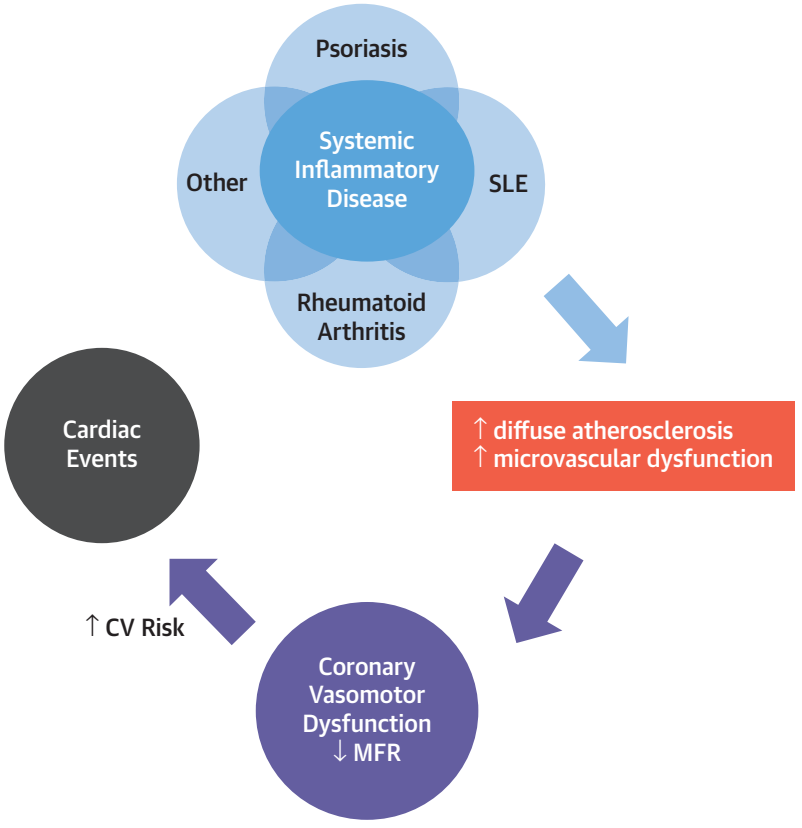
DISCUSSION

Autoimmune systemic inflammatory diseases are associated with coronary vasomotor dysfunction, reflecting a combination of diffuse atherosclerosis in conduit vessels and structural and functional abnormalities in the coronary microcirculation (13-19). The present data extend the previous observations of higher coronary vasodilator dysfunction burden in patients with systemic inflammatory disorders by demonstrating that such vascular dysfunction is associated with adverse outcomes, including death (Central Illustration). These results are novel and support the hypothesis of a link between systemic inflammation, coronary vascular dysfunction and adverse outcomes in this population.

The mechanisms through which measurements of abnormal myocardial flow reserve are associated with adverse outcomes cannot be determined from this study. However, it is possible that high serum levels of proinflammatory cytokines including interleukin (IL)-17, IL-6, interferon-alfa, and tumor necrosis factor, all of which are elevated in systemic inflammatory disorders (30-33), perturb endothelial function and vascular health, resulting in accelerated epicardial atherosclerosis and coronary microvascular dysfunction. Indeed, the inverse association between serum CRP concentration and MFR observed in the subsample of patients in this cohort supports this hypothesis. The authors have recently shown that impaired coronary vasodilator reserve is associated with subclinical injury (34) and abnormalities in cardiac structure and function (29,35,36), and adverse outcomes (29,35,36) in patients without systemic inflammatory disorders. Whether there is 1 common proinflammatory pathway associated with coronary vascular dysfunction in patients with systemic inflammatory disorders is not known.

Dysregulated immune responses, often involving excessive off-target inflammatory activity, are seen in

CENTRAL ILLUSTRATION **Systemic Inflammatory Disease, Coronary Vasodilator Dysfunction and Adverse Outcomes**



Weber, B.N. et al. J Am Coll Cardiol Img. 2021;■(■):■–■.

