

Improvement in coronary circulatory function in morbidly obese individuals after gastric bypass-induced weight loss: relation to alterations in endocannabinoids and adipocytokines

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Aims

To investigate the effect of surgical gastric bypass-induced weight loss and related alterations in endocannabinoids (ECs) and adipocytokine plasma levels on coronary circulatory dysfunction in morbidly obese (MOB) individuals.

Methods and results

Myocardial blood flow (MBF) responses to cold pressor test (CPT) from rest (Δ MBF) and during pharmacologically induced hyperaemia were measured with ¹³N-ammonia PET/CT in 18 MOB individuals with a body mass index (BMI) > 40 kg/m² at baseline and after a median follow-up period of 22 months. Gastric bypass intervention decreased BMI from a median of 44.8 (inter-quartile range: 43.3, 48.2) to 30.8 (27.3, 34.7) kg/m² ($P < 0.0001$). This decrease in BMI was accompanied by a marked improvement in endothelium-related Δ MBF to CPT and hyperaemic MBFs, respectively [0.34 (0.18, 0.41) from 0.03 (−0.08, 0.15) mL/g/min, $P = 0.002$; and 2.51 (2.17, 2.64) from 1.53 (1.39, 2.18) mL/g/min, $P < 0.001$]. There was an inverse correlation between decreases in plasma concentrations of the EC anandamide and improvement in Δ MBF to CPT ($r = -0.59$, $P = 0.009$), while increases in adiponectin plasma levels correlated positively with hyperaemic MBFs ($r = 0.60$, $P = 0.050$). Conversely, decreases in leptin plasma concentrations were not observed to correlate with the improvement in coronary circulatory function ($r = 0.22$, $P = 0.400$, and $r = -0.31$, $P = 0.250$).

Conclusions

Gastric bypass-related reduction of BMI in MOB individuals beneficially affects coronary circulatory dysfunction. The dysbalance between ECs and adipocytokines appears to be an important determinant of coronary circulatory function in obesity.

Keywords

Adipocytokines • Coronary circulation • Endocannabinoids • Endothelium • Myocardial blood flow • Obesity • Positron emission tomography

Introduction

The prevalence of obesity in adults in the USA and in industrialized countries continues to exceed 30% in most sex-age groups, and ~6–8% have morbid or severe obesity [body mass index

(BMI) ≥ 40 kg/m²].¹ Epidemiological investigations have demonstrated that obesity is associated with increased cardiovascular morbidity and mortality.² In individuals with increasing body weight, progressive worsening of coronary endothelial function may ensue, while the functional abnormality may extend to an

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impairment of the total coronary vasodilator capacity in obesity.³ Although an impairment of coronary circulatory function has been appreciated as functional precursor of the coronary atherosclerotic disease (CAD) process, the exact mechanism by which obesity initiates and accelerates CAD is still poorly understood. As we have recently shown,⁴ increased endocannabinoid (EC) plasma levels of anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which are predominantly produced and released from the adipose tissue in obese individuals, are associated with coronary circulatory dysfunction. This observation may suggest increases in EC plasma levels as a novel endogenous cardiovascular risk factor in obesity. Interestingly, in morbid obesity, potential adverse effects of ECs and insulin-resistant syndrome on coronary circulatory function appear to be balanced, at least in part, by a seven-fold increase in leptin plasma levels.⁵ Yet, the role of leptin to alter coronary circulatory function still remains a matter of ongoing debate.³ Also, adiponectin as another adipocytokine has been widely realized to exert beneficial effects on the function of the coronary circulation.⁶ Weight loss by lifestyle interventions combined with anti-obesity medications or gastric bypass, however, has been demonstrated to improve endothelial function of the peripheral circulation in obese or morbidly obese (MOB) individuals.^{7,8} The effect of gastric bypass-induced weight loss on ECs, adipocytokines, and coronary circulatory dysfunction in MOB individuals, however, still remains to be characterized.

With this in mind, we investigated whether surgical bypass-induced weight loss in MOB individuals ($\text{BMI} \geq 40 \text{ kg/m}^2$) improves coronary circulatory dysfunction after a follow-up (FU) period of at least 12 months and how this beneficial effect on the coronary circulation is related to changes in body weight, EC, adiponectin, and leptin plasma levels.

Methods

Study population and design

In a prospective, baseline, and longitudinal FU study, coronary circulatory function was assessed with ^{13}N -ammonia and PET/CT (64-slice Biograph HiRez TruePoint PET-CT scanner, Siemens, Erlangen, Germany) by measuring myocardial blood flow (MBF) at rest and its response to vasomotor stress in 18 MOB individuals ($\text{BMI} \geq 40 \text{ kg/m}^2$) without arterial hypertension, hypercholesterolaemia, smoking, and diabetes mellitus before and after a FU of at least 12 months of gastric bypass (bariatric) surgery as a weight reduction treatment.⁹ The standard operation involved Roux-en-Y gastric bypass surgery with an isolated gastric pouch <2 ounces and a 100 cm distal bowel limb. In addition, MBF values were compared with those in 18 healthy, normal weight, age- and gender-matched controls (CON; $\text{BMI} < 25 \text{ kg/m}^2$), who served as reference to define the normal range of coronary circulatory function. Among the initial 25 MOB individuals who underwent PET baseline examination,⁵ 18 repeated the PET examination after an FU of at least 12 months (median FU: 22 months and inter-quartile range, IQR: 14–28 months), while 7 MOB individuals did not repeat study examinations simply for convenience and lack of interest. Study applicants were recruited only for study purpose in the absence of any cardiac or vasoactive medication such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, statins, or β -blockers, a history

of variant angina, a family history of premature CAD, current or previous smoking, or clinically manifested cardiovascular or any other systemic disease. In addition, throughout the study period, no cardiac or vasoactive medication was initiated in any study participants. Following, the applicants underwent an initial screening visit including a physical examination, electrocardiogram, blood pressure measurements, and routine blood chemistry in a fasting state entailing lipid profile and plasma levels of triglycerides, insulin, glucose, high-sensitive C-reactive protein (CRP), and haemoglobin Alc. Physical examination and electrocardiogram were normal in all study applicants. In addition, study applicants with evidence of left ventricular hypertrophy on echocardiography were not recruited for current study. Subsequently, each study participant underwent dual X-ray absorptiometry (Hologic QDR4500A, Hologic, Bedford, MA, USA) to measure body composition, total fat burden, and fat distribution.⁵ This was followed by ^{13}N -ammonia PET/CT assessment of myocardial perfusion and MBF. A prerequisite for the study inclusion was a normal stress–rest perfusion imaging on ^{13}N -ammonia PET/CT, which widely excluded the presence of flow-limiting CAD lesions. Controls and all MOB individuals were part of previous baseline investigations determining the effect of altered EC, adiponectin, and leptin plasma levels in obesity and morbid obesity on coronary circulatory function.^{4,5} Routine blood chemistry, EC such as AEA and 2-AG, adiponectin, and leptin plasma levels were assessed as previously described.⁴ 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.

