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ORIGINAL RESEARCH

IMAGING

PET/CT Assessment of Flow-Mediated Epicardial Vasodilation in Obesity and Severe Obesity

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ABSTRACT

BACKGROUND It is not known whether the transition from obesity and severe obesity, as 2 different metabolic disease entities, affect flow-mediated and, thus, endothelium-dependent epicardial vasodilation.

OBJECTIVES The purpose of this study was to investigate the effect of obesity and severe obesity on flow-mediated epicardial vasomotion with positron emission tomography/computed tomography-determined longitudinal decrease in myocardial blood flow (MBF) from the base-to-apex direction of the left ventricle or gradient.

METHODS ^{13}N-ammonia positron emission tomography/computed tomography evaluated global MBF during pharmacologically induced hyperemia and at rest for assessment of coronary microvascular function. In addition, the Δ longitudinal MBF gradient (hyperemia minus rest) was determined. Patients were then grouped according to the body mass index (BMI) into normal weight (NW) (BMI 20.0-24.9 kg/m^2, n = 27), overweight (OW) (BMI 25.0-29.9 kg/m^2, n = 29), obesity (OB) (BMI 30.0-39.9 kg/m^2, n = 53), and severe obesity (morbid obesity: BMI ≥40 kg/m^2, n = 43).

RESULTS Compared to NW, left ventricular Δ longitudinal MBF gradient progressively declined in OW and OB (0.04 ± 0.09 mL/g/min vs −0.11 ± 0.14 mL/g/min and −0.15 ± 0.11 mL/g/min; $P \leq 0.001$, respectively) but not significantly in SOB (−0.01 ± 0.11 mL/g/min, $P = 0.066$). Regadenoson-induced global hyperemic MBF was lower in OB than in NW (1.88 ± 0.40 mL/g/min vs 2.35 ± 0.32 mL/g/min; $P \leq 0.001$), while comparable between NW and SOB (2.35 ± 0.32 mL/g/min vs 2.26 ± 0.40 mL/g/min; $P = 0.302$). The BMI of the study population was associated with the Δ longitudinal MBF gradient in a U-turn fashion (r = 0.362, standard error of the estimate = 0.124; $P < 0.001$)

CONCLUSIONS Increased body weight associates with abnormalities in coronary circulatory function that advances from an impairment flow-mediated, epicardial vasodilation in overweight and obesity to coronary microvascular dysfunction in obesity, not observed in severe obesity. The U-turn of flow-mediated epicardial vasomotion outlines obesity and severe obesity to affect epicardial endothelial function differently. (JACC Adv 2024;3:100936) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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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.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CMD = coronary microvascular dysfunction

CT = computed tomography

CVR = coronary vascular resistance

HDL = high-density lipoprotein

hsCRP = high-sensitivity C-reactive protein

LV = left ventricular

MBF = myocardial blood flow

MFR = myocardial flow reserve

PET = positron emission tomography

PPG = pullback pressure gradient

RPP = rate-pressure product

SBP = systolic blood pressure

SEE = standard error of the estimate

NW = normal weight

OW = overweight

OB = obesity

Since obesity has been widely appreciated as a risk factor of cardiovascular morbidity and mortality, the increasing prevalence of obesity in industrialized nations arises as a major health concern.[1] In patients with known coronary vascular disease, increasing obesity, in particular visceral obesity, is inversely related to mortality.[2] Yet, in patients with known cardiovascular disease, the relationship between obesity and cardiovascular outcome may be more complex and even paradoxical as large-scale clinical studies outline.[1,3] The latter contention may also be supported by postmortem studies of forensic autopsy cases and also in vivo imaging with computed tomography (CT)-determined coronary artery calcifications[4-6] that unraveled very low coronary atherosclerotic disease burden in advanced or severe obesity as compared to obesity. Similarly, positron emission tomography (PET) flow studies to identify coronary microvascular dysfunction (CMD)[7] reported the highest major adverse event rate in obese individuals with a body mass index (BMI) ranging from 30 to 39 kg/m^2, but much less in patients with severe obesity, while the cardiovascular risk profile was similar. In a more recent investigation,[6] PET-determined hyperemic flows demonstrated indeed a U-turn of global hyperemic myocardial blood flow (MBF) from obesity to severe obesity outlining an obesity paradox at the level of the coronary microcirculation in unhealthy obesity.

The effect of obesity and severe obesity specifically on epicardial vasodilator function as the primary site of the initiation and progression of coronary artery disease (CAD), however, remains to be investigated. PET assessment of an abnormal decrease in MBF from the base to the apex direction of the left ventricle during hyperemic flows has been put forth to provide more specific information on structural and functional alterations of epicardial artery in cardiovascular risk individuals.[8-10] The validity and value of the PET-determined longitudinal MBF gradient as a specific probe of diffuse CAD and/or impaired flow-mediated epicardial vasodilation has been demonstrated by correlates of the hyperemic longitudinal MBF gradient with invasively determined fractional flow reserve pressure pullbacks.[11-14]

With this in mind, we specifically aimed to evaluate the presence and pattern of PET-determined hyperemic longitudinal MBF gradient contingent on increasing body weight from normal weight, overweight, metabolically unhealthy obesity, and severe obesity with predominantly medically controlled cardiovascular risk factors.

