Impairment of Skin Vasoconstrictive Response to Sympathetic Activation in Obese Patients: Influence of Rheological Disorders

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Alterations of cardiac vagosympathetic activity have been suggested in obesity. We have previously shown that the skin vasoconstrictive response to sympathetic activation is reduced in non–insulin-dependent diabetic patients. The present study investigates the skin vasoconstrictive response to sympathetic activation in nondiabetic obese patients and the influence of clinical and rheological factors. Fifty-seven obese and 18 healthy women were investigated. The resting cutaneous blood flow (CBF) and CBF response to three tests that activate the sympathetic nervous system (deep breathing, Valsalva maneuver, and sitting to standing) were measured by a laser Doppler device. The red blood cell (RBC) filtration index (FI) and RBC aggregation were measured using a Hanss hemorrheometer and a Myrenne aggregometer (Myrenne, Roetgen, Germany), respectively. Resting CBF was not significantly different in obese and control subjects. The vasoconstrictive response to the deep-breathing and sitting-to-standing tests expressed as the decrease in CBF was significantly lower in obese patients versus controls (43.9% ± 3.1% *v* 73.7% ± 17.9%, $P = .01$, and 67.1% ± 3.8% *v* 89.8% ± 12.0%, $P = .02$, respectively). The spontaneous basal CBF variations and the downward slope of the CBF reduction during the Valsalva and sitting-to-standing tests correlated negatively with age in obese patients ($P = .042$, .022, and .008, respectively). During the sitting-to-standing test, the percent change in CBF correlated positively with RBC aggregation at a shear rate of 0 and 3 s^{-1} ($P = .011$ and .017, respectively). In conclusion, (1) CBF assessment by laser Doppler flowmetry is an effective noninvasive method to investigate sympathetic nervous function in obese patients; (2) obesity is associated with a significant reduction in the vasoconstrictive response to two tests for sympathetic activation, the deep-breathing and sitting-to-standing tests; (3) the severity of this reduction increases with age; and (4) RBC aggregation may contribute to the increase in the vasoconstrictive response and may thus increase the risk of widespread cardiovascular disease.

AUTONOMIC NERVOUS SYSTEM dysfunction has been associated with obesity in humans and animals. Alterations in vagosympathetic activity have been suspected in different animal models of obesity.[1] Both a reduction in sympathetic activity and an increase in parasympathetic activity have been reported in rats with experimentally induced lesions of the ventromedial hypothalamus.[2]

In obese adults, cardiac parasympathetic control as evaluated by spontaneous variations in the heart rate during standardized tests is often impaired.[3-5] However, sympathetic nervous system activity is more difficult to investigate in humans. It has been found to be either increased[6,7] or decreased.[4] Spectral analysis of variations in heart rate and blood pressure has been proposed to study cardiovascular sympathetic and parasympathetic activity.[8-10] The spontaneous fluctuations in hand and foot blood flow are probably mediated by changes in peripheral sympathetic tone, and a reduction in these fluctuations has been found to be related to autonomic neuropathy in diabetic patients.[11] However, resting blood flow is dependent on several factors such as the room temperature, the patient's emotional state, the ambient noise, and the patient's cooperation, which suggests that these factors probably account for a large part of the high intersubject variability in cutaneous blood flow (CBF).[12] Measurement of the vasoconstrictive response to maneuvers that involve sympathetic activation has been proposed during a deep-breathing test,[13] cold pressure test,[14-16] Valsalva maneuver,[17] or sitting-to-standing test,[18] which similarly induce peripheral skin vasoconstriction mediated by sympathetic nervous system activation. Vasoconstrictive responses may be measured by plethysmography, Doppler ultrasound, or thermography.[16,19,20] Some investigators have also suggested that laser Doppler flowmetry may be used to study skin vasomotor reflexes.[15,21,22] We have also used this method to study these reflexes with standardized tests,[23] and it has proved to be an effective noninvasive tool to investigate sympathetic nervous function in different diseases. Our results in non–insulin-dependent diabetic patients also suggest that rheological blood properties and metabolic factors may strongly influence resting CBF and vasomotor reflexes.[23]

Hemorrheological disorders such as an increase in blood and plasma viscosity or erythrocyte hyperaggregation are also associated with obesity.[24,25] We have recently shown that erythrocyte filterability is also decreased in nondiabetic obese subjects and correlates with insulin resistance.[25] Since these disorders contribute to slowing the blood flow, they may modify CBF and its changes during sympathetic stimulation.

