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PET-determined epicardial-microvascular dysfunction and association with cardiovascular events

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TITLE:

PET-determined epicardial-microvascular dysfunction and association with cardiovascular events

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Abstract

Background: To investigate whether a progressive worsening of coronary function from epicardial artery to coronary microcirculation confers worse cardiovascular outcome in cardio-metabolic disease.

Methods: ^{13}N-ammonia positron emission tomography (PET) determined rest and pharmacologic-stress myocardial blood flow (MBF) and correspondingt myocardial flow reserve (MFR) in 329 patients. Normal MFR was defined ≥ 2.0, while abnormal MFR of < 2.0 signified coronary microvascular dysfunction (CMD). Subsequently, was then sub-grouped into classical and endogen type. In addition, an abnormal hyperemic longitudinal MBF gradient (MBF-GRAD) ≥ -0.10 mL/g/min, surrogate for impaired epicardial vasodilation, was determined. Patients were assigned into four following groups: group 1, normal MFR and no MBF-GRAD; group 2, normal MFR and MBF-GRAD; group 3 with classical CMD; and group 4 with endogen CMD. Major adverse cardiovascular events (cardiovascular death (CVD), acute coronary syndrome (ACS), myocardial infarction, percutaneous transluminal coronary angioplasty (PCI), coronary artery bypass grafting (CABG), ischemic stroke, or hospitalization due to HFpEF (H-HFpEF)) were assessed.

Results: During a mean follow-up of 581±288 days, four of group 1 patients H-HFpEF occurred and one patient had a stroke. In group 2, 3, and 4, cardiovascular events occurred in 6 (3 CVD, 1 PCI, and 2 H-HFpEF), 15 (3 CVD, 2 ACS, 5 PCI, 1 CABG, and 5 H-HFpEF), and 2 H-HFpEF, respectively. Patients in group 3 demonstrated a significantly higher incidence of cardiovascular events compared to group 1, 2 and 4, respectively ($p<0.001$ log-rank test).

Conclusions: A progressive worsening of coronary function from epicardial to coronary microcirculation associates with a worse cardiovascular outcome.

Key words: cardio-metabolic risk, coronary microvascular function, myocardial blood flow, myocardial flow reserve, myocardial perfusion, positron emission tomography, prognostication

ABBREVIATIONS

CAD = coronary artery disease

CMD = coronary microvascular dysfunction

CT = computed tomography

HDL = high-density lipoprotein

LDL = low-density lipoprotein

hsCRP = high-sensitivity C-reactive protein

LV = left ventricular

MBF = myocardial blood flow

MFR = myocardial flow reserve

PET = positron emission tomography

RPP = rate-pressure product

Introduction

Normal functional responses of the coronary circulation ascertain pivotal and predominantly flow-mediated and thus endothelium-dependent anti-atherosclerotic and antithrombotic effects [1, 2]. Coronary circulatory dysfunction, on the other hand, may precede or accompany obstructive and non-obstructive coronary artery disease (CAD) and it may confer an increased risk for worse clinical outcomes [3-9]. Specific assessment of coronary circulatory function is commonly performed invasively during coronary angiography determining alterations in intracoronary flow velocity in response to acetylcholine-stimulation of endothelial-derived nitric oxide and/or flow-dependent responses of the epicardial artery diameter [1, 10, 11]. Coronary flow increases can also be stimulated by intracoronary administration of smooth muscle-cell-relaxing substances such as papaverine and adenosine identifying and characterizing predominantly endothelium-independent coronary arteriolar function [2, 10]. The invasive nature of coronary angiography, however, does not permit a more widespread clinical application. In this respect, positron emission tomography (PET)-measured myocardial flow reserve (MFR) enables the non-invasive identification and characterization of coronary circulatory dysfunction [2, 3, 5, 12, 13]. Notably, phenotyping of PET-determined CMD into classical type (predominantly related to alterations in hyperemic MBFs) and endogen type (predominantly related to alterations in resting MBF) carries important prognostic information and it provides a farmework for individualized and specific treatment options[1, 4, 14]. In recent years, PET flow measurements of an abnormal decrease in MBF from the base to the apex of the LV during hyperemic flows, a so-called flow gradient, has been established to non-invasively probe downstream hemodynamic effects early functional and/or structural diffuse CAD on coronary flows during hyperemic stimulation [15-18]. In a more recent PET flow study [5], in nearly fifty percent of cardiovascular risk patients with normal global MFR concurrently presented an abnormal hyperemic decrease in longitudinal MBF, indicative of an impairment of flow-mediated

epicardial vasodilation, that may confer an increased risk for cardiovascular events as invasive investigations have previously outlined [19-21].

