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CLINICAL RESEARCH

Skin Vasodilator Function and Vasomotion in Patients with Morbid Obesity: Effects of Gastric Bypass Surgery

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Abstract Obesity-associated microvascular dysfunction (MVD) involves different body tissues, including skin, and concurs to increased cardiovascular risk in obese patients (Ob-P). Generalized improvement of MVD is an important goal in obesity treatment. Since skin MVD mirrors generalized systemic MVD, skin microvascular investigation in prospective studies in Ob-P may surrogate microvascular investigation in organs more important for cardiovascular risk of the studied patients. In this prospective study, we measured forearm skin post-occlusive reactive hyperaemia (PORH), as percentage flow increase from baseline, and skin vasomotion in 37 Ob-P before Roux-en-Y gastric bypass (RYGB), and in 24 of them about 1 year after RYGB, using laser Doppler flowmetry (LDF). The spectral contribution of skin LDF signal oscillations in the frequency intervals of 0.01–0.02 Hz, 0.02–0.06 Hz, and 0.06–0.2 Hz—corresponding to endothelial-, sympathetic-, and myogenic-dependent vasomotion, respectively, was measured by means of spectral Fourier analysis. The same measurements were also performed in 28 healthy, lean subjects (HLS). Before RYGB, Ob-P had a significant reduction in PORH and in the all vasomotion parameters investigated, compared with HLS. After RYGB, Ob-P who completed the follow-up, had a significant weight loss (~40 kg on average), together with a full normalisation in PORH and in vasomotion parameters, regardless of diabetes status. Surgically induced sustained weight loss resulted in full normalisation of skin microvascolar function in Ob-P about 1 year after RYGB. This result suggests a beneficial effect of sustained weight loss on generalized MVD of the studied Ob-P.

Keywords Obesity · Weight loss surgery · Roux-en-Y gastric bypass · Microvascular function · Skin vasomotion · Post-occlusive reactive hyperemia · Laser Doppler flowmetry

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Introduction

Obesity carries a high cardiovascular risk [1, 2]. Recently, a number of experimental and laboratory findings indicate that obesity is associated with microvascular dysfunction [3–5], which includes impaired vasodilator function of resistance vessels, reduced recruitment of capillaries during hyperaemia [3], impaired microvascular endothelial function [3, 5], and reduced vasomotion [6]. Obesity-associated microvascular dysfunction may compromise oxygen and nutrient supply to body tissues and concur to the characteristic high cardiovascular risk of obese patients. Furthermore, some authors suggest that microvascular dysfunction may contribute to arterial hypertension [3] and insulin resistance [3, 4, 7], which importantly concur to increased cardiovascular risk in obese patients. Indeed, improvement of generalized microvascular dysfunction of obese patients is considered an important goal in the treatment of obesity. In spite of this, the majority of studies that investigated the effect of weight loss on vascular system in obese patients

were focused on conduit arteries [8–10]. Only one recent study in obese patients [11] investigated the effect of surgically induced weight loss on endothelial-dependent and endothelial-independent vasodilator response at the level of skeletal muscle microcirculation.

Recently, skin microcirculation has emerged as an accessible and potentially representative vascular bed to examine the mechanisms of microcirculatory function and dysfunction [12]. Pathology-induced skin microvascular dysfunction (including impaired vasodilator function and reduced vasomotion) is evident in the skin microcirculation [13–15], and it has been suggested to mirror generalized systemic microvascular dysfunction in magnitude and underlying mechanisms [12, 16]. Therefore, investigation of skin microcirculation in prospective studies involving obese patients may surrogate the study of microvascular function in other body tissues, such as the myocardium, which are more important for the cardiovascular risk of obese patients.

Thus, the aim of this prospective study was to investigate the long-term (1 year) effect of weight loss induced by Roux-en-Y gastric bypass (RYGB) on skin vasodilator function and on skin vasomotion in morbidly obese patients in order to argue its impact on the overall microvasculature of the investigated patients.

Materials and Methods

Study Design and Subjects

In this prospective study, we planned to involve severely obese subjects consecutively selected from January 2008 to June 2008, from patients who attended our Department. Patients were selected on the basis of the following criteria: to be candidate to RYGB in the following 3 weeks from the recruitment, aged between 30 and 60 years, BMI≥40 kg/m^2, with or without associated comorbility such as hypertension, type 2 diabetes, dyslipidemia, or obstructive sleep apnea syndrome.