The aim of the present study was to assess peripheral sympathetic function in nondiabetic obese patients by measuring resting CBF variations and the vascular response to stimuli involving sympathetic activation with a laser Doppler device, and to evaluate the factors that may modify the responses, particularly the rheological parameters.

SUBJECTS AND METHODS

Patients

Fifty-seven obese women were investigated. All were free of clinical signs of dysautonomia and postural hypotension and had no known diabetes. Table 1 shows the general characteristics of the patients. The mean age was 37.4 years (range, 16 to 69) and the mean body mass index (BMI) was 33.9 kg/m^2 (range, 30 to 53). None of the subjects had hypertension, cardiac or pulmonary disease, or anemia. All were free of peripheral vascular disease, and patients on medications known to modify blood flow (eg, vasodilators, calcium-channel blockers, angio-

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Table 1. Clinical Parameters for 57 Obese Patients

Parameter	Mean ± SEM
Age (yr)	37.4 ± 1.7
Weight (kg)	89.1 ± 2.4
BMI (kg/m^2)	33.7 ± 0.8
Waist to hip ratio	0.85 ± 0.02
Systolic blood pressure (mm Hg)	124 ± 2.1
Diastolic blood pressure (mm Hg)	78 ± 1.7

tensin-converting enzyme inhibitors, adrenergic agents, nitrates, and β-blockers) were excluded from the study. Patients taking anti–platelet aggregation agents or pentoxifylline were also excluded. The results of an oral glucose tolerance test were normal according to 1985 World Health Organization criteria in all but 4 patients, who had glucose intolerance.

The data were compared with two series of healthy female controls with normal body weight (BMI, 19 to 25 kg/m^2; mean, 22.3). There were 18 women aged 20 to 71 years (mean, 37.5) for the laser Doppler flowmetry parameters and 19 women aged 20 to 65 years (mean, 35.7) for the rheological parameters.

Laser Doppler Flowmetry

The PF2 Periflux device (Perimed, Stockholm, Sweden) was used to measure CBF as previously described.[23] This device consists of a low-power (5 mW) helium-neon laser source. The laser light was delivered to the skin via flexible graded-index fiberoptic guides. The wavelength transmission was 632 nm. The laser probe was attached to the right index finger with the beam aimed at the palmar side, the subject being seated for at least 10 minutes in a quiet room with the temperature set at 22° to 24°C. Measurements were performed between 9 and 11 AM. Basal CBF was monitored for 5 minutes with the subject at rest. The mean and standard deviation (SD) for basal CBF were obtained. The patient was asked to practice three vasomotor tests, which were then performed as previously described.[5,26,27] Velocimeter flow was monitored during the tests, and all data were recorded by a computerized system.

During the deep-breathing test consisting of 6 deep respirations in 1 minute, CBF decreased during each inspiration and then increased during expiration, and the mean value for the three cycles that showed the greatest decrease was calculated. During the Valsalva maneuver consisting of a forced exhalation at a pressure of 40 mm Hg for 10 seconds in the sitting position, a decrease in CBF occurred during the active phase. For the sitting-to-standing test, the subject remained in the standing position for 1 minute, which induced a decrease in CBF within the first few seconds. For each test, the maximum decrease in CBF was expressed as a percentage of the previous basal value and as the downward slope of CBF between the basal and minimum levels of CBF. The reproducibility of these tests was previously evaluated, and the mean coefficient of variation was 24.9% to 25.9%.[23]

