β-Adrenergic Stimulation and Abdominal Subcutaneous Fat Blood Flow in Lean, Obese, and Reduced-Obese Subjects

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The present study was designed to investigate whether the β-adrenergically mediated blood flow response of abdominal subcutaneous adipose tissue (per unit adipose tissue weight) was altered in obesity and to study the effect of weight reduction on this response. Body composition (underwater weighing) and fat blood flow were determined in a group of lean (n = 9; % body fat, 11.6 ± 3.9) and obese (n = 9; % body fat, 28.3 ± 1.8) subjects. In seven obese subjects, measurements were also performed after a 4-week period of weight reduction induced by a very-low-calorie diet (% body fat after diet 23.4 ± 3.3). After an overnight fast, abdominal subcutaneous fat blood flow was determined by the ^{133}xenon washout technique during a 30-minute period of supine rest and during 30-minute periods of infusion of the β-agonist isoprenaline (ISO) with and without simultaneous infusion of the β_1-blocker atenolol (AT). Basal abdominal fat blood flow was significantly higher in lean as compared with obese subjects, whereas weight reduction significantly increased basal fat blood flow (obese *v* reduced-obese, $P < .05$). There was a significant increase in abdominal fat blood flow as a result of ISO infusion in lean and obese subjects before and after weight reduction. During ISO + AT infusion, abdominal fat blood flow was still significantly increased as compared with control values in lean and obese subjects. The increase in blood flow during ISO was significantly higher in lean subjects than in obese subjects, whereas the ISO + AT–induced blood flow response was comparable. These data suggest that especially the β_1-mediated blood flow response is blunted in obese subjects. Although the increase in the ISO-induced blood flow response was not significantly different after as compared with before the diet, there was a significant positive relationship between the decrease in percent body fat and the change in the ISO-mediated abdominal blood flow as a result of weight loss ($P < .05$). In conclusion, the present study shows that the β-adrenergically mediated abdominal fat blood flow response (expressed per unit weight) is diminished in obesity. This decreased blood flow response tended to change in a direction toward the condition seen in lean subjects after partial weight reduction.

ADIPOSE TISSUE blood flow may play an important role in adipose tissue metabolism by delivering substrates, lipolytic hormones, and carrier proteins, responsible for the transport of fatty acids in the bloodstream, to the tissue.[1-3] Since triglyceride synthesis and the mobilization of fatty acids are the principal events in adipose tissue, the relationship between adipose tissue blood flow and net lipolysis is of special interest. By means of the ^{133}xenon clearance technique, it has been shown that in several metabolic situations characterized by an increased mobilization of the fat stores, such as fasting,[4] exercise,[5] or infusion of epinephrine,[6] adipose tissue blood flow is increased.

Previous studies have shown that adipose tissue blood flow (per unit adipose tissue weight) may be decreased in obesity.[4,7,8] In addition, a blunted abdominal adipose tissue blood flow response to glucose ingestion has been reported in obese subjects.[7] In previous studies we found that the lipolytic response as a result of infusion of the β_1- and β_2-agonist isoprenaline (ISO) is lower in obese subjects than in lean subjects, as reflected by lower ISO-induced increases in arterial fatty acid and glycerol levels.[9] This may favor the maintenance (and perhaps development) of large fat stores. The impaired lipolytic response in obesity may be associated with a decreased blood flow per unit adipose tissue weight, since a diminished blood flow response may affect the delivery of ISO and transport proteins for fatty acids to adipose tissue.[1,3] In addition, a model has been proposed that raises the possibility that the release and reuptake of fatty acids by adipocytes within adipose tissue may be controlled by adipose tissue perfusion.[2]

The present study was designed to investigate whether the adipose tissue blood flow response as a result of β-adrenergic stimulation was altered in obesity and to study the effect of weight reduction on this response.

