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Coronary Vasomotor Control in Obesity and Morbid Obesity

Contrasting Flow Responses With Endocannabinoids, Leptin, and Inflammation

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OBJECTIVES This study sought to investigate abnormalities in coronary circulatory function in 2 different disease entities of obese (OB) and morbidly obese (MOB) individuals and to evaluate whether these would differ in severity with different profiles of endocannabinoids, leptin, and C-reactive protein (CRP) plasma levels.

BACKGROUND There is increasing evidence that altered plasma levels of endocannabinoids, leptin, and CRP may affect coronary circulatory function in OB and MOB.

METHODS Myocardial blood flow (MBF) responses to cold pressor test from rest and during pharmacologically induced hyperemia were measured with N-13 ammonia positron emission tomography/computed tomography. Study participants (n = 111) were divided into 4 groups based on their body mass index (BMI) (kg/m^2): 1) control group (BMI: 20 to 24.9, n = 30); 2) overweight group (BMI: 25 to 29.9, n = 31), 3) OB group (BMI: 30 to 39.9, n = 25); and 4) MOB group (BMI ≥40, n = 25).

RESULTS The cold pressor test–induced change in endothelium-related MBF response (ΔMBF) progressively declined in overweight and OB groups when compared with the control group [median: 0.19 (interquartile range [IQR] 0.08, 0.27) and 0.11 (0.03, 0.17) vs. 0.27 (0.23, 0.38) ml/g/min; p ≤ 0.01, respectively], whereas it did not differ significantly between OB and MOB groups [median: 0.11 (IQR: 0.03, 0.17) and 0.09 (−0.01, 0.19) ml/g/min; p = 0.93]. Compared with control subjects, hyperemic MBF subjects comparably declined in the overweight, OB, and MOB groups [median: 2.40 (IQR 1.92, 2.63) vs. 1.94 (1.65, 2.30), 2.05 (1.67, 2.38), and 2.14 (1.78, 2.76) ml/g/min; p ≤ 0.05, respectively]. In OB individuals, ΔMBF was inversely correlated with increase in endocannabinoid anandamide (r = −0.45, p = 0.044), but not with leptin (r = −0.02, p = 0.946) or with CRP (r = −0.33, p = 0.168). Conversely, there was a significant and positive correlation among ΔMBF and elevated leptin (r = 0.43, p = 0.031) and CRP (r = 0.55, p = 0.006), respectively, in MOB individuals that was not observed for endocannabinoid anandamide (r = 0.07, p = 0.740).

CONCLUSIONS Contrasting associations of altered coronary endothelial function with increases in endocannabinoid anandamide, leptin, and CRP plasma levels identify and characterize OB and MOB as different disease entities affecting coronary circulatory function. (J Am Coll Cardiol Img 2012;5: 805–15) © 2012 by the American College of Cardiology Foundation

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As obesity has been recognized as a risk factor of cardiovascular morbidity and mortality, the worldwide global epidemic of obesity with an increasing prevalence, not only in adults but also among children and adolescents, has raised major health concerns (1). Recent investigations have demonstrated a close association between obesity and an abnormal function of the coronary circulation (2,3), which is commonly regarded as a functional precursor of the coronary artery disease (CAD) process (4,5). Increasing attention has been directed to a novel concept that plasma proteins originating from the adipose tissue, so-called adipocytokines, such as adiponectin, leptin, and/or endocannabinoids (EC) as well as metabolically triggered inflammation may alter vascular function (6–8). Whereas adiponectin has been widely appreciated to beneficially affect nitric oxide–mediated, endothelium-dependent vasomotion (6), the role of leptin altering coronary circulatory function in humans remains controversial (2). As regards the role of EC in obesity, we have shown recently that increases in EC plasma levels such as of anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are inversely associated with coronary circulatory dysfunction in obese individuals (3). This would suggest that elevated EC plasma levels exert adverse effects on the function of the coronary circulation (4). Systemic inflammation also seems to play an important role in altering coronary circulatory function in cardiovascular risk individuals (9,10). Conversely, its role in affecting the function of the coronary circulation in individuals with an excess of body weight still remains a matter of ongoing debate (2,11). Notably, obesity and morbid obesity have been suggested to represent 2 different disease entities with differences in adipocytokine profile, lipid and glucose metabolism, and systemic inflammation rather than a disease continuum (1,7).

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With this in mind, we aimed to investigate the presence of abnormalities in coronary circulatory function in 2 different disease entities of obese and morbidly obese individuals and to evaluate whether these would differ in severity with different profiles of EC, leptin, and high-sensitivity C-reactive protein (hsCRP) plasma levels.

ABBREVIATIONS AND ACRONYMS

2-AG = 2-arachidonoylglycerol
AEA = anandamide
ANOVA = analysis of variance
BMI = body mass index
CAC = coronary artery calcification
CAD = coronary artery disease
CI = confidence interval
CON = control subject(s)
CPT = cold pressor test
CT = computed tomography
CVR = coronary vascular resistance
EC = endocannabinoid(s)
HDL = high-density lipoprotein
hsCRP = high-sensitivity C-reactive protein
MBF = myocardial blood flow
MFR = myocardial flow reserve
MOB = morbid obesity
OB = obesity
OW = overweight
PET = positron emission tomography
RPP = rate-pressure product
SBP = systolic blood pressure

METHODS

Study population and design. The study population consisted of 30 normal weight control subjects (CON) (body mass index [BMI]: 20 to 24.9 kg/m^2), 31 overweight (OW) (BMI: 25 to 29.9 kg/m^2), and 50 obese individuals (BMI: ≥30 kg/m^2) without arterial hypertension, smoking, and diabetes mellitus (Table 1) (3). The obese group was subsequently subdivided according to their BMI into common obesity (OB) (BMI: 30.0 to 39.9 kg/m^2, n = 25) and morbid obesity (MOB) (BMI: ≥40 kg/m^2, n = 25). Whereas in the OB group, no individuals had hypercholesterolemia, 4 individuals in the MOB group had cholesterol plasma levels mildly above 240 mg/dl. Study applicants had been recruited by flyers and newspaper advertisements. A study prerequisite was the absence of any cardiac or vasoactive medication, a history of variant angina, a family history of premature CAD, or clinically manifested cardiovascular or any other systemic disease. The applicants subsequently underwent an initial screening visit that comprised a physical examination,