Rheological Investigations

Erythrocyte filterability and aggregation were evaluated in most of the patients by previously described methods.[25,28,29] Measurements were performed within 1 hour following venous blood sampling at fasting. Erythrocyte filterability was measured using the Hanss hemorrheometer. Briefly, the device consists of an upper plastic block with a central capillary surrounded by a sheath of water circulating from a thermostat-controlled bath. The end of the capillary is cone-shaped and attached to the Nuclepore membrane (diameter, 13 mm; pore diameter, 5 μm; Nuclepore, Pleasanton, CA). The central capillary was filled with a red blood cell (RBC) suspension or the buffer alone (Hanks, pH 7.40). Two level detectors 9 mm apart at the top of the capillary activated and then stopped an electronic chronometer when the meniscus of the liquid moved during the filtration procedure. The time lapse measured first was proportional to the flow rate and therefore to the overall fluidity of the filtered liquid. For the liquid as a suspension and the buffer alone, the time lapse was called ts and tb, respectively, and was proportional to the initial flow rate. The result was expressed in terms of a filtration index (FI), defined as FI = ([ts − tb]/tb) × (100/H), where H is the hematocrit. High FI values indicate low RBC deformability.

Erythrocyte aggregation was evaluated with an MA2 erythrocyte aggregometer (Myrenne, Roetgen, Germany), based on the analysis of the incident infrared light transmitted through the blood sample. The device consists of a transparent cone-plate chamber in which blood cells were first sheared (shear rate = 600 s^{-1}) by rotation of the cone for 10 seconds to dissociate RBC aggregates. The rotation of the cone was then either abruptly stopped to allow rouleau formation in stasis (shear rate = 0) or greatly slowed (shear rate = 3 s^{-1}) to allow rouleau formation at a very low shear rate. A photoelectrical device analyzed the variation of light transmitted through the blood sample. The mean erythrocyte aggregation indices (MEA1 and MEA2) were obtained, corresponding to aggregation at a shear rate of 0 or 3 s^{-1}.

Other Investigations

Fasting blood glucose, fructosamine (Roche Diagnostic System, Neuilly/Seine, France; normal <285 μmol/L), hemoglobin A_{1c} ([HbA_{1c}] microcolumn chromatography; normal <6.25%), serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, and creatininemia were determined. The blood glucose level was also measured 120 minutes after 75 g glucose administered orally. Plasma insulin levels at fasting and 120 minutes after glucose were measured by radioimmunoassay (Behring, Mahrburg, Germany). Biological characteristics of the obese patients are shown in Table 2.

Statistical Analyses

Results are expressed as the mean ± SEM. All of the continuous variables studied were reasonably close to a normal distribution. Comparisons were made using 1-way ANOVA. Associations between continuous variables were tested using linear and partial Pearson correlations. All statistical calculations were performed on a Hewlett-Packard personal computer (Evry, France) using SPSS statistical software (SPSS, Chicago, IL).

Table 2. Biological Parameters for 57 Obese Patients

Parameter	Mean ± SEM
Blood glucose (mmol/L)	
Fasting	4.30 ± 0.07
120 min after glucose	5.39 ± 0.12
Fructosamine (μmol/L)	202 ± 3
HbA_{1c} (%)	4.94 ± 0.11
Plasma insulin (pmol/L)	
Fasting	77 ± 4
120 min after glucose	241 ± 20
Total cholesterol (mmol/L)	5.34 ± 0.16
HDL cholesterol (mmol/L)	1.37 ± 0.04
Triglycerides (mmol/L)	1.26 ± 0.08
Creatininemia (μmol/L)	81.5 ± 1.3
Uricemia (μmol/L)	262 ± 9
FI*	10.00 ± 0.26
MEA1*	6.13 ± 0.14
MEA2*	9.95 ± 0.24

*Determined in 47 obese patients.