METHODS

STUDY POPULATION. The initial screening population consisted of 573 patients who were consecutively referred for ^{13}N-ammonia PET/CT for assessment of obstructive CAD and/or CMD between November 1, 2018 and July 31, 2023. Patients with proven COVID-19 infection and also those with post COVID-19 syndrome,[15] as documented in the patient chart, were excluded from analysis. Furthermore, only patients with normal pharmacologic stress and rest myocardial perfusion imaging and wall motion analysis, as determined by gated ^{13}N-ammonia PET/CT that widely ruled out the presence of hemodynamically significant obstructive CAD, were included for study evaluation. Overall, 196 patients had COVID-19 infection with or without post-COVID-19 syndrome, 71 patients presented ischemia, 15 patients had infarction with peri-infarct ischemia, 21 patients had infarction only, 46 had hypertensive arterial blood pressures (≥140/95 mm Hg) on the day of the PET study, and 72 patients had congestive heart failure, and thus were excluded from the study. Consequently, the final study population consisted of 152 symptomatic patients having a low likelihood of flow-limiting obstructive CAD predominantly with medically treated cardiovascular risk factors like dyslipidemia, arterial hypertension, and type 2 diabetes mellitus (**Table 1**). A total of 106 patients from a previous PET study[6] assessing the effect of increasing body weight on global hyperemic MBF were included in this retrospective analysis. Patients were then grouped according to the BMI into normal weight (NW) (BMI 20.0-24.9 kg/m^2, n = 27), overweight (OW) (BMI 25.0-29.9 kg/m^2, n = 29), obesity (OB) (BMI 30.0-39.9 kg/m^2, n = 53), and morbid obesity (BMI ≥40 kg/m^2, n = 43). Vasoactive medications such as calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statin as well as beta-blockers, and diuretics were held at least 24 h before PET/CT myocardial perfusion-flow assessment. All patients refrained from caffeine-containing beverages for at least 24 h and from smoking for at least 12 h prior to the cardiac PET/CT study.[6] The study was approved by the Washington University in St. Louis (No.201812037), and each participant signed a clinical approved informed consent form.

TABLE 1 Characteristics of Study Population (n = 152)

	NW	OW	*P* Value	OB	*P* Value	MOB	*P* Value
Female/male	16/11	13/16	0.393	26/27	0.264	31/12	0.06
BMI, kg/m^2	23.9 ± 1.35	28.3 ± 1.25	0.001	35.2 ± 2.60	0.001	48.68 ± 6.17	0.001
Weight, kg	70.8 ± 8.17	83.6 ± 8.97	0.001	103.0 ± 13.7	0.001	135.7 ± 22.3	0.001
Height, cm	171 ± 8.4	172 ± 9.6	0.978	171 ± 9.8	0.616	167 ± 10.4	0.029
Age, y	57.5 ± 13.8	56.9 ± 10.5	0.861	62.4 ± 12.3	0.062	54.9 ± 9.3	0.397
Cardiovascular risk factors							
Hypertension	6 (22%)	16 (55%)	0.026	29 (53%)	0.003	30 (69%)	0.001
Dyslipidemia	7 (26%)	15 (52%)	0.102	35 (64%)	0.001	17 (58%)	0.004
Diabetes mellitus	3 (11%)	4 (13%)	0.922	21 (38%)	0.008	10 (23%)	0.209
Smoking	0 (0%)	1 (3%)	0.209	9 (16%)	0.049	3 (6%)	0.432
Family history of CAD	2 (7%)	6 (20%)	0.101	10 (18%)	0.179	2 (5%)	0.652
Lipid status							
Total cholesterol, mg/dl	172 ± 34	167 ± 50	0.679	152 ± 43	0.034	156 ± 36	0.074
LDL cholesterol, mg/dl	95 ± 34	89 ± 42	0.588	81 ± 35	0.096	81 ± 25	0.080
HDL cholesterol, mg/dl	57 ± 19	54 ± 12	0.563	51 ± 17	0.258	48 ± 12	0.023
Triglyceride, mg/dl	106 ± 56	151 ± 49	0.008	129 ± 75	0.182	149 ± 83	0.019
Glucose, mg/dl	98 ± 13	105 ± 10	0.048	117 ± 34	0.008	114 ± 33	0.006
hsCRP, mg/l	0.75 ± 0.79	2.94 ± 0.92	0.001	11.55 ± 15.9	0.027	7.79 ± 12.41	0.046
HbA_{1c}, %	5.5 ± 0.48	5.9 ± 0.51	0.117	6.25 ± 0.99	0.007	6.49 ± 1.30	0.004

Values are n, mean ± SD or n (%). *P* values vs CON (Mann-Whitney *U* test for independent samples).

BMI = body mass index; CAD = coronary artery disease; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MOB = morbid obesity; NW = normal weight; OB = obesity; OW = overweight.

CARDIAC ^{13}N-AMMONIA PET/CT STUDY. Following the topogram, used to determine the axial field of view and a low-dose CT scan (120 kV, 30 mA) for attenuation correction, ^{13}N-ammonia PET concurrently assessed myocardial perfusion and MBF in ml/min/g with dynamic image acquisition (Biograph mCT PET-CT scanner, Siemens Healthineers, Erlangen, Germany) and a 2-compartment tracer kinetic model during regadenoson-stimulated hyperemia and at rest, respectively.[6] The ^{13}N-ammonia PET/CT protocol for the assessment of myocardial perfusion, MBF, and analysis thereof is described in detail in the Supplemental Appendix. PET assessment of the left ventricular (LV) hyperemic longitudinal MBF gradient served for the identification of an impairment of flow-mediated, epicardial vasodilation, while the evaluation of global hyperemic MBF and global myocardial flow reserve (MFR), respectively, denoted the function of the coronary arteriolar vessels.

STATISTICAL ANALYSIS. Data are presented as the mean ± SD for quantitative and absolute frequencies for qualitative variables. For comparison of differences, appropriate *t*-tests for independent or paired samples were used. A comparison of regadenoson-related MBFs, MFR, and longitudinal MBF gradient among the different groups was performed by 1-way analysis of variance followed by Scheffe multiple comparison tests. Pearson's correlation coefficients (r), assuming a linear regression and the standard error of the estimate (SEE), were calculated to investigate possible associations among BMI, MBFs and coronary vascular resistance (CVR), hemodynamic and cardiovascular risk parameters. Multivariate analysis was performed by means of a linear stepwise regression model adjusting for the following a priori selected predictors of the hyperemic longitudinal MBF gradient: gender, age, BMI, systolic blood pressure (SBP), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, and high-sensitivity C-reactive protein (hsCRP). All test procedures were 2-tailed, and $P \leq 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS (Statistics version 27.0, IBM) for Windows 27.0. Based on a standard deviation of 0.17 of hyperemic MBF,[6] and a minimum clinically relevant difference in hyperemic MBF of 0.22 ml/g/min, $\alpha = 0.05$, and a power of 0.8, the number of patients necessary for the cross-sectional analysis was calculated to be 23.

