



PET-determined prevalence of coronary microvascular dysfunction and different types in a cardio-metabolic risk population

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ABSTRACT

Background: The aim was to investigate the prevalence of “classical” (predominantly related to alterations in hyperemic MBFs) and “endogen” (predominantly related to alterations in resting MBF) normal coronary microvascular function (nCMF) or coronary microvascular dysfunction (CMD) in a clinical population without flow-limiting obstructive CAD.

Methods: We prospectively enrolled 239 symptomatic patients with normal pharmacologically-stress and rest myocardial perfusion on ¹³N-ammonia PET/CT. ¹³N-ammonia PET/CT concurrently assessed myocardial flow reserve (MFR = MBF stress/MBF rest). Normal nCMF was defined by a MFR of ≥ 2.0 , while an abnormal MFR of < 2.0 signified CMD. In addition, patients were subgrouped into classical and endogen type of nCMF and CMD, respectively.

Results: In the whole study population, CMD was present in 54% (130/239). The classical type was more prevalent than the endogen type of CMD (65% vs 35%, $p \leq 0.008$). The classical type of CMD was paralleled by a high prevalence of diabetes mellitus, metabolic syndrome, and obesity, while the endogen type of CMD was accompanied by a higher prevalence of arterial hypertension, obesity, and/or morbid obesity. Further, the classical type of nCMF was more frequently observed than the endogen type (74% vs. 26%, $p \leq 0.007$). The endogen type of nCMF was related to lower heart rate and/or arterial blood pressures.

Conclusions: In this contemporary clinical study population, slightly more than half of symptomatic patients had CMD with predominance of the classical type. These observations emphasize the need for standardized reporting of CMD to gear individualized and/or intensified medical treatment to improve symptoms and/or clinical outcome in these patients.

1. Introduction

Chest pain and/or dyspnea but without obstructive coronary artery disease (CAD) has been realized as a frequent defiance in clinical practices that constitutes an increasing public health concern [1]. For example, in a large cohort of 398,978 patients referred for invasive coronary angiography, only 38% had obstructive CAD with an epicardial narrowing exceeding 50% stenosis diameter [2]. While non-cardiac causes like costochondritis, musculoskeletal alterations, and/or gastroesophageal reflux disease need to be taken into consideration, underlying coronary microvascular dysfunction (CMD) as functional substrate may frequently account for these symptoms as invasive studies outline [3–5]. CMD is commonly caused by detrimental effects of cardiovascular

risk factors on endothelium- or endothelium-independent coronary circulatory function, hypersensitivity of the arteriolar vascular smooth muscle cells, or both [4]. As the invasive assessment of CMD is performed in a highly selected study population referred for coronary angiography, the prevalence of CMD in patients with non-obstructive CAD in a more general clinical population remains uncertain. In this respect, PET-determined myocardial perfusion and myocardial blood flow (MBF) in absolute terms in milliliters per minute per gram (mL/min/g) during pharmacologically-induced hyperemia and at rest with derived myocardial flow reserve (MFR) affords a non-invasive means for the detection and characterization of CMD [6–8]. Such PET-determined CMD carries important diagnostic and prognostic information amenable to specific medical treatment that improve symptoms and potentially

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patient outcome [9]. Notably, an expert panel consensus document suggests a standardization of PET-determined CMD into classical type (predominantly related to alterations in hyperemic MBFs) and endogen type (predominantly related to alterations in resting MBF), respectively, to provide a framework for the detection of microvascular angina with subsequent individualized and, thus, optimized patient care [10].

To this end, we aimed to investigate the prevalence of PET-determined CMD in a clinical population without flow-limiting obstructive CAD.

2. Methods

2.1. Patient population

The initial study population analysed consisted of 272 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) who were consecutively referred for ^{13}N -ammonia PET/CT for assessment of obstructive CAD and/or CMD between 1st November 2018 and 31st December 2022. 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, did serve for study analysis. From these patients, 25 patients presented ischemia, 2 patients had infarction with *peri*-infarct ischemia, 6 patients had infarction only when evaluated on gated ^{13}N -ammonia stress-rest PET/CT images, and thus were excluded from the study. For subanalysis,

Table 1

Patient characteristics with and without CMD, and hemodynamic findings during PET/CT exam.