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Table 1. Characteristics of Study Population (N = 111)

	CON (n = 30)	OW (n = 31)	p Value	OB (n = 25)	p Value	MOB (n = 25)	p Value
BMI, kg/m^2	21.9 (20.7, 22.9)	26.7 (25.9, 28.2)	0.0001	31.7 (31.0, 34.9)	0.0001	45.0 (43.2, 47.5)	0.0001
Waist/hip ratio	0.85 (0.81, 0.89)	0.90 (0.85, 0.93)	0.019	0.94 (0.91, 0.98)	0.0001	0.97 (0.84, 1.06)	0.010
Waist, cm	83.0 (80.0, 85.0)	98.0 (92.62, 103.0)	0.0001	111.0 (106.0, 117.5)	0.0001	124.0 (116.0, 140.2)	0.0001
Total fat amount, g	12,872 (10,509, 15,961)	20,341.0 (17,323, 23,628)	0.0001	29,310 (27,328, 35,281)	0.0001	60,871 (50,090, 66,404)	0.0001
Percentage of body fat	19.7 (14.8, 26.1)	23.6 (21.5, 28.3)	0.008	29.7 (28.5, 31.4)	0.0001	47.8 (40.9, 50.7)	0.0001
Android/gynoid fat mass	0.89 (0.80, 1.18)	1.43 (1.12, 1.89)	0.001	1.59 (1.42, 1.83)	0.0001	1.69 (1.19, 2.19)	0.0001
Central fat distribution	0.40 (0.38, 0.45)	0.48 (0.43, 0.54)	0.001	0.52 (0.50, 0.56)	0.0001	0.56 (0.46, 0.61)	0.0001
Age, yrs	40 (30, 46)	44 (33, 51)	0.159	44 (36, 57)	0.158	42 (35, 54)	0.233
Female/male	9/12	11/19		8/17		10/15	
AEA, ng/ml	0.56 (0.49, 0.71)	0.52 (0.42, 0.67)	0.267	0.65 (0.50, 0.73)	0.179	0.70 (0.58, 0.77)	0.002
2-AG, ng/ml	1.50 (0.60, 5.47)	1.40 (0.72, 2.09)	0.605	1.92 (1.21, 2.66)	0.755	2.67 (1.37, 5.23)	0.576
Adiponectin, μg/ml	3.78 (2.3, 5.4)	3.25 (1.67, 5.27)	0.430	2.76 (0.5, 4.5)	0.250	2.11 (0.4, 3.6)	0.041
Leptin	5.47 (2.3, 11.2)	12.66 (8.04, 25.84)	0.001	16.03 (9.4, 22.9)	0.001	110.50 (59.8, 147.5)	0.0001
Lipid status							
Cholesterol levels, mg/dl	191 (168, 230)	207 (170, 230)	0.723	211 (172, 226)	0.533	187 (158, 213)	0.960
LDL level, mg/dl	122 (105, 145)	129 (111, 152)	0.401	122 (99, 152)	0.899	119 (103, 137)	0.969
HDL level, mg/dl	58 (41, 66)	46 (39, 55)	0.010	44 (37, 49)	0.008	42 (39, 46)	0.017
Triglyceride level, mg/dl	54 (48, 101)	93 (67, 120)	0.012	123 (95, 191)	0.0001	122 (83, 167)	0.0001
Glucose level, mg/dl	93 (82, 101)	97 (88, 103)	0.150	97 (92, 108)	0.020	103 (96, 118)	0.011
Insulin, mUI/l	3.2 (1.9, 5.2)	6.1 (3.3, 10.9)	0.004	8.1 (5.2, 10.6)	0.001	28.6 (17.3, 38.1)	0.0001
HOMA	0.7 (0.44, 1.03)	1.4 (0.7, 2.8)	0.008	1.9 (1.2, 3.9)	0.0001	8.3 (4.5, 13.2)	0.0001
hsCRP levels, mg/l	0.9 (0.9, 3.0)	1.0 (0.9, 2.0)	0.847	2.9 (1.4, 5.2)	0.008	8.0 (4.9, 13.0)	0.0001
HbA_{1c}, %	5.2 (4.9, 5.5)	5.2 (5.0, 5.4)	0.961	5.4 (5.0, 5.7)	0.338	5.45 (5.4, 5.7)	0.008

Values are median (Q1, Q3). Central fat distribution is calculated as trunk fat mass/total body fat mass × 100. P values versus CON (Mann-Whitney *U* test for independent samples).
2-AG = 2-arachidonoylglycerol; AEA = anandamide; BMI = body mass index; CON = control subjects; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; HOMA = Homeostasis Model Assessment; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MOB = morbid obesity; OB = obesity; OW = overweight; Q = quartile.

electrocardiogram, blood pressure measurements, and routine blood chemistry in a fasting state. Physical examination revealed normal findings in all applicants and they had normal resting electrocardiograms. Each study participant then underwent dual x-ray absorptiometry (Hologic QDR4500A, Hologic, Bedford, Massachusetts) to measure body composition, total fat amount burden, and fat distribution as described previously (12). Subsequently, N-13 ammonia positron emission tomography (PET)/computed tomography (CT) measurements of myocardial blood flow (MBF) at rest and during vasomotor stress were performed in a fasting state to assess coronary circulatory function. Twenty-one control (CON), 26 OW, 17 OB, and 13 MOB subjects were part of a previous investigation assessing the effect of elevated EC plasma levels in obesity on coronary circulatory function (3). Routine blood chemistry of EC such as AEA and 2-AG, leptin and adiponectin plasma levels were determined (3). The study was approved by the University Hospitals of Geneva Institutional Review Board (No. 07-183), and each participant signed the approved informed consent form.