In this respect, we aimed to investigate whether a progressive worsening of coronary circulatory function expanding from the epicardial artery to the coronary microcirculation is paralleled by increasing risk of developing cardiovascular in a metabolic risk population.

Materials and Methods

Study population

The study population implied 329 symptomatic patients (115 men and 214 women, mean age, 61±13 years) with predominant metabolically unhealthy obesity having a low likelihood of flow-limiting obstructive CAD with widely medically controlled cardiovascular risk factors such as dyslipidemia, arterial hypertension, and/or type 2 diabetes mellitus (Table 1) [22]. These patients were consecutively referred to rest-stress myocardial perfusion and myocardial blood flow (MBF) with ^{13}N-ammonia positron emission tomography/ computed tomography (PET/CT) to evaluate the presence of obstructive CAD and/or CMD between February 2023 and April 2026. The prevalence of the abnormal hyperemic longitudinal MBF among different types of coronary flow regulation in this population was published more recently [5]. For study purpose, only patients with normal rest and pharmacologic-stress ^{13}N-ammonia PET/CT myocardial perfusion images, that widely excluded the presence of hemodynamically significant obstructive CAD, as well as normal wall motion analysis on gated ^{13}N-ammonia PET were included [12, 22]. Screening was conducted by attainable complete history, physical examination, and laboratory analyses. Patients with a history of acute coronary syndrome; myocardial infarction; hypertrophic obstructive and nonobstructive cardiomyopathy; congestive heart failure; malignant hypertension; valvular heart disease; or significant endocrine, hepatic, renal, or inflammatory disease were not included in the study. Vasoactive medications, including calcium-channel blockers, angiotensin converting enzyme inhibitors, statins, long-acting nitrates, and beta-blockers were withheld from the participant at least 24 h before the PET study. All study participants refrained from caffeine-containing beverages for at least 24 h and from smoking for at least 12 h prior to the cardiac PET/CT perfusion-flow study [12, 22].

Ethical approval

The study was approved by the Washington University in St. Louis (No.201812037), and each participant signed a clinical approved informed consent form.

Cardiac ^{13}N-ammonia PET/CT study protocol

After an initial topogram to denote the axial field of view and a low-dose CT scan (120 kV, 30 mA) for attenuation correction, ^{13}N-ammonia PET determined myocardial perfusion and MBF in ml/min/g with serially acquired images (Biograph mCT PET-CT scanner, Siemens Healthineers, Erlangen, Germany) and a two-compartment tracer kinetic model at rest and during regadenoson-induced hyperemia, respectively [12, 22]. PET ten-minutes list mode data acquisition was started immediately after injection of ≈259 MBq and ≈518 MBq ^{13}N-ammonia as a bolus and subsequent infusion of 10 mL saline solution over 30 s (0.33 mL/sec) via infusion pump (e.g. Aitecs Syringe Pump) at rest and during regadenosonon-stimulation of hyperemia (0.4 mg intravenous bolus injection over 10- and 20-seconds interval), respectively [12, 22]. Myocardial perfusion at rest and during pharmacologic-induced hyperemic flow stimulation was analyzed visually on reoriented short-and long-axis myocardial slices and semi quantitatively on the corresponding polar map from the last static 10-min transaxial PET image. Semiquantitative evaluation of ^{13}N-ammonia PET perfusion images was performed with a standard 17-segment model and a five-point grading system by two expert observers. Summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were acquired. Only patients with normal rest-stress myocardial perfusion as defined by a SDS < 2, and normal wall motion on gated PET with a LVEF ≥45% were selected for study analysis [12, 22].

For the quantification of myocardial blood flow in ml/g/min, left ventricular (LV) contours and input function region were acquired automatically with minimal operator intervention using Corridor4DM software (Cardiac; 4DM PET CFR) version 2016 (INVIA Medical