RESULTS

CLINICAL CHARACTERISTICS. The clinical characteristics of the study population are given in Table 1. As regards sex, it was comparable among patients evaluated except for SOB. The age was comparable among groups, while it tended to be higher in OB. In

TABLE 2 Global MBF, Left Ventricular Longitudinal MBF Gradient, and Hemodynamic Findings

	NW	OW	*P* Value	OB	*P* Value	MOB	*P* Value
Global myocardial flow							
Global MBF-rest	1.07 ± 0.24	0.97 ± 0.15	0.081	1.01 ± 0.18	0.262	1.17 ± 0.25	0.123
Global NMBF-rest	1.24 ± 0.27	1.12 ± 0.18	0.065	1.13 ± 0.23	0.079	1.28 ± 0.26	0.471
Global MBF-stress	2.35 ± 0.32	2.13 ± 0.41	0.350	1.88 ± 0.40	0.001	2.26 ± 0.40	0.302
Global MFR	2.29 ± 0.53	2.22 ± 0.48	0.613	1.90 ± 0.43	0.003	1.99 ± 0.38	0.016
Global CVR-rest	91 ± 27	94 ± 15	0.303	96 ± 22	0.342	82 ± 18	0.099
Global CVR-stress	34 ± 5	39 ± 8	0.014	44 ± 9	0.001	36 ± 7	0.079
Longitudinal flow gradient							
LV MBF gradient-rest	−0.01 ± 0.06	−0.01 ± 0.06	0.504	−0.01 ± 0.06	0.850	−0.01 ± 0.06	0.964
LV MBF gradient-stress	0.03 ± 0.06	−0.12 ± 0.14	0.001	−0.16 ± 0.11	0.001	−0.02 ± 0.12	0.045
LV ΔMBF gradient	0.04 ± 0.09	−0.11 ± 0.14	0.001	−0.15 ± 0.11	0.001	−0.01 ± 0.11	0.066
LV CVR gradient-rest	0.64 ± 3.78	0.87 ± 4.89	0.856	0.52 ± 4.66	0.902	0.13 ± 4.48	0.607
LV CVR gradient-stress	−0.39 ± 0.78	1.28 ± 2.57	0.001	2.99 ± 1.72	0.001	0.34 ± 1.53	0.013
LV ΔCVR gradient	−1.03 ± 3.90	1.87 ± 2.08	0.052	2.47 ± 4.52	0.001	0.21 ± 4.12	0.210
Hemodynamics							
Rest HR, beats/min	68 ± 11	69 ± 8	0.584	71 ± 10	0.285	72 ± 11	0.092
Stress HR, beats/min	90 ± 14	94 ± 16	0.304	90 ± 13	0.982	93 ± 12	0.314
Rest-SBP, mm Hg	129 ± 11	127 ± 8	0.356	129 ± 8	0.829	127 ± 12	0.342
Stress-SBP, mm Hg	114 ± 13	115 ± 9	0.986	114 ± 10	0.794	115 ± 12	0.976
Rest-RPP	8,810 ± 1,754	8,794 ± 1,147	0.970	9,097 ± 1,413	0.466	9,200 ± 1,699	0.363
Stress-RPP	10,370 ± 2,165	10,852 ± 2,120	0.422	10,274 ± 1,814	0.843	10,790 ± 2,055	0.424
ΔRPP, pharmacologic − rest	1,560 ± 1,449	2,057 ± 1,490	0.229	1,177 ± 1,381	0.262	1,589 ± 1,532	0.936

Values are mean ± SD. *P* values vs CON (Mann-Whitney *U* test for independent samples). Global MBF-stress and global MFR to characterize coronary microvascular (dys) function. Stress-related left ventricular longitudinal flow gradient serves to denote impairment of flow-mediated epicardial vasodilation.