PET/CT assessment of myocardial perfusion and flow

Myocardial perfusion and MBF, measured in mL/min/g , were determined with ^{13}N -ammonia PET/CT, serial PET image acquisition, and a two-compartment tracer kinetic model as described previously.⁴ The gated PET emission data were used for the analysis of the relative ^{13}N -ammonia uptake of the left ventricle, and thus, myocardial perfusion was evaluated visually on reoriented short- and long-axis myocardial slices and semi-quantitatively on the corresponding polar map from the last static 18 min transaxial PET image. For the semi-quantitative analysis of the PET perfusion images, a 17-segment model and a 5-point grading system by two expert observers were used.⁴ Myocardial blood flow was measured at rest, during sympathetic stimulation with cold pressor testing (CPT), reflecting predominantly endothelium-dependent circulatory function, and during dipyridamole-stimulated hyperaemic flow increases ($140 \mu\text{g/kg/min}$ dipyridamole), reflecting predominantly flow increases due to vascular smooth muscle relaxation of coronary arteriolar vessel.³ The increase in MBF from rest to CPT was defined as endothelium-related ΔMBF (mL/min/g). The myocardial flow reserve (MFR) was calculated as the ratio of adenosine MBF over rest MBF. Heart rate, blood pressure, and a 12-lead electrocardiogram were recorded continuously during each MBF measurement. The rate–pressure product (RPP), which is a product of the mean heart rate and systolic blood pressure (SBP) during the first 2 min of image acquisition, served as an index of cardiac work. Further, 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 (mmHg) 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; $\text{NMBF} = \text{MBF}$ divided by RPP multiplied by 10 000).

Statistics

Because continuous variables are not always normally distributed, they are presented as median and IQR (25th to 75th percentile: quartile 1, quartile 3). For comparison of differences between MOB individuals and CON, we used the Mann–Whitney *U* test for independent samples (SAS Institute, Cary, NC, USA), while when analysing differences between MOB-baseline and MOB-FU, we used the Wilcoxon test for related samples. A comparison of CPT-induced change in MBF and dipyridamole MBFs among the different groups was performed by one-way analysis of variance followed by Scheffe multiple comparison tests. Pearson correlation coefficients (*r*), assuming a linear regression and the standard error of the estimate, were calculated to investigate the associations between CPT- and dipyridamole-induced changes in MBFs and laboratory parameters. All test procedures were two-tailed, and $P \leq 0.05$ was considered statistically significant. Using an SD of 0.18 of Δ MBF to vasomotor stress, and a minimum clinically relevant difference in Δ MBF of 0.20 in flow response, $\alpha = 0.05$, and a power ($1 - \beta$) of 0.8, a minimum sample size of 10 individuals was estimated to be needed for repeat long-term PET flow studies.^{10,11}

Clinical characteristics, haemodynamics, and myocardial blood flow measurements at baseline

The clinical characteristics, anthropometrical measurements, and dual X-ray absorptiometry-determined total fat burden and fat distribution of the study groups can be appreciated in *Table 1*. There were no significant differences in clinical characteristics, haemodynamics, and MBFs in MOB groups with and without FU at baseline (*Tables 1* and *2*). Thus, there are no baseline characteristics that could be identified (with the given power/sample size) to have influenced lack of FU.

Resting heart rate was higher in MOB individuals than in CON, while SBP did not differ significantly (*Table 2*). Due to the higher heart rate at rest in MOB individuals, the resting RPP was significantly higher in MOB individuals than in CON. The higher RPP at rest in MOB individuals was associated with a significantly higher resting MBF than in CON (*Table 2*). When adjusted for the RPP, the normalized MBF (NMBF) at rest, however, was comparable among groups. CPT-induced sympathetic stimulation did lead to a significant increase in the heart rate and SBP in each group, so that the RPP was significantly higher during CPT than at baseline (*Table 2*). CPT-related increase in SBP, however, was higher in MOB individuals than in CON, while it was comparable for the heart rates. Although the RPP during CPT was also higher in MOB individuals than in CON, MBFs during CPT tended to be lower in MOB than in CON individuals. When adjusted for RPP, the NMBF during CPT was significantly lower in MOB individuals than in CON. Further, when looking at the CPT-related increase in RPP from rest (Δ RPP), it was comparable between CON and MOB individuals, whereas the corresponding change in MBF from rest to CPT (Δ MBF) was significantly less in MOB individuals than in CON (*Table 2, Figure 1A*). Thus, despite comparable increases in cardiac work with CPT, the endothelium-related change in MBF was significantly impaired in MOB individuals. These observations are further substantiated by evaluating changes in CVR to CPT. As can be seen further in *Table 2*, changes of CVR mirrored those of MBF for each study group. The observed differences in haemodynamic responses therefore did not account for altered MBF responses to CPT. With regard to dipyridamole-stimulated hyperaemic MBFs and MFR, they were significantly lower in MOB individuals than in CON (*Table 2, Figure 1B*). Further, we related hyperaemic MBFs to the mean arterial

blood pressure in order to account for potential interindividual variations in coronary driving pressure. The resulting CVR during dipyridamole stimulation was abnormally increased when compared with CON.