Obese patients were grouped as diabetic or non-diabetic based on ADA criteria [17]. Diabetic subjects who were not taking insulin were considered to have type 2 diabetes (T2DM), as well as insulin-taking diabetic subjects whose age of diabetes onset was ≥40 years. Subjects with a history of alcohol abuse, end-stage renal disease, cardiac failure, HVB or HCV chronic hepatitis, thyroid disease, or on thyroid supplementation were excluded from the study.

Healthy non-obese subjects were also recruited as a control group.

Recruited patients underwent laser Doppler flowmetry (LDF) and laboratory tests 2 weeks before RYGB. Control subjects underwent the same tests in the day after their recruitment in the study. Obese recruited patients were asked to attend our Unit 1 year after RYGB in order to repeat LDF and laboratory tests.

Laser Doppler Flowmetry

Subjects were asked to abstain from food, drugs, tobacco, alcohol, coffee, or tea for 8 h prior to the LDF and had 20 min of acclimatisation in the supine position at a room temperature of 22–24°C. LDF was performed with the subject in the supine position using a LDF apparatus (Periflux PF4001, Perimed, Jarfallan, Sweden) equipped with a non-heated probe (PF408). LDF probe was fixed to the medial surface of the right forearm of the studied subject. The LDF apparatus used had the following characteristics: 780 nm wavelength, 10 Hz–19 kHz bandwidth, 0.1 s time constant, 32 Hz sampling frequency. Before each measurement, LDF calibration was performed using colloidal latex particles whose Brownian motion provides the standard value. LDF output was recorded continuously by an interfaced computer (Acer, Travelmate 202 T) equipped with a Perisoft dedicated software. This software allows the measurement of skin blood flow at the level of the illuminated tissue, in conventional perfusion units (PU, 1 PU=10 mV).

Using the described method, skin right forearm blood flow was continuously recorded in each subject under basal conditions (15 min) and during a post-occlusive reactive hyperaemia (PORH) test (3 min ischemia, 10 min following ischemia). The PORH test was performed using a method previously reported [13]. Briefly, right forearm skin ischemia was induced by inflating a pneumatic cuff positioned on the right arm to 30 mmHg above systolic blood pressure for 3 min. After 3 min, pneumatic cuff was instantaneously deflated. Basal skin blood flow was taken as the mean value during 5 min before occlusion; maximal blood flow was the higher blood flow value recorded after cuff pressure release. The PORH was expressed as the percent change in blood flow above baseline.

Skin Vasomotion Investigation

Skin vasomotion was investigated by means of the spectral Fourier analysis of the skin LDF signal recorded during a period of 15 min before cuff inflation. The spectral Fourier analysis was performed using a Perisoft dedicated software (Perimed, Jarfallan, Sweden), as previously described [13–15]. Briefly, this software measures—in PU^2/Hz—the power spectral density (PSD) of each LDF frequency interval investigated. Based on previous studies [18, 19], the frequency range 0.01–1.6 Hz was divided into five intervals: 0.01–0.02 Hz (associated to the endothelial-dependent vasomotion (EDVM)), 0.02–0.06 Hz (related to the sympathetic-dependent vasomotion (SDVM)), 0.06–

0.2 Hz (related to the myogenic-dependent vasomotion (MDVM)), 0.2–0.6 Hz (related to the respiratory activity) and 0.6–1.6 Hz (synchronous with heart activity).

For the purpose of the present study (aimed to investigate skin vasomotion and not the all blood flow-motion) we only examined the three skin blood flow oscillations in the frequency range of 0.01–0.2 Hz, that are related to vasomotion.

The highest PSD value measured in each of these three frequency intervals was taken to be the PSD of that interval. The PSD of the of 0.01–0.2 Hz interval related to the overall vasomotion (OVM) was obtained by the sum of the PSD value of the 0.01–0.02 Hz, 0.02–0.06 Hz, and 0.06–0.2 Hz intervals.

Since skin vasomotion measurements are influenced by changes in skin blood flow [20, 21], we normalised PSD (N-PSD) for the resting blood flow values measured from the same time-window.