Table 3. Correlation Coefficients Between Parameters of the Laser Doppler Flowmetry in Control Subjects

Parameter	Mean Basal CBF	CBF SD	Deep Breathing			Standing			Valsalva		
			Decrease in CBF	%	Slope	Decrease in CBF	%	Slope	Decrease in CBF	%	Slope
Mean basal CBF		.661	.701	−.475	.701	.840	−.412	.529	.792		.594
CBF SD	.661					.738		.467	.582		.527
Deep breathing											
Decrease	.701								.469		
%	−.475						.818			.619	
Slope	.701								.470		
Standing											
Decrease	.840	.738							.723		.571
%	−.412			.818						.751	
Slope	.529	.467							.558		.794
Valsalva											
Decrease	.792	.582	.469		.470	.723		.558			
%				.619			.751				
Slope	.594	.527				.571		.794			

NOTE. Only significant correlations are shown.

RESULTS

CBF at Rest and During Vasomotor Tests in the Controls

In the control group, age had no effect on the mean basal CBF, the SD of basal CBF, or CBF changes during the three vasomotor tests. The decrease in CBF and the downward slope of the CBF reduction during the three tests correlated significantly. They also correlated with the mean basal CBF and the SD of basal CBF (Table 3).

CBF at Rest and During Vasomotor Tests in the Obese Patients

In the obese patients, the SD of basal CBF and the downward slope of CBF during the Valsalva and sitting-to-standing tests correlated negatively with age ($r = -.270$, $P = .042$, $r = -.302$, $P = .022$, and $r = -.348$, $P = .008$, respectively; Fig 1). The decrease in CBF and the downward slope of CBF during the three vasomotor tests also correlated significantly with each other and with the mean basal CBF and the SD of basal CBF (Table 4). Mean basal CBF and the SD at rest did not differ significantly in the obese patients and the control group (Table 5). In 6 obese patients, the SD was below the lowest limit (=6.00 perfusion units) found in the control group. During the deep-breathing test, the reduction in CBF was significantly lower in the obese patients than in the controls, and 10 obese patients had a reduction in CBF and a CBF downward slope below the lowest value found in the controls (23% and 4, respectively). During the sitting-to-standing test, the decrease in CBF was also significantly lower in the obese patients versus the controls, and 8 obese patients had a reduction in CBF below the lowest value found in the controls (35%). During the Valsalva maneuver, there was only a trend (nonsignificant) for a lower decrease in CBF in the obese patients (Table 6).

Rheological Parameters

The RBC FI did not differ significantly in obese and control subjects (10.40 ± 0.28 *v* 10.50 ± 0.42). The two erythrocyte aggregation indexes, namely MEA1 and MEA2, were significantly higher in the obese patients versus the controls (6.13 ± 0.14 *v* 4.30 ± 0.35, $P < .001$, and 9.95 ± 0.24 *v*

Table 4. Correlation Coefficients Between Parameters of the Laser Doppler Flowmetry in Obese Patients

Parameter	Mean Basal CBF	CBF SD	Deep Breathing			Standing			Valsalva		
			Decrease in CBF	%	Slope	Decrease in CBF	%	Slope	Decrease in CBF	%	Slope
Mean basal CBF		.423	.538	−.293	.537	.669		.717	.751		.611
CBF SD	.423		.505		.505	.373		.472	.396		.262
Deep breathing											
Decrease	.538	.505				.518		.579	.554		.311
%	−.293						.323				
Slope	.537	.505				.518		.580	.553		.310
Standing											
Decrease	.669	.373	.518		.518				.620		.453
%				.323							
Slope	.717	.472	.579		.580				.613		.555
Valsalva											
Decrease	.751	.396	.554		.553	.620		.613			
%											
Slope	.611	.262	.311		.310	.453		.555			

NOTE. Only significant correlations are shown.