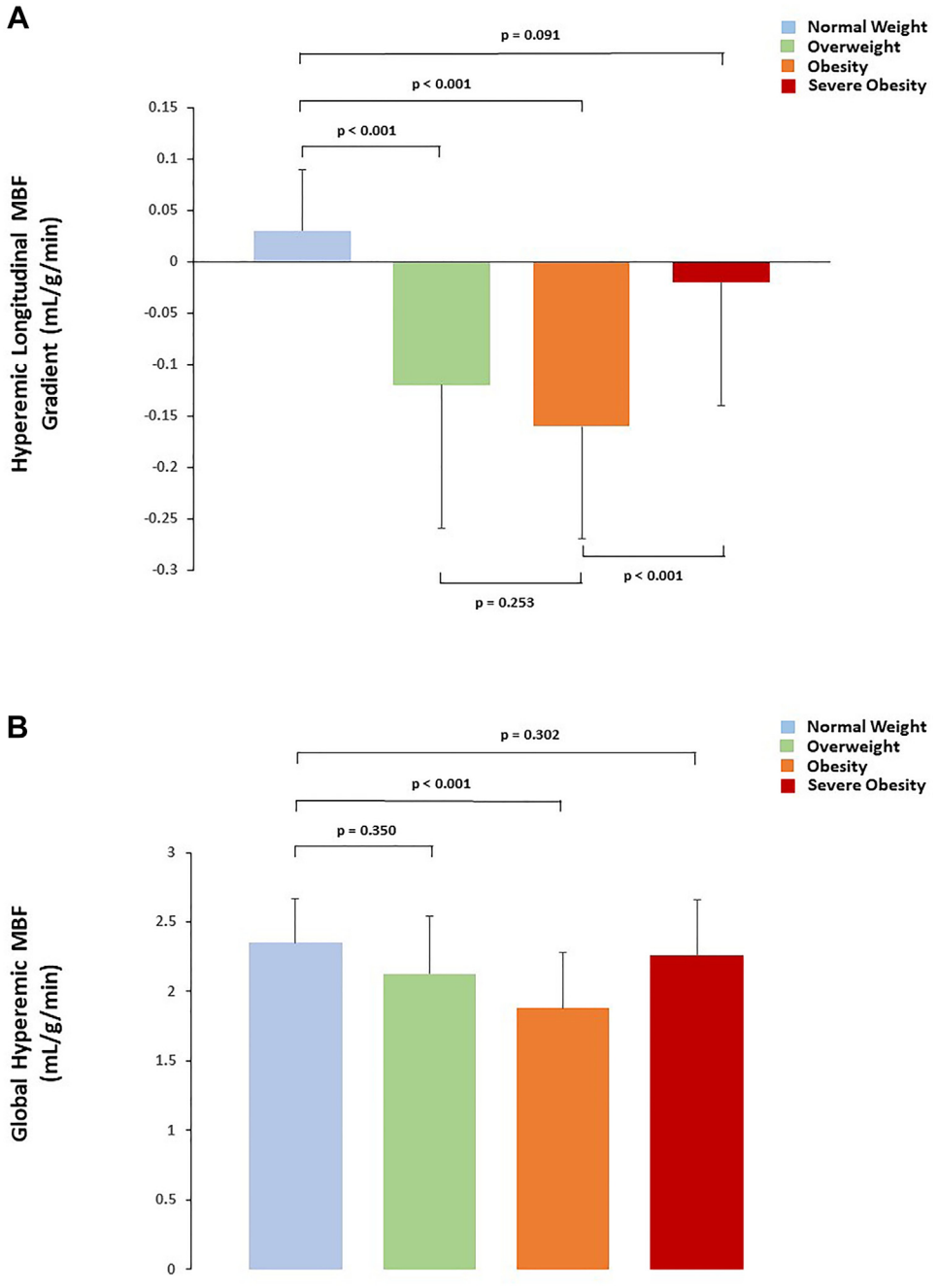
CVR = coronary vascular resistance; HR = heart rate; LV = left ventricular; MBF = myocardial blood flow; MFR = myocardial flow reserve; NMBF = normalized MBF; RPP = rate-pressure product; SBP = systolic blood pressure; other abbreviations as in Table 1.

view of the cardiovascular risk profile, the prevalence of medically treated arterial hypertension and dyslipidemia was comparable among OW, OB, and SOB, but lowest in NW. There was an increase in diabetes mellitus from NW, OW to OB followed by a mild decrease from OB to SOB. In NW, no smoker but 1, 9, and 3 in OW, OB, and SOB, respectively, were noted. Furthermore, 2 in NW, and 6, 10, and 2 in OW, OB, and SOB, respectively, had a family history of CAD. Regarding the lipid profile, total cholesterol was comparable between NW and OW but lower in OB and SOB. Furthermore, LDL cholesterol was within normal range, and it did not differ between groups, while HDL was lowest in SOB. As regards triglyceride levels, they increased from NW to OW with a subsequent mild decrease in OB and SOB. Plasma glucose levels progressively increased from NW, OW, to OB, while comparable between OB and SOB. Furthermore, hsCRP progressively increased from NW, OW to OB, and then mildly dropped in SOB. Glycosylated hemoglobin mildly but progressively increased with increasing body weight.

HEMODYNAMICS. Resting heart rate, SBP, and the corresponding rate-pressure product (RPP) were comparable between groups analyzed (Table 2). During pharmacologic vasodilation with regadenoson to stimulate hyperemic flow increase, the heart rate significantly increased in all study groups, while SBP decreased. The change in RPP (ΔRPP) during regadenoson stimulation was similar between groups.

IMPAIRED, FLOW-MEDIATED EPICARDIAL VASODILATION, AND BODY WEIGHT. Segmental resting regional MBF was mildly but nonsignificantly less in the mid-distal than in the mid-left ventricle that did lead to a minimal and similar longitudinal decline in flow among groups, respectively (Table 2). Regadenoson-stimulated hyperemic MBFs did cause a significant and progressive decline in LV longitudinal MBF from the base to apex direction from OW to OB, but widely disappeared again in SOB but still less than in NW (Table 2), which was also paralleled by the results of the Δlongitudinal MBF gradient in these groups (Table 2, Figure 1A). Furthermore, the calculation of the longitudinal CVR gradients at rest, during pharmacologic stress, and the Δlongitudinal CVR gradient mirrored longitudinal MBF values of all groups (Table 2) ruling out confounding effects of interindividual variations in coronary driving pressure. The group comparison of the hyperemic longitudinal MBF gradient, Δlongitudinal MBF gradient, and

FIGURE 1 **Hyperemic Longitudinal MBF Gradient and Global Hyperemic MBF in Individuals With Increasing Body Weight**



(A) Longitudinal myocardial blood flow (MBF) gradient and increasing body weight. Longitudinal MBF gradient during hyperemic flow stimulation for the 4 study groups. (B) Global hyperemic MBF and increasing body weight. Global MBF during hyperemic flow stimulation for the 4 study groups.

corresponding ΔCVR gradient in NW was significantly altered when compared to OW and OB, respectively (both <0.001 and $P = 0.005$), but not from SOB, respectively ($P = 0.091$, $P = 0.066$, and $P = 0.214$). As regards the relationship between hyperemic longitudinal MBF with BMI in the whole study population, a significant quadratic correlation was observed, respectively (r = 0.373, SEE = 0.125) (Figure 2A), and similarly for the Δlongitudinal MBF gradient and BMI relationship (r = 0.362, SEE = 0.124; $P < 0.001$). Finally, on univariate analysis, only hsCRP plasma levels were significantly associated with hyperemic longitudinal MBF gradient (Table 3), while on multivariate analysis, hsCRP level remained an independent predictor, in addition to BMI, for the hyperemic longitudinal MBF gradient. By univariate and multivariate analysis, only hsCRP plasma levels were predictive of the Δlongitudinal MBF, respectively.