Assessment of coronary artery calcification and myocardial perfusion with PET/CT. Prior to PET flow studies, we used 64-slice multidetector computed tomography of the Biograph HiRez TruePoint PET/CT scanner (Siemens, Erlangen, Germany) to determine coronary artery calcium score (13). Following, myocardial perfusion was determined with N-13 ammonia PET/CT (3). In all study participants, visual evaluation and polar map analysis of the N-13 ammonia distribution at rest and during vasomotor stress revealed homogeneous tracer uptake. In addition, MBF was determined in ml/g/min from serial transaxial N-13 ammonia PET/CT image acquisition in conjunction with a 2-compartment tracer kinetic model (3). N-13 ammonia PET/CT determined left-ventricular MBFs at rest, then during the cold pressor test (CPT), and during pharmacologically induced hyperemia with standard infusion of dipyridamole (140 mg/kg/min) (3,4). Heart rate, blood pressure, and a 12-lead electrocardiogram were recorded continuously during each MBF measurement. From the average of 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. To account for possible interindividual variations in coronary driving pressure, an index of global coronary vascular resistance (CVR) was determined as the ratio of mean arterial blood pressure (mm Hg) to MBF (ml/g/min). In addition, MBF was normalized to the RPP, and thus myocardial work (averaged during the first 2 min of image acquisition; MBF divided by RPP multiplied by 10^3) was determined.

Statistical analysis. Because continuous variables are not always normally distributed, they are presented as median and interquartile range (25th to 75th percentile: quartile 1, quartile 3). For comparison of differences, we used the Mann-Whitney *U* test for independent samples (SAS Institute, Cary, North Carolina). A comparison of CPT-induced change in MBF and dipyridamole MBFs among the different groups was performed by 1-way analysis of variance (ANOVA) followed by Scheffe multiple comparison test. Pearson correlation coefficients (r), assuming a linear regression and the standard error of the estimate (SEE), were calculated to investigate the associations between CPT- and dipyridamole-induced changes in MBFs and laboratory parameters. Multivariate analysis was performed with stepwise forward regression of variables with significance on univariate analysis. All test procedures were 2-tailed, and $p \leq 0.05$ was considered statistically significant.

RESULTS

Patient characteristics and metabolic profile. The clinical characteristics, anthropometrical measurements, and dual x-ray absorptiometry–determined total fat amount burden and fat distribution of the study groups are given in Table 1. For the entire study population, coronary artery calcification (CAC) was found in 14% (15 of 111). In the CON group, the prevalence of CAC was 17% (5 of 30) with a coronary artery calcium score of 6.8 ± 6.7. Conversely, in the OW, OB, and MOB groups only 12% (4 of 31), 16% (4 of 25), and 8% (2 of 25) had CAC with coronary artery calcium score of 96.5 ± 94.4, 11.9 ± 9.2, and 57.7 ± 27.4, respectively. Regarding the CAC distribution, the highest prevalence was in the left anterior descending artery (n = 14), followed by the right coronary (n = 7) and left circumflex (n = 5) arteries, respectively.

Correlations among fat parameters, EC, and adipocytokines. In the entire study population, Pearson regression analysis denoted a significant correlation between BMI and total fat amount as estimated by dual x-ray absorptiometry (r = 0.95; p = 0.0001). Significant and positive correlations were noted among BMI, total fat, percentage of body fat, or trunk fat amount and leptin, AEA, and hsCRP, respectively, whereas they correlated inversely with adiponectin (Table 2). Further, central fat distribution, as the trunk fat and total fat ratio, was significantly associated with leptin and AEA and

Table 2. Entire Study Population

	Leptin, ng/ml	Adiponectin, μg/ml	AEA, ng/ml	2-AG, ng/ml	hsCRP, mg/l
Waist, cm	r = 0.54	r = –0.20	r = 0.16	r = 0.16	r = 0.31
	p = 0.0001	p = 0.133	p = 0.240	p = 0.220	p = 0.013
Waist/hip ratio	r = 0.17	r = –0.24	r = 0.24	r = 0.24	r = 0.08
	p = 0.168	p = 0.043	p = 0.043	p = 0.040	p = 0.479
BMI, kg/m^2	r = 0.69	r = –0.29	r = 0.35	r = 0.14	r = 0.54
	p = 0.0001	p = 0.003	p = 0.0001	p = 0.167	p = 0.0001
Total fat amount, g	r = 0.73	r = –0.23	r = 0.33	r = 0.13	r = 0.59
	p = 0.0001	p = 0.019	p = 0.001	p = 0.207	p = 0.0001
Percentage of body fat	r = 0.75	r = –0.15	r = 0.21	r = 0.09	r = 0.62
	p = 0.0001	p = 0.135	p = 0.034	p = 0.390	p = 0.0001
Trunk fat amount, g	r = 0.74	r = –0.27	r = 0.41	r = 0.19	r = 0.49
	p = 0.0001	p = 0.008	p = 0.0001	p = 0.068	p = 0.0001
Central fat distribution	r = 0.27	r = –0.23	r = 0.32	r = 0.14	r = 0.06
	p = 0.010	p = 0.025	p = 0.001	p = 0.175	p = 0.596
Android/gynoid fat mass	r = 0.12	r = –0.21	r = 0.37	r = 0.17	r = 0.07
	p = 0.258	p = 0.044	p = 0.0001	p = 0.108	p = 0.537

Central fat distribution = trunk fat mass/total fat mass × 100. Android/gynoid fat mass = trunk fat amount/leg fat amount. Abbreviations as in Table 1.

inversely with adiponectin. As regards the android/gynoid fat mass distribution, it significantly correlated with AEA and inversely with adiponectin. The waist circumference was significantly associated with leptin and hsCRP, whereas the waist/hip ratio correlated inversely with adiponectin and positively with AEA and 2-AG, respectively. As regards the OB group, only central fat distribution and android/gynoid fat mass ratio were inversely correlated with leptin ($r = -0.58$; $p = 0.011$ and $r = -0.53$; $p = 0.024$), whereas android/gynoid fat mass ratio also correlated positively with AEA ($r = 0.51$; $p = 0.030$). In the MOB group again, there were significant associations among total fat amount and AEA ($r = 0.52$; $p = 0.011$) and 2-AG ($r = 0.45$; $p = 0.031$), whereas percentage of body fat correlated with leptin ($r = 0.43$; $p = 0.035$) and hsCRP ($r = 0.62$; $p = 0.002$), respectively. Also, trunk fat amount correlated with adiponectin ($r = 0.43$; $p = 0.047$), AEA ($r = 0.65$; $p = 0.001$), and 2-AG ($r = 0.66$; $p = 0.001$), respectively. Finally, there were also significant associations among android/gynoid fat mass distributions and leptin ($r = 0.49$; $p = 0.020$), and 2-AG ($r = 0.48$; $p = 0.023$).