Imaging Solutions, Ann Arbor, MI) [12, 22]. Starting with intravenous ^{13} N-ammonia i.v. injection, serial transaxial emission images were acquired (dynamic frames: 1 × 5 sec, 12 × 10 sec, 4 × 30 sec, 4 × 60 sec, 1 × 120 sec) with PET/CT, and time-activity curves from the first 2 min in concert with a two-compartment tracer kinetic model were used to quantify regional and global MBF in ml/g/min [12, 22]. On the polar map of the last 600-s image set, regions of interest (ROIs) were allocated to the territories of the main three coronary arteries using the 17-segment model. Applying the Corridor4DM software package, MBF was calculated in ml/g/min. Regional MBFs of the LAD, LCx, and RCA territory were averaged on a polar map and the determined mean MBF of the left ventricle was denoted as global MBF. Following, segmental MBF from the mid to mid-distal left ventricular myocardium was assessed from the polar map to denote a MBF difference (ml/g/min) indicative of a longitudinal MBF gradient. Described in more detail, longitudinal MBFs in the mid and mid-distal myocardial segment of the LV corresponding to the vascular territories of the LAD (segments: 7–8 and 13–14), LCx (segments: 11–12 and 16), and RCA (segments: 9–10 and 15) were determined [15]. Basal segments (LAD: 1–2, LCx: 5–6, and RCA: 3–4) and the apical segment (LAD: 17), however, were not considered for this evaluation due to possible count variability caused by the membranous septum, by a certain variability in locating the last apical slice, and by partial volume errors resulting from object size at the apex [15]. Thus, regional longitudinal MBF gradients of the LAD, LCx, and RCA territory were then averaged on a polar map and the computed mean longitudinal MBF gradient of the left ventricle was defined as global longitudinal MBF gradient at rest and during hyperemic MBFs on a patient level. In view of prior PET flow studies [5, 12, 15], the absence of a longitudinal decrease in hyperemic MBF or mild decline within < −0.10 mL/g/min defined the absence of a longitudinal MBF gradient, whereas a value ≥ −0.10 mL/g/min was regarded as sufficient to signify an abnormal hyperemic longitudinal MBF gradient

Heart rate, blood pressure, and a 12-lead electrocardiogram were acquired continuously during each MBF measurement. From the mean heart rate and systolic blood pressure during the first 2 min of each image acquisition, the rate-pressure product (RPP) was derived as an index of cardiac work.

Definitions of coronary microvascular (dys)function and grouping

In view of an expert panel consensus document (iJACC), coronary microvascular function (nCMF) was defined by a MFR of ≥ 2.0, while an abnormal MFR of < 2.0 (predominantly due to decreases in hyperemic MBF) signified the classical type of coronary microvascular dysfunction (CMD), or (predominantly related to increases in resting MBF ≥ 1.0 mL/g/min) denoted the endogen type of CMD [1, 5]. Further, an abnormal hyperemic longitudinal MBF gradient (MBF-GRAD) ≥ -0.10 mL/g/min, as surrogate for impaired epicardial vasodilation, was determined. Subsequently, ppatients were assigned into four following groups: group 1, normal MFR and no MBF-GRAD; group 2, normal MFR and MBF-GRAD; group 3 with classical CMD; and group 4 with endogen CMD.

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Outcomes

Patients chart via EPIC were evaluated retrospectively for the assessment of major adverse cardiovascular events (cardiovascular death, acute coronary syndrome, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, or ischemic stroke or HFpEF hospitalization) cardiovascular events. The date of the last consultation was applied to determine follow-up. Time to first event was evaluated. All information regarding potential cardiovascular events was validated by documentation, including the analysis of repeated coronary angiograms, hospital discharge letters, and hospital chart reviews. Death from any cause was documented. For an event to be classified as admission for nonfatal myocardial infarction, discharge with a primary hospitalization diagnosis of myocardial infarction was required. Acute coronary syndrome was defined as hospitalization due to unstable angina pectoris of Braunwald classification IIB or IIIB. All hospitalization events occurred >30 days following imaging.

Statistical analysis

Data of baseline characteristics, MFR, and cardiovascular events during follow-up are expressed as mean ± SD or n (%). Comparison between groups was performed by the Wilcoxon or the Kruskal-Wallis test for quantitative variables and by the Fisher exact test for qualitative data with Bonferroni after adjusting for multiple comparisons. Cumulative event rates for groups were estimated by the method of Kaplan- Meier by log-rank test. The log-rank test was used for univariate comparisons of groups with no event. Multivariate analysis using Cox regression techniques was applied to evaluate the potential interactions among the entered covariates. The variables included in the model were age, gender, arterial hypertension, dyslipidemia, smoking, diabetes mellitus, positive family history for coronary artery disease, body mass index, C-reactive protein levels, hyperemic longitudinal MBF gradient, and MFR. Medical therapy was not entered into the multivariate model as co-

medication was highly correlated with its indications (cardiovascular risk factors). Results are presented as relative risks with corresponding 95% confidence intervals and p values from Wald's test. Statistical significance was assumed if the null hypothesis could be rejected at the $p \leq 0.05$ level.