	Normal MFR \geq 2.0	Abnormal MFR $<$ 2.0	p Value
N (numbers)	109	130	
Sex (female/male)	56/53	83/47	0.065
BMI, kg/m ²	36.4 \pm 10.44	39.8 \pm 10.96.54	0.014
Age, yrs	57.0 \pm 11.1	60.9 \pm 12.2	0.110
Cardiovascular risk factors			
Hypertension, n	64 (58.7)	101 (77.6)	0.002
Dyslipidemia, n	59 (54.1)	81 (62.3)	0.236
Diabetes mellitus, n	27 (24.7)	53 (40.8)	0.009
Smoking, n	6 (5.5)	8 (6.2)	0.787
Family history of CAD, n	13 (11.9)	21 (16.2)	0.458
Obesity, n	59 (54.1)	91 (70.0)	0.016
Morbid obesity, n	35 (32.1)	59 ((45.4)	0.062
Lipid status			
Total cholesterol, mg/dl	160 \pm 45	150 \pm 36	0.113
LDL cholesterol, mg/dl	91 \pm 37	75 \pm 27	0.001
HDL cholesterol, mg/dl	51 \pm 16	50 \pm 15	0.747
Triglyceride, mg/dl	126 \pm 69	127 \pm 65	0.869
Glucose, mg/dl	116 \pm 44	131 \pm 46	0.028
hs CRP, mg/l	4.86 \pm 6.50	10.42 \pm 15.78	0.042
HbA _{1c} , %	6.19 \pm 1.23	6.59 \pm 1.41	0.085
MBF, ml/g/min			
MBF at rest	0.99 \pm 0.22	1.21 \pm 0.28	0.0001
MBF during hypereamia	2.37 \pm 0.53	1.95 \pm 0.48	0.0001
MFR	2.41 \pm 0.35	1.63 \pm 0.25	0.0001
Hemodynamics at rest			
Heart rate, beats/min	69 \pm 12	72 \pm 11	0.076
SBP, mm Hg	132 \pm 18	138 \pm 18	0.030
DBP, mm Hg	78 \pm 11	76 \pm 11	0.444

Values are mean \pm standard deviation (SD). P values versus Normal MFR (Mann-Whitney *U* test for independent samples). BMI = body mass index; CMD = coronary microvascular dysfunction; CT = computed tomography; DBP = diastolic blood pressure; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MBF = myocardial blood flow; MFR = myocardial flow reserve; PET = positron emission tomography; SBP = systolic blood pressure.

patients were also grouped according to the number of components of the metabolic syndrome with BMI in place of waist circumference [7,11]. In this direction, the five thresholds used were triglycerides level \geq 150 mg/dl, high-density lipoprotein cholesterol (HDL-C) $<$ 40 mg/dl in men and $<$ 50 mg/dl in women, systolic blood pressure \geq 130 mmHg or diastolic blood pressure \geq 85 mmHg, fasting glucose \geq 110 mg/dl, and BMI $>$ 28.8 kg/m². Following, patients were grouped according to the number of features of the metabolic syndrome (none, one or two, three or more). Vasoactive medications such as calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statin as well as b-blockers, and diuretics were withheld at least 24 h before PET/CT myocardial perfusion- flow examination [7]. All study 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.

