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Insulin-Mediated Increase in Blood Flow Is Impaired in the Elderly

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ABSTRACT

It has recently been recognized that the ability of insulin to augment blood flow is reduced in insulin-resistant conditions such as obesity and noninsulin-dependent diabetes mellitus. Normal aging is characterized by resistance to insulin-mediated glucose uptake. We undertook the following studies with the hypothesis that the resistance to insulin-mediated glucose uptake that occurs with aging is caused in part by a reduction in insulin-mediated blood flow. These experiments were conducted on healthy young (n = 13; age, 24 ± 1 yr; body mass index: 22.2 ± 0.6 kg/m^2) and old (n = 13; age, 77 ± 1 yr; body mass index: 24.2 ± 0.5 kg/m^2) subjects. Each subject underwent two studies. In the control study, saline was infused for 4 h. In the euglycemic clamp study, insulin was infused for 4 h at a rate of 40 mU/m^2·min in the young subjects and 34 mU/m^2·min in the old subjects. Blood samples were taken, and calf blood flow was measured using venous occlusion plethysmography at regular intervals in each study. Basal calf blood flow was lower in the elderly (young subjects: 1.51 ± .08 mL/100 mL tissue per min; old subjects: 1.15 ± 0.07 mL/100 mL tissue per min, $P < 0.002$). During the euglycemic clamp studies, steady-state insulin and glucose values were similar in the two age groups. Glucose disposal rates were significantly higher in the young subjects ($P = 0.01$ by analysis of variance). Mean arterial pressure values were significantly higher in the elderly ($P < 0.001$ by analysis of variance) throughout the clamp, but there was no significant change over time in either age group. The mean incremental blood flow rate at steady-state (180–240 min) was significantly higher in the young subjects (0.76 ± 0.23 mL/100 mL tissue per min) than in the old subjects (0.05 ± 0.09 mL//100 mL tissue per min, $P < 0.01$). There was a significant correlation between steady-state glucose disposal rate values and incremental blood flow rates in the young subjects ($r = 0.59$, $P < 0.05$) but not in the old subjects ($r = 0.21$, P = NS). We conclude that normal aging is characterized by an impairment in the ability of insulin to modulate blood flow, which may contribute in part to the insulin resistance of aging. (*J Clin Endocrinol Metab* **80:** 1899–1903, 1995)

NORMAL aging is characterized by a progressive impairment in carbohydrate tolerance (1). One of the major contributing factors to the glucose intolerance of aging is resistance to insulin-mediated glucose uptake (IMGU) (2–5). IMGU occurs primarily in skeletal muscle. Insulin is thought to increase glucose uptake into muscle by activating glucose transporters, which increase cellular glucose uptake. It has been demonstrated recently that insulin may also act by increasing skeletal muscle blood flow, thereby increasing the delivery of insulin and glucose to muscle tissue (6–14). Because there is a close correlation between the reduction in insulin-mediated blood flow and the resistance to IMGU in obesity, insulin-dependent diabetes mellitus, noninsulin-dependent diabetes mellitus, and hypertension, it has recently been proposed that alterations in insulin-mediated blood flow may have a role to play in the insulin resistance that occurs in these conditions (15–20).

We undertook the following study with the hypothesis that the resistance to IMGU which occurs with aging is caused in part by a reduction in insulin-mediated blood flow.

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Materials and Methods

Experimental Subjects

These studies were performed in healthy nonobese young and elderly subjects (Table 1). All subjects had a normal history and physical examination, normal laboratory tests (including hepatic and renal function), a normal electrocardiogram, and a normal glucose tolerance test, as defined by the National Diabetes Data Group criteria. None of the subjects were taking medication. No subject had symptoms of claudication. Pedal pulses were normal, and there were no clinical signs of peripheral vascular insufficiency. In addition, all subjects had blood pressure values in both ankles that were greater than or equal to blood pressure values in the arms, as measured with a sphygmomanometer. This study was approved by the committee on human investigation at the University of British Columbia. All subjects gave written informed consent before participation.