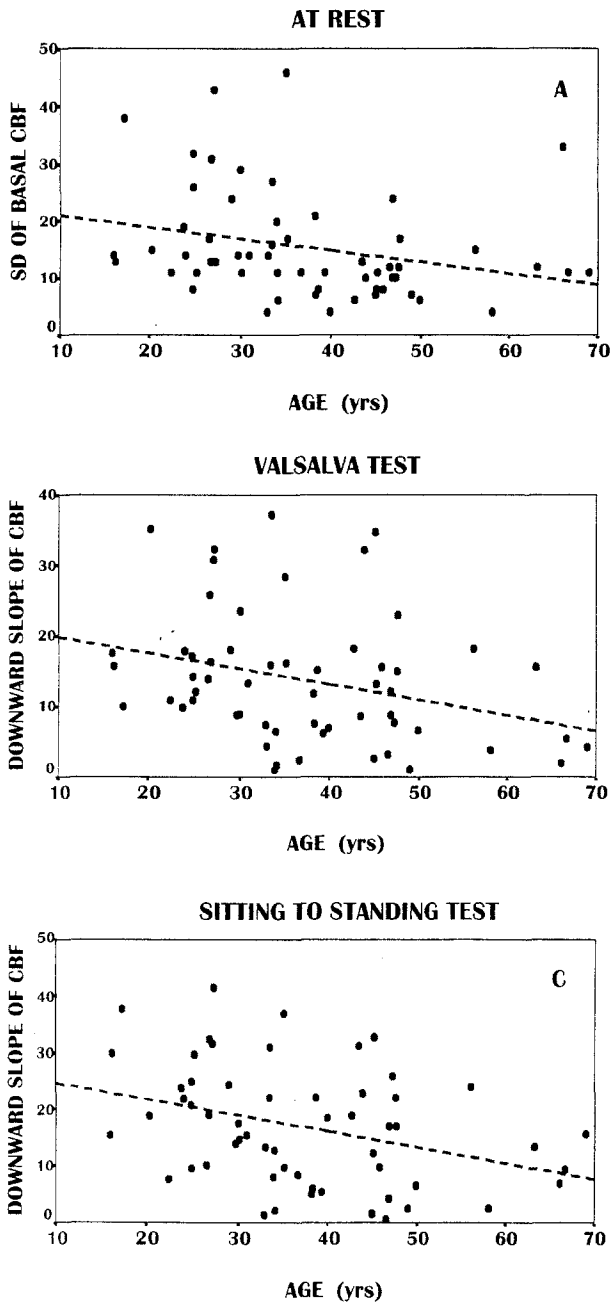

Fig 1. Correlations between age and the SD of basal CBF (A, $r = -.270$, $P = .042$) and the downward slope of CBF during the Valsalva (B, $r = -.302$, $P = .022$) and sitting-to-standing (C, $r = -.348$, $P = .008$) tests in the obese group.

7.11 ± 0.50, $P < .001$, respectively). In the obese group, MEA1 correlated negatively with age ($r = -.329$, $P = .033$) and both MEA1 and MEA2 correlated significantly with body weight ($r = .308$, $P = .047$ and $r = .395$, $P = .010$, respectively).

Table 5. Resting CBF (arbitrary perfusion units)

Group	Mean CBF	SD
Obese patients (n = 57)	121.5 ± 6.6	15.4 ± 1.3
Controls (n = 18)	114.9 ± 20.4	12.9 ± 1.7

Correlations of CBF With Clinical and Biological Parameters in the Obese Patients

Body weight correlated significantly with the downward slope of CBF during the Valsalva test ($r = .307$, $P = .02$). There was no significant correlation between laser Doppler parameters and the other clinical parameters. During the sitting-to-standing test, the percent change in CBF correlated positively with MEA1 ($r = .389$, $P = .011$) and MEA2 ($r = .368$, $P = .017$; Fig 2). There was no significant correlation between laser Doppler parameters and the other biological parameters. Controlling for age, body weight, and the mean basal CBF, the partial correlation coefficients between the percent change in CBF during the sitting-to-standing test and MEA1 and MEA2 were .400 ($P = .012$) and .342 ($P = .033$), respectively.