2.2. Cardiac PET/CT perfusion and flow studies

After conducting the topogram to determine the axial field of view and a low-dose CT scan (120 kV, 30 mA) for attenuation correction, ^{13}N -ammonia PET assessed 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 during regadenoson-stimulated hyperemia and at rest, respectively [7]. PET image acquisition was performed during regadenoson-stimulated hyperemia (0.4 mg intravenous bolus injection over 10 and 20 s interval) was started immediately after injection of \approx 370 MBq ^{13}N -ammonia as a bolus followed subsequent infusion of 10 mL saline solution over 30 s (0.33 mL/sec) via infusion pump (e.g. Aitecs Syringe Pump) and also at least 40 min later at rest for a total duration of 10-min list-mode PET data acquisition, respectively [7]. Myocardial perfusion during pharmacologic-induced hyperemia and at rest was assessed evaluated visually on reoriented short-and long-axis myocardial slices and semiquantitatively 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 [7,12]. Summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were assessed. Only patients with a SDS $<$ 2, ruling out myocardial ischemia, and normal wall motion on gated PET were considered for the study analysis. Image interpretation was visually performed in consensus by two nuclear cardiologists. In the case of disagreement between observers, consensus was obtained in a joint reading. For 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) [7]. Starting with intravenous ^{13}N -ammonia i.v. injection, serial transaxial emission images were acquired (dynamic frames: 1 \times 5 sec, 12 \times 10 sec, 4 \times 30 sec, 4 \times 60 sec, 1 \times 120 sec) with PET/CT, 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 [7,12]. On the polar map of the last 600-s image set, regions of interest (ROIs) were aligned to the territories of the main three coronary arteries using the 17-segment model [7,12]. Using the Corridor4DM software package, MBF was determined in ml/g/min. Regional MBFs of the LAD, LCx, and RCA territory were averaged on a polar map and the calculated mean MBF of the left ventricle was defined as global MBF. Heart rate, blood pressure, and a 12-lead electrocardiogram were acquired 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.

In addition, resting 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 10 000). [7].

2.3. Definitions of CMD

According to an expert panel consensus document [10], normal coronary microvascular function (nCMF) was defined by a MFR of ≥ 2.0 , while an abnormal MFR of < 2.0 signified coronary microvascular dysfunction (CMD). These groups were then subgrouped into classical type (predominantly related to alterations in hyperemic MBFs) and endogen type (predominantly related to alterations in resting MBF). An increase in resting MBF was defined ≥ 1.30 mL/g/min [10].

2.4. Statistical analysis

Data are presented as the mean \pm SD for quantitative and absolute frequencies for qualitative variables. For comparison of differences, appropriate t-tests for independent samples were used. A comparison of MBFs and MFR among the different groups was performed by 1-way analysis of variance (ANOVA) followed by Scheffe multiple comparison test. Multivariate analysis was performed by means of a linear step-wise regression model adjusting for the following a priori selected predictors of the hyperaemic MBF: gender, age, BMI, SBP, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, high-sensitive C-reactive protein, and glycosylated hemoglobin. Differences in prevalence of gender, cardiovascular risk factors and coronary microvascular (dys)function among groups were analysed with the χ^2 test. All test procedures were 2-tailed, and $p \leq 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS for Windows 27.0 (SPSS).

2.5. Ethics and registration

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

informed consent form.

3. Results

3.1. CMD and clinical characteristics

The clinical characteristics of the study population having a low likelihood of flow-limiting obstructive CAD are demonstrated in Table 1. Sex was widely balanced in the whole study group. As it can be observed, patients with CMD had a higher prevalence of arterial hypertension, diabetes mellitus, and obesity than in those without CMD, while it did not differ significantly for dyslipidemia, smoking, family history for CAD, and morbid obesity. Further, BMI, plasma glucose, and hsCRP were significantly higher in CMD patients, while LDL cholesterol was higher in those without CMD. Total cholesterol, HDL cholesterol, triglycerides, and glycosylated hemoglobin did not differ significantly among both groups. As regards the hemodynamic findings, they were widely comparable except for higher resting SBP and lower DBP during pharmacologic stress in CMD patients than in those without CMD.

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

Table 2 demonstrates the clinical characteristics and hemodynamic findings for the classical and endogen type of normal coronary microvascular function (nCMF) or coronary microvascular dysfunction (CMD) in a clinical population without flow-limiting obstructive CAD. In the whole study population, CMD was present in 54%. The classical type was more prevalent than the endogen type of CMD (65% vs 35%, $p \leq 0.008$) (Fig. 1). The classical type of CMD was paralleled by a high prevalence of diabetes mellitus, metabolic syndrome, and obesity, while the endogen type of CMD was accompanied by a higher prevalence of

Table 2

Patient characteristics and different types of normal coronary microvascular function (nCMF) and coronary microvascular dysfunction (CMD), and hemodynamic findings during PET/CT study.