Follow-up studies after gastric bypass-induced weight loss in morbidly obese individuals

As expected, gastric bypass surgery produced a median decrease of 31.8% (28.3, 36.5) in BMI and 50.5% (41.7, 61.8) in fat mass, respectively (*Table 1*). While nine of the initial MOB individuals had achieved BMI < 30 kg/m², nine remained between 30 and 35 kg/m². After FU, plasma total cholesterol, LDL cholesterol, triglyceride, glucose, insulin, HOMA, and CRP had significantly declined from baseline in MOB individuals, whereas HDL cholesterol had increased (*Table 1*). The gastric bypass-induced weight loss was paralleled by a significant decrease in AEA, 2-AG, and leptin plasma levels. Contrary to this, weight loss resulted in a significant increase in adiponectin plasma at the FU. In addition, AEA and 2-AG plasma levels after the FU were lower ($P = 0.792$ and $P = 0.012$), while leptin and adiponectin plasma levels were higher when compared with CON ($P = 0.550$ and $P = 0.035$).

Haemodynamics and myocardial blood flow measurements at follow-up

Also at the FU, ¹³N-ammonia PET rest–stress perfusion examination was normal in all MOB individuals. Resting heart rate, SBPs, and RPPs were lower at the FU than at baseline in MOB individuals (*Table 2*). As a consequence, resting MBF on repeat assessment tended to be lower. When adjusted for the RPP, however, the NMBF at rest was similar between baseline and FU examination (*Table 2*). During sympathetic stimulation with CPT, heart rate, SBPs, and RPPs were also significantly lower at the FU than at baseline. Conversely, MBFs during CPT were significantly higher at the FU than at baseline. This improvement in CPT-related MBFs during the FU was also confirmed when MBFs were adjusted for RPP. Also here, the NMBF during CPT was significantly higher at the FU than at baseline. Further, the CPT-related increase in RPP from rest (Δ RPP) between baseline and FU examination did not differ significantly, while the Δ MBF to CPT was significantly higher at the FU when compared with baseline (*Table 2, Figure 1A*). This improvement in endothelium-related Δ MBF was comparable with those of CON (*Figure 1A*). As regards dipyridamole-stimulated hyperaemic MBFs at the FU, they were also observed to be significantly higher than at baseline and comparable with those of CON (*Table 2, Figure 1B*). The improvement in hyperaemic MBFs after the FU was also paralleled by a significant decrease in CVR at the FU when compared with baseline in MOB individuals.

Comparison of myocardial blood flow responses, changes in body fat, adipocytokines, and endocannabinoid concentrations

Alterations in routine blood chemistry, EC such as AEA and 2-AG, adiponectin, and leptin plasma levels from baseline to the FU were expressed as the difference in concentrations at baseline and the FU. Changes in BMI, fat mass, and laboratory parameters in MOB individuals were compared with those of improvement in the flow response to CPT and dipyridamole stimulation, respectively. These changes were defined as the difference in Δ MBF to CPT and hyperaemic MBF between the FU and baseline (e.g. difference in Δ MBF to

Table 1 Characteristic of the study population

	CON	MOB base only	MOB base	P-value vs. CON	P-value vs. MOB base only	MOB follow-up	P-value vs. MOB base
Age, years	41 (36, 47)	46 (41, 51)	43 (36, 52)	0.317	0.463	44 (37, 53)	0.0001
Gender, F/M	8/10	3/4	8/10			8/10	
Total fat amount, g	12 461 (9906, 15 470)	62 484 (51 240, 67 359)	57 009 (50 469, 61 180)	0.0001	0.072	28 222 (19 288, 35 677)	0.0001
BMI, kg/m ²	22 (21, 23)	44 (41, 46)	45 (43, 49)	0.0001	0.084	31 (28, 35)	0.0001
Percentage of body fat, %	20 (15, 26)	49 (44, 51)	45 (41, 49)	0.0001	0.443	29 (25, 40)	0.0001
Central fat distribution	0.40 (0.38, 0.44)	0.55 (0.50, 0.57)	0.56 (0.46, 0.62)	0.0001	0.425	0.50 (0.42, 0.52)	0.001
Waist, cm	82 (80, 85)	132 (127, 143)	124 (119, 139)	0.0001	0.315	100 (96, 103)	0.012
Waist/hip ratio	0.84 (0.81, 0.88)	0.99 (0.96, 1.09)	0.91 (0.82, 1.01)	0.539	0.147	0.83 (0.80, 0.92)	0.012
AEA, ng/mL	0.56 (0.49, 0.68)	0.74 (0.69, 0.82)	0.70 (0.58, 0.93)	0.016	0.540	0.5 (0.5, 0.7)	0.003
2-AG, ng/mL	1.80 (1.00, 5.70)	3.03 (1.6, 4.7)	2.9 (1.3, 4.4)	0.753	0.599	1.0 (0.8, 1.4)	0.001
Leptin, ng/mL	4.5 (1.9, 10.1)	142.9 (59.3, 159.8)	101.3 (67.0, 113.7)	0.0001	0.240	7.2 (3.5, 13.4)	0.0001
Adiponectin, ng/mL	3.4 (2.0, 5.3)	0.41 (0.3, 0.5)	2.6 (2.1, 3.8)	0.207	0.067	6.0 (2.2, 10.5)	0.007
Cholesterol levels, mg/dL	191 (168, 238)	169 (162, 192)	180 (157, 201)	0.231	0.464	144 (123, 177)	0.006
LDL level, mg/dL	128 (106, 148)	111 (104, 130)	118 (99, 130)	0.066	0.931	77 (65, 98)	0.0001
HDL level, mg/dL	55 (39, 63)	42 (39, 42)	43 (37, 54)	0.095	0.118	49 (43, 81)	0.018
Triglyceride level, mg/dL	54 (48, 106)	77 (60, 99)	115 (81, 144)	0.0001	0.378	77 (55, 99)	0.001
Glucose level, mg/dL	94 (83, 103)	103 (85, 120)	99 (95, 111)	0.024	0.691	86 (75, 96)	0.004
Insulin, mU/L	2.8 (1.9, 5.0)	16.4 (10.8, 24.9)	21.3 (6.0, 28.6)	0.0001	0.899	4.1 (1.9, 10.0)	0.005
HOMA	0.7 (0.5, 1.2)	3.7 (2.7, 6.7)	5.0 (0.8, 8.6)	0.004	0.851	0.9 (0.4, 3.5)	0.005
C-reactive protein levels, mg/L	0.9 (0.9, 3.0)	10.2 (7.5, 15.5)	6.5 (3.3, 9.5)	0.0001	0.512	0.9 (0.9, 1.4)	0.003
HbA _{1c} , %	5.2 (5.0, 5.5)	5.3 (5.2, 5.4)	5.4 (5.3, 5.7)	0.053	0.219	5.1 (4.8, 5.2)	0.007

Values are median (Q1, Q3). Base, baseline examination; CON, controls; MOB, morbid obesity; AEA, anandamide; 2-AG, 2-arachidonoylglycerol; BMI, body mass index; bA1c, haemoglobin A1c; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein.