SUBJECTS AND METHODS

In this study, abdominal subcutaneous fat blood flow was determined in lean (n = 9) and obese (n = 9) men recruited by an advertisement in the local newspaper. In seven obese subjects, measurements were also performed after weight reduction (n = 7, reduced-obese subjects). All subjects were outpatients throughout the study. Physical characteristics are indicated in Table 1. The subjects were medically screened by a questionnaire and physical examination. All subjects had normal glucose tolerance and had no or only very mild hypertension (diastolic blood pressure < 95 mm Hg). None were taking medication or had clinical evidence of illness apart from obesity. The study protocol was reviewed and approved by the Ethics Committee of the University of Limburg, and all volunteers provided written consent. The study protocol consisted of two experiments with 1 week in between. In the first experiment the β-agonist ISO was infused in increasing standardized doses, and during each infusion period plasma concentrations of ISO were determined (ISO infusion test). In the second experiment, abdominal subcutaneous adipose tissue blood flow was studied during ISO infusion with and without infusion of the β_1-blocker atenolol ([AT] blood flow measurement). To reduce the variability in the blood flow experiment, the dose of ISO in this experiment was individually determined and was the dose that increased plasma ISO to a fixed value of 165 pg/mL. The two experiments above were repeated after weight reduction when the subjects had been weight-stable for at least 4 to 5 days. During the experiments, room temperature was kept between 21° and 23°C.

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Table 1. Characteristics of Lean, Obese, and Reduced-Obese Men

	Lean (n = 9)	Obese (n = 9)	Obese (n = 7)	Reduced-Obese (n = 7)
Age (yr)	22.2 ± 0.7	33.0 ± 1.8†	33.7 ± 1.3†	33.7 ± 1.3†
Weight (kg)	73.3 ± 3.9	103.5 ± 2.9†	98.4 ± 2.9†	89.6 ± 2.7†§
Body mass index (kg/m^2)	22.3 ± 1.0	32.5 ± 1.2†	31.4 ± 0.9†	27.6 ± 0.5†§
% body fat	11.6 ± 3.9	28.3 ± 1.8†	27.1 ± 1.2†	23.4 ± 3.3†§
Fat mass (kg)	9.0 ± 1.4	29.5 ± 2.5†	27.0 ± 0.6†	21.1 ± 1.3†§
FFM (kg)	64.6 ± 3.4	74.0 ± 2.2*	71.8 ± 1.9*	68.6 ± 1.2*‡
Lipid fraction adipose tissue	0.47 ± 0.02	0.68 ± 0.02†	0.67 ± 0.02†	0.62 ± 0.01†‡
Partition coefficient for xenon	5.3 ± 0.2	7.4 ± 0.2†	7.2 ± 0.1†	6.7 ± 0.1†‡

NOTE. Results are the mean ± SEM.

*$P < .01$, †$P < .001$: lean *v* obese or reduced-obese (unpaired *t* test).

‡$P < .01$, §$P < .001$: obese, before *v* after (Student's paired *t* test).

Diet

During the first 4 weeks of the diet period, subjects consumed a very–low-calorie diet of 2,000 kJ/d, which provided 52 g protein, 50 g carbohydrate, 7 g fat, and 1.3 g sodium per day and a micronutrient content that meets the Dutch recommended daily allowances. In the fifth week, subjects returned within 2 to 3 days to a status of near energy balance.

ISO Infusion Test

In this experiment, ISO was infused in increasing doses of 6, 12, 23, and 46 ng/kg fat-free mass (FFM) · min, with each dose infused for 30 minutes. The dose is related to ISO sulfate, 69% of which corresponds to ISO-free base. Body density was determined by hydrostatic weighing with simultaneous lung volume measurement (Volugraph 2000, Mijnhardt, The Netherlands). Body composition was calculated according to the formula of Siri.[10] After 15 minutes in each infusion period, a blood sample was taken with a heparinized syringe and placed into a glutathione-containing tube in ice. The sample was immediately centrifuged at 3,000 rpm at 4°C, and the plasma was stored at −50°C. In the plasma samples, concentrations of isoprenaline were determined by high-performance liquid chromatography.[11] During the experiments the heart rate was continuously recorded; when the heart rate had increased by 30 beats per minute, the infusion was stopped.