Hemodynamic parameters. At baseline, heart rate did not differ significantly among the CON, OW, and OB groups, but it was significantly higher in the MOB group (Table 3). Systolic blood pressure (SBP) among groups was comparable. Due to the higher heart rate in the MOB group, however, the resting RPP was significantly higher in the MOB subjects than in CON and OW subjects, whereas it did not differ significantly between the OB and MOB groups. Sympathetic stimulation with CPT induced a significant increase in heart rate and SBP among groups, so that the RPP was significantly higher during CPT than at baseline. The increase in the RPP (ΔRPP) as a result of the CPT-induced

Table 3. MBF and Hemodynamic Findings During PET/CT Exam

	Groups						
	CON	OW	p Value	OB	p Value	MOB	p Value
MBF, ml/min/g							
MBF at rest	0.69 (0.65, 0.75)	0.70 (0.62, 0.76)	0.761	0.68 (0.57, 0.79)	0.914	0.83 (0.71, 0.98)	0.003
NMBF at rest	0.92 (0.85, 1.13)	0.96 (0.83, 1.09)	0.332	0.88 (0.78, 1.03)	0.250	0.98 (0.90, 1.17)	0.382
MBF during CPT	1.00 (0.89, 1.18)	0.86 (0.78, 1.04)	0.026	0.75 (0.71, 0.90)	0.0001	0.93 (0.81, 1.08)	0.141
ΔMBF to CPT from rest	0.27 (0.23, 0.38)	0.19 (0.08, 0.27)	0.005	0.11 (0.03, 0.17)	0.0001	0.09 (−0.01, 0.19)	0.0001
NMBF during CPT	1.05 (0.92, 1.15)	0.93 (0.84, 1.06)	0.053	0.78 (0.71, 0.87)	0.0001	0.77 (0.71, 0.98)	0.001
MBF during hyperemia	2.40 (1.92, 2.63)	1.94 (1.65, 2.3)	0.006	2.05 (1.67, 2.38)	0.014	2.14 (1.78, 2.42)	0.053
MFR	3.40 (2.97, 3.82)	2.88 (2.31, 3.27)	0.007	3.15 (2.36, 3.28)	0.050	2.53 (2.13, 2.76)	0.0001
MBF hyperemia/NMBF rest	2.33 (1.94, 2.70)	1.93 (1.57, 2.52)	0.055	2.18 (1.26, 2.76)	0.012	2.04 (1.76, 2.40)	0.0001
CVR, mm Hg/ml/min/g							
At rest	117 (102, 134)	130 (116, 138)	0.045	119 (109, 149)	0.357	104 (94, 128)	0.099
During CPT	96 (76, 110)	117 (99, 134)	0.002	132 (117, 151)	0.0001	119 (99, 138)	0.001
Change to CPT from rest	−23 (−33, −15)	−9 (−31, 4)	0.049	6 (−9, 13)	0.0001	7 (−4, 18)	0.0001
Pharmacologic vasodilation	33 (27, 39)	43 (35, 50)	0.001	43 (37, 50)	0.001	43 (37, 55)	0.002
Hemodynamics at rest							
Heart rate, beats/min	62 (54, 70)	63 (55, 68)	0.928	66 (57, 73)	0.408	67 (66, 74)	0.006
SBP, mm Hg	114 (103, 123)	120 (113, 128)	0.051	122 (106, 133)	0.233	120 (110, 132)	0.201
RPP	6,788 (6,159, 7,756)	7,134 (6,527, 8,024)	0.440	7,488.0 (6,738, 9,021)	0.140	8,284 (7,293, 8,964)	0.003
CPT							
Heart rate, beats/min	72 (64, 83)	69 (60, 78)	0.206	72 (62, 77)	0.456	76 (70, 84)	0.224
SBP, mm Hg	134 (122, 141)	136 (127, 148)	0.324	148 (126, 156)	0.088	148 (141, 158)	0.003
RPP	9,098 (8,511, 1,0913)	9,525 (8,340, 10,764)	0.908	9,450 (8,628, 11,503)	0.597	11,376 (10,293, 12,528)	0.003
ΔRPP, CPT-rest	2,448 (1,811, 3,270)	1,902 (1,329, 2,951)	0.148	1,786 (1,336, 3,279)	0.597	3,096 (1,840, 4,075)	0.285
Pharmacologic vasodilation							
Heart rate, beats/min	84 (73, 92)	84 (80, 91)	0.669	87 (81, 95)	0.461	95 (83, 102)	0.065
SBP, mm Hg	111 (103, 118)	117 (111, 122)	0.031	120 (111, 129)	0.010	120 (118, 131)	0.002
RPP	8,901 (8,129, 10,375)	9,840 (8,692, 10,998)	0.125	10,512 (9,366, 11,538)	0.013	11,880 (10,438, 12,365)	0.0001
ΔRPP, pharmacologic-rest	1,887 (1,013, 2,668)	2,147 (1,549, 3,738)	0.349	2,392 (1,648, 4,051)	0.297	3,324 (2,035, 4,314)	0.109

Values are median (Q1, Q3). p values versus CON (Mann-Whitney *U* test for independent samples).
CPT = cold pressor test; CT = computed tomography; CVR = coronary vascular resistance; MBF = myocardial blood flow; MFR = myocardial flow reserve; NMBF = normalized myocardial blood flow; PET = positron emission tomography; RPP = rate-pressure product; SBP = systolic blood pressure; other abbreviations as in Table 1.

sympathetic stimulation was not significantly different among the CON, OW, OB, and MOB subjects (Table 3), signifying comparable increases in myocardial workload among the study groups. During pharmacologic vasodilation with dipyridamole to induce hyperemic flows, the heart rate significantly increased among study groups, whereas SBP mildly decreased in the CON, OW, and OB groups and remained unchanged in the MOB group. The change in RPP (ΔRPP) during dipyridamole stimulation was comparable among the study groups (Table 3).