Systemic inflammatory disorders including psoriasis, SLE, RA, and possible others increase the frequency of impaired coronary vasodilator function, resulting from an increased burden of diffuse atherosclerosis in conduit vessels and coronary microvascular dysfunction. In this study, we observed that the lowest myocardial flow reserve tertile (MFR <1.65) had worse adjusted overall survival and worse adjusted cardiovascular event-free survival in patients with systemic inflammatory disease (SLE, RA, psoriasis). RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

numerous conditions and include common comorbidities such as atherosclerosis and obesity (12,37,38). Given that each systemic inflammatory disease in this study has unique biologic targets and different immunopathobiology, the authors hypothesize that there are probably multiple immune dysregulatory mechanisms that can perturb vascular health, and this is likely context specific. The link between specific immune dysregulation pathways and coronary vascular dysfunction is currently under investigation (e.g., Lipids, Inflammation, and CV Risk in RA; LiiRA [NCT02714881]; and MIcrovascular dysfuNction In Moderate-severe Psoriasis [MINIMA]; NCT04271540). The association between coronary vasodilator dysfunction and outcomes in patients with SLE, RA, and PsO suggest that MFR could be used to identify patients with these diseases who are at risk for adverse CV events (39,40). Excess CV risk in these populations is increasingly becoming recognized. Indeed, the 2019 American College of Cardiology/American Heart Association 10-year CV risk factor guidelines have released updated guidance that systemic inflammatory diseases are considered a "risk enhancer." These new recommendations can be used to stratify patients who are at intermediate risk in whom primary prevention statin therapy is being considered in clinical practice (41).

STUDY LIMITATIONS. Limitations include the lack of validated disease-specific measurements of disease activity for each disease at the time of cardiac PET and the anti-inflammatory treatment history. Although PsO, RA, and SLE are diseases characterized

by systemic inflammation, each disease is distinct and has unique characteristics and immune dysregulation. The small sample size for each disease limits the ability to interpret hard outcomes, including all-cause mortality and MACE, within each disease. However, there were similar values of MFR across the diseases, suggesting that impaired coronary vasodilator reserve is a common finding across each disease state. In addition, it is possible that there was the potential for a small number of missed MACE events that might have occurred outside our health system. Furthermore, the patients in this cohort were commonly clinically referred for symptoms of dyspnea or chest pain, thus likely representing a higher risk population. Whether the present results also apply to the younger patients (<40) with PsO, RA, and SLE without symptoms warrants additional studies. However, even after excluding overt obstructive CAD and left ventricle dysfunction, it was found that patients with systemic inflammatory diseases and impaired MFR had higher all-cause mortality and MACE. In addition, a comparator arm of patients without systemic inflammatory disease was not included in this study as this study was not designed to compare the prevalence of impaired MFR, as this has been previously shown in all 3 diseases (14,15,17-19). However, this study was designed to understand how MFR may be used as a biomarker for further risk stratification of this population. Coronary angiography was infrequent in our patient cohort without regional perfusion defects on PET scanning. However, the blunted stress MBF and MFR are likely a reflection of both coronary microvascular dysfunction and diffuse nonobstructive atherosclerosis. Future studies including coronary CT angiography would be required to decipher the relative role of diffuse nonobstructive atherosclerosis and microvascular dysfunction.