RESULTS

Coronary microvascular (dys)function, different types, and clinical characteristics

Table 1 outlines the clinical characteristics and hemodynamic findings for the four groups in a symptomatic cardiometabolic disease population. The prevalence of normal coronary artery function (group 1) in the whole study population was 34%. When regarding the groups with an abnormal function of the coronary artery, the prevalence of normal MFR but an abnormal hyperemic longitudinal MBF gradient (group 2) with 35% was highest, whereas intermediate for the classical type of CMD with 20%, and lowest for the endogen type of CMD (group 4) with 11%, respectively (Table 1). As regards sex, female was more prevalent in group1, group 2, and group 4, while balanced in group 3 (Table 1). Group 3 and group 4 had a higher prevalence of arterial hypertension versus group 1 and group 2. The prevalence of dyslipidemia was highest in group 3, while comparable among the other groups. Interestingly, the prevalence of diabetes mellitus was highest in group 3, followed by group 4, and comparable between groups 1-2. The prevalence of obesity was widely comparable between groups, while it was lowest for morbid obesity in group 2. As regards the prevalence of smoking and a family history for CAD, it was relatively low and similar among groups. Concerning the lipid profile, total cholesterol was highest in group 2, while HDL cholesterol was lowest in group 3. LDL cholesterol, triglycerides, glucose, and HbA_{1c} levels we comparable among groups, but hsCRP levels were highest in group 3. By study definition, MFR values were normal in groups 1 and 2, while significantly reduced in groups 3 and 4 (Table 1). The abnormal decrease in MFR in group 3 and group 4 were related to significant reductions in hyperemic MBFs and elevations in resting MBF, respectively. Concerning the hemodynamic, rest and stress systolic blood pressure and thus also the rate pressure product were highest in group 4, while comparable between groups 1 to 3. This is also reflected by corresponding values of the RPP at rest and during stress stimulation.

Cardiovascular events during follow-up

Cardiovascular events are summarized in Table 2. The mean period of follow-up was 581±288 days. During follow-up, 28 of 329 patients (9%) suffered cardiovascular events. In group 1, four patients were hospitalized due to HFpEF decompensation (H-HFpEF) and one patient experienced a transient ischemic stroke. In groups 2, 3, and 4, cardiovascular events occurred in 6, 15, and 2 patients, respectively ($p \leq 0.0001$, univariate by log-rank test). In group 2, three cardiovascular deaths, one percutaneous coronary intervention, and two H-HFpEF were noted. The highest event rate was observed in group 3 with three cardiovascular deaths, two acute coronary syndromes, five percutaneous coronary intervention, one coronary artery bypass graft, and five H-HFpEF, while the lowest in group 4 with two H-HFpEF. The cumulative proportion of cardiovascular event-free survival among groups 1-4 is demonstrated in Figure 1. Overall, patients in group 3 demonstrated a significantly higher incidence of cardiovascular events compared to group 1, 2 and 4, respectively ($p<0.001$ log-rank test). As regards the occurrence of cardiovascular death only, patients in group 2 and group 3 demonstrated a borderline significant higher incidence of cardiovascular death than in group 1 and 3 ($p \leq 0.056$, log-rank test) (Figure 2).

Determinants of prognosis

Alterations in MFR and hsCRP levels were associated with the occurrence of cardiovascular events during the follow-up on univariate analysis, whereas the hyperemic longitudinal MBF gradient, age, sex, BMI, positive family history for CAD, arterial hypertension, dyslipidemia and diabetes mellitus were not (Table 3). To test whether alterations in MFR were associated with developing cardiovascular events in an independent fashion, a multivariate analysis was conducted. As denoted in Table 3, alterations in MFR were not an independent predictor of future cardiovascular events. In addition, the hyperemic longitudinal MBF gradient, age, sex, smoking, positive family history for CAD, arterial hypertension, dyslipidemia, and diabetes

mellitus did not have a significant effect on the multivariate analysis. Conversely, BMI and hsC-reactive protein levels were independently associated with the occurrence of cardiovascular events. Thus, in the current cardiometabolic risk population, MFR and also hyperemic longitudinal MBF gradient were not independent predictors for a higher risk for the development of cardiovascular events. Furthermore, Table 4 denotes the additional univariate and multivariate analysis implying cardiovascular deaths only. In this sub analysis, on univariate as well as multivariate analysis, hsCRP levels were predictive for a higher risk for cardiovascular death during the follow-up period.

Discussion

The findings of the present study are first of its kind to demonstrate that a progressive worsening of coronary artery function expanding from the epicardial artery to the coronary microcirculation associates with the risk of cardiovascular events in a cardiometabolic risk population during an average follow-up of 581 days. Such observations may agree with previous results of invasive angiographic assessment of coronary artery function [19, 20, 23-25] in cardiovascular risk patients with normal coronary angiogram and/or non-obstructive CAD but extend the latter observations now to phenotyping of the epicardial and coronary microvascular function by PET-determined estimates of MBF responses to hyperemic flow stimulation.