Blood Flow Measurements

After an overnight fast, blood flow through the abdominal subcutaneous adipose tissue was determined during a 30-minute period of supine rest and during 30-minute periods of intravenous infusion of the nonselective β-agonist ISO with or without simultaneous infusion of the β_1-blocker AT. After the resting period, intravenous infusion of ISO was administered for 60 minutes, with AT added during the last 30 minutes. For each subject, the dose of ISO (per kilogram fat-free mass) leading to a plasma concentration of 165 pg/mL was infused. The mean infusion dose of ISO was 20 ± 1 ng/kg FFM · min (range, 16 to 24 ng/kg fat-free mass FFM · min). Before the simultaneous infusion of ISO and AT (0.11 mg/kg FFM · min) was started, a priming dose of AT (0.08 mg/kg FFM) was administered over 5 minutes.

Subcutaneous adipose tissue blood flow was measured by the ^{133}xenon washout method on the abdomen a little distal and lateral to the umbilicus.[8] A dose of ^{133}xenon dissolved in saline was injected subcutaneously with a very fine needle (0.5 × 16 mm). A probe with NaI detector (Atomic Products, Intequip, Almere, The Netherlands) was placed in a fixed position 15 cm above the abdomen. The registration of ^{133}xenon was started 45 minutes after the injection, at which time the washout is usually monoexponential. From the regression of count rate against time, the rate of disappearance of ^{133}xenon over the last 20 minutes of each measurement period was determined.

Tissue-Blood Partition Coefficient

For the calculation of quantitative values of fat blood flow (per 100 grams tissue), the relative solubility of xenon between tissue and blood, ie, the partition coefficient, must be known. The highest solubility coefficients for xenon are found for lipids and hemoglobin, which implies that the magnitude of the partition coefficient will mainly depend on the lipid content of adipose tissue and the hematocrit value of the blood perfusing it.[5,12] In a study by Martin et al,[13] the relationship between percent adiposity and the lipid fraction (V) of adipose tissue was determined by underwater weighing of all portions of adipose tissue from human cadavers (range % body fat, 17.8 to 43.9) and was as follows:

$$V = 0.327 + 0.0124 \times \% \text{ adiposity } (r = 0.95, P < .005). \quad \text{Eq 1}$$

Given that the solubility of xenon in a tissue equals the weighted mean of the solubility in the individual tissue components,[14] the following equations can be applied on the basis of the data of Chen et al[12]:

$$S_B = HtS_C + (1 - Ht)S_P, \quad \text{Eq 2}$$

whereby S_B, S_C, and S_P are the solubility in blood, red blood cells, and plasma, respectively, and Ht is the hematocrit.

Assuming that the solubility of xenon in water and protein within adipose tissue equals that of plasma yields the following equation:

$$S_A = VS_L + (1 - V)S_P, \quad \text{Eq 3}$$

whereby S_A, S_L, and S_P are the solubilities in adipose tissue, lipid, and plasma, respectively, and V is the lipid fraction of adipose tissue.

The tissue-blood partition coefficient of xenon for adipose tissue (λ) can then be expressed as

$$\lambda = \frac{S_A}{S_B} = \frac{V(S_L/S_P - 1) + 1}{Ht(S_C/S_P - 1) + 1}, \quad \text{Eq 4}$$

whereby S_P is 0.0939 mL/mL, S_L is 1.8276 mL/g, and S_C is 0.2710 mL/mL.

On the basis of equations 1 and 4, the tissue-blood partition coefficient was calculated for each individual. The hematocrit was assumed to be 45%, a value previously found for both lean and obese men.[9]

Statistics

Data are represented as the mean ± SEM. Plasma ISO concentrations and blood flow values within groups were tested by repeated-measures ANOVA. Post hoc testing was performed with

a Student's paired t test, and P values for the post hoc comparisons were corrected according to Bonferroni's inequalities. Differences between lean and obese subjects were tested with a one-way ANOVA. Comparisons between values for before and after weight reduction were made with a Student's paired t test. A P value less than .05 was regarded as statistically significant.

RESULTS

Body Composition

As a result of the diet, there was an 8.7-kg weight loss, which can be accounted for by 67% as fat mass and 33% as FFM (Table 1).