Experimental Protocol

Each subject underwent two glucose clamp studies in random order, performed according to the method of Andres *et al.* (21). Each study was separated by at least 2 weeks. All studies commenced at 0730 h in our

TABLE 1. Subject characteristics and fasting glucose and hormone levels

	Young (n = 13)	Old (n = 13)
Age (yr)	24 ± 1	77 ± 1
Male/female	7/6	7/6
BMI (kg/m^2)	22.2 ± 0.6	24.2 ± 0.5[a]
Body fat (%)	20.9 ± 1.7	24.3 ± 2.3
Waist-hip ratio	0.81 ± 0.02	0.92 ± 0.02[a]
VO_2 max (mL/kg · min)	48.2 ± 2.3	22.1 ± 1.7[b]
MAP (mm Hg)	87 ± 2	99 ± 2[b]
Glucose (mmol/L)	5.2 ± 0.1	5.4 ± 0.1
Insulin (pmol/L)	27 ± 14	32 ± 7
Epinephrine (pmol/L)	126 ± 19	95 ± 17
Norepinephrine (nmol/L)	0.73 ± 0.05	1.61 ± 0.12[b]

BMI, body mass index; MAP, mean arterial pressure.
[a] $P < 0.05$ young *vs.* old.
[b] $P < 0.001$ young *vs.* old.

Clinical Research Centre after an overnight fast. In all studies, iv lines were inserted into an antecubital vein for infusion of glucose and insulin or saline solution and into a contralateral hand vein for sampling of arterialized venous blood (22). Three heparinized blood samples were taken at 10-min intervals from −20 to 0 min to measure basal glucose, insulin, and catecholamine values. At time 0, glucose clamp studies were commenced and were continued for 240 min. In one study, regular human insulin (Eli Lilly, Indianapolis, IN) was infused at a rate of 40 mU/m^2·min in the young subjects and 34 mU/m^2·min in the old subjects. These insulin infusion rates were chosen because insulin clearance decreases with age (23), and we showed previously that infusing insulin in this way results in equivalent peripheral insulin levels in young and old subjects (5). In the control study, subjects received 500 mL saline via an iv in the hand and 600 mL saline via an antecubital vein. In the euglycemic clamp studies, subjects received 500 mL saline via a peripheral vein and variable amounts of glucose via an antecubital vein. Blood samples were taken at 5-min intervals to measure plasma glucose and every 30 min to measure insulin and catecholamines in each study. The coefficient of variation of plasma glucose did not exceed 5% in any study. During each study, blood pressure was measured at baseline and at 30-min intervals using an automated blood pressure cuff (Dinamap; Critikon, Tampa FL). Mean arterial pressure (MAP) was calculated from the diastolic blood pressure plus one third of the pulse pressure.

Bilateral calf blood flow was determined by venous occlusion plethysmography, using calibrated mercury in SILASTIC brand strain gauges, as previously described (24). This technique was used because it reliably measures changes in blood flow in response to insulin infusion (7, 8, 19, 25, 26). Each leg was supported at 15 cm above the right atrium. Venous occlusion pressure was 40 mm Hg at the lower thigh, and ankle cuff occlusion pressure was 200 mm Hg. The venous occlusion cuff was inflated for 10 sec and deflated for 10 sec for a period of 3 min. The mean of the final five measurements of each recording period was used for analysis. Blood flow was measured at 10-min intervals from −30 to 0 min and then at 30-min intervals for the rest of the study.

VO_{2max} was determined by performing a graded maximal exercise test on a bicycle ergometer, as previously described (27). Waist/hip ratio was determined by dividing the abdominal girth at the umbilicus by the hip circumference at the greater trochanter. Bioelectrical impedance was measured using a machine from RJL Systems (Detroit, MI), and the percentage body fat was calculated as previously described (28).

Analytic Methods

Plasma glucose was measured immediately in all studies by the glucose oxidase method in a YSI glucose analyzer (Yellowsprings Instruments, Yellow Springs, OH). The remaining blood was placed in prechilled test tubes containing aprotonin (400 KIU/mL) and EDTA (1.5 mg/mL) and was centrifuged at 4 C. The plasma was stored promptly at −70 C until assay. All samples from each subject were analyzed in the same assay. Insulin assays were performed using a kit from Linco Research (St. Louis, MO). Catecholamines were analyzed using high performance liquid chromatography with electrochemical detection, as previously described (29).