More recently, Mikhail et al [4] demonstrated in 287 patients with normal ^{13}N-ammonia PET/CT pharmacologic stress and rest myocardial perfusion imaging that reductions in global MFR predominantly related to alterations in hyperemic MBFs or classical type of CMD are paralleled with the risk of developing cardiovascular events over a mean follow-up period of 2.52 years in a cardiometabolic risk population. This, however, was not so much the case when global MFR was reduced owing to relative increases in resting but normal stress MBFs or so-called endogen type of CMD[4]. Conversely, in another study conducted by Kadoya et al. [14] assessing coronary microvascular dysfunction phenotypes in 3,317 patients with normal rest and dipyridamole stress ^{82}rubidium PET perfusion images, CMD subtyping was indeed an independent predictor for major cardiovascular events such as all-cause death, nonfatal myocardial infarction, or sustained ventricular arrhythmia during a median follow-up of 8.5 years. Notably, classical CMD conferred the highest risk with a mean hazard ratio of 1.97, while it was a bit less for endogen CMD with 1.71. The reason for these in part discordant outcome observations for the endogen type of CMD between both studies [4, 14] remains uncertain but may be related to differences in numbers of patients, duration of follow-up, and cardiovascular risk profile. Phenotyping of the CMD for more specific cardiovascular

risk assessment is also supported by a seminal report of Sayed et al. [26] conducting a retrospective study in a large cohort of 8131 patients over a mean follow-up of 520 days. And indeed, PET-assessed reductions in stress MBF did confer a greater risk for subsequent ischemic outcomes, whereas relative elevations in resting MBF reflected a greater risk for future death or heart failure hospitalization. Such observations may also stress the importance of not normalizing the global MFR to increases in heart rate and/or systolic blood pressures as it would mask the presence of endogen CMD leading to a suboptimal cardiovascular risk stratification [27]. Gould et al. [28] were first having raised the concept that even subclinical functional and/or structural alterations of the epicardial arterial wall my cause down-stream hemodynamic effects resulting in a longitudinal decrease in hyperemic MBF from the base to the apical direction during hyperemic coronary flow stimulation [12, 15, 16, 29]. Early and subclinical CAD-related functional and/or structural changes may indeed be accompanied by an impairment of flow-mediated epicardial vasodilation. Under such conditions, the resistance to higher coronary flow increases is not balanced by a flow-mediated coronary vasodilation and a progressive proximal-to-distal decline in intracoronary pressure along the epicardial artery may ensue [30], associated relative and mild decrease in longitudinal MBF from the base to the apical segments of the left ventricle [15, 17, 31]. As previous [18, 28] and current investigation put forth, the identification and characterization of the abnormal hyperemic, longitudinal MBF gradient by PET imaging may indeed carry important diagnostic and prognostic information.

There is abundance of evidence that PET-determined normal global MFR confers indeed an improved outcome than compared to those with abnormal reductions in global MFR in non-obstructive as well as in obstructive CAD [6, 7, 9, 32-34]. In the clinical setting, myocardial perfusion PET imaging and quantification of the MFR has emerged as a mainstay for improving the diagnostic yield and prognostication of patients with known and/or suspected CAD. Conversely, a PET-determined normal MFR may not necessarily confer a complete

risk-free warranty period in certain cardiovascular risk individuals [4, 32, 33]. Conceptually, in patients with normal rest-stress PET-determined myocardial perfusion and global MFR, the additional identification of an abnormal hyperemic longitudinal MBF gradient may be of help to unmask a subset of patients at risk for cardiovascular events. Current study findings, albeit small in number, may provide some first evidence that even in the presence of PET-measured normal global MFR, the additional identification of an abnormal hyperemic longitudinal MBF gradient may be associated with a certain risk for future cardiovascular events. Notably, the incidence of cardiovascular events increased with the degree of coronary vasomotor abnormality expanding from the epicardial artery to the microcirculation during pharmacologic stress stimulation. In this direction, invasive investigations have demonstrated [23-25, 35] that early functional abnormalities of the epicardial artery may exist before alteration of the coronary arteriolar vessels may ensue in cardiovascular risk patients. More recent non-invasive PET studies [3, 5, 12] could also demonstrate that functional or structural alterations of the epicardial artery may precede coronary microvascular function ranging between 30% and 50%. Given that an impairment of flow-mediated and thus endothelium-dependent epicardial vasodilation may be predictive of future cardiovascular events [35], a PET-determined abnormal hyperemic longitudinal MBF gradient could reflect indeed a mechanistic link between early functional and/or structural alterations of the epicardial artery and cardiovascular outcomes even in the presence of a normal global MFR in cardiovascular risk individuals warranting, however, further clinical testing in a large population.

In the current study, the lowest cardiovascular event rate was observed in the group with normal global MFR without a hyperemic longitudinal MBF gradient and the group with endogen CMD with four and two cardiovascular events, respectively. When looking into more detail in the group with normal coronary artery function, these events were widely related to arterial hypertension induced acute heart failure decompensation in HFpEF and one stroke in patients with normal coronary artery function. Similarly, in patients with endogen

CMD, the two observed two acute heart failure decompensations in HFpEF likely were also related to intermittent hypertensive arterial blood pressure regulation.