Myocardial blood flow. At baseline, MBF was comparable among the CON, OW, and OB groups, but it was significantly higher in the MOB group (Table 3). When adjusted for RPP, the normalized MBF at rest did not differ significantly among groups. The endothelium-related change of MBF during CPT from rest (ΔMBF to CPT) and the normalized MBF during CPT were significantly less in the OW, OB, and MOB groups than in the CON group, whereas they were comparable between the OB and MOB groups, respectively (Table 3). The group comparison between the ΔMBF to CPT and normalized MBF during CPT in CON subjects was significant as compared with OW, OB, and MOB subjects, respectively ($p = 0.0001$ by ANOVA). In addition, changes of CVR widely mirrored those of MBF for each study group (Table 3). Thus, differences in hemodynamic responses can be widely ruled out as a possible cause for the observed alteration in MBF during CPT.

Dipyridamole-stimulated hyperemic MBFs were significantly lower in OW, OB, and MOB subjects than in CON subjects (Table 3, Fig. 1). The MFR, or total coronary vasodilator capacity, declined from the CON group to the OW and OB groups, but was comparable between the OW and OB groups. In addition, the MFR was significantly less in the MOB group than in the CON, OW, and OB groups, respectively. The group comparison of dipyridamole MBFs and MFR in the CON group was significantly different from those in the OB and MOB groups ($p = 0.015$ and $p = 0.002$ by ANOVA). The CVR during dipyridamole stimulation, accounting for possible interindividual variations in coronary driving pressure, was significantly higher in the OW, OB, and MOB groups than in the CON group and thus confirmed the reduced vasodilatory capacity in individuals with increasing body weight (Table 3). Also here, the group comparison of CVR during dipyridamole stimulation in the CON group was significantly different from those in the OW, OB, and MOB groups ($p = 0.002$ by ANOVA).

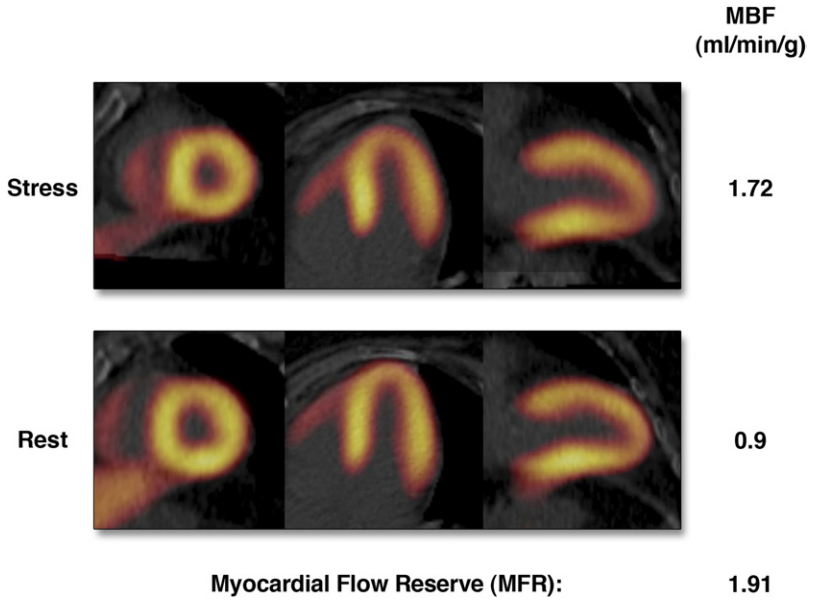

Figure 1. N-13 Ammonia PET/CT Perfusion Images

Example of a normal stress and rest myocardial perfusion study on short-, horizontal-, and vertical-axis images of N-13 ammonia positron emission tomography (PET)/computed tomography (CT) in a 55-year-old morbidly obese woman (body mass index: ≈43 kg/m^2). Conversely, the myocardial flow reserve (MFR = myocardial blood flow [MBF] stress/MBF rest) of 1.91 is mildly reduced, signifying an impairment of the coronary vasodilatory capacity.

Determinants of ΔMBF to CPT and hyperemic MBF. In the entire study population, on univariate analysis age, total fat amount, sex, AEA, 2-AG, SBP, and triglyceride plasma levels were inversely, whereas HDL cholesterol was positively correlated with endothelium-related changes in MBF from rest to CPT (ΔMBF) (Table 4). By multivariate analysis, only total fat amount and sex remained independently associated with ΔMBF (beta: −0.380 [95% confidence interval (CI): 0.0001 to 0.0001]; p = 0.001, and beta: −0.338 [95% CI: −0.212 to −0.046], p = 0.003). Further, hyperemic MBFs correlated inversely with age, sex, AEA, and 2-AG, but positively with HDL cholesterol plasma levels, respectively. Conversely, only age, sex, and 2-AG plasma levels proved to be independently associated with hyperemic MBFs, respectively (beta: −0.234 [95% CI: −0.018 to −0.002], p = 0.016; beta: −0.202 [95% CI: −0.408 to −0.007]; p = 0.043, and beta: −0.194 [95% CI: −1.061 to 0.009]; p = 0.054).