ISO Infusion Test

All subjects showed dose-related increases in plasma ISO (for all groups by ANOVA, $P < .001$). The mean plasma ISO concentrations with the increasing standardized doses (per kilogram FFM) were similar in lean, obese, and reduced-obese subjects (plasma ISO values were 0 ± 0, 62 ± 5, 108 ± 8, 195 ± 10, and 390 ± 28 pg/mL in lean subjects, 0 ± 0, 50 ± 7, 104 ± 12, 222 ± 20, and 388 ± 28 in obese subjects, and 0 ± 0, 31 ± 6, 96 ± 8, 223 ± 15, and 380 ± 30 in reduced-obese subjects).

Blood Flow Measurements

As indicated in Table 1, the calculated lipid fraction of adipose tissue was significantly higher in obese as compared with lean subjects. As expected, weight reduction resulted in a significant decrease in the lipid content of adipose tissue. Estimated values for the tissue-blood partition coefficient for adipose tissue were significantly higher in obese as compared with reduced-obese and lean subjects and significantly higher in reduced-obese than in lean subjects.

The abdominal subcutaneous adipose tissue blood flow in normal-weight, obese, and reduced-obese subjects is indicated in Table 2. The basal abdominal fat blood flow was significantly higher in lean than in obese subjects, whereas weight reduction in obese subjects resulted in an increase in basal abdominal fat blood flow (obese v reduced-obese, $P < .05$). There was a significant negative relationship between percent body fat and basal fat blood flow in the total group ($r = .51, P < .05$).

There was a significant increase in abdominal fat blood flow as a result of ISO infusion in lean and obese and reduced-obese subjects. During ISO + AT infusion, fat blood flow was still significantly increased as compared with control values in lean and obese subjects, whereas in reduced-obese subjects this value tended to be higher than control values ($P = .10$). With ISO, the absolute abdominal fat flow (Table 2) and the change in abdominal fat flow from the control value (Fig 1) were significantly higher in lean than in obese subjects, whereas with ISO + AT there were no significant differences between both groups. Furthermore, there was a significant negative relationship between percent body fat and the increase in blood flow during ISO in the total group ($r = .53, P = .03$).

During ISO and ISO + AT, absolute values for the abdominal fat blood flow and the change in abdominal flow from the control value were not significantly different in reduced-obese as compared with lean or obese subjects. However, there was a positive relationship between the decrease in percent body fat and the weight loss–induced change in ISO-mediated abdominal blood flow values (Fig 2).

DISCUSSION

The main purpose of the present study was to investigate whether the β-adrenergically stimulated abdominal subcutaneous fat blood flow was altered in obesity, and if so, how weight reduction would affect this. For calculating quantitative blood flow values from the washout curves of ^{133}xenon, the adipose tissue-blood partition coefficient must be known. The highest solubility coefficients for xenon are found for lipids and hemoglobin, which implies that the lipid content of adipose tissue and the hematocrit of the blood perfusing it will be major determinants of the partition coefficient. In the present study hematocrit values were not directly determined, but were assumed to be 45% as found previously for both lean and obese men.[9] However, a variation in hematocrit values within the range from 40% to 50% can maximally account for 10% of the difference in blood flow response between lean and obese subjects. Although the variation in the lipid content of human subcutaneous adipose tissue as reported by Martinsson[15] would only slightly affect the magnitude of the partition coefficient, Bülow et al[16] reported a much higher variation in lipid content. However, in both studies exact data on the percentage of adiposity of the subjects are not given. The relationship between percent body fat and the lipid content of total adipose tissue in the study by Martin et al[13] has not previously been reported, to our knowledge. Since subcutaneous adipose tissue comprises approximately two thirds of

Table 2. Abdominal Subcutaneous Adipose Tissue Blood Flow (mL/100 g · min) During Rest and During Infusion of the β-Agonist ISO With and Without Simultaneous Infusion of the β_1-Blocker AT in Lean, Obese, and Reduced-Obese Men

	Control	ISO	ISO + AT	P (ANOVA)
Lean (n = 9)	2.60 ± 0.65	10.57 ± 2.45‡	5.50 ± 1.33§‖	.001
Obese (n = 9)	1.02 ± 0.21*	3.95 ± 0.57*§	3.25 ± 0.42§	.001
Obese (n = 7)	0.85 ± 0.16*	4.00 ± 0.71*§	3.26 ± 0.53§	.001
Reduced-obese (n = 7)	2.06 ± 0.66†	6.11 ± 1.64§	4.25 ± 1.12	.003

NOTE. Results are the mean ± SE. Values for repeated-measures ANOVA are indicated in the far-right column.