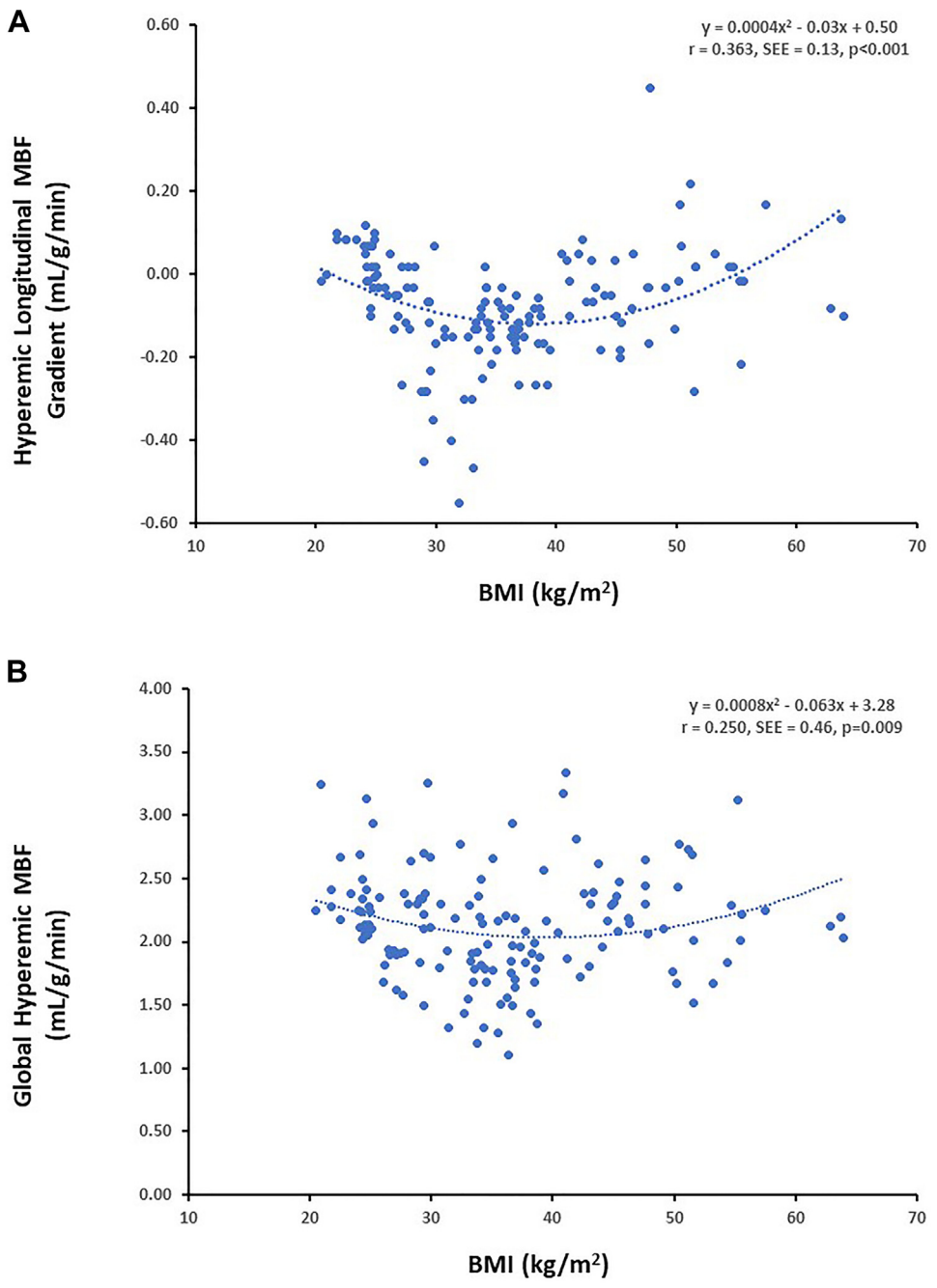
CORONARY MICROVASCULAR FUNCTION AND BODY WEIGHT. Global MBF at rest did not differ significantly between groups but tended to be mildly higher in SOB (Table 2). Global hyperemic MBF during regadenoson-stimulation did not differ significantly between NW and OW but it was markedly lower in OB to denote CMD, whereas it increased again in SOB like NW, respectively (Figure 1B). The global MFR was similar between NW and OW but significantly declined in OB and SOB with comparable reduced values. The group comparison of regadenoson-stimulated global hyperemic MBFs in NW was significantly altered when compared to OW and OB, respectively (both <0.001), while it did not differ between NW and SOB ($P = 0.327$). The corresponding global MFR was significantly altered between NW, OW, OB, and SOB ($P < 0.001$). To account for possible interindividual variations in coronary driving pressure, the CVR during regadenoson application was determined. The CVR progressively increased from NW, OW to OB, while it was comparable between SOB and NW (Table 2). The group comparison of CVR during regadenoson application in NW was significantly different from those in OW and OB ($P < 0.001$) but not from SOB ($P = 0.106$). Furthermore, the relationship between global hyperemic MBF and BMI was investigated for the entire study population in a quadratic fashion that proved to be significant (r = 0.214, SEE = 0.422; $P \leq 0.033$) (Figure 2B), and similarly for the relationship between global MFR and BMI (r = 0.250, SEE = 0.458; $P \leq 0.009$). Following, we did assess the determinants of global hyperemic MBF in this study population. On univariate analysis, gender, age, total cholesterol, LDL-cholesterol, HDL-cholesterol, and plasma glucose levels were significantly associated with hyperemic MBF increases (Table 4). By multivariate analysis, however, only age and HDL levels proved to be independent predictors of hyperemic MBF. Furthermore, BMI, age, SBP, total cholesterol, LDL-cholesterol, plasma glucose- and glycosylated hemoglobin-levels were associated with global MFR on univariate analysis, while only LDL-cholesterol levels remained an independent predictor of global MFR.