Laboratory Tests

Subjects were examined in the morning after an overnight (12–14 h) fast.

Peripheral blood samples were obtained for determination of the lipid profile, plasma glucose, HbA_{1c} and insulin concentrations. Fasting and 2-h post-load plasma glucose concentration was measured on a Beckman Glucose Analyzer 2 (Beckman, Fullerton, CA, USA). Fasting concentrations of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides serum levels were also measured (Synchron CX4, Beckman Instruments, Inc., Brea, CA, USA). Plasma insulin was measured by radioimmunoassay (Linco Research, St. Charles, Missouri, USA).

Statistical Analysis

All the data were expressed as mean ± standard error (SEM) or as mean ± standard deviation (SD). Comparison between control subjects and obese patients before surgery was performed using the analysis of variance (ANOVA) for unpaired data or the Kruskal–Wallis test, depending on data distribution. Comparison of obese patients before and after surgery was performed using ANOVA for repeated measures or Wilcoxon's test depending on data distribution. A p value ≤ 0.05 was considered as statistically significant. Statistical analysis was performed using GraphPad Prism Software Inc.

Results

From January 2008 to June 2008 we selected 37 obese patients, 18 with T2DM (Ob-T2DM) and 19 without T2DM (Ob-NGT), who fitted the inclusion criteria of the study. These patients underwent LDF and laboratory tests before RYGB, as well as RYGB in the 3 weeks following their recruitment. Twenty-four of the 37 recruited patients (11 Ob-NGT and 13 Ob-T2DM) completed the follow-up and underwent LDF and laboratory tests 12±2 months after RYGB. Thirteen patients did not undergo to LDF and laboratory tests 1 year after RYGB because they did not accept to complete their follow-up. We recruited also 28 non-obese healthy subjects as a control group.

Pre-surgery Results

Clinical and metabolic characteristics of the 37 obese patients enrolled in the study and the 28 control subjects are reported in Table 1. Ob-T2DM and Ob-NGT patients had similar clinical phenotypes, but diastolic blood pressure, fasting and 2-h plasma glucose and HbA_{1c} concentrations were higher in Ob-T2DM than Ob-NGT patients.

Results of baseline LDF and vasomotion measurements are reported in Table 2.

Both Ob-T2DM and Ob-NGT patients showed a significantly higher basal skin blood flow as compared to control subjects (12.03±0.97 and 13.59±1.40 vs 9.14±0.84 PU, respectively, $p=0.03$). After ischemia, there was a significant increase in skin blood flow in the all three groups, but the obese patients had a significantly lower PORH as compared with control subjects (481±62% and 419±50% for Ob-NGT and Ob-T2DM, respectively,

Table 1 Clinical and metabolic characteristics of 37 obese patients before surgery and of 28 control subjects

	Ob-NGT (19)	Ob-T2DM (18)	CS (37)
Number	19	18	28
Sex (F/M)	14/5	13/5	21/7
Age (years)	40±8	45±9	44±10
BMI (kg/m^2)*	47.0±11.8	48.3±7.1	22.7±2.3
SBP (mmHg)*	133±20	135±16	124±8
DBP (mmHg)°	78±7	85±6	79±5
Triglycerides (mg/dl)	123±49	168±105*	94±20
Total cholesterol (mg/dl)	193±38	193±35	191±9.5
HDL-cholesterol (mg/dl)	44±11	44±10	47±3
Fasting glucose (mg/dl)	92±10°	131±53	96±7
2-h glucose (mg/dl)	114±27°	227±29	115±12
Fasting insulin (μU/ml)	18.5±8.5	24.6±13.1*	7.6±0.6
HbA_{1c} (%)	5.4±0.6°	6.6±2.0	5.2±0.2

Ob-NGT normal glucose tolerance obese patients, *Ob-T2DM* type 2 diabetes obese patients, *CS* control subjects, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

* $p\leq 0.05$ vs control group; Data are mean±SD $p\leq 0.05$ vs Ob-T2DM

Table 2 Skin blood flow and vasomotion parameter investigated in 37 obese patients (before surgery) and in 28 control subjects