Comparisons between control values: lean v obese or reduced-obese (unpaired t test), *$P < .05$; obese v reduced-obese (Student's paired t test), †$P < .05$.

Within-group comparisons: control v ISO or ISO + AT (Student's paired t test, Bonferroni), ‡$P < .05$, §$P < 0.01$; ISO v ISO + AT, ‖$P < .05$.

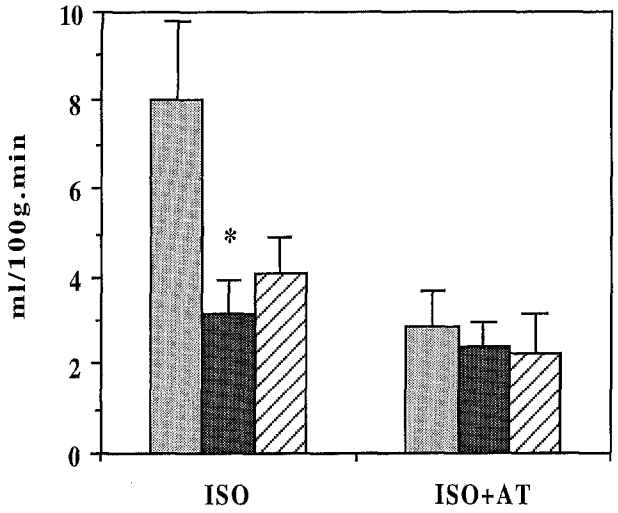

Fig 1. Changes in abdominal subcutaneous fat blood flow during infusion of the nonselective β-agonist ISO with and without simultaneous infusion of the β_1-blocker AT in (□) lean (n = 9), (■) obese (n = 7), and (▨) reduced-obese (n = 7) subjects. Mean ± SE. Unpaired *t* test: lean *v* obese, *P < .05.

total adipose tissue,[17] it may be assumed that the magnitude and variation of the lipid content of total adipose tissue gives a reasonable representation of the lipid content in subcutaneous adipose tissue. Moreover, the range in lipid content that we found (0.40 to 0.85) seems comparable to the range reported by Bülow et al[16] for subcutaneous adipose tissue on the abdomen and thigh. The values for the partition coefficient in the present experiment are somewhat lower than values reported by Bülow et al,[16] which may be explained by the higher blood hematocrit values and the lower average lipid fraction we used to calculate the partition coefficient.

Basal abdominal adipose tissue blood flow was significantly higher in lean than in obese subjects, as previously reported.[4,7,8] Furthermore, the ISO-induced increase in abdominal fat blood flow was significantly higher in lean as compared with obese subjects (Fig 1). Moreover, there was a negative relationship between the increase in blood flow as a result of ISO infusion and percent body fat. A blunted peripheral blood flow response has been reported before in obesity.[7,9,18] Laakso et al[18] found that the insulin-mediated increase in skeletal muscle blood flow was impaired in obese subjects during a hyperinsulinemic, euglycemic clamp, whereas Jansson et al[7] found a blunted adipose tissue blood flow response to glucose ingestion in obese subjects. In addition, we have recently found a diminished skeletal muscle blood flow response during β-adrenergic stimulation in obese as compared with lean subjects.[9] It has been previously reported that catecholamines may influence human adipose tissue blood flow.[6] However, the blunted response to β-adrenergic stimulation in abdominal subcutaneous adipose tissue in obese subjects has not previously been reported, to our knowledge.

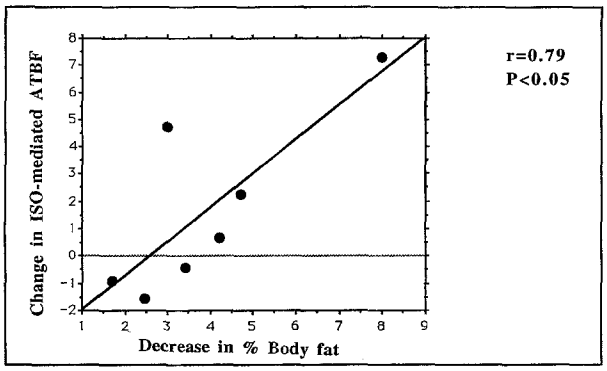

Fig 2. Relationship between the decrease in % body fat and the weight loss–induced change in abdominal subcutaneous adipose tissue blood flow ([ATBF] after minus before) during infusion of the nonselective β-agonist ISO. Reduced-obese, n = 7. Standard error of estimate for ISO, 2.43 mL/100 g · min.