DISCUSSION

The present findings are unique as they unravel a U-turn pattern of the observed hyperemic longitudinal MBF gradient with a progressive worsening from normal weight, overweight, to obesity, while it normalized again in severe obesity comparable to those individuals with normal weight (Central Illustration). Such observations are in keeping with previously demonstrated U-turn pattern of global hyperemic MBFs or coronary microvascular function across the range of increasing body weight,[6] but extend these findings to a larger cohort with the abnormal hyperemic longitudinal MBF gradient as a noninvasive probe for an impairment of flow-mediated epicardial vasodilation.[9,11,12]

An abnormal MBF gradient from the base-to-apex direction during pharmacologically stimulated hyperemia has been reported previously for obstructive and nonobstructive CAD in individuals with cardiovascular risk factors.[9,13,16,17] The reported hyperemic MBF gradient has been related to downstream fluid dynamic effects of CAD-induced diffuse luminal narrowing and/or functional alterations of the epicardial coronary conduit vessels.[9,11] Such observations may also agree, for example, with a well-elaborated invasive investigation evaluating the distribution of epicardial resistance along the epicardial artery with pressure pullback measurements during continuous hyperemia in patients with stable CAD patients.[12] Based on evaluations of invasive coronary angiography, the CAD pattern was judged as focal, diffuse, or a combination of both. Subsequently, the distribution of epicardial resistance was evaluated using the hyperemic pullback pressure gradients (PPGs). A so-called PPG index was then computed to determine the pattern of CAD and low PPG index signified the presence of diffuse CAD. Overall, applying the PPG index, 36% of CAD patterns were reclassified as compared to angiography. Notably, a mean PPG index <0.58 was suggested to signify diffuse CAD associated with a drop in intracoronary pressure from the proximal to distal epicardial artery segment during

FIGURE 2 Correlation Between Hyperemic Longitudinal MBG Gradient, Global Hyperemic MBF, and Body Mass Index



(A) Correlation between hyperemic longitudinal MBF gradient and body mass index (BMI). Quadratic correlation between hyperemic longitudinal MBF gradient and BMI in the entire study group. (B) Correlation between global hyperemic MBF and BMI. Quadratic correlation between global hyperemic MBF and BMI in the entire study group. MBF = myocardial blood flow; SEE = standard error of the estimate.

TABLE 3 Predictors of Impaired, Flow-Mediated Epicardial Vasodilation

	Hyperemic Longitudinal MBF Gradient			Δ Longitudinal MBF Gradient		
		Multivariate Analysis			Multivariate Analysis	
	Univariate *P* Value	Standardized Coefficient	*P* Value	Univariate *P* Value	Standardized Coefficient	*P* Value
Sex	0.391	/	/	0.447	/	/
BMI, kg/m^2	0.377	0.286	0.039[a]	0.689	/	/
Age, y	0.437	/	/	0.988	/	/
SBP at rest, mm Hg	0.154	/	/	0.238	/	/
Total cholesterol, mg/dL	0.894	/	/	0.311	/	/
LDL cholesterol, mg/dL	0.978	/	/	0.608	/	/
HDL cholesterol, mg/dL	0.962	/	/	0.666	/	/
Triglyceride, mg/dL	0.546	/	/	0.366	/	/
Glucose, mg/dL	0.705	/	/	0.783	/	/
HsCRP, mg/L	0.024[a]	−0.300	0.031[a]	0.038[a]	−0.282	0.043[a]
HbA_{1c}, %	0.901	/	/	0.894	/	/

[a]Significant difference by analysis of variance.

BMI = body mass index; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MBF = myocardial blood flow; SBP = systolic blood pressure.

hyperemia stimulation. Current results of a progressive worsening the hyperemic MBF gradient from normal weight, overweight to obesity may add a novel and specific flow parameter to the PET perfusion-flow assessment of CAD by unraveling early alterations in flow-mediated and, thus, endothelial-dependent epicardial vasoreactivity amenable to preventive medical cares and/or appropriate lifestyle changes. Adding information of an abnormal longitudinal decrease of myocardial flow therefore may lead to a further fine-tuning of the diagnosis and prognostication of subclinical and clinically manifest CAD[8,9,14] deserving further large-scale clinical investigations.

The current study population consisted predominantly of patients with metabolically unhealthy obesity as most patients were treated medically for cardiovascular risk factors such as arterial hypertension, hypercholesterolemia, and/or diabetes mellitus.[6] Thus, apart from increases in body weight, some adverse effects of other cardiovascular risk factors, albeit medically treated, may have contributed to the observed progressive worsening of the abnormal hyperemic MBF gradient in patients with overweight and with obesity. Furthermore, underlying components of the metabolic syndrome, commonly accompanied by visceral obesity, such as increases in total cholesterol, triglycerides, plasma glucose, systemic inflammation, and arterial blood pressure are likely to have added to the reported progressive worsening of impaired flow-mediated epicardial vasodilation with increasing body weight to obesity. In this respect, it is important to note that CT-determined coronary artery calcification burden provided evidence of a higher prevalence of subclinical CAD burden in metabolically healthy obesity than in those individuals with normal weight.[18] Thus, albeit that metabolically healthy obesity is characterized by lower amount of visceral adipose tissue, high insulin sensitivity, favorable lipid profile, and low pro-inflammatory cytokine levels in plasma and adipose tissue, even metabolic risk factors at level below those considered as abnormal, may still promote the initiation of subclinical CAD.[18] In the current study population including predominantly patients with unhealthy obesity high-sensitive CRP or microinflammation was predictive of the observed hyperemic MBF gradient. By multivariate analysis, however, both BMI and high-sensitive CRP plasma levels emerged as independent predictors of the hyperemic longitudinal MBF gradient. The independent predictive value of BMI for the hyperemic longitudinal MBF gradient emphasizes complex interactions among components of the metabolic syndrome clustering impacts of arterial blood pressure, insulin resistance, and microinflammation on the endothelium of the epicardial coronary artery.[5,19,20] Conversely, inflammation as independent predictor of the abnormal hyperemic MBF gradient may outline an inflammatory vascular environment as common denominator of various cardiovascular risk burden altering epicardial coronary endothelial function that also conforms with results of invasive assessment of epicardial vasomotor function.[21,22]