As regards the OB group, the univariate analysis demonstrated sex, AEA, and 2-AG plasma levels as well as SBP to be significantly and inversely associated with ΔMBF (Table 5, Fig. 2A). By multivariate analysis, only 2-AG plasma levels were independently associated with ΔMBF (beta: −0.484 [95% CI: −0.021 to −0.001]; p = 0.030). Further, univariate analysis showed hyperemic MBFs to be significantly associated only with 2-AG plasma levels. Conversely, the univariate analysis in MOB (Table 5, Fig. 2B) demonstrated leptin and hsCRP plasma levels to be significantly and positively associated with ΔMBF. By multivariate analysis, only increases in hsCRP plasma levels were associated with ΔMBF in an independent fashion (beta: 0.522 [95% CI: 0.002 to 0.013]; p = 0.014). Regarding the hyperemic MBFs, they correlated with total fat amount, sex, SBP, HDL cholesterol, and hsCRP plasma levels, respectively, whereas on multivariate analysis only sex was independently associated with MBFs during dipyridamole stimulation (beta: −0.459 [95% CI: −0.691 to −0.061]; p = 0.022).

DISCUSSION

The results of the current study provide several new findings. At first, there was a progressive decrease in endothelium-dependent MBF responses to CPT from normal weight CON subjects to OW and OB subjects, whereas it did not differ significantly between the OB and MOB groups. In addition, hyperemic MBFs were comparably altered among groups with increases in body weight. Thus, despite marked increases in body weight from OB to MOB subjects, there was no further progressive worsening of coronary circulatory function. Secondly, increases in EC plasma levels of AEA and 2-AG were inversely associated with an impairment of coronary endothelial function in OB subjects, which is sug-

Table 4. Entire Study Population

	Univariate Analysis			
	ΔMBF to CPT		Hyperemic MBF	
	Coefficient Beta (95% CI)	p Value	Coefficient Beta (95% CI)	p Value
Age, yrs	−0.202 (−0.006 to 0.0001)	0.037	−0.286 (−0.020 to −0.004)	0.003
Total fat amount, g	−0.370 (0.0001 to 0.0001)	0.0001	−0.074 (0.0001 to 0.0001)	0.457
Male	−0.252 (−0.164 to −0.024)	0.009	−0.299 (−0.496, −0.116)	0.002
AEA, ng/ml	−0.295 (−0.483 to −0.104)	0.003	−0.234 (−1.165 to −0.106)	0.019
2-AG, ng/ml	−0.220 (−0.018 to −0.001)	0.028	−0.210 (−0.048 to −0.002)	0.037
Adiponectin, μg/ml	0.171 (−0.002 to 0.024)	0.087	0.177 (−0.004 to 0.067)	0.078
Leptin, ng/ml	−0.152 (−0.001 to 0.0001)	0.128	0.038 (−0.002 to 0.002)	0.704
SBP, mm Hg	−0.203 (−0.006 to 0.0001)	0.036	−0.147 (−0.014 to 0.002)	0.133
Total cholesterol, mg/dl	−0.080 (−0.001 to 0.001)	0.424	0.026 (−0.002 to 0.003)	0.797
LDL cholesterol, mg/dl	−0.107 (−0.002 to 0.001)	0.297	−0.034 (−0.003 to 0.002)	0.740
HDL cholesterol, mg/dl	0.239 (0.001 to 0.005)	0.015	0.278 (0.003 to 0.015)	0.004
Triglycerides, mg/dl	−0.295 (−0.001 to 0.0001)	0.003	−0.095 (−0.002 to 0.001)	0.346
Glucose, mg/dl	−0.098 (−0.002 to 0.001)	0.322	−0.095 (−0.005 to 0.002)	0.340
HOMA	−0.200 (−0.020 to 0.001)	0.074	−0.098 (−0.043 to 0.017)	0.388
hsCRP, mg/l	−0.114 (−0.009 to 0.002)	0.255	0.012 (−0.015 to 0.017)	0.906

p values determined by analysis of variance.
CI = confidence interval; other abbreviations as in Tables 1 and 3.

Table 5. Obesity and Morbid Obesity Groups

	OB				MOB			
	ΔMBF to CPT		Hyperemic MBF		ΔMBF to CPT		Hyperemic MBF	
	Coefficient Beta (95% CI)	p Value	Coefficient Beta (95% CI)	p Value	Coefficient Beta (95% CI)	p Value	Coefficient Beta (95% CI)	p Value
Age, yrs	−0.27 (−0.008 to 0.002)	0.257	−0.31 (−0.034 to 0.007)	0.190	−0.27 (−0.008 to 0.002)	0.194	0.08 (−0.019 to 0.024)	0.775
Total fat amount, g	0.12 (0.0001 to 0.0001)	0.625	0.27 (0.0001 to 0.0001)	0.280	−0.07 (0.0001 to 0.0001)	0.748	−0.67 (0.0001 to 0.0001)	0.028
Male	−0.46 (−0.498 to 0.009)	0.043	−0.32 (−1.723 to 0.353)	0.182	−0.30 (−0.194 to 0.029)	0.140	−1.22 (−1.379 to −0.537)	0.002
AEA, ng/ml	−0.45 (−0.660 to −0.010)	0.044	−0.18 (−2.503 to 0.961)	0.455	−0.07 (−0.386 to 0.278)	0.740	−0.17 (−1.238 to 0.462)	0.293
2-AG, ng/ml	−0.63 (−0.023 to −0.005)	0.004	−0.46 (−0.080 to 0.001)	0.057	−0.26 (−0.056 to 0.005)	0.224	0.19 (−0.13 to 0.044)	0.223
Adiponectin, μg/ml	0.005 (−0.026 to 0.026)	0.985	0.02 (−0.098 to 0.105)	0.944	−0.33 (−0.026 to 0.006)	0.112	−0.19 (−0.125 to 0.037)	0.220
Leptin, ng/ml	−0.02 (−0.007 to 0.006)	0.946	−0.10 (−0.031 to 0.021)	0.698	0.43 (0.0001 to 0.002)	0.031	−0.13 (−0.005 to 0.003)	0.483
SBP, mm Hg	−0.51 (−0.009 to −0.001)	0.021	−0.11 (−0.025 to 0.016)	0.654	−0.14 (−0.007 to 0.004)	0.515	0.81 (0.017 to 0.041)	0.002
Total cholesterol, mg/dl	−0.18 (−0.002 to 0.001)	0.462	0.01 (−0.006 to 0.006)	0.992	−0.01 (−0.001 to 0.001)	0.978	4.15 (−0.053 to 0.135)	0.353
LDL cholesterol, mg/dl	−0.24 (−0.002 to 0.001)	0.344	−0.03 (−0.006 to 0.006)	0.915	−0.00 (−0.002 to 0.002)	0.991	−0.39 (−0.012 to 0.003)	0.158
HDL cholesterol, mg/dl	0.05 (−0.005 to 0.007)	0.838	0.21 (−0.014 to 0.033)	0.401	0.12 (−0.004 to 0.007)	0.584	−0.44 (−0.026 to −0.003)	0.022
Triglycerides, mg/dl	0.08 (−0.001 to 0.001)	0.740	−0.06 (−0.004 to 0.003)	0.805	−0.23 (−0.002 to 0.001)	0.298	0.22 (−0.001 to 0.005)	0.171
Glucose, mg/dl	0.02 (−0.002 to 0.002)	0.950	−0.10 (−0.009 to 0.006)	0.629	0.29 (−0.001 to 0.003)	0.183	0.19 (−0.003 to 0.003)	0.347
HOMA	−0.11 (−0.037 to 0.024)	0.657	0.04 (−0.117 to 0.133)	0.888	0.12 (−0.009 to 0.014)	0.612	−0.13 (−0.035 to 0.016)	0.396
hsCRP, mg/l	−0.33 (−0.022 to 0.004)	0.168	−0.34 (−0.087 to 0.016)	0.163	0.55 (0.002 to 0.013)	0.007	0.34 (0.003 to 0.024)	0.020