Weight reduction resulted in a significant increase in basal blood flow and a tendency toward an increase in the ISO-induced change in blood flow. Although the mean β-adrenergically mediated increase in blood flow was not significantly different before as compared with after weight reduction, there was a linear relationship between the decrease in percent body fat and the change in the ISO-induced blood flow response as a result of weight loss (Fig 2). These data suggest that the blunted blood flow response as a result of β-adrenergic stimulation in obese subjects is secondary to the expanded fat mass, with a constant or decreased blood flow per adipose cell,[19,20] and it is hypothesized that it will return toward the condition seen in lean subjects after more severe weight reduction. However, since our obese subjects were still slightly overweight, we cannot exclude the possibility that postobese subjects totally normalized in body weight still have a defect in the blood flow response.

In lean and obese subjects, the blood flow response was higher during ISO infusion (nonselective β-adrenergic stimulation) than during ISO + AT infusion (mainly β_2-adrenergic stimulation), whereas the blood flow during ISO + AT was still significantly elevated as compared with control values. Since the administered dose of the β_1-blocker AT was sufficient for an effective[21,22] and selective[23] β_1-blockade, this indicates that both β_1- and β_2-adrenoceptors are involved in the blood flow response as a result of ISO. Furthermore, whereas the ISO-induced increase in adipose tissue blood flow was significantly higher in lean than in obese subjects, the ISO + AT–induced increase in adipose tissue blood flow was comparable, which suggests that especially the β_1-mediated blood flow response is blunted in obese subjects.

A factor that may have biased our data is the significant age difference. There was a significant positive relationship between age and percent body fat in our lean and obese subjects, which might have affected the relationship between percent body fat and blood flow. However, a study by Larsen et al[8] reported no association between age and abdominal subcutaneous adipose tissue blood flow, which implies that age was no confounding factor in the present study.

In previous studies,[9] we have found that the lipolytic response as a result of infusion of the β_1- and β_2-agonist ISO is decreased in obese subjects, as reflected by lower ISO-induced increases in arterial fatty acid and glycerol levels. This impaired lipolytic response in obesity may be related to the decreased blood flow response per unit weight, since a lower blood flow may diminish the delivery of ISO[3] and transport proteins for fatty acids[1] to adipose tissue and increase the rate of fatty acid reesterification.[2] However, in another study,[24] we found that weight reduction did not change the impaired lipolytic response during ISO infusion in obese subjects, but rather decreased the release of nonesterified fatty acids from (visceral) adipose tissue, as suggested by a decreased ketogenesis. This might suggest that mechanisms other than the blunted blood flow response are responsible for the impaired lipolysis in (reduced) obese subjects. However, no firm conclusions about the role of blood flow in the impaired lipolytic response in (reduced) obese subjects can be drawn from the present study, since the blood flow and lipolytic response as a result of β-adrenergic stimulation were measured in different groups of subjects and the observed changes in blood flow response were relatively small.

Recently, interdepot adipose tissue analyses have become more common, since regional differences in the metabolism of adipose tissue may be one of the factors involved in the cardiovascular risk of obesity. It has been shown that the lipolytic and blood flow response (per unit adipose tissue weight) to fasting,[4] glucose ingestion,[25] or catecholamine infusion[26] may be more pronounced in abdominal subcutaneous tissue than in other subcutaneous fat depots such as femoral and gluteal fat. In accordance with these findings, we found that the blood flow response in abdominal adipose tissue was much higher than the previously reported values for forearm subcutaneous fat flow in lean and obese subjects.[9]

In summary, the present study shows that the β-adrenergically mediated blood flow response (per unit weight) is diminished in obesity. The decreased blood flow response in adipose tissue in obese subjects tended to change in a direction toward conditions seen in lean subjects after partial weight reduction.

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