Data Analysis

All data are presented as mean ± SE. Leg blood flow was calculated as previously described (24). The blood flow values obtained in both legs were averaged to give the mean value at each time point. Incremental blood flow was calculated by subtracting the blood flow value obtained during the control study from the blood flow value at the same time point in the euglycemic clamp. The metabolic rate of glucose (M) was calculated as previously described (30) and then corrected for lean body mass. Differences between young and old subjects were determined by Student's *t* test for unpaired samples and by two-way repeated measures analysis of variance (ANOVA) using the program Super ANOVA (Abacus Concepts, Berkeley, CA). Correlation coefficients were determined by the method of least squares. *P* less than 0.05 was considered significant in all analyses.

Results

Subject characteristics are shown in Table 1. The elderly had a higher body mass index, waist-hip ratio, and MAP, and a lower VO_{2max}. Percentage body fat was slightly but not significantly higher in the elderly. Fasting glucose, insulin, and epinephrine values before the euglycemic clamp studies were similar in the two groups (Table 1). Fasting norepinephrine values were higher in the elderly. Glucose, insulin, and catecholamine values remained constant during the control studies in both age groups (data are not shown). Glucose, insulin, and catecholamine values during the euglycemic clamp are shown in Fig. 1. Steady-state (30–240 min) glucose values (young subjects: 5.0 ± 0.1 mmol/L; old subjects: 5.2 ± 0.1 mmol/L, *P* = NS) were similar. As anticipated from our previous work, steady-state insulin values (young subjects: 371 ± 45 pmol; old subjects: 381 ± 53 pmol/L, *P* = NS) were

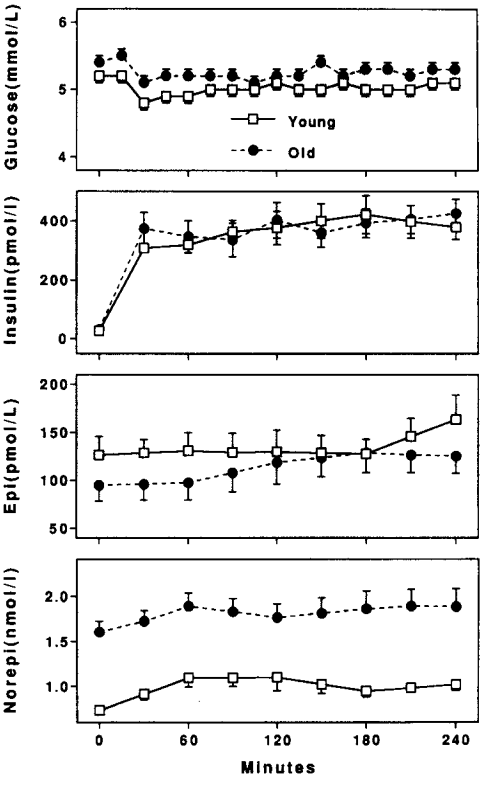

FIG. 1. Glucose, insulin, and catecholamine values in young and old subjects during the euglycemic clamp studies.

similar in both age groups, even though we used a lower insulin infusion rate in the elderly. There was a significant increase in NE values over time in both age groups by ANOVA (young subjects: df = 8, f = 3.67, $P < 0.05$; old subjects: df = 8, f = 3.13, $P < 0.05$). Although epinephrine values seemed to increase over time as well, there was no significant change by ANOVA. At baseline, calf blood flow was lower in the elderly (young subjects: 1.51 ± 0.08 mL/100 mL tissue/min; old subjects: 1.15 ± 0.07 mL/100 mL tissue/min, $P < 0.002$). M values, MAP, pulse, and incremental blood flow rates during the clamp are shown in Fig. 2. M values were significantly higher in the young subjects throughout the study (f = 7.07, df = 1, $P = 0.01$), and there was a significant age/time interaction (f = 6.31, df = 8, $P = 0.01$). Steady-state (180–240 min) M values were also higher in the young subjects (young: 11.17 ± 0.58 mg/kg lean body mass/min; old: 8.72 ± 0.79 mg/kg LBM/min) ($P = 0.02$). MAP values were significantly higher in the elderly throughout the study ($P < 0.001$ by ANOVA), but there was no significant change over time in either group. Pulse rates were not significantly different between young and old subjects by ANOVA. However, there was a significant age/time interaction (f = 4.23, df = 8, $P < 0.001$), indicating a different pattern of change over time in the two groups. When a repeated measures ANOVA was conducted in each age group separately, there was a significant increase in pulse rate over time in the young (f = 12.098, df = 8, $P = <0.001$) but not the old subjects (f = 1.96, df = 8, $P = 0.14$). The increase in calf blood flow from baseline blood flow rates was significantly higher in the young subjects (f = 11.55, df = 1, $P < 0.002$). There was a significant age-time interaction (f = 3.33, df = 8, $P < 0.002$), indicating a different pattern of change over time in the two groups. The steady-state (180–240 min) incremental blood flow values were significantly greater in the young (0.76 ± 0.23 mL/100 mL tissue/min) than in the old subjects (0.05 ± 0.09 mL/100 mL tissue/min, ($P < 0.01$). There was a significant correlation between steady-state M values and incremental blood flow rates in the young (r = 0.59, $P < 0.05$) but not in the old subjects (r = 0.21, P = NS).