p values determined by analysis of variance.
Abbreviations as in Tables 1, 3, and 4.

gestive of adverse effects of ECs on the coronary endothelium, but this association was not more observed in MOB subjects. Thirdly, elevations in leptin and hsCRP plasma levels were correlated with endothelium-related MBF responses to CPT in the MOB group, although positively, whereas there was no such association in the OB group. Increases in leptin and hsCRP plasma levels therefore were associated with relatively higher, though diminished, endothelium-mediated MBF increases to CPT in the MOB group, stressing some beneficial effects on coronary endothelial function. These contrasting associations of altered coronary endothelial function with increases in AEA, leptin, and hsCRP plasma levels, however, confirm the hypothesis that OB and MOB reflect 2 different disease entities, rather than a simple continuation of increases in body weight, affecting coronary circulatory function.

Metabolic profile. As expected, total cholesterol and low-density lipoprotein cholesterol were similar among groups with increasing body weight (1). Conversely, HDL cholesterol progressively decreased and triglyceride increased from CON subjects to OW and OB subjects, but no further alterations were noted between the OB and MOB groups. When regarding plasma markers of the insulin-resistance syndrome and chronic inflammation, they also continuously increased but across the whole spectrum of increasing body weight. Notably, apart from glucose plasma levels, there was a striking and nonlinear increase in insulin resistance, plasma levels of insulin, and hsCRP from the OB to MOB groups. Consequently, a marked increase of body weight from the OB to MOB groups did not further alter the lipid profile, HDL cholesterol, or triglycerides, whereas plasma glucose levels were only mildly affected. This observation can be explained by differences in adipose tissue distribution and metabolic activity between the OB and MOB groups. Visceral adipose tissue accumulation exerts more deleterious metabolic effects than subcutaneous fat accumulation does, mainly due to the higher fatty acid supply from the abdominal area, which contributes to metabolic abnormalities (1). Contrary to intra-abdominal fat depots, subcutaneous adipose tissue accumulation may be rather protective owing to a lower lipolytic response to catecholamines, a higher antilipolytic sensitivity to insulin, and an enhanced lipoprotein lipase activity (14). Also, distinct visceral adipose tissue, such as round ligament and mesenteric adipose tissues, which pose a higher sensibility to effects of insulin in stimulating lipoprotein lipase activity and lipogenesis and in inhibiting lipolysis, is likely to have contributed to reduced metabolic effects at the expense of an increased fat accumulation (1,14,15). This also provides a rationale why plasma glucose levels were only slightly higher in MOB subjects than in OB subjects

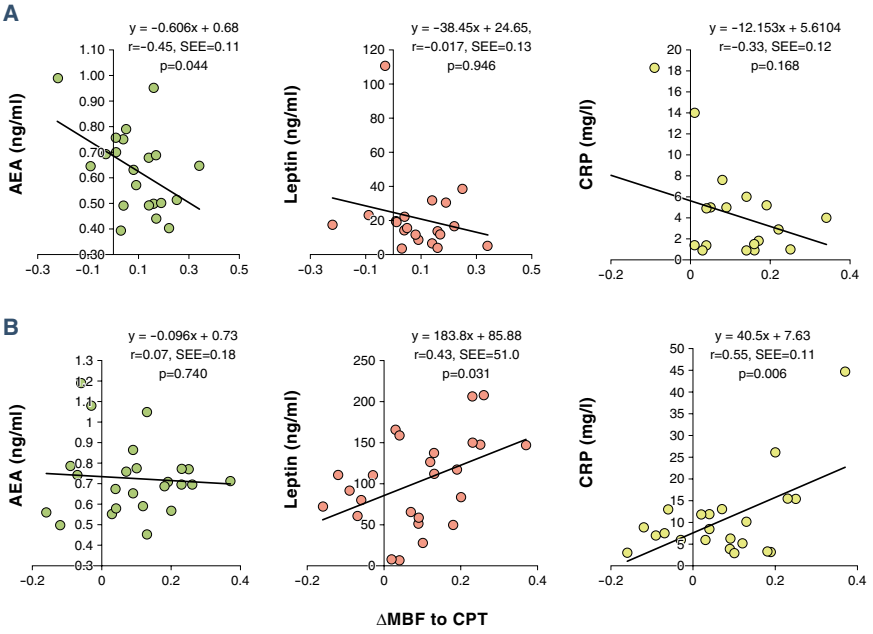

Figure 2. Relationships Among AEA, Leptin, Inflammation, and Coronary Endothelial Function

Correlations among **(A)** anandamide (AEA), leptin, and high-sensitivity C-reactive protein (CRP) plasma levels and change of endothelium-related myocardial blood flow (ΔMBF) during cold pressor testing (CPT) in the obese group, respectively, and **(B)** correspondingly in the morbid obesity group. SEE = standard error of the estimate.

despite a progressive increase in insulin plasma levels and insulin resistance.