DISCUSSION

This study was performed in nondiabetic obese patients without clinical signs of autonomic neuropathy and without postural hypotension, to detect early signs of cardiovascular sympathetic dysfunction. Although the three vasomotor tests used here involved different afferent pathways,[13,30] all of them share the same sympathetic efferent system as the final common pathway. This makes it possible to evaluate a peripheral sympathetic defect by analyzing the changes in skin blood flow during these tests. For example, during the standing test, these changes provide a sympathetic index, since it has been shown that the time to CBF recovery after the decrease induced by standing correlates with the change in blood pressure and heart rate immediately after standing and that this time is prolonged by phentolamine, a sympatholytic agent.[22]

The mean basal CBF measured by laser Doppler flowmetry was not significantly different in the obese patients and control subjects. The correlations between the mean basal CBF and the decrease in CBF during each of the three vasomotor tests suggest that the higher the resting CBF, the deeper the decrease during sympathetic activation. The mean value for the SD of basal CBF was also very similar in both groups. However, it was decreased in 6 obese patients. The correlation between the SD of basal CBF and the decrease in CBF during sympathetic activation tests in the controls (which is even more marked in the obese patients) is in agreement with previous studies showing that spontaneous variations in the blood flow of the extremities are under sympathetic control.[11] Therefore, the decrease in the SD in some obese patients suggests a decrease in sympathetic activity.

The most significant result in the obese patients consisted of a smaller decrease in CBF during the deep-breathing and sitting-to-standing tests. There was also a trend for a lower decrease in CBF during the Valsalva maneuver. The most frequent (10 of 57) disorder consisted of a reduced decrease in CBF during the deep-breathing test. Most of these results are close to our previous findings in non–insulin-dependent diabetic patients.[23] The lower decrease in CBF might result from a difference in blood pressure and cardiac output at baseline and during the tests between the obese and control subjects. In the obese subjects, blood pressure was normal but was not measured throughout the tests. Cardiac output and humeral blood flow were not measured in the present study. Cardiac output has been

Table 6. Changes in CBF During the Three Vasomotor Tests

Group	Deep Breathing		Valsalva		Standing	
	Decrease in CBF (%)	Slope	Decrease in CBF (%)	Slope	Decrease in CBF (%)	Slope
Obese patients (n = 57)	43.9 ± 3.1	10.0 ± 0.8	64.8 ± 3.5	13.8 ± 1.2	67.1 ± 3.8	16.8 ± 1.4
Controls (n = 18)	73.7 ± 17.9	11.8 ± 1.4	77.6 ± 16.4	14.1 ± 3.2	89.8 ± 12.0	14.1 ± 2.9
P	.01	NS	NS	NS	.02	NS

found to be increased in patients with massive obesity,[31] which was not the case in our patients. On the contrary, in less severely obese patients, cardiac systolic function has been shown to be negatively related to fat accumulation.[32] Therefore, the lower vasoconstrictive response to sympathetic activation is unlikely to result from an increase in basal cardiac output. During a standardized 5-minute handgrip test, another test of sympathetic activation, we found that the increase in blood pressure was reduced in nondiabetic obese patients with cardiac parasympathetic dysfunction compared with a control group.[33] This is in agreement with the present finding of a lower vasoconstrictive response to sympathetic activation. Altogether, these data are well consistent with a decrease in sympathetic activation.

Certain factors seem to be associated with the responses to the vasomotor tests. In the obese group, both the SD of basal CBF and the downward slope of CBF during two of the vasomotor reflexes correlated negatively with age. The influence of age was not found in the control group, possibly because of the smaller number of subjects. However, the influence of age in the obese group might be related to the duration of overweight. The influence of age on the results of the cardiac parasympathetic tests has been clearly demonstrated.[5,27,34] The influence of age seems far less clear for sympathetic nervous activity.[11] Cardiovascular responsiveness to β-adrenergic stimulation seems to decrease with age.[35,36] But no information is available regarding α-adrenoceptors. Increased sympathetic nervous activity has been proposed as a compensatory phenomenon, due to a diminished responsiveness to noradrenaline with age.[37,38] The lower response to vasomotor reflexes with age in obese subjects may result from various mechanisms, including a reduction in the activation of the sympathetic nervous system, a decrease in α-adrenoceptors, alterations in the adrenergic signal transduction pathway within vascular smooth muscle cells, endothelial dysfunction, or an excess of advanced glycosylation end products.