Parameter	Ob-NGT (19)	Ob-T2DM (18)	CS (37)	*p*
Basal SBF (PU)	12.03±0.97	13.59±1.40	9.14±0.84	0.03
PORH (%)	481±62	419±50	611±37	
OVM (PU/Hz%)	8.88±0.83	8.43±0.79	12.90±1.09	0.0021
SDVM (PU/Hz%)	3.40±0.36	3.55±0.37	4.80±0.41	0.013
MDVM (PU/Hz%)	2.15±0.26	2.07±0.28	3.76±0.46	0.0055
EDVM (PU/Hz%)	3.33±0.42	2.81±0.27	4.32±0.46	

Ob-NGT normal glucose tolerance obese patients, *Ob-T2DM* type 2 diabetes obese patients, *CS* control subjects, *SBF* skin blood flow, *PU* perfusion unit, *PORH* post-occlusive reactive hyperaemia, *OVM* overall vasomotion, *SDVM* sympathetic-dependent vasomotion, *MDVM* myogenic-dependent vasomotion, *EDVM* endothelial-dependent avsomotion. Data are mean ± SEM. The asterisk indicates that the *p* value is only related to the difference between control subjects and type 2 diabetes obese patients

p=0.013 vs 611±37% of controls) regardless for diabetes status.

Similarly, N-PSD of OVM, SDVM, and MDVM were each lower in obese patients than in controls, regardless of diabetes status. N-PSD of EDVM was lower in obese patients, but the difference was only significant for the Ob-T2DM group (p=0.04).

Post-surgery Results

A major weight loss (~40 kg on average) occurred in the 24 patients who completed the follow-up about 1 year after RYGB. As expected, fasting plasma glucose and HbA_{1c} in Ob-T2DM patients was reduced 1 year after surgery in comparison to before surgery in the same patients (Table 3). Blood pressure was reduced 1 year after surgery both in Ob-T2MD and in Ob-NGT patients in comparison to before surgery in the same patients (Table 3).

Basal skin blood flow decreased and PORH significantly increased (by ~50% each) in obese patients 1 year after RYGB in comparison to before RYGB, similarly in Ob-NGT and Ob-T2DM (Fig. 1), with complete normalisation of PORH (no significant difference in comparison with control subjects was observed). No significant difference in PORH was observed between Ob-NGT and Ob-T2DM patients after RYGB. After RYGB, all measures of skin vasomotion (N-PSD of OVM, SDVM, MDVM, and ESDM) significantly increased as compared to before surgery (with respective p values of 0.0014, 0.008, 0.008, and 0.0048) (Fig. 2), with their complete normalisation (no significant difference in post-surgery vasomotion measures was observed in comparison with control subjects). Moreover, no significant difference in all measures of skin vasomotion was observed between Ob-NGT and Ob-T2DM patients after RYGB. However, the post-surgery N-PSD value of the MDVM component tended to be higher in Ob-T2DM than in Ob-NGT, with a difference between Ob-T2DM and Ob-NGT very near to the statistical significance (p=0.06).

On the pooled pre- and post-surgery data, a significant inverse correlation was found between BMI and PORH (r^2= 0.20, p=0.0013) (Fig. 3). No significant correlation was found between BMI and PORH in each sub-groups of Ob-NGT and Ob-T2DM patients.

Discussion

The main finding of the present study was that surgically induced major weight loss in severely obese patients

Table 3 Clinical and metabolic characteristics of 24 obese patients before surgery and in the same patients 1 year after surgery

	NGT-pt		T2DM-pt	
	Before surgery	After surgery	Before	After
Sex (F/M)	8/3	10/3		
Age (years)	40±9	41±9	45±9	46±9
BMI (kg/m^2)*	47.1±7.8	32.3±6.9	49.5±6.3	32.7±4.4
SBP (mmHg)*	136±21	116±13	142±13	134±12
DBP (mmHg)*	79±7	74±9	87±6	79±7
Fasting glucose (mg/dl)*	85±6	80±7	101±11	83±13
HbA_{1c} (%)*	5.6±0.7	5.4±0.4	5.9±0.9	5.5±0.4

NGT-pt normal glucose tolerance patients, *T2DM-pt* type 2 diabetes patients, *CS* control subjects, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