CONCLUSIONS

In conclusion, these findings demonstrate that all 3 of these distinct autoimmune systemic inflammatory disorders may be associated with impaired coronary vasodilator reserve in a subset of patients. When present, this vascular dysfunction was associated with an increased risk of adverse CV outcomes and all-cause mortality.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Supported by National Heart, Lung, and Blood Institute (NHLBI) grant T32 HL094301 (to B.W., S.D.), grant T32 T32HL007604 (J.B.), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) grant K24 AR066109 (to K.C.), National Institutes of Health (NIH) grant K23 HL135438 (to V.T.), and National Heart, Lung, and Blood Institute grant R01HL150342 (to S.D.). Dr. Di Carli receives grants from Gilead Sciences and Spectrum Dynamics; and is a consultant for Janssen and Bayer, outside the submitted work. Dr. Dorbala receives grants from Pfizer and GE Healthcare; and is a consultant for GE Healthcare and Pfizer, outside the submitted work. Dr. Blankstein receives grants from Amgen and Astellas; and is a consultant for Amgen, outside of the submitted work. Dr. Merola receives grants from and is a consultant for Merck, Abbvie, Dermavant, Eli Lilly, Novartis, Janssen, Union Chimique Belge (UCB), Celgene, Sanofi, Regeneron, Arena, Sun Pharma, Biogen, Pfizer, EMD Sorono, Avotres, and Leo Pharma. Dr. Massarotti receives grants from Bristol-Myers Squibb; and is a consultant for UCB and Exagen; and serves on data safety monitoring board for EMD Serono. Dr. Costenbader receives grants from Merck, AstraZeneca, Janssen, and Glaxo Smith Kline; and is a consultant for Merck. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Marcelo F. Di Carli, Brigham and Women's Hospital, ASB-L1 037-C, 75 Francis Street, Boston, Massachusetts 02115, USA. E-mail: mdicarli@bwh.harvard.edu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: There is an increasing recognition of the role of inflammation in CV disease. Patients with systemic inflammatory disease conditions are known to be at elevated CV risk; yet current risk stratification strategies underestimate this risk. Advanced CV imaging techniques can enable early diagnosis, risk stratification, and patient management in patients with suspected or known CVD. Quantification of MBF and flow reserve using PET may serve as a marker of risk and improve risk prediction in patients with systemic inflammatory disease.

TRANSLATIONAL OUTLOOK: The integration of multiparametric imaging approaches, including cardiac PET, into routine clinical practice have become powerful tools for both clinical care and research. MFR by using PET provides a robust and reproducible measurement of the burden of diffuse atherosclerosis and microvascular dysfunction on coronary vasomotor function. There is a need for future studies to investigate the link between specific immune dysregulation pathways and coronary vascular dysfunction and whether inhibition of specific pathways can improve coronary vascular health.

REFERENCES

1. Liao KP. Cardiovascular disease in patients with rheumatoid arthritis. Trends Cardiovasc Med 2017; 27:136–40.

2. Teague H, Mehta NN. The link between inflammatory disorders and coronary heart disease: a look at recent studies and novel drugs in development. Curr Atheroscler Rep 2016;18:3.

3. Liu Y, Kaplan MJ. Cardiovascular disease in systemic lupus erythematosus: an update. Curr Opin Rheumatol 2018;30:441–8.

4. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J 2010;31:1000–6.

5. Skaggs BJ, Hahn BH, McMahon M. Accelerated atherosclerosis in patients with SLE–mechanisms and management. Nat Rev Rheumatol 2012;8: 214–23.

6. Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc 2013;2: e000062.

7. Azfar RS, Seminara NM, Shin DB, Troxel AB, Margolis DJ, Gelfand JM. Increased Risk of Diabetes and Likelihood of Receiving Diabetes Treatment in Patients with Psoriasis. Arch Dermatol 2012;148:995–1000.

8. Petri M, Perez-Gutthann S, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. Am J Med 1992;93:513–9.

9. del Rincón I, Polak JF, O'Leary DH, et al. Systemic inflammation and cardiovascular risk factors predict rapid progression of atherosclerosis in rheumatoid arthritis. Ann Rheum Dis 2015;74: 1118–23.

10. Gupta A, Taqueti VR, van de Hoef TP, et al. Integrated non-invasive physiological assessment of coronary circulatory function and impact on cardiovascular mortality in patients with stable coronary artery disease. Circulation 2017;136: 2325–36.

11. Osborne MT, Bajaj NS, Taqueti VR, et al. Coronary microvascular dysfunction identifies patients at high risk of adverse events across cardiometabolic diseases. J Am Coll Cardiol 2017; 70:2835–7.

12. Libby P, Ridker PM, Hansson GK, Leducq Q. Transatlantic network on atherothrombosis inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol 2009;54: 2129–38.

13. Recio-Mayoral A, Mason JC, Kaski JC, et al. Chronic inflammation and coronary microvascular dysfunction in patients without risk factors for coronary artery disease. Eur Heart J 2009;30: 1837–43.

14. Amigues I, Russo C, Giles JT, et al. Myocardial microvascular dysfunction in rheumatoid arthritis quantitation by 13N-ammonia positron emission tomography/computed tomography. Circ Cardiovasc Imaging 2019;12:e007495.