	nCMF			CMD			
	Classical Type	Endogen Type	p Value	Classical Type	p Value	Endogen Type	p Value
N (numbers)	81	28		84		46	
Sex (female/male)	46/35	83/47	0.188	48/36	0.876	35/11	0.023
BMI, kg/m ²	36.4 \pm 10.68	36.2 \pm 9.88	0.915	38.5 \pm 10.1	0.186	41.7 \pm 12.2	0.016
Age, yrs	56.2 \pm 10.9	58.4 \pm 11.6	0.220	62.9 \pm 11.2	0.0001	58 \pm 13.1	0.436
Cardiovascular risk factors							
Hypertension, n	45 (55.5)	18 (64.3)	0.514	60 (71.4)	0.053	41 (89.1)	0.0001
Dyslipidemia, n	45 (55.5)	14 (50.0)	0.664	55 (65.5)	0.270	27 (58.7)	0.852
Diabetes mellitus, n	18 (22.2)	9 (32.1)	0.317	30 (35.7)	0.041	22 (47.8)	0.005
Smoking, n	3 (3.7)	3 (10.7)	0.070	5 (5.9)	0.498	3 (6.5)	0.667
Family history of CAD, n	7 (8.6)	6 (21.4)	1.00	16 (19.1)	0.095	5 (10.9)	0.756
Obesity, n	15 (18.5)	8 (28.5)	0.666	23 (27.4)	0.053	11 (23.9)	0.004
Morbid obesity, n	27 (33.3)	8 (28.5)	0.815	32 (38.1)	0.062	25 (54.3)	0.025
Lipid status							
Total cholesterol, mg/dl	169 \pm 44	126 \pm 46	0.001	148 \pm 36	0.003	158 \pm 35	0.171
LDL cholesterol, mg/dl	98 \pm 36	68 \pm 31	0.001	72 \pm 28	0.0001	81 \pm 25	0.009
HDL cholesterol, mg/dl	53 \pm 17	44 \pm 11	0.010	50 \pm 15	0.329	51 \pm 13	0.493
Triglyceride, mg/dl	124 \pm 72	130 \pm 42	0.716	126 \pm 73	0.849	129 \pm 64	0.740
Glucose, mg/dl	111 \pm 53	109 \pm 21	0.065	122 \pm 34	0.120	144 \pm 61	0.002
hs CRP, mg/l	4.89 \pm 6.82	4.72 \pm 4.98	0.948	7.60 \pm 15.32	0.415	14.73 \pm 15.94	0.007
HbA _{1c} , %	6.11 \pm 1.25	6.43 \pm 1.19	0.354	6.24 \pm 1.21	0.611	7.00 \pm 1.57	0.007
MBF, ml/g/min							
MBF at rest	1.06 \pm 0.21	0.78 \pm 0.08	0.0001	1.05 \pm 0.16	0.632	1.50 \pm 0.19	0.0001
Normalized MBF at rest	1.14 \pm 0.28	0.99 \pm 0.19	0.0001	1.14 \pm 0.22	0.957	1.40 \pm 0.28	0.0001
MBF during hyperaemia	2.57 \pm 0.45	1.77 \pm 0.16	0.0001	1.74 \pm 0.35	0.0001	2.31 \pm 0.47	0.002
MFR	2.46 \pm 0.38	2.26 \pm 0.18	0.008	1.66 \pm 0.21	0.0001	1.55 \pm 0.28	0.0001
Hemodynamics at rest							
Heart rate, beats/min	71 \pm 12	65 \pm 10	0.009	70 \pm 11	0.671	75 \pm 11	0.066
SBP, mm Hg	135 \pm 18	126 \pm 15	0.021	133 \pm 14	0.542	147 \pm 20	0.001
DBP, mm Hg	78 \pm 10	73 \pm 12	0.038	76 \pm 10	0.071	77 \pm 14	0.346
RPP	9692 \pm 2455	8150 \pm 1352	0.002	9398 \pm 1795	0.379	11103 \pm 2479	0.003

Values are mean \pm standard deviation (SD). P values versus Classical Type of nCMF (Mann-Whitney U test for independent samples). Abbreviations as in Table 1. In addition, normalized MBF at rest = MBF/RPP \times 10000.