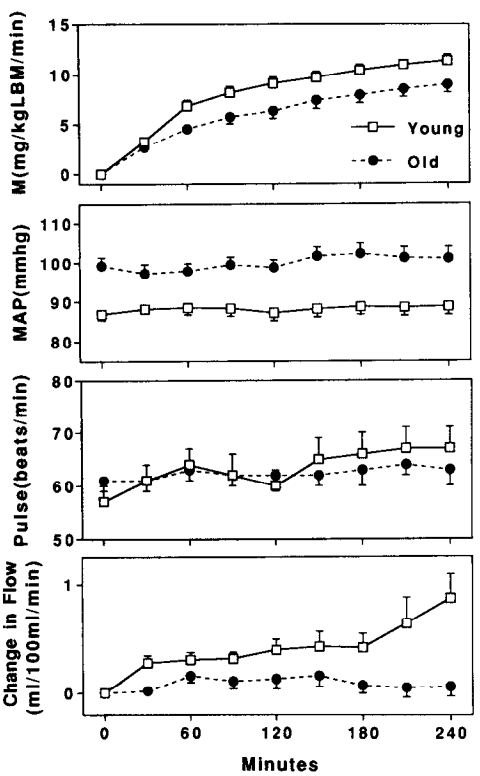

FIG. 2. M values, MAP, pulse, and incremental calf blood flow rates in young and old subjects during the euglycemic clamp studies.

Discussion

We found that the ability of insulin to augment blood flow was attenuated in healthy elderly subjects. Several potential factors may have contributed to the reduction in insulin's ability to augment blood flow in our subjects. It is unlikely that they had undetected vascular disease. Our volunteers were active and nonsmoking, had no symptoms or signs of peripheral vascular disease, and had ankle/brachial blood pressure ratios of equal to or greater than 1. Our elderly subjects had MAP values that were higher than those of the young subjects. Hypertension is known to influence insulin-mediated blood flow in younger subjects (20). Our older subjects had a higher body mass index and a slightly higher percentage of body fat. Obesity is known to impair the ability of insulin to increase blood flow (9). Our elderly subjects also had a more central distribution of body fat. This pattern of fat deposition is more likely to be associated with alterations in insulin-mediated blood flow (12). Our elderly subjects had a lower VO_{2max}. Athletes are known to have significantly higher blood flow rates than those of inactive individuals (31), and our elderly subjects may have had lower blood flow rates because they were less fit. Nonetheless, we believe that our findings are applicable to normal aging in community-dwelling elderly persons inasmuch as our subjects had no identifiable diseases, took no medications, had normal glucose tolerance tests, were free of disability, and led active lives.

Boden *et al.* (26) found no age-related difference in leg blood flow during euglycemic clamp studies in six healthy young and six healthy elderly men. Our young subjects were younger and our older subjects were older than those of Boden *et al.*, which may have made it easier for us to detect differences. There seemed to be greater basal and insulin-stimulated blood flow in the younger subjects in the study of Boden *et al.*, which could have become significant with a larger sample size. Although Boden *et al.* do not provide data on VO_{2max}, our elderly subjects may have been less fit. Although Boden *et al.* did not report MAP values, their elderly subjects may have had MAP values closer to those of the young controls. Because we studied women as well as men, subtle gender differences may have influenced our results. Additional studies are needed to assess the effect of age on insulin-stimulated blood flow.