The presence of endogen CMD or reduced MFR due to increases in myocardial metabolism paralleled by increases in resting MBF but normal hyperemic MBFs and also without a longitudinal MBF gradient may indeed signify less vulnerability of the coronary arterial wall accounting for the absence of typical structural CAD related cardiovascular events in this study population. As endogen CMD is frequently caused by arterial hypertension and/or type 2 diabetes mellitus, subclinical remodeling of the left ventricle and/or even left ventricular hypertrophy may have been present causing hospitalization due to acute heart failure decompensation in HFpEF condition. Similarly, in the group with normal MFR and coronary artery function, the observed four cases of hospitalization due to HFpEF decompensation likely were related to the presence of arterial hypertension and/or type 2 diabetes mellitus related left ventricular remodeling as described in prior studies conducted by Taqueti et al. [33]**.** Notably, all observed six cardiovascular deaths occurred in patients with normal MFR but an abnormal hyperemic longitudinal MBF gradient and classical type of CMD with three cases in both groups, respectively. The exact reasons for observed cardiovascular deaths remain uncertain and needs further investigations. While the presence of left-ventricular hypertrophy may have caused ventricular arrhythmia with sudden cardiac death, observed coronary artery dysfunction in both groups may have accelerated the progression of the atherosclerotic process and plaque rupture paralleled by athero-thrombotic sequelae and fatal outcome. Interestingly, when evaluating further the cardiovascular events in both groups, coronary revascularization was substantially higher in patients with classical CMD compared to those with the presence of the abnormal hyperemic flow gradient only (five versus one case). Such observations may suggest that with increasing severity of coronary artery function extending from the epicardial artery to the microcirculation, as an integrating index of the

overall burden inflicted by a variety of risk factors on the arterial wall, a higher cardiovascular event rate is likely to ensue [2, 35].

Thus, an impairment of coronary arterial function expanding from the epicardial artery to the microcirculation may indeed represent a pivotal mechanistic link between early stages of structural arterial disease and adverse cardiovascular outcome in this study population. These observations may also link increasing systemic inflammation to a risk of cardiovascular events in this cardiometabolic disease population which may not be surprising given well-known pro-atherosclerotic and pro-thrombotic state of the metabolic syndrome with increasing body weight [22]. Interestingly, after adjusting for known cardiovascular risk factors by multivariate analysis, only body mass index and systemic inflammation proved to be independent predictors of cardiovascular events. Thus, alterations in MFR were not independently associated with the occurrence of cardiovascular events. The exact reasons may remain uncertain; they may be related to the clustering adverse effects of cardiometabolic risk parameters within the metabolic syndrome in obesity on the coronary circulatory function. While these assumptions may be intuitively correct, further confirmation in larger cardiovascular imaging trials are needed.

Limitations

There are important limitations worthy of contemplation in the interpretation of current observations. First, we did not conduct intracoronary ultrasound and/or contrast computed tomography of the epicardial artery to better characterize the arterial wall structure. Thus, we cannot describe the presence and extent of diffuse coronary atherosclerosis and/or excentric plaques of the epicardial arteries. Second, the outcome findings presented were derived from a symptomatic and predominant cardiometabolic disease risk population. These observations in cardiovascular outcomes related to PET-determined epicardial-microvascular dysfunction therefore cannot be extrapolated to populations with different cardiovascular risk profiles in

the primary care setting. Third, the relatively small sample size of the study population with 329 patients, short-term mean follow-up of 581 days, and medically treated cardiovascular risk factors may account for the observed relatively low cardiovascular event rate of 9%. Current findings therefore do not yield a definite answer, but they may foster further large-scale clinical investigations in this rapidly emerging research field.

Conclusions

A progressive worsening of coronary function from the epicardial artery to the coronary microcirculation is associated with a worse cardiovascular outcome in a cardiometabolic disease population. Such observations may signify differences in cardiovascular risk stringent on the phenotype of epicardial and/or coronary microvascular dysfunction, warranting further large-scale clinical investigations.

Declarations

Author contributions

All authors contributed to the study design. Material preparation and data collection: SM, EO, IV, MHA, AP, SJ, TS. Imaging analysis: SM, EO and IV, supervised by TS. Data analysis: SM, EO, IV, MHA, AP, SJ, TS. Data interpretation: SM, EO, IV, MHA, AP, SJ, TS. Draft of the manuscript: SM, EO, IV, MHA, AP, SJ, TS. All authors read and approved of the final manuscript.

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Data availability

The data underlying this article will be shared at reasonable request to the corresponding author.