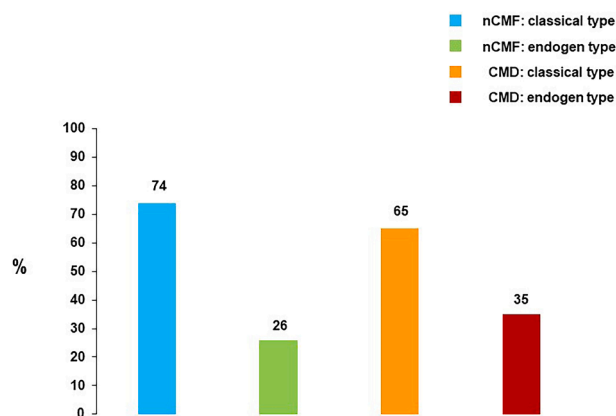


Fig. 1. Prevalence of classical and endogen types of normal coronary microvascular function (nCMF) and coronary microvascular dysfunction (CMD).

arterial hypertension, obesity, and/or morbid obesity (Table 2, Fig. 1). Further, the classical type of nCMF was more frequently observed than the endogen type (74% vs. 26%, $p \leq 0.007$). Notably, the endogen type of nCMF was related to lower heart rate and/or arterial blood pressures (Table 2).

As regards nCMF, the endogen type had a higher prevalence of female patients than in the classical type, while cardiovascular risk were comparable. Further, total cholesterol, LDL cholesterol, and HDL cholesterol were lower in the endogen type when compared to the classical type. Plasma levels of triglycerides, glucose, hsCRP, and glycosylated hemoglobin were comparable among these groups. As expected, resting and hyperaemic MBF were lower in the endogen type than in the classical type of nCMF that was also paralleled by lower heart rates, and arterial blood pressures in the endogen type. The MFR was by definition normal but a bit less in the endogen as compared to the classical type of nCMF. With respect to CMD, both types were compared to the classical nCMF. As can be appreciated, there was a higher prevalence of females in the classical type of CMD versus classical nCMF. Patients in the classical CMD were more advanced in age and they had a higher prevalence of diabetes mellitus and obesity than in classical nCMF. Total cholesterol and LDL cholesterol were lower in classical CMD than in classical nCMF, while the remaining laboratory parameters did not differ significantly. As expected, resting MBF was comparable between both groups, while hyperaemic MBF and MFR were significantly less in classical CMD than in patients with classical nCMF. Hemodynamic at rest were comparable, while heart rate and diastolic blood pressures during pharmacologic stress were a bit lower in classical CMD than in classical nCMF. As regards the endogen type of CMD, also here a higher prevalence of females than in nCMF was noted. Endogen type of CMD had significantly higher BMI and markedly higher prevalence of arterial hypertension, diabetes mellitus, obesity, and morbid obesity when compared to classical nCMF. As regards the laboratory parameters, HDL cholesterol was significantly lower, while plasma glucose, hsCRP, and glycosylated hemoglobin markedly higher in the group with endogen type of CMD than in classical type of nCMF. As expected, resting MBF was higher in the endogen type of CMD than in the classical type of nCMF. Hyperaemic MBF was in normal range in the endogen type of CMD but still significantly less than in classical nCMF. Due to the high resting MBF, the MFR was markedly reduced in endogen type of CMD than in classical nCMF. Of further interest, the normalized MBF at rest was significantly higher in the endogen type of CMD than in the endogen type of nCMF (Table 2), that may indicate, at least in part, other factors than the increases in myocardial workload, reflected by the RPP, to account for observed increase in resting MBF in the endogen type of CMD. As regards hemodynamic, rest systolic blood pressure and thus also the rate pressure product were higher in the endogen type of CMD than in the classical type of nCMF. During pharmacologic stress,

systolic blood pressure was higher while diastolic blood pressure lower among these groups.

3.3. Metabolic syndrome and CMD

Table 3 demonstrates characteristics and differences in MBFs and MFR in the three groups with no features, one or two features, and three or more features. There is a progressive increase in BMI, triglycerides, plasma glucose, HbA1c, hsCRP and systolic blood pressure, while LDL- and HDL-cholesterol non-significantly decreased with increasing number of features of the metabolic syndrome. Concerning resting MBFs, they did not differ among groups with increasing features of the metabolic syndrome ($p = 0.333$ by ANOVA). Conversely, hyperaemic MBFs and MFR progressively decreased with increasing features of the metabolic syndrome ($p \leq 0.003$ and ≤ 0.0001 by ANOVA).