When looking specifically at EC and adiponectin, plasma levels of EC mildly but progressively increased, whereas adiponectin declined with increases in body weight (1,3). Interestingly, the EC, AEA, and 2-AG were positively, whereas adiponectin plasma levels were inversely, associated with the total fat amount but also with surrogate markers for visceral adipose tissue burden such as waist/hip ratio, central fat, and android/gynoid fat distribution. Thus, apart from the total fat amount increase, the visceral adipose tissue appears to reflect a predominant source of alterations in EC and adiponectin plasma levels in individuals with increasing body weight as reported previously (1,3). The progressive decrease of adiponectin plasma levels in obese individuals with increasing body weight has been related to a state of metabolic stress associated with increases in catecholamines, glucocorticoids, and insulin, which of all exert inhibitory effects on the expression and release of adiponectin from the adipose tissue (1). As regards leptin plasma levels, they were significantly higher in OB subjects than in CON and OW subjects (2). Notably, there was a 7-fold higher increase in leptin plasma levels in MOB subjects versus OB subjects. Plasma levels of leptin have been shown to correlate more closely with total and subcutaneous tissue than with visceral adipose tissue (1). For this reason, circulating leptin plasma levels are generally higher in women, who commonly develop more subcutaneous fat than men do (1). In the current study, the striking increase in leptin plasma levels was correlated with the total percentage of body fat and an android pattern of fat distribution in MOB subjects, suggesting the increase in adipose tissue as a whole and also visceral fat mass distribution as predominant sources of the marked increase in leptin plasma levels. This may be partly surprising (1) but most likely is related to the lower prevalence of women versus men in the MOB group.

Coronary circulatory function and interrelations. When regarding the MFR or total coronary vasodilator capacity, it significantly declined from the CON to the OW group with a mild increase from the OW to the OB group, whereas it was then lowest in the MOB group. The relatively low MFR in the MOB group was primarily related to the augmentation in resting MBF induced by higher resting heart rates, SBP, and resulting RPP, which are indicative of the myocardial workload. This finding also accords with previous investigations in the assessment of coronary circulatory function in

obesity (3,16). An increase in myocardial workload in obese individuals, associated with higher resting MBF, is commonly related to an activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (16). Addressing specifically the OB group, increases in EC such as AEA and 2-AG plasma levels were inversely correlated with alterations in coronary circulatory function. These findings confirm and extend a recent report (3), emphasizing that, apart from effects related to obesity such as low HDL cholesterol, insulin resistance, and inflammation, increases in EC plasma levels play a pivotal role in mediating coronary circulatory dysfunction in OB subjects. As mentioned before, we did not observe a further worsening of coronary circulatory function from OB to MOB subjects. This somehow astounding observation may be supported by recent results in the assessment of brachial artery function in severe obesity (11). Flow-mediated and, thus, endothelium-dependent vasodilation was paradoxically higher in severely obese individuals than in obese and normal weight individuals. This paradoxical preservation in flow-mediated vasodilation in individuals with severe obesity was suggested to be related to an enhanced inflammatory environment associated with a greater mobilization of endothelial progenitor cells and reduced activation of the immune system (11). In addition, another investigation in 29 morbidly obese individuals with various traditional cardiovascular risk factors, including the metabolic syndrome (7), demonstrated that carotid-femoral pulse-wave velocity, as a reflection of arterial stiffness, was only mildly elevated. Interestingly, elevations in hsCRP were inversely related to pulse-wave velocity, when the opposite might have been expected (9,10). Contrary to common opinion, therefore, metabolically triggered chronic microinflammation in severe obesity may be associated with preserved flow-mediated vasodilation and relatively low arterial stiffness than was assumed previously. In this direction, the results of the current study provide first evidence that increases in leptin and hsCRP plasma levels correlated positively with altered and endothelium-related MBF responses to CPT in MOB subjects. Arterial increases in leptin concentrations and a metabolically triggered systemic inflammation, therefore, confer some beneficial effects on coronary endothelial function against adverse effects of body fat on the endothelium in MOB subjects. On multivariate analysis, increases in hsCRP plasma levels remained independently associated with the CPT-induced change in MBFs, signifying in particular inflammatory factors to mediate direct protective effects on the coronary endothelium in MOB subjects. Visceral adipose tissue is characterized by an infiltration of macrophages, which have been demonstrated as a major source of inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-6, and interleukin-10 in obesity (1). For example, increases in anti-inflammatory interleukin-10 have been shown to protect vascular endothelial function by reducing increases in superoxide formation within the arterial wall in an experimental model (17). Also clinical studies lend further evidence of a potential vascular protective role of interleukin-10 (18,19). If interleukin-10 serum levels were increased in CAD patients with elevated CRP plasma levels, no impairment of acetylcholine-stimulated forearm blood flow response was noted (18). This reported preservation of endothelium function in the presence of inflammatory-triggered increases in interleukin-10 plasma levels in CAD patients (18) might also provide a mechanistic link between a better clinical outcome after acute coronary syndromes and reduced increased risk associated with elevated CRP plasma levels (19). Because we did not measure interleukin-10 plasma levels and other parameters potentially involved in the adipose tissue–triggered inflammatory process, further investigations are certainly needed to identify the exact mechanism of the inflammatory response mediating protective effects on the coronary endothelium in MOB.

CONCLUSIONS

Contrasting associations of altered coronary endothelial function with increases in AEA, leptin, and hsCRP identify and characterize OB and MOB as different disease entities, rather than as a simple continuation of increases in body weight, affecting coronary circulatory function.

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Key Words: adiponectin ■ blood flow ■ circulation ■ coronary disease ■ endocannabinoids ■ endothelium ■ leptin ■ obesity.