Ethics approval and consent to participate

The study was approved by the Washington University in St. Louis (No.201812037) and was in accordance with the Helsinki Declaration. All participants gave written informed consent.

Consent for publication

All patients offered the informed consents for their images in Figures to be published.

Competing interests

The authors declare no competing interests.

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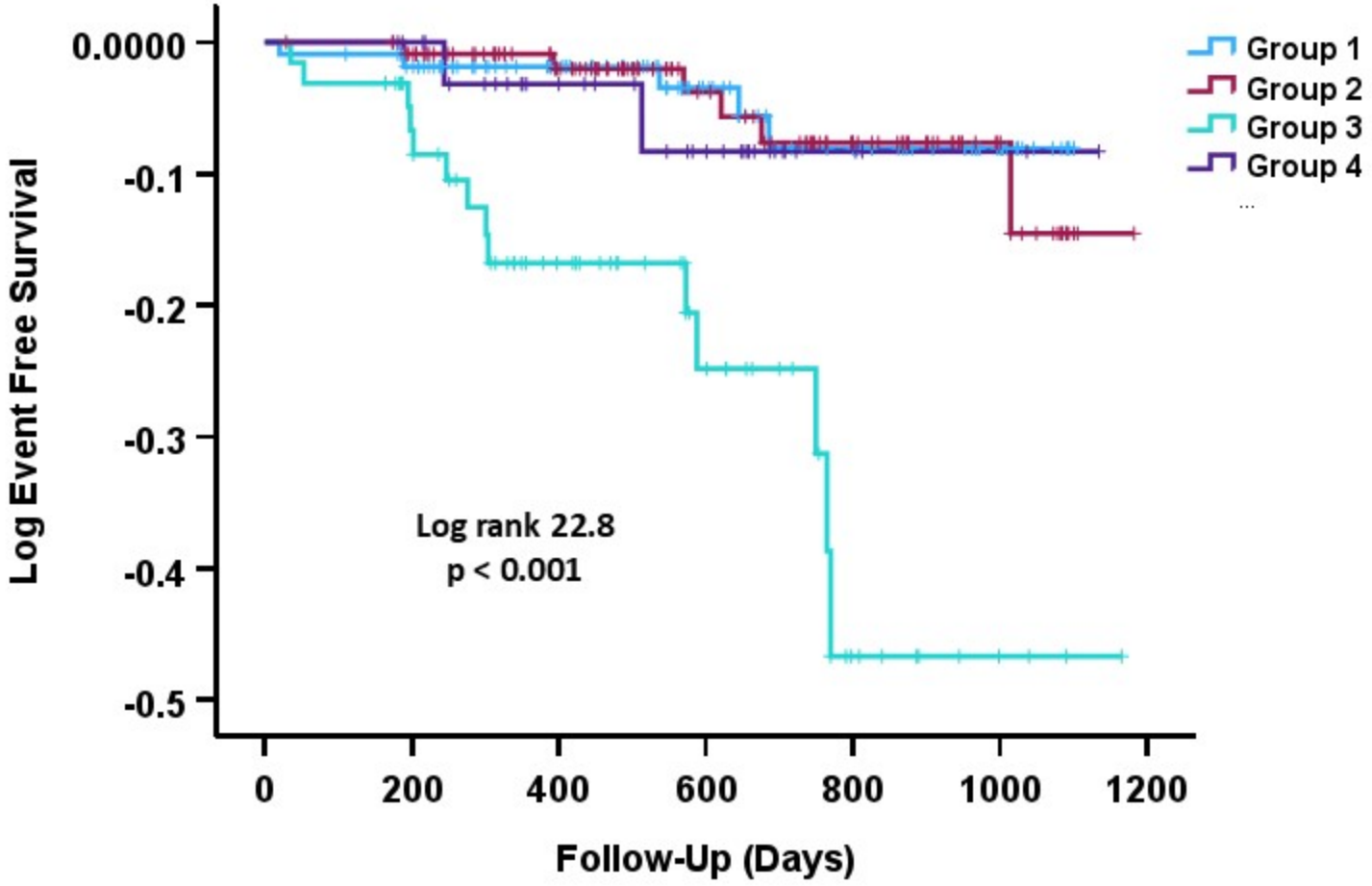
Figure Legends

Figure 1. Kaplan-Meier analysis demonstrates the proportion of patients without cardiovascular events during follow-up in patients with normal global MFR and no longitudinal gradient (group1), normal global MFR but with longitudinal gradient (group 2), as well as those with with classical and endogen type of CMD, respectively (group 3 and group 4).