3.4. Determinants of CMD

Further, we evaluated potential determinants of CMD in this study population. In the whole study group, on univariate analysis gender, BMI, age, systolic blood pressure, LDL cholesterol, plasma glucose, high-sensitive CRP, and glycosylated hemoglobin levels were significantly associated with MFR (Table 4). By multivariate analysis, however, only age and glycosylated hemoglobin remained statistically independent predictors of MFR.

4. Discussion

In this contemporary clinical study population, slightly more than half of symptomatic patients had CMD without evidence of hemodynamically obstructive CAD. With respect to the type of CMD, the classical type was more prevalent than the endogen type with 65% to 35%, respectively. Notably, while the classical type of CMD was accompanied

Table 3
Metabolic syndrome categories, MBFs, and MFR during PET/CT exam.

	Patients with features of metabolic syndrome				
	No features	1-2 features	p Value	≥ 3 features	p Value
N (numbers)	28	114		97	
Sex (female/male)	16/12	68/46	0.833	56/41	1.000
BMI, kg/m ²	26.7 ± 3.35	37.0 ± 9.64	0.0001	43.0 ± 10.71	0.0001
Age, yrs	57.6 ± 12.8	58.9 ± 12.3	0.611	59.9 ± 11.0	0.398
Lipid status					
Total cholesterol, mg/dl	160 ± 34	155 ± 45	0.748	152 ± 41	0.380
LDL cholesterol, mg/dl	94 ± 32	83 ± 33	0.236	81 ± 32	0.156
HDL cholesterol, mg/dl	56 ± 17	56 ± 13	0.977	44 ± 11	0.130
Triglyceride, mg/dl	89 ± 31	97 ± 33	0.346	158 ± 76	0.0001
Glucose, mg/dl	96 ± 9	108 ± 34	0.142	144 ± 52	0.0001
hs CRP, mg/l	3.66 ± 2.21	6.58 ± 13.18	0.207	11.54 ± 14.17	0.008
HbA _{1c} , %	5.76 ± 0.77	5.75 ± 0.82	0.878	6.98 ± 1.47	0.002
MBF, ml/g/min					
MBF at rest	1.03 ± 0.20	1.12 ± 0.28	0.083	1.12 ± 0.29	0.081
MBF during hyperaemia	2.32 ± 0.35	2.21 ± 0.56	0.203	2.00 ± 0.55	0.005
MFR	2.29 ± 0.38	2.03 ± 0.51	0.006	1.83 ± 0.43	0.0001

Values are mean ± standard deviation (SD). P values versus No Features (Mann-Whitney U test for independent samples). Abbreviations as in Table 1.

Table 4

Entire study group.

	MFR		Multivariate Analysis	
	Univariate			
	p Value	Standardized Coefficient		p Value
Gender	0.029*	/	/	/
BMI, kg/m ²	0.001*	/	/	/
Age, yrs	0.001*	-0.280		0.049*
SBP at rest, mmHg	0.014*	/	/	/
Total cholesterol, mg/dl	0.132	/	/	/
LDL cholesterol, mg/dl	0.011*	/	/	/
HDL cholesterol, mg/dl	0.931	/	/	/
Triglyceride, mg/dl	0.481	/	/	/
Glucose, mg/dl	0.008*	/	/	/
Hs CRP, mg/l	0.021*	/	/	/
HbA _{1c} , %	0.045*	-0.330		0.010*

Significant difference by analysis of variance.

Abbreviations as in Table 1.

by a high prevalence of diabetes mellitus, metabolic syndrome, and obesity, the endogen type of CMD was associated with a higher prevalence of arterial hypertension, obesity, and/or morbid obesity. These observations may emphasize the need for standardized reporting of CMD to gear individualized and/or intensified medical treatment to improve symptoms and/or clinical outcome in these patients needing further investigations.