Like in prior investigations with PET-determined hyperemic MBFs in individuals with increasing body

weight,[6] we did observe a U-turn of the hyperemic MBF gradient from patients with obesity to those patients with severe obesity (**Central Illustration**). This paradoxical normalization of the abnormal hyperemic MBF gradient in individuals with severe obesity suggests less vulnerability of epicardial coronary function even when other traditional cardiovascular risk factors may be present. Indeed, there is a well-reported shift from the predominant pro-atherogenic impact of visceral adipose tissue to a less atherogenic lipid profile, alterations in the inflammatory-metabolic environment, changes in the adipocytokine pattern, and yet-unknown mechanisms owing to a striking increase in subcutaneous adipose tissue in patients with severe obesity.[3,5] For example, a more favorable lipid profile, metabolically triggered chronic microinflammation and/or related but yet unknown factors, and marked increases in leptin plasma levels may be associated with maintained coronary endothelial or brachial artery function, respectively.[5,23] Such maintained coronary endothelial function may also translate in less CAD burden in patients with severe obesity than in patients with obesity as also demonstrated in vivo with CT-determined coronary artery calcification burden or in postmortem studies.[4,5] It is also possible that obesity-related increases in circulating progenitor cells derived from the bone marrow may add to vascular repair and regeneration via direct and/or paracrine mechanisms and, therefore, may account, at least in part, for the observed U-turn of flow-mediated epicardial vasomotor function from patients with obesity to patients with severe obesity. Such contention would also agree with more recently reported obesity paradox of improved outcomes in CAD patients that was limited to those patients with obesity and intact regenerative capacity of circulating progenitor cells.[24]

As regards the assessment of coronary microvascular function with PET-determined global hyperemic MBFs and global MFR, respectively, in agreement with prior investigation but smaller in numbers,[6] we observed a progressive worsening of coronary microvascular function from normal weight, overweight to patients with obesity, while it widely normalized again in patients with severe obesity. Interestingly, only age and HDL remained independent predictors for global hyperemic MBFs, and LDL cholesterol for the global MFR. Suboptimal neuroendocrine modulation of the cardiovascular system and a diminished impact of regadenoson and its metabolites on vascular smooth muscle cell relaxation of the coronary microcirculation may account for observed CMD in obesity.[25] Furthermore, advanced age and/or the period that obese patients were exposed to components of the metabolic syndrome likely also account for observed CMD.[22] The independent predictive value of HDL cholesterol levels for alterations in coronary microvascular function in individuals with increasing body weight also emphasizes complex interactions between components of the metabolic syndrome such as arterial blood pressure, BMI, insulin resistance, and CRP plasma levels impacting the function of the coronary arteriolar vessels.[5,6,19,20] The offset of CMD from patients with obesity to severe obesity in previous[6] and current analysis may be related to major change in adipocytokine profiles, inflammation, lipid and glucose metabolism, and yet unknown factors.[5] Such a favorable shift for coronary microvascular function from patients with obesity to severe obesity, however, may be associated with striking increases in adipocytokines, such as a 7-fold increase in leptin plasma levels, and activation of myocardial matrix metalloproteinases that may lead to LV hypertrophy and interstitial fibrosis leading to diastolic, and finally systolic heart failure recognized as the most common cause of sudden cardiac death in patients with severe obesity.[1,3,26]

There are important limitations to be recognized in the interpretation of the current study data. First, albeit that we excluded patients with proven COVID-19 infection with or without post COVID-19

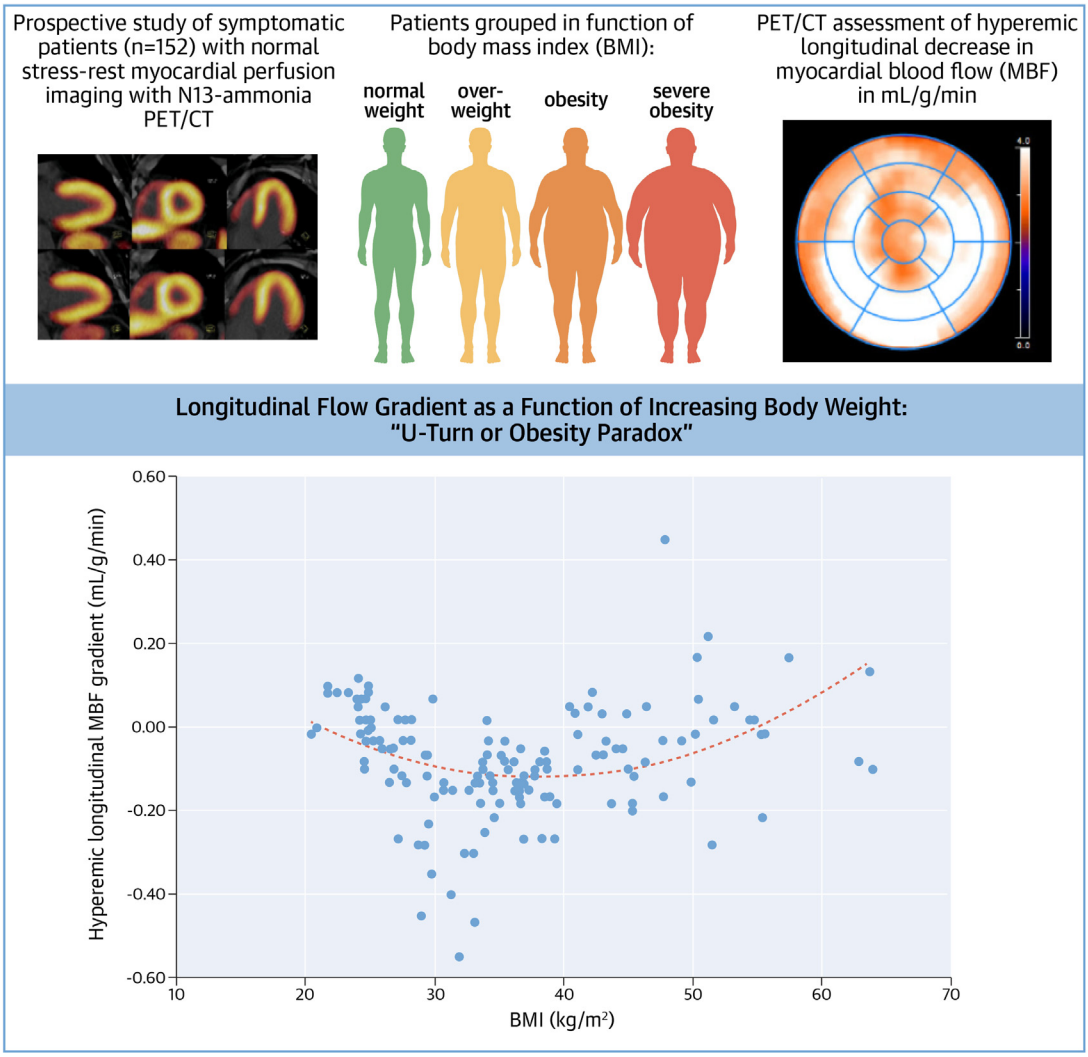
TABLE 4 Predictors of Coronary Microvascular Dysfunction