Figure 2. Kaplan-Meier analysis demonstrating the proportion of patients without cardiovascular death during follow-up in groups 1 to 4. (Same abbreviations for groups 1-4 as in Figure 1)

CENTRAL ILLUSTRATION: Group 1: Normal Global MFR and No Longitudinal MBF Gradient; Group 2: Normal Global MFR but with Longitudinal MBF Gradient; Group 3: Classical Type of CMD; and Group 4: Endogen Type of CMD.

Legend: CMD = coronary microvascular dysfunction, MACE = major adverse cardiovascular events; MFR = myocardial flow reserve; MBF = myocardial blood flow


0.0000
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Log Event Free Survival
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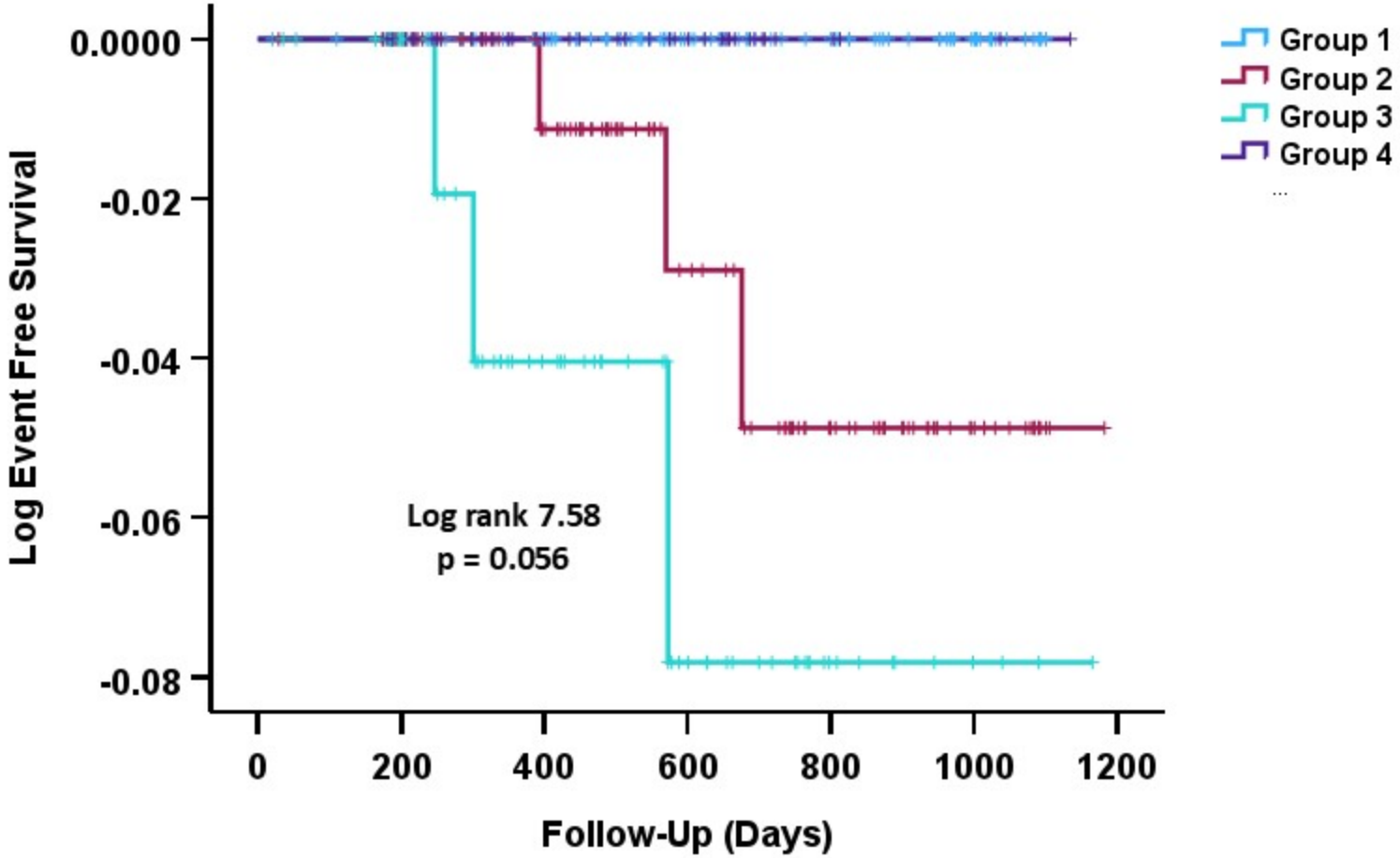
Follow-Up (Days)
Log rank 22.8
p < 0.001
Group 1
Group 2
Group 3
Group 4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Log Event Free Survival
0
200
400
600
800
1000
1200
Follow-Up (Days)
Log rank 7.58
p = 0.056
Group 1
Group 2
Group 3
Group 4

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