Table 2 Haemodynamic and myocardial blood flow findings during PET/CT examinations

	Groups			P-value vs. CON	P-value vs. MOB base only	MOB follow-up	P-value vs. MOB base
	CON	MOB base only	MOB base				
Haemodynamics at rest							
Heart rate (b.p.m.)	61 (53, 69)	68 (61, 73)	68 (66, 78)	0.010	0.454	60 (57, 69)	0.067
SBP (mmHg)	114 (109, 123)	123 (114, 126)	115 (110, 128)	0.486	0.605	106 (103, 119)	0.006
RPP	6745 (6192, 7749)	8317 (6941, 9444)	8144 (7310, 9354)	0.018	0.842	6601 (5806, 8056)	0.031
CPT							
Heart rate (b.p.m.)	70 (63, 84)	79 (73, 86)	74 (69, 84)	0.330	0.514	70 (61, 80)	0.0001
P-value vs. heart rate at rest	0.0001	0.022	0.046			0.001	
SBP (mmHg)	135 (125, 142)	151 (147, 159)	148 (131, 158)	0.013	0.288	134 (120, 140)	0.008
P-value vs. SBP at rest	0.0001	0.0001	0.001			0.001	
RPP	9088 (8618, 10 824)	1232 (11 233, 13 525)	10 902 (9588, 11 801)	0.007	0.295	8911 (7860, 11 200)	0.022
P-value vs. RPP at rest	0.0001	0.0004	0.001			0.001	
ΔRPP (CPT-rest)	2469 (1693, 3192)	3711 (2812, 4411)	2813 (1283, 3823)	0.581	0.199	1989 (1765, 3672)	0.744
Pharmacological vasodilation							
Heart rate (b.p.m.)	85.0 (73, 91)	93 (83, 100)	84 (75, 100)	0.645	0.345	91 (80, 94)	0.422
P-value vs. heart rate at rest	0.0001	0.0002	0.001			0.002	
SBP (mmHg)	114 (105, 118)	124 (120, 131)	119 (112, 137)	0.028	0.656	101 (95, 122)	0.008
P-value vs. SBP at rest	0.050	0.362	0.528			0.480	
RPP	8970 (8030, 10 375)	11 590 (10 199, 12 403)	11 418 (8850, 12 294)	0.029	0.319	9660 (8000, 11 011)	0.381
P-value vs. RPP at rest	0.0001	0.0002	0.002			0.005	
ΔRPP (pharmacological rest)	1740 (1302, 2794)	3283 (2514, 3809)	2420 (1102, 4080)	0.528	0.259	2614 (892, 4576)	0.619
MBF (mL/min/g)							
MBF at rest	0.69 (0.61, 0.78)	0.82 (0.78, 0.94)	0.87 (0.66, 1.02)	0.013	0.600	0.73 (0.66, 0.90)	0.396
NMBF at rest	0.95 (0.86, 1.14)	1.12 (1.05, 1.17)	1.05 (0.88, 1.16)	0.446	0.607	1.19 (0.99, 1.34)	0.170
MBF during CPT	1.00 (0.83, 1.19)	0.89 (0.77, 0.97)	0.93 (0.80, 0.98)	0.107	0.804	1.08 (0.91, 1.34)	0.034
P-value vs. MBF at rest	0.0001	0.596	0.298			0.0001	
ΔMBF to CPT from rest	0.26 (0.23, 0.41)	0.07 (−0.03, 0.14)	0.00 (−0.11, 0.18)	0.0001	0.870	0.36 (0.18, 0.44)	0.001
NMBF during CPT	1.05 (0.92, 1.15)	0.80 (0.61, 0.89)	0.84 (0.64, 1.00)	0.001	0.739	1.11 (0.97, 1.42)	0.001
P-value vs. NMBF at rest	0.041	0.004	0.004			0.519	
MBF during pharmacological vasodilation	2.39 (1.95, 2.57)	1.74 (1.57, 1.88)	1.53 (1.39, 2.18)	0.001	0.713	2.51 (2.17, 2.64)	0.001
P-value vs. MBF at rest	0.0001	0.0005	0.0001			0.0001	
MFR	3.40 (3.00, 3.80)	1.95 (1.79, 2.25)	2.08 (1.59, 2.54)	0.0001	0.467	3.24 (2.33, 3.99)	0.004

Continued

Table 2 Continued

	Groups		P-value vs. CON	P-value vs. MOB base only	P-value vs. MOB	MOB follow-up	P-value vs. MOB base
	CON	MOB base only					
CVR (mmHg/mL/min/g)							
At rest	119 (105, 134)	102 (93, 113)	0.127	0.339	106 (96, 126)	108 (89, 121)	0.711
During CPT	96 (74, 111)	126 (113, 143)	0.002	0.666	128 (97, 135)	90 (72, 116)	0.014
P-value vs. CVR at rest	0.0001	0.021			0.032	0.009	
Δ change to CPT from rest	-25 (-37, -16)	17 (14, 33)	0.0001	0.962	18 (-5, 36)	-10 (-25, 1.4)	0.002
Pharmacological vasodilation	34 (27, 38)	51 (48, 56)	0.0001	0.894	58 (42, 64)	33 (28, 41)	0.001
P-value vs. CVR at rest	0.0001	0.0001			0.0001	0.0001	

Values are median (Q1, Q3). Base, baseline exam; CON, controls; MOB, morbid obesity; RPP, rate-pressure product; CPT, cold pressor test; MBF, myocardial blood flow; NMBF, normalized MBF; MFR, myocardial flow reserve; CVR, coronary vascular resistance.