Although that the underlying mechanism of CMD is likely to be multifactorial, a common final pathway may be seen in an increase reactive oxygen species via NADPH oxidase stimulation of the arterial wall that neutralizes from the endothelium released and athero-protective nitric oxide to even produce peroxynitrite, another short-acting peroxide causing further functional and structural disturbances to the arterial wall [13]. Initial alteration in coronary arterial function is commonly limited to the endothelium, while more intense and long-lasting exposure to cardiovascular risk factors confers an extension of functional vascular alterations also to the vascular smooth muscle cell layer of the coronary arteriolar resistance vessels [13]. In the current study, CMD was indeed present in 54% of symptomatic patients with cardiovascular risk profile, of whom 65% presented the classical type of CMD. It is important to consider that the majority of patients presented metabolically unhealthy obesity as they were commonly treated medically for cardiovascular risk factors such as arterial hypertension, dyslipidemia, and/or diabetes mellitus. In view of this, we also analyzed the effect of underlying metabolic syndrome, commonly paralleled with increases in visceral adipose tissue, on coronary microvascular function. When grouping the study population with a metabolic syndrome classification adapted to the presence of three or more National Cholesterol Education Program (NCEP) diagnostic criteria, then there was a progressive decrease of the MFR from those patients without features to the one with features of the metabolic syndrome as also described more recently [7]. Since resting MBFs did not differ among groups without and with metabolic syndrome, the progressive decrease in MFR was related to parallel decrease in hyperaemic MBFs and thus to an impairment of coronary arterial function. In the current study in predominant unhealthy obese individuals components of the metabolic syndrome such as increases in BMI, arterial blood pressures, triglycerides, plasma glucose, and systemic inflammation can be assumed to predominantly account for the observed classical type of CMD. Such classical type of CMD may not only reflect a functional substrate for microvascular angina in patients without hemodynamically obstructive CAD but it may also confer a risk for the initiation and development of CAD and worse clinical outcome [14,15].

As regards the endogen type of CMD, it was present in 35% of symptomatic patients with CMD and predominately related to the presence of arterial hypertension, obesity, and in particular morbid obesity. Resting MBF was significantly higher than in patients with

normal coronary microvascular function or classical type of CMD, while hyperemic MBFs were comparable. Resting MBF, as determined with PET, has been reported to range from 0.7 to 1.2 mL/g/min depending on the left ventricular myocardial workload and, thus, oxygen demand in healthy volunteers [3,16,17]. At resting condition, MBF therefore increases in function of myocardial workload to meet myocardial oxygen or metabolic demands. Studies have demonstrated a close correlation between resting MBF and the rate-pressure product (defined as product of systolic blood pressure and heart rate) as a non-invasive probe of cardiac workload and therefore myocardial oxygen demand [18,19]. In this direction, cardiovascular conditions that increase myocardial oxygen consumption such as tachycardia, arterial hypertension, increased myocardial contractility, increased left-ventricular wall stress, and/or sympathetic activation cause a commensurate increase in resting MBF [10]. And indeed, increases in resting MBF in the endogen type of CMD were related to higher resting heart rates, SBPs, indicative of the myocardial workload in individuals with arterial hypertension observed predominantly in morbid obesity.

It is important to keep in mind that nervousness and/or even anxiety of a patient just before the stress test and PET imaging may represent a confounding factor leading to an increase in heart rate and/or arterial blood pressures associated with higher resting flows and thus given normal hyperemic MBFs diagnosed as endogen CMD that may not be present during daily activities with normal heart rate and arterial blood pressures associated with normal resting MBF. Thus, the diagnosis of endogen CMD therefore needs to cautiously be interpreted in the appropriate clinical context and/or cardiovascular risk constellation. Since resting MBF depends on the metabolic and thus oxygen demand, however, resting MBF values may be increased in the presence of e.g. arterial hypertension and, thus, the MFR may have been widely consumed already. In this respect, the resting MBF can be normalized to the rate-pressure product ($RPP = \text{heart rate} \times \text{systolic blood pressure}$). This enable the calculation of the so-called normalized MFR ($nMFR = \text{stress MBF} / \text{normalized rest MFR}$) as a reflection of coronary artery function independent of the actual measured resting MBF. Such calculations are commonly performed for an accurate comparison of coronary circulatory function among groups in research studies. This, however, does not seem advisable in the clinical setting as it may mask physiological flow abnormalities. For example, a reduced MFR due to increases in resting MBF related to high arterial blood pressures (endogen type of CMD) may account for chest pain and/or shortness of breath and provides a specific treatment target, that otherwise may be missed by the calculation of the normalized MFR.