*$p \leq 0.05$ for the time factor by repeated measures ANOVA

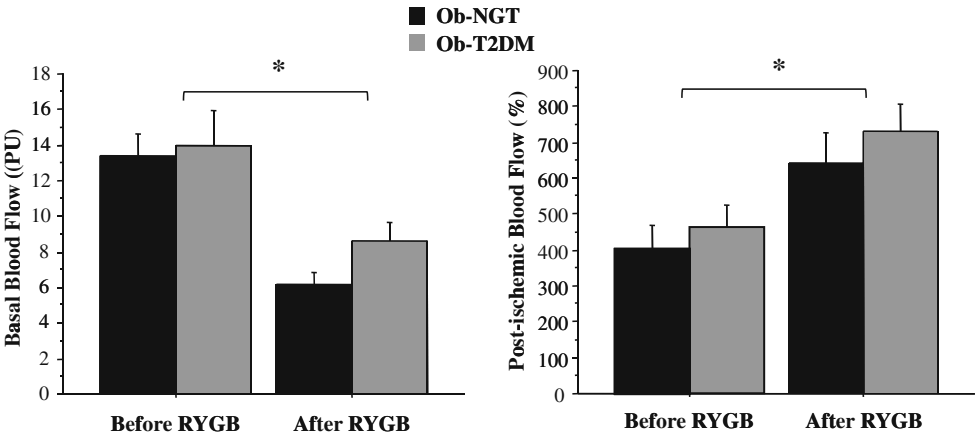

Fig. 1 Basal and post-ischemic skin blood flow in morbidly obese subjects with (*Ob-T2DM*) or without (*Ob-NGT*) type 2 diabetes, before and 1 year following weight reduction by Roux-en-Y gastric bypass surgery (*RYGB*). Data are mean and SEM, asterisks indicate differences at the $p \leq 0.05$ level

resulted in a full normalisation in skin vasodilator function and in skin vasomotion about 1 year after RYGB. Changes in skin vasodilator function and skin vasomotion following weight loss were essentially similar in obese patients with or without diabetes. A further finding of the present study was that skin vasodilator function and skin vasomotion were reduced in severely obese patients before RYGB in comparison with lean, healthy subjects.

To our knowledge, this is the first study which prospectively investigated the effect of surgically induced sustained weight loss on skin microvascular function in obese patients. Recently, skin microvascular function has been suggested to mirror microvascular function in other body tissues [12, 16]. Skin vasodilator function, which can be easily and non-invasively investigated by means of LDF, is generally considered such as an indicator of the overall skin