CPT = ΔMBF to CPT FU - ΔMBF to CPT baseline). As can be appreciated in Table 3, although the decrease in BMI and fat mass after the FU was paralleled by a normalization of coronary circulatory function, no association was observed with the improvement in endothelium-related MBF responses to CPT. Similarly, the gastric bypass-induced alterations in 2-AG, adiponectin, leptin, CRP, lipid profile, triglycerides, glucose, and HOMA did not correlate with the difference in ΔMBF to CPT, while there was a significant association between the decrease in AEA plasma levels and the improvement in endothelium-related MBF responses to CPT (Figure 2A). In order to account for haemodynamic differences between baseline and FU studies, we also related alterations of ΔCVR to CPT to gastric bypass-induced weight loss and metabolic parameters (Table 3). Indeed, the observed correlation was also maintained when alterations in ΔCVR were related to the decrease in AEA plasma levels. In addition, there was also a trend of association between alterations in ΔCVR and the decrease in total fat amount but it did not reach statistical significance ($P = 0.088$). As regards the increase in hyperaemic MBFs between baseline and the FU, it was only significantly associated with the increase in adiponectin plasma levels (Figure 2B), and inversely with the decrease in glucose plasma levels (Table 3). When evaluating the corresponding change in CVR during dipyridamole stimulation, it correlated only with the increase in adiponectin plasma levels. In order to evaluate whether an improvement in endothelium-related MBF response to CPT also contributed to the observed increase in hyperaemic MBFs after the FU, we evaluated a possible association between the difference in ΔMBF to CPT and difference in hyperaemic MBF. Indeed, the difference in ΔMBF to CPT significantly correlated with the difference in hyperaemic MBF ($r = 0.50$, $P < 0.0001$) (Figure 3).

Discussion

The results of the current investigation provide several unique observations. At first, gastric bypass-induced weight loss in MOB individuals widely normalized coronary circulatory dysfunction. In addition, the decrease in ECs plasma levels of AEA, associated with the weight loss, was closely associated with the normalization of coronary endothelial function. This close association between the decrease in EC plasma levels and improvement in endothelium-related MBF response to CPT provides further evidence of adverse effect of elevated EC plasma levels on obesity-related coronary vasculopathy.^{4,5} Secondly, gastric bypass-induced weight loss in MOB individuals was paralleled by a marked increase in adiponectin plasma levels, which was significantly associated with the improvement in hyperaemic flow increases. Weight loss-induced increases in adiponectin plasma levels, therefore, were associated with relatively higher increases in hyperaemic flows, which could possibly reflect a beneficial effect of adiponectin in concert with the weight loss, and/or adiponectin-related but still undetermined factors on total integrated coronary vasodilator capacity. Thirdly, the decrease in leptin plasma levels with decreasing body weight was not observed to be related to the improvement in coronary circulatory function at the FU. This observation may emphasize that beneficial effect of leptin plasma levels on endothelium-related coronary function may operate predominantly in MOB individuals with a seven-fold increase of its concentration to counterbalance the adverse effects of obesity on coronary circulatory dysfunction as described previously.⁵ Fourthly, as we observed a significant association between the improvement in endothelium-related MBF

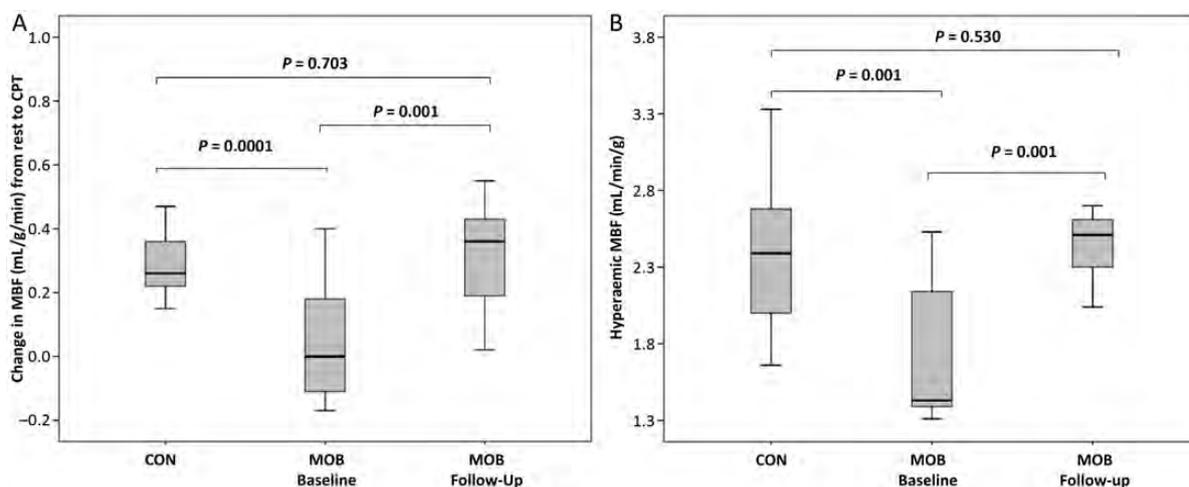


Figure 1 Myocardial blood flows (MBF) during vasomotor stress in controls (CON) and morbidly obese (MOB) individuals. Change in MBF to cold pressor testing from rest (A) and in hyperaemic MBF (B) in CON and in MOB individuals at baseline and at the follow-up.

response to CPT and hyperaemic MBFs, the increase in hyperaemic MBFs after gastric bypass-induced weight loss appears to be related by $\sim 24\%$ to the concurrent improvement in flow-mediated and, thus, endothelium-dependent coronary vasomotor function. This consideration also accords with previous investigations,¹² which have demonstrated that shear-sensitive components of the coronary endothelium contribute through a flow-mediated vasodilation by 20–25% to hyperaemic flow increases. Taken together, the weight loss-induced decrease in ECs and the increase in adiponectin plasma levels in initial MOB individuals contribute, at least in part, to the normalization of coronary circulatory function, demonstrating that the (dys)balance between ECs, adiponectin, and leptin is an important determinant of coronary circulatory function in obesity.