Insulin is believed to increase blood flow by opening previously underperfused or nonperfused arterioles, which exposes more muscle cells to insulin and glucose. Support for this concept comes from studies showing that there is a correlation between capillary density in muscle and insulin

sensitivity (32). Early work suggests that insulin-induced vasodilation may be mediated by the sympathetic nervous system (7, 8, 19, 25). Recent studies showed that insulin-induced vasodilatory responses are not altered by propanolol or atropine infusion, implying that β-adrenergic or cholinergic mechanisms do not contribute importantly to insulin-induced vasodilation in humans (33). Recently, Steinberg *et al.* (34) demonstrated conclusively that insulin-mediated vasodilation occurs via increased synthesis or release of endothelium-derived nitric oxide. The reduced vasodilatory effects of insulin in the elderly could be caused by a decreased ability of insulin to stimulate endothelium-derived nitric oxide production.

Our data are consistent with other studies showing that elderly subjects have increased NE values (35) and that hyperinsulinemia increases NE values (11, 19). Because NE infusion does not alter insulin-mediated blood flow (10), it is unlikely that increased NE levels had a significant effect on leg blood flow. β-Adrenergic-mediated vasodilation (36) is diminished with age. Our data suggest that insulin-mediated vasodilation is also impaired. However, other vasodilators (37) and exercise (38) produce comparable vasodilation in young and old subjects. Insulin increases cardiac output (12). In our elderly subjects, heart rate increased in the young and not in the old. Although this could relate to differences in venous return, venous filling pressures, *etc.*, it is possible that insulin may have a greater effect on cardiac output in the young. Additional studies with direct measurements of cardiac output will be needed to address this issue.

It would have been ideal in our study to correlate calf blood flow directly with calf glucose uptake. However, previous studies found a strong correlation between leg and whole body glucose uptake (11). The changes we report in calf blood flow are similar to those occurring in other vascular beds, inasmuch as previous studies have found a close correlation between calf and forearm blood flow measurements (39).

It is possible that fat infiltrated between the muscles of elderly subjects. Thus, blood flow expressed per milliliter of tissue would be reduced in the elderly because of a greater fat/muscle ratio and because of decreased flow to muscle tissue *per se*. We did not quantitate calf muscle and fat mass in our subjects. However, previous investigators found that, although elderly subjects have an increase in intraabdominal fat, leg fat is actually approximately 50% less (40). Thus, we believe that a greater leg fat content is unlikely to explain our results. Furthermore, subjects acted as their own controls, which should factor out differences in fat content.

Venous occlusion plethysmography measures the increase in volume of the leg when venous outflow is prevented. It is possible but unlikely that venous pooling was a component of what was measured in our study. The time-constant required to achieve steady-state for measurements of venous pressure/volume relationship is 2–4 min. We documented a linear increase in calf volume during 10 sec of cuff occlusion and a rapid return to baseline on cuff deflation, indicating no residual congestion between deflations. If the technique had not been performed properly, it would be evident from the plethysmographic record because the increase in limb volume would not be linear (41). This did not occur in our study.

Blood flow increased in the young but not in the old subjects throughout the study, and glucose disposal rates increased in parallel in the two age groups. If blood flow is important in regulating insulin-mediated glucose disposal, blood flow and glucose disposal patterns should correspond closely. We suspect that the ability of insulin to activate glucose transporters is relatively similar in young and old subjects (flow-independent glucose uptake), which explains the parallel increase in IMGU in the two age groups. Because insulin-mediated blood flow is impaired in the elderly, flow-dependent glucose uptake is reduced, and the absolute rates of glucose disposal are less. This would explain the correlation between IMGU and blood flow in the young but not in the old subjects. In the young subjects, IMGU and blood flow increased in parallel for the first 180 min, but flow seemed to increase at a more rapid rate than IMGU from 180–240 min. For reasons that are unclear, the variance in blood flow measurements increased during the last hour. It is entirely possible that the rate of increase was, in fact, similar for IMGU and blood flow during this time.

Our findings may have clinical implications. An increase in tissue perfusion could increase IMGU and improve glucose tolerance in insulin-resistant conditions such as aging. Several studies have found that angiotensin converting enzyme-inhibitors increase limb blood flow, decrease glucose levels, and increase IMGU in middle-aged patients with non-insulin-dependent diabetes mellitus (42–44). Moreover, angiotensin converting enzyme-inhibitors have been shown to improve insulin sensitivity in elderly nondiabetic subjects with hypertension (45).

We conclude that normal aging may be characterized by an impairment in the ability of insulin to modulate blood flow. This could contribute, in part, to the insulin resistance of aging.

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