The findings of an increase in myocardial workload in morbid obesity associated with higher resting MBFs accords with a previously demonstrated activation of the sympathetic nervous system and renin-angiotensin-aldosterone system and an increase in resting MBF in obesity [20]. Of further interest, when the resting MBF was normalized to the rate-pressure-product or myocardial workload, the normalized MBF was still significantly higher in the endogen type of CMD than in the endogen type of nCMD. Such observations may strongly suggest that in a subset of patients the increase in myocardial workload, as reflected by an increase in rate-pressure-product, be paralleled by a disproportionate increases in the RPP commonly seen in advanced obesity and/or type 2 diabetes mellitus likely related to additional metabolic conditions such as the insulin resistant state [21].

Notably, the identification of an impairment of MFR due to increases in resting MBF may be responsible for chest pain and/or shortness of breath and provides a specific treatment target, otherwise missed by semi quantitative calculation of MFR only [3]. It is intriguing to speculate that the endogen type of CMD likely confers a cardiovascular risk with left ventricular hypertrophy triggered manifestation of heart failure, ventricular arrhythmia and sudden cardiac death as opposed to the classical type of CMD with CAD induced athero-thrombotic events that warrants further investigation with large-scale clinical outcome trials.

In the entire study population, gender, BMI, age, LDL cholesterol,

high-sensitive CRP, plasma glucose, and glycosylated hemoglobin were predictive of a CMD. By multivariate analysis, however, only age and glycosylated hemoglobin remained independent predictors of the CMD. Advancing age has been reported to be associated with a mild and progressive decrease in hyperaemic MBFs that has been related to some alterations in the neuroendocrine regulation of the cardiovascular system and increase in arterial vessel stiffness [22]. Apart from this, not only the numbers of cardiovascular risk components but also the duration of its exposures may be critical in the development of CMD [13,17]. In addition, increasing severity of insulin-resistance and carbohydrate intolerance has been demonstrated to be paralleled by a progressive worsening of CMD [23]. The independent predictive value of glycosylated hemoglobin for CMD likely is a reflection of complex interactions between components of the metabolic syndrome such as increases in body weight, arterial hypertension, insulin resistance, and micro-inflammation to alter coronary microvascular function [20,23]. Of further interest, the classical type of normal CMF with MFR ≥ 2.0 is commonly related to normal hyperaemic MBFs also with values ≥ 2.0 mL/g/min as observed for ^{13}N -ammonia PET flow studies [10]. This classical type of normal CMF was observed in 74% as opposed to the endogen type in 26% in the current study. The endogen type of normal CMF is related to lower resting MBFs commonly related to lower heart rate and/or arterial blood pressures leading with a lower metabolic demand as observed in the current study. The relative decrease in resting MBF then also lowers the threshold of the hyperemic MBF as lower arterial blood pressures cause reductions in intracoronary driving pressure leading to lower hyperaemic MBFs [10]. In this respect, it is important to realize that in the presence of the endogen type of normal CMF, mild down-stream effects of diffuse CAD and/or an impairment of flow-mediated coronary vasodilation during hyperemic flows stimulation may not become apparent [24].

There are some limitations worthy of considerations. At first, we did study a population with a low likelihood of flow-limiting obstructive CAD with a predominant cardio-metabolic risk profile. Thus, the current results likely are biased to this specific study population analyzed for the prevalence and different types of CMD. The relatively small sample size and single center study design may have also contributed to this selection bias. Albeit that the prevalence of CMD was high enough to draw conclusions on differences between CMD phenotypes in this specific study population, larger prospective and multicenter investigations in symptomatic and cardiovascular risk patients are warranted. Further, echocardiography was not systematically performed to identify aortic stenosis and/or left ventricular hypertrophy that may account for increases in resting flow.

5. Conclusions

In this contemporary clinical study population, slightly more than half of symptomatic patients had CMD with predominance of the classical over the endogen type. These observations underline the necessity for standardized reporting of CMD for an individualized and/or optimized medical treatment to improve symptoms and/or clinical outcome in these patients that, however, warrants further large-scale clinical investigations.

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Not applicable.

CRediT authorship contribution statement

Anita R. Bhandiwad: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing. **Ines Valenta:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing. **Sudhir Jain:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – review & editing. **Thomas H. Schindler:** Investigation, Resources, Data curation, Writing – original draft, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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