Morbidly obese individuals but without traditional cardiovascular risk factors such as smoking, hypercholesterolaemia, or arterial hypertension were investigated aiming to exclude possibly confounding effects of these cardiovascular risk factors on coronary circulatory function. The dramatic weight loss after a median FU period of 22 months following gastric bypass surgery normalized coronary circulatory function in these individuals when compared with an age- and gender-matched CON population. Yet, nine individuals were still overweight with BMI $< 30 \text{ kg/m}^2$ and nine individuals were still in the lower range of obesity with a BMI between 30 and 35 kg/m^2 after the FU. Thus, although this range of body weight is commonly associated with an abnormal function of the coronary circulation,^{3,4} in these initial MOB individuals, coronary circulation was normalized after a median BMI decrease from 45 to 30 kg/m^2 . These observations may suggest some kind of positive 'rebound' phenomenon on coronary circulatory function after a striking weight loss, whose exact underlying mechanisms remain to be clarified. Of particular interest, ECs were lower, while leptin and adiponectin plasma levels were higher after the FU when compared with CON. This also did hold true for ECs and adiponectin plasma levels when compared with findings in

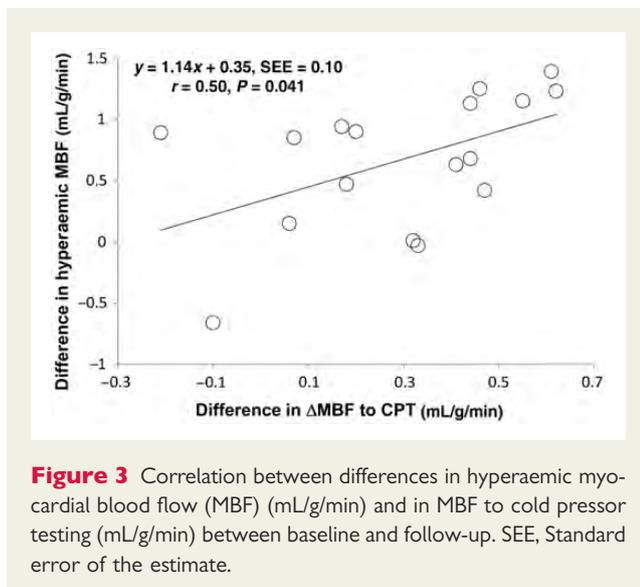
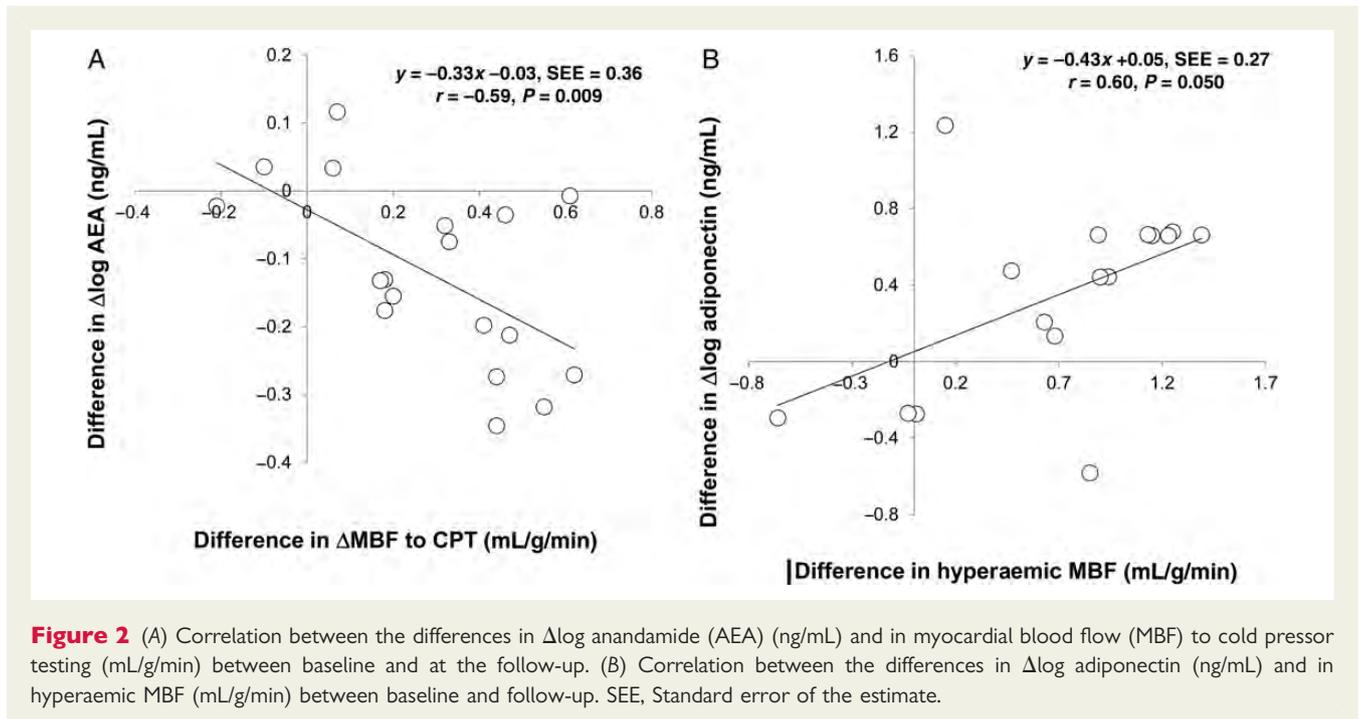
overweight and obesity, respectively,⁵ while leptin plasma levels were lower. Thus, the gastric bypass-related weight loss manifested in a relative rebound phenomenon of ECs and adipocytokines, which may explain, at least in part, the normalization of coronary circulatory function despite the fact that initial MOB individuals remained overweight or relatively obese. In addition, it is conceivable that the gastric bypass-induced weight loss, associated with an improvement in lipid profile, insulin resistance syndrome, and reductions in arterial pressure, did lead to a marked reduction in the formation of oxidative stress burden via NADPH oxidase, abnormalities in LDL subfractions and LDL oxidation, while at the same time beneficial effects of increases in HDL cholesterol and unopposed NOS activity may have prevailed. This, in fact, may have led to a positive dysbalance in favour of endothelium-derived nitric oxide formation and other yet-unknown mechanisms associated with a normalization of coronary circulatory function.¹² The marked reduction in body weight, therefore, may have conferred an enhanced beneficial effect on the production and endothelial release of atheroprotective nitric oxide within the arterial wall, similar to the one that has been described for statin withdrawal but in the other direction.¹³ Conceptually, the observations of a normalization of coronary circulatory function after a marked weight loss as compared with healthy CON could also reflect, at least in part, an issue of statistical power. The sample size of 18 MOB individuals undergoing gastric bypass to reduce body weight burden vs. 18 CON may simply not have been large enough to identify these relatively small differences in MBF responses to vasomotor stress given the relative weight differences when compared with baseline values. On the other hand, a positive rebound phenomenon on coronary circulatory function after gastric bypass-induced weight loss appears to be consistent with a recent one in MOB individuals with various traditional cardiovascular risk factors and assessment of brachial artery function.⁷ A mean decrease in BMI of $\sim 25\%$ was accompanied by an improvement in flow-mediated brachial artery dilation in the mean to 10%,