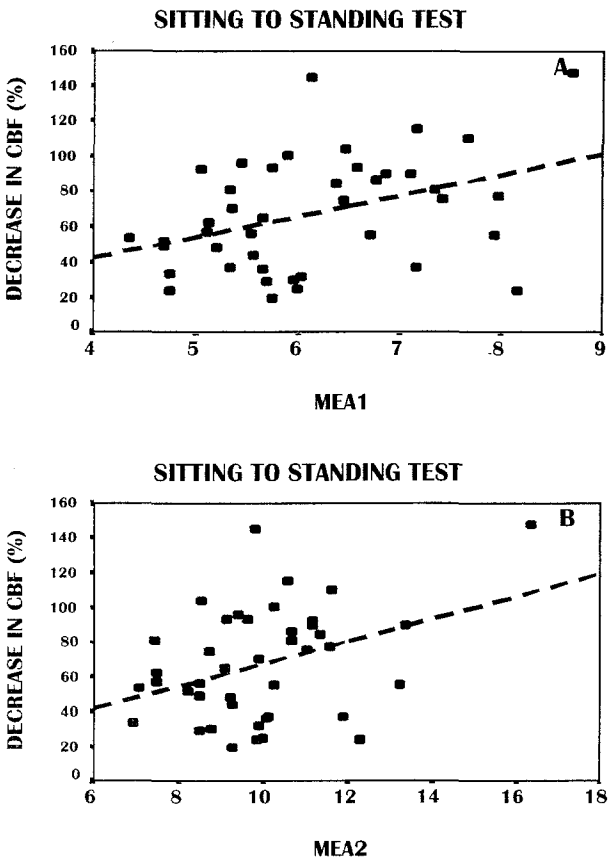

Fig 2. Correlations between the percent change in CBF during the sitting-to-standing test and RBC aggregation indexes MEA1 and MEA2 (A and B, *r* = .389, *P* = .011 and *r* = .368, *P* = .017, respectively) in the obese group.

The present study confirms our previous results and others showing that aggregation is increased in obese patients and correlates with body weight.[23,25,39] A positive correlation was found here between RBC aggregation indexes and the CBF response to the sitting-to-standing test, and these correlations were significant even after controlling for age, body weight, and mean basal CBF. In non–insulin-dependent diabetic patients, we have shown that RBC rheologic factors may strongly influence resting CBF and vasomotor reflexes.[23] In the obese patients, the positive correlation between RBC aggregation and the vasoconstrictive response to sympathetic activation suggests that RBC stasis contributes to the decrease in microcirculatory blood flow during these maneuvers. Since erythrocyte rheological changes have been mainly shown to affect patients with central obesity[39] and to be a component of the insulin resistance syndrome in obese patients,[25] we may hypothesize that the associated increase in the vasoconstrictive response might aggravate insulin resistance by reducing blood flow and glucose uptake.[40] Moreover, rheological alterations together with an increase in the vasoconstrictive response to sympathetic activation can reflect severe blood flow dysregulation, which may increase the risk of developing widespread vascular disease.

In conclusion, this study demonstrates that the peripheral vasoconstrictor response to sympathetic activation is reduced in nondiabetic obese subjects. The vascular response, particularly during the deep-breathing or sitting-to-standing tests, shows that the procedure involving the measurement of CBF by laser Doppler flowmetry is simple, sensitive, and reproducible,

affording an effective noninvasive way to investigate sympathetic nervous function in obese subjects. The decrease in cutaneous vasoconstriction during these tests is consistent with a decrease in sympathetic activation. However, our data cannot exclude the involvement of a reduction of either the vasoconstrictive response or large blood vessel flow response to normal sympathetic activation. The influence of age and probably the duration of obesity seem to be important determinants of the lower vasoconstrictive response during these tests. On the other hand, erythrocyte hyperaggregation by induction of vascular stasis amplifies the effect of sympathetic activation on the reduction of CBF. This suggests that hemorrheological agents might afford an effective way to prevent morbid vascular complications. Finally, obesity per se may partly account for the alterations in diabetic patients in the tests involving sympathetic nervous system activation,[23] as shown for the alterations in tests mainly involving the parasympathetic nervous system.[41,42]

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