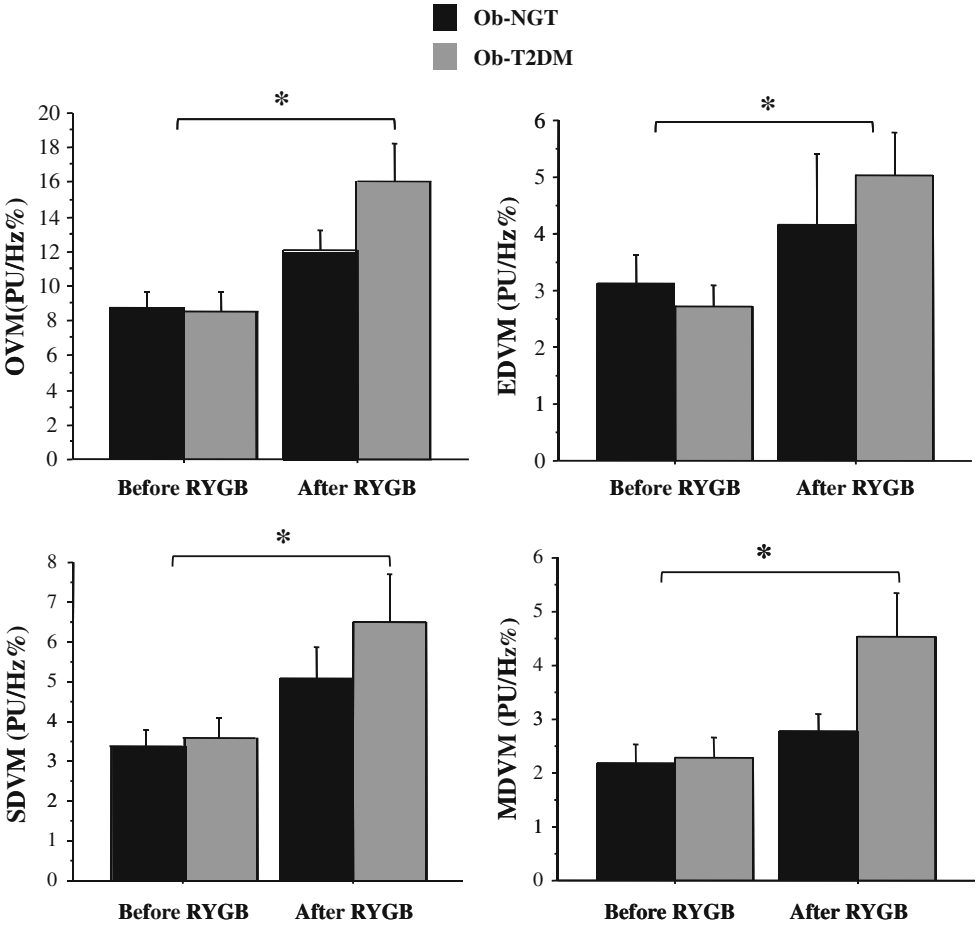

Fig. 2 Indices of vasomotion in morbidly obese subjects with (Ob-T2DM) or without type 2 diabetes (*Ob-NGT*) before and 1 year following weight reduction by Roux-en-Y gastric bypass surgery (*RYGB*). Data are mean and SEM, *asterisks* indicate differences at the $p \leq 0.05$ level. *OVM* overall vasomotion, *EDVM* endothelial-dependent vasomotion, *SDVM* sympathetic-dependent vasomotion, *MDVM* myogenic-dependent vasomotion

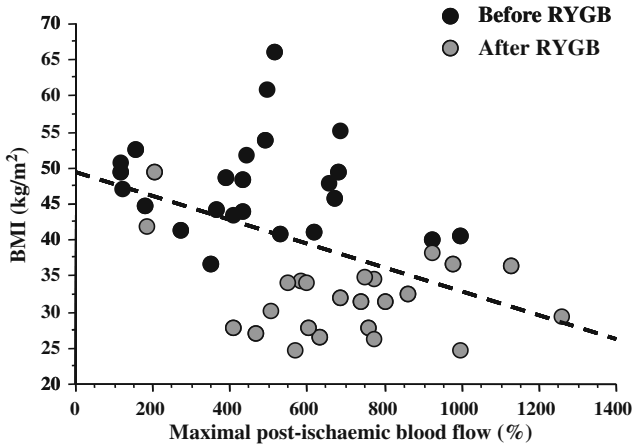

Fig. 3 Inverse correlation between BMI and post-ischemic vasodilatation in morbidly obese subjects before and 1 year after surgically induced weight loss (r^2=0.20, p=0.0013)

microvascular function, including endothelial-dependent and endothelial-independent mechanisms [15, 16, 22]. Using LDF technique, the sudden rise in skin blood flow occurring after the release of arterial occlusion, as the consequence of microvessel smooth muscle relaxation distal to the site of circulatory arrest [23], can be monitored and measured. Some evidence also suggests that this test is a reliable indicator of cardiovascular risk of investigated subjects [24].

Skin vasomotion is the rhythmic variation of skin microvessel diameter due to rhythmic contraction and dilatation of microvessel walls. Vasomotion is responsible for skin microcirculatory blood flow oscillations in microvessels, the so-called blood flow motion [25]. Results of studies based on the theoretical analysis of complex oscillations in multibranched microvascular networks [26, 27] suggest that stimulated vasomotion can increase the mean blood flow by 40–60% as compared to steady perfusion conditions. More recently, an in vivo study in rabbit ear skin clearly demonstrated that increase in microvascular vasomotion enhances tissue perfusion and promotes material exchange between tissue and blood [28]. Three mechanisms have been invoked for skin vasomotion: activity of microvessel endothelial cells [18, 19], sympathetic discharge [29, 30], and spontaneous activity of the microvessel smooth muscle cells [31]. Each of these vasomotion mechanisms is responsible for a specific blood flow motion component within a given frequency interval. In particular, the flow motion components with frequency interval of 0.01–0.02 Hz, 0.02–0.06 Hz, and 0.06–0.2 Hz have been showed to be related to endothelium-dependent, sympathetic-dependent, and myogenic-dependent vasomotion, respectively [18]; their spectral density has been suggested to reflect the efficiency of the corresponding mechanism [13, 15, 18, 19].