	Hyperemic MBF			MFR		
		Multivariate Analysis			Multivariate Analysis	
	Univariate *P* Value	Standardized Coefficient	Univariate *P* Value	*P* Value	Standardized Coefficient	*P* Value
Sex	0.001[a]	/	/	0.633	/	
BMI, kg/m^2	0.85	/	/	0.009[a]	/	
Age, y	0.001[a]	−0.454	0.005[a]	0.025[a]	/	
SBP at rest, mm Hg	0.669	/	/	0.014[a]	/	
Total cholesterol, mg/dL	0.001[a]	/	/	0.010[a]	/	
LDL cholesterol, mg/dL	0.018[a]	/	/	0.003[a]	0.321	0.020*
HDL cholesterol, mg/dL	0.001[a]	0.379	0.003[a]	0.591	/	
Triglyceride, mg/dL	0.364	/	/	0.902	/	
Glucose, mg/dL	0.010*	/	/	0.005[a]	/	
HsCRP, mg/L	0.330	/	/	0.075	/	
HbA_{1c}, %	0.415	/	/	0.021[a]	/	

[a]Significant difference by analysis of variance.

BMI = body mass index; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MBF = myocardial blood flow; MFR = myocardial flow reserve; SBP = systolic blood pressure.

CENTRAL ILLUSTRATION **Relationship Between Hyperemic Longitudinal MBF Gradient and BMI**



Valenta I, et al. JACC Adv. 2024;3(5):100936.

Quadratic correlation between hyperemic longitudinal MBF gradient and BMI in the entire study group. The U-turn of the hyperemic longitudinal MBF gradient, as noninvasive surrogate for flow-mediated epicardial vasodilation, signifies obesity and severe obesity to alter epicardial endothelial function differently. CT = computed tomography; PET = positron emission tomography.

syndrome, as documented in the patient chart, some confounding effects of undetected COVID infection on the observed abnormal hyperemic longitudinal MBF gradient, as described more recently,[15] cannot be entirely excluded. Secondly, we did not conduct noninvasive contrast CT coronary angiography or invasive coronary ultrasound of the epicardial artery to identify early and diffuse CAD may have been present and contributed to the manifestation of the abnormal longitudinal MBF gradient during hyperemic flow stimulation.[9] Notably, the hyperemic MBF gradient was determined from the mid and mid-distal LV segments measurements and, therefore, over a relatively short longitudinal distance striving to avoid confounding count variability in the basal segments and partial volume effects in the apical segment on flow measurements.[16,27] Thus, our diagnostic approach to determine the MBF gradient during hyperemic flows may be associated with some underestimation of the flow gradient as reported by

Gould et al.[9] Conceptually, such limitation may be overcome by a different analysis approach such as mapping LV flows on a pixel basis that would allow to include the basal and apical segments.[9,14,28]

CONCLUSIONS

Increased body weight associates with abnormalities in coronary circulatory function that advances from an impairment flow-mediated, epicardial vasodilation in overweight and obesity to CMD in obesity not observed in severe obesity. The U-turn of flow-mediated epicardial vasomotion outlines obesity and severe obesity to affect epicardial endothelial function differently. These findings further support the value and validity of the hyperemic longitudinal MBF gradient as noninvasive probe of epicardial endothelial function warranting further clinical investigations.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The observed U-turn of the PET-determined abnormal hyperemic longitudinal MBF gradient from patients with obesity to those with severe obesity may signify a functional "obesity paradox" suggesting less vulnerability of epicardial endothelial function with severe obesity. The relative offset of epicardial endothelial dysfunction from obesity to severe obesity likely is related to major alterations in adipocytokine profiles, inflammation, lipid and glucose metabolism, and yet unknown factors, deserving further investigations.

TRANSLATIONAL OUTLOOK: Since epicardial endothelial dysfunction is commonly seen as functional precursor of CAD, a PET-determined flow gradient, as noninvasive probe of epicardial endothelial vasoreactivity, may open new avenues for research and clinical investigations.

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KEY WORDS **blood flow, CAD, circulation, coronary circulatory function, coronary microvascular function, flow gradient, MFR, myocardial perfusion, PET, vasomotion**

APPENDIX **For supplemental materials and methods, please see the online version of this paper.**