Table 3 Determinants of alterations in myocardial blood flow response to vasomotor stress after follow-up in a univariate analysis

Difference	Difference in Δ MBF to CPT		Difference in Δ CVR to CPT		Difference in hyperaemic MBF		Difference in CVR during hyperaemia	
	Coefficient β (95% CI)	P-value	Coefficient β (95% CI)	P-value	Coefficient β (95% CI)	P-value	Coefficient β (95% CI)	P-value
Log BMI	0.249 (–1.383, 3.986)	0.319	0.285 (–204.09, 726.42)	0.251	–0.174 (–8.81, 4.52)	0.504	–0.199 (–230.85, 102.94)	0.429
Log fat amount	0.236 (–0.739, 1.827)	0.379	0.440 (–30.95, 392.88)	0.088	–0.133 (–4.08, 2.59)	0.636	–0.243 (–110.19, 43.11)	0.364
Log AEA	–0.593 (–1.830, –0.299)	0.009	–0.576 (–317.21, –44.87)	0.012	0.285 (–0.72, 2.43)	0.267	–0.217 (–80.98, 33.12)	0.387
Log 2-AG	–0.103 (–0.497, 0.335)	0.685	0.058 (–65.10, 81.06)	0.820	0.158 (–0.70, 1.27)	0.544	–0.122 (–31.39, 19.60)	0.631
Log adiponectin	0.135 (–0.190, 0.315)	0.606	0.197 (–28.26, 60.77)	0.449	0.597 (0.00, 1.16)	0.050	0.462 (–0.784, 27.52)	0.052
Log leptin	0.218 (–0.202, 0.478)	0.400	0.089 (–51.79, 71.78)	0.735	–0.305 (–1.33, 0.37)	0.250	–0.120 (–26.40, 16.88)	0.646
Log glucose	–0.146 (–2.019, 1.137)	0.562	–0.380 (–458.62, 58.15)	0.120	–0.675 (–7.863, –1.96)	0.003	–0.406 (–164.64, 14.474)	0.095
Log HOMA	0.107 (–0.470, 0.614)	0.768	0.277 (–65.32, 136.58)	0.439	–0.070 (–1.25, 1.05)	0.847	–0.073 (–36.07, 30.15)	0.842
Log total cholesterol	0.136 (–0.981, 1.668)	0.590	0.249 (–116.98, 336.68)	0.320	–0.347 (–4.95, 0.97)	0.172	–0.223 (–114.61, 45.59)	0.375
Log LDL cholesterol	0.151 (–1.484, 0.820)	0.550	0.154 (–142.21, 261.03)	0.541	–0.273 (–4.12, 1.31)	0.289	–0.257 (–103.85, 34.54)	0.304
Log HDL cholesterol	0.172 (–0.505, 1.002)	0.494	0.068 (–116.39, 150.79)	0.788	–0.334 (–2.94, 0.64)	0.191	–0.121 (–57.343, 35.930)	0.633
Log triglycerides	0.446 (–0.040, 1.303)	0.064	0.379 (–27.78, 215.54)	0.121	–0.169 (–2.43, 1.27)	0.516	0.123 (–35.088, 56.446)	0.628
Log C-reactive protein	–0.245 (–0.742, 0.275)	0.343	–0.283 (–144.68, 43.74)	0.271	–0.274 (–2.09, 0.70)	0.304	–0.070 (–41.27, 31.97)	0.790

MBF, myocardial blood flow; CPT, cold pressor testing; BMI, body mass index; AEA, anandamide; 2-AG, 2-arachidonoylglycerol; SBP, systolic blood pressure; LDL cholesterol, low-density lipoprotein cholesterol; HDL cholesterol, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment for insulin resistance.

P-values by analysis of variance, significance value $P \leq 0.05$.



which is substantially higher when compared with a flow-mediated brachial artery dilation in the mean of 4.8% in a healthy study population of 4739 adults.¹⁴ Yet, it remains to be answered whether the observed improvement in, or normalization of, coronary circulatory function after a marked weight loss is sustained in the long-term in these initial MOB individuals, who are otherwise still considered overweight or mildly obese. Most likely, behavioural interventions related to weight, diet, and physical activity may be needed to stabilize the achieved normalization in coronary circulatory function.^{7,8}

Notably, the aforementioned investigation in the assessment of brachial artery function⁷ demonstrated a marked improvement in

endothelial function with a weight loss intervention after gastric bypass in MOB individuals but with other, in part, medically treated traditional cardiovascular risk factors, while the non-endothelium vascular smooth muscle cell function was not affected. Therefore, it is equally possible that the improvement in brachial artery function was related not only to surgical weight loss but also to an improved and medically treated cardiovascular risk profile of diabetes mellitus, arterial hypertension, and hypercholesterolaemia.⁷ In this scenario, the current study demonstrates the first proof that gastric bypass-induced weight loss in MOB individuals, paralleled by alterations in lipid profile, a decrease in plasma markers of the insulin resistance syndrome, and chronic inflammation, widely normalized not only endothelium-related MBF responses to CPT but also hyperaemic flow reserve. In current and previous investigation of brachial artery function in MOB individuals,⁷ the extent in the improvement in coronary circulatory dysfunction did not correlate with the degree in weight loss or decrease in total fat amount after gastric bypass. The observation of an absence of any correlation between the weight loss or decrease in total fat amount and the normalization in coronary circulatory function, respectively, most likely is also related to the striking and non-linear decrease in body weight overriding the observed improvement in coronary circulatory function. Of further interest, improved hyperaemic MBFs with weight loss correlated mildly with the decrease in plasma glucose levels. This may put forth that also a mild increase in plasma glucose levels even when within the normal range of plasma glucose levels may contribute to impairment in hyperaemic MBFs in obesity. Altered glycaemic status associated with weight loss, therefore, may reflect an important determinant of coronary vascular homeostasis in non-diabetic obese individuals, which merits further investigations.