Findings obtained in the present study represent a substantial advance in the knowledge of the effect of surgically induced sustained weight loss on peripheral microcirculation in obese patients. Only one previous study demonstrated an improvement in endothelial-dependent vasoreactivity at the level of skeletal muscle microcirculation in obese patients after sustained weight loss [11].

The full normalisation in skin vasodilator function and in skin vasomotion we observed in obese patients following surgically induced major weight loss argues for a complete recovery of skin microvascular dysfunction in the studied patients. Accordingly with the suggested property of skin microcirculation of reflecting generalized systemic microvascular dysfunction in magnitude and underlying mechanisms [12], results of the present study argue for a beneficial effect of surgically induced sustained weight loss on microvascular dysfunction at the level of other body tissues in the studied obese patients. This hypothetical and more generalized positive effect could have more important implications for cardiovascular risk of obese patients than the normalisation of microvascular dysfunction only at the level of skin.

With regard to the different vasomotion components, the spectral contribution of the all three frequency intervals of skin LDF signal investigated, was normalised after sustained weight loss in our patients (both in diabetics and non-diabetics). This suggests that sustained weight loss was associated with normalisation of the all three mechanisms responsible for vasomotion, such as the endothelial-, sympathetic-, and myogenic-dependent mechanism.

With regards to possible differences in skin vasomotion between Ob-2MD and Ob-NGT, its investigation was not the aim of our study. However, since type 2 diabetes was present in a sub-group of our obese subjects, we investigated possible changes in skin vasomotion not only in the whole sample of obese subjects, but also in the sub-groups of diabetics and non-diabetics. Before surgery we found a reduced EDVM in Ob-T2DM but not in Ob-NGT. This agrees with the results of previous studies in non-obese type 2 diabetic subjects [21, 32] which showed reduced vasomotion in patients compared with that observed in controls. On the contrary, we did not observe significant differences in post-surgery vasomotion measurements between Ob-T2DM and Ob-NGT. This last result could be due to the small sample of our study. Next studies aimed to investigate possible differences between Ob-T2DM and Ob-NGT in vasomotion changes associated to sustained weight loss should involve a bigger number of subjects.

The finding of a reduced skin vasodilator function and skin vasomotion, which we observed in obese patients before RYGB in comparison with lean healthy subjects, agrees with data obtained in previous studies [3–5]. This confirms that obesity impairs skin microvascular function.

Other findings of this study are the higher skin blood flow we found in obese patients before surgery compared to lean control subjects, as well as its reduction after weight loss. Both these findings are difficult to be explained. In particular, the first one disagrees with previous observations showing no difference in basal skin perfusion between obese patients and lean subjects [3]. Here, it is pertinent to recall that microvessel tone in glabrous skin areas—such as the forearm skin where we took our flow measurements—is predominantly mediated by sympathetic cholinergic vasodilator nerves [33]. An increased sympathetic tone could account for the higher skin blood flow in obese patients before weight loss, while, in its turn, a reduction in sympathetic over-activity after weight loss could account for the post-surgical reduction in basal skin blood perfusion. Nevertheless, differences in basal skin blood perfusion between obese patients and control subjects (as well as before and after weight loss in obese patients) did not influence our results on skin vasomotion and PORH, since the measurements of these parameters were normalised values for resting skin blood flow.

One weak point of our study is the small study sample, which might have interfered with some statistical comparisons. Further studies in a higher number of obese patients are needed in order to confirm our results. The inverse correlation between BMI and skin PORH, which we observed in our patients by pooling pre- and post-surgery data, needs to be verified by comparing surgically induced changes in BMI and PORH.

In conclusion, the present study shows that sustained weight loss due to RYGB resulted in a full normalisation in skin microvascuolar function in the studied obese patients. Findings of the present study argue for an improvement of generalized microvascular dysfunction in obese treated patients that could have positive implications for their cardiovascular risk. Further prospective studies in a higher number of obese patients are needed to verify these findings as well as the impact of surgically induced sustained weight loss on cardiovascular risk of obese patients.

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Conflicts of interest The authors declare no conflict of interest.

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