15. Liao KP, Huang J, He Z, et al. Coronary Microvascular Dysfunction in Rheumatoid Arthritis Compared to Diabetes Mellitus and Association With All-Cause Mortality. Arthritis Care Res (Hoboken) 2021;73:159–65.

16. Zanatta E, Colombo C, D'Amico G, d'Humiéres T, Dal Lin C, Tona F. Inflammation and coronary microvascular dysfunction in autoimmune rheumatic diseases. Int J Mol Sci 2019;20.

17. Ishimori ML, Martin R, Berman DS, et al. Myocardial ischemia in the absence of obstructive coronary artery disease in systemic lupus erythematosus. J Am Coll Cardiol Img 2011;4:27–33.

18. Weber B, Perez-Chada LM, Divakaran S, et al. Coronary microvascular dysfunction in patients with psoriasis. J Nucl Cardiol 2020 May 17 [E-pub ahead of print].

19. Osto E, Piaserico S, Maddalozzo A, et al. Impaired coronary flow reserve in young patients affected by severe psoriasis. Atherosclerosis 2012; 221:113–7.

20. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.

21. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25: 1271–7.

22. Liao KP, Cai T, Gainer V, et al. Electronic medical records for discovery research in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2010;62:1120–7.

23. El Fakhri G, Kardan A, Sitek A, et al. Reproducibility and accuracy of quantitative myocardial blood flow assessment with Rb PET: comparison with (13)N-ammonia PET. J Nucl Med 2009;50: 1062–71.

24. Lortie M, Beanlands RSB, Yoshinaga K, Klein R, Dasilva JN, DeKemp RA. Quantification of myocardial blood flow with 82Rb dynamic PET imaging. Eur J Nucl Med Mol Imaging 2007;34: 1765–74.

25. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. Circulation 2011;124: 2215–24.

26. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol 2018:25285.

27. Hicks Karen A, Tcheng James E, Bozkurt Biykem, et al. 2014 ACC/AHA Key data elements and definitions for cardiovascular endpoint events in clinical trials. Circulation 2015; 132:302–61.

28. Morise AP, Haddad WJ, Beckner D. Development and validation of a clinical score to estimate the probability of coronary artery disease in men and women presenting with suspected coronary disease. Am J Med 1997;102:350–6.

29. Taqueti VR, Solomon SD, Shah AM, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. Eur Heart J 2018;39:840–9.

30. Feldmann M, Brennan FM, Maini R. Cytokines in autoimmune disorders. Int Rev Immunol 1998; 17:217–28.

31. Dean GS, Tyrrell-Price J, Crawley E, Isenberg DA. Cytokines and systemic lupus erythematosus. Ann Rheum Dis 2000;59:243–51.

32. Brembilla NC, Senra L, Boehncke W-H. The IL-17 family of cytokines in psoriasis: IL-17A and beyond. Front Immunol 2018;9:1682.

33. Sidiropoulos PI, Siakka P, Pagonidis K, et al. Sustained improvement of vascular endothelial function during anti-TNFalpha treatment in rheumatoid arthritis patients. Scand J Rheumatol 2009;38:6–10.

34. Taqueti VR, Everett BM, Murthy VL, et al. Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease. Circulation 2015;131: 528–35.

35. Bajaj NS, Singh A, Zhou W, et al. Coronary microvascular dysfunction, left ventricular remodeling, and clinical outcomes in patients with chronic kidney impairment. Circulation 2020;141: 21–33.

36. Zhou W, Brown JM. Hypertensive coronary microvascular dysfunction: a subclinical marker of end organ damage and heart failure. Eur Heart J 2020;41:2366–75.

37. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. Nat Rev Endocrinol 2017;13:633–43.

38. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol 2012;32:2045–51.

39. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377: 1119–31.

40. Tardif J-C, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med 2019;381: 2497–505.

41. Arnett Donna K, Blumenthal Roger S, Albert Michelle A, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;140: e596–646.

KEY WORDS inflammation, microvascular dysfunction, nuclear imaging, PET

APPENDIX For supplemental tables and figures, please see the online version of this paper.