As regards alterations in EC plasma levels, decreases in AEA plasma levels owing to the gastric bypass-induced weight loss

were closely associated with the normalization in endothelium-related MBF responses to CPT. As abnormal coronary circulatory function has been recognized as a functional precursor of the CAD process and future cardiovascular events,¹² the observed association between decreases in AEA plasma levels and the normalization of coronary endothelial function after gastric-bypass-induced weight loss provides further *in vivo* evidence that increases in AEA plasma levels may reflect indeed a potential novel risk factor for cardiovascular risk in obesity.^{4,5} Regarding the weight loss-induced decrease in 2-AG plasma levels, however, we did not observe an association neither with the normalization of endothelium-related MBF responses nor with hyperaemic MBF increases. Thus, it is possible that decreases in 2-AG plasma levels contribute to the observed normalization of coronary circulatory function after weight loss only in concert with increases in HDL and decreases in insulin resistance and inflammation. In this regard, at least in viscerally obese men, lifestyle-induced reduction of BMI and waist circumference has been demonstrated to cause reductions in 2-AG levels that are directly correlated with increases in HDL and decreases in insulin resistance.¹⁵ Independent of the exact molecular mechanisms of ECs altering the function of the arterial wall, current and recent investigations^{4,5} put forth that increases in EC plasma levels in obesity confer adverse effects on coronary circulatory function.

In the current study in MOB individuals, we did not find a significant or close association between alterations in lipid profile, insulin resistance, triglycerides, and CRP plasma levels, and the normalization of coronary circulatory function after gastric bypass-induced weight loss as someone might have expected. The reason for this astounding observation remains unclear but is likely to be related to the relatively small sample size of MOB individuals studied. Furthermore, in view of the striking decrease in gastric bypass-induced total fat, which did lead to a normalization of coronary circulatory function after a median FU of 22 months, it is also possible that coronary circulatory function normalized before the total decrease in fat amount was achieved. This, in fact, might also have added to the observed dissociation between non-linear decrease in body weight and normalization in coronary circulatory function after the FU, as also observed for flow-mediated brachial artery function.⁷

Limitations

There are some limitations worthy of consideration. The current investigation did not establish a causal relationship between plasma levels of EC, adipocytokines, and obesity-related coronary vasculopathy. Thus, further experimental investigations are certainly needed to unmask the exact mechanisms of ECs and adipocytokines in altering coronary circulatory function in obesity. In addition, although no study participants had echocardiographic evidence of left ventricular hypertrophy at baseline examination, there is still a likely possibility that the observed improvement in coronary circulatory function after weight loss may also be secondary to changes in cardiac remodelling,¹⁶ as opposed to a solely primary effect on the function of the coronary circulation. Finally, a multitude of comparisons are presented but in view of the relatively low numbers of MOB individuals without adjustment for multiplicity.

Conclusions

In this study, we have demonstrated a normalization of coronary circulatory function related to a gastric bypass-induced weight loss in MOB individuals. The associated decreases in AEA and increases in adiponectin plasma levels were associated with the normalization of coronary circulatory function after weight loss, signifying that the (dys)balance between ECs and adipocytokines may be seen as an important determinant of coronary circulatory function in obesity. As an impairment of coronary circulatory function is commonly seen as a functional precursor of the CAD process, its normalization after weight loss may reduce the association between obesity and cardiovascular risk, which, however, remains to be clinically tested.

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Conflict of interest: none declared.

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CARDIOVASCULAR FLASHLIGHT

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ST elevation myocardial infarction treated with bioresorbable vascular scaffold: rationale and first cases

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Bioresorbable vascular scaffolds (BVS) have the potential to start new era in interventional cardiology. First clinical studies in stable coronary artery disease have demonstrated a good safety profile and promising results. The use of BVS in ST elevation myocardial infarction (STEMI) has not yet been reported.

The first two implantations of BVS Absorb[®] during primary PCI for STEMI in humans performed at our institution in December 2012 are described. Both patients have given written informed consent. The first patient, a 54-year-old male, presented with typical chest pain of 90 min duration, ST elevation in inferior leads on ECG and thrombotic occlusion of the right coronary artery. This lesion was predilated and BVS Absorb 3.0/18 mm was implanted with slow 1 Atm/s inflation to 16 Atm, angiographic result was optimal. Optical coherence tomography (OCT) performed with a Fourier-domain, non-occlusive catheter (C7 Dragonfly, St Jude Medical, USA) demonstrated excellent BVS apposition to vessel wall and small residual thrombi as the site of occlusion. Our second patient, a 52-year-old male, was admitted with anterior STEMI. Coronary angiography demonstrated critical thrombotic stenosis of proximal left anterior descending (LAD) artery involving the origin of a diagonal branch (Panel A). LAD was predilated with 3.0/12-mm balloon and subsequent slow flow in the diagonal branch was treated by ostial dilatation with 2.5/15-mm balloon. Optical coherence tomography demonstrated a ruptured plaque beginning 8 mm proximal from the diagonal branch (Panel B); a maximal thrombus burden was detected just proximal from the diagonal branch (Panel C). There was no thrombus or ruptured plaque distal to diagonal branch. Bioresorbable vascular scaffold Absorb 3.5/28 mm was implanted with 1 Atm/s inflation to 16 Atm for 30 s with optimal result (Panel D). Flow in the diagonal branch remained normal. Final OCT demonstrated optimal scaffold apposition (longitudinal view on Panels E and F), widely patent ostium of the diagonal branch with clearly visible residual thrombi (Panel E) and perfect sealing of the ruptured plaque (Panel F). Both patients were treated with dual antiplatelet therapy and in-hospital course was uneventful with discharge on Day 4.

The authors believe that primary PCI in the STEMI setting might represent a suitable BVS indication. Patients with STEMI tend to be younger and any possible benefits of BVS are more likely to become evident with longer term follow-up. Despite the theoretical advantages, there are no clinical data regarding safety of BVS in thrombotic lesions. It seems prudent to ensure that every BVS implanted in highly thrombotic milieu is optimally expanded.

