Depressor Action of Insulin on Skeletal Muscle Vasculature: A Novel Mechanism for Postprandial Hypotension in the Elderly

MARK T. KEARNEY, DM, ALAN J. COWLEY, MD, TRACY A. STUBBS, BSc, ALISON EVANS, BSc, IAN A. MACDONALD, PhD

Nottingham, England, United Kingdom

Objectives. We sought to assess the role of insulin in postprandial blood pressure regulation in the elderly.

Background. Insulin is both a positive inotropic and chronotropic hormone that also vasodilates skeletal muscle vasculature. Insulin may thus mediate aspects of postprandial cardiovascular homeostasis.

Methods. Ten healthy elderly subjects were studied in the fasting state on three separate days. After baseline supine hemodynamic and neurohumoral measurements were taken (cardiac output and superior mesenteric artery blood flow were measured using Doppler ultrasound, and calf blood flow was measured using venous occlusion plethysmography), subjects ate on one occasion a 2.5-MJ high carbohydrate meal and on the other two occasions, an isoenergetic high fat meal. One high fat meal was accompanied by an insulin infusion reproducing the plasma insulin profile seen after a high carbohydrate meal while main-

taining the glycemic profile seen after a high fat meal alone. After meal ingestion, measurements were repeated every 20 min for 2 h.

Results. After the three meals, there were similar increments in cardiac output and heart rate. After the high carbohydrate meal and high fat meal with insulin, mean arterial blood pressure fell by between 8 to 10 mm Hg, but did not change after the high fat meal. After the high carbohydrate meal and the high fat meal with insulin, calf vascular resistance did not change, whereas after the high fat meal, it increased by 15.5 ± 4.4 U (mean ± SEM).

Conclusions. Insulin contributes to the failure of calf vasoconstriction seen after a high carbohydrate meal. By this vasodepressor action, insulin is at least in part responsible for the fall in blood pressure after a high carbohydrate meal.

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The hemodynamic and neurohumoral responses accompanying meal ingestion in healthy young subjects are well established (1). After eating a meal there is a decline in splanchnic vascular resistance, leading to an overall fall in systemic vascular resistance. To meet the metabolic demands of digestion and in defense of blood pressure, there is an increase in heart rate and stroke volume, leading to an increase in cardiac output of up to 50% (2). Meals with the majority of energy content as fat are accompanied by vasoconstriction in the calf (the bulk of which is skeletal muscle), unlike meals rich in carbohydrates (1). Despite this apparent failure of vasoconstriction after a high carbohydrate meal, blood pressure is well maintained by greater increments in heart rate and cardiac output compared with that after a high fat meal (1). After a meal, particularly one rich in carbohydrates, there is an increase in sympathetic activity, especially in the skeletal

muscle (3,4) and renal vascular beds (4). This muscle sympathetic activity is thought to occur in vasoconstrictor nerves (5). After a meal rich in carbohydrates, there is a greater increase in plasma insulin than after a high fat meal, and this response contributes to the increased sympathetic activity occurring as a result of carbohydrate ingestion (6).

Healthy elderly subjects (7,8) and frail institutionalized elderly (9) can suffer a significant postprandial decline in blood pressure, particularly after meals of high carbohydrate content (8). The mechanisms modulating postprandial cardiovascular homeostasis in both healthy young and old and frail old subjects are unclear. The elderly have an attenuated compensatory chronotropic (7) and inotropic response to both high fat and high carbohydrate meals (8). It is thus intriguing, that despite this, blood pressure is well maintained after a high fat meal but falls after a high carbohydrate meal (8). After a high fat meal in both the elderly and the young, there is a significant increase in calf vascular resistance that is absent after a high carbohydrate meal (1,8). This, allied to the reduced chronotropic and inotropic responses, may lead to the fall in blood pressure seen in the elderly after a high carbohydrate meal.

Recent work has focused on the cardiovascular effects of insulin (for review, see Baron [10]). It is now well established that insulin, in its upper "physiologic" range, vasodilates skeletal muscle vasculature (11) despite sympathoactivation (12), the major part of which is likely to be targeted at the

Abbreviations and Acronyms

ANOVA = analysis of variance
CVR   = calf vascular resistance
SMA   = superior mesenteric artery
SMABF = superior mesenteric artery blood flow
SMAVR = superior mesenteric artery vascular resistance

skeletal muscle vascular bed. In their original paper describing postprandial hypotension, Lipsitz et al. (9) suggested that it may be due to a failure of insulin-mediated sympathoactivation. In a subsequent report (13), the same group demonstrated a failure to maintain norepinephrine levels in an elderly cohort of patients with postprandial syncope (13). However, in a further study no link between insulin-mediated sympathoactivation and postprandial hypotension could be found (14). In support of this it has been shown (15) that glucose ingestion in the elderly results in greater sympathoactivation than in the young.

The present study aimed to establish the role of insulin in the cardiac and regional vascular responses to a high carbohydrate meal in the elderly. To this end, we gave a group of healthy elderly people three meals; on one occasion a high carbohydrate meal and on two occasions an isoenergetic high fat meal, which on one occasion was accompanied by an insulin infusion, reproducing the plasma insulin profile seen after the high carbohydrate meal. We have previously demonstrated (16) that a similar insulin infusion administered after high fat meal ingestion in healthy young subjects prevented the increase in calf vascular resistance occurring after high fat meal alone, but was associated with a greater chronotropic and inotropic response than after the high fat meal (16). We thus hypothesized that in the elderly where the cardiac response to meal ingestion is attenuated (7,8), the vasodilatory action of insulin contributes significantly to the decline in systemic blood pressure occurring after a high carbohydrate meal.

Methods

Subjects. Ten healthy elderly subjects took part in the study (eight men; mean age 72.3 ± 2.3 years; mean body mass index 24.9 ± 0.6 kg/m^2, range 21.8 to 27.4). All subjects were normotensive and had no history of cardiorespiratory disease. Subjects were biochemically euthyroid and had normal fasting blood glucose, urea and electrolytes levels and normal results on liver function tests. In addition, they had normal results on the 12-lead electrocardiogram. Subjects gave written informed consent to take part in the study, which was approved by the University of Nottingham Medical School Research Ethics Committee. Before taking part, subjects visited the laboratory and were fully familiarized with the experimental techniques and undertook standard tests of autonomic function (17).

Experimental protocol. On three subsequent occasions at least 1 week apart, after a fast of 6 to 10 h, subjects arrived at the laboratory, which was temperature controlled ($26 \pm 2°$C).

After emptying their bladder, subjects rested for 30 min, during which time monitoring equipment was attached, and a cannula for blood sampling was inserted retrogradely into a vein on the dorsum of the left hand. The cannula was kept patent by slowly infusing 150 mmol/liter NaCl, and the hand rested in a box circulated with hot air (55° to 60°C) to "arterialize" the venous blood sample (18). A second cannula was inserted antegradely into a vein in the left antecubital fossa for infusion of insulin and glucose or a saline placebo. After a further 15-min rest, measurements of all variables were taken. After these measurements, subjects sat up and ate on two occasions a high fat meal (volume 350 ml) with an energy content of 2.5 MJ, 71% as fat, and on another occasion an isoenergetic high carbohydrate meal (volume 600 ml) with 75% energy as carbohydrate (7). All subjects completed the meals (the order of which was chosen at random for each subject) within 10 min and then returned to the supine position. Measurements were repeated every 20 min for 2 h commencing 15 min after meal completion. On one occasion, immediately after completing one of the high fat meals, an insulin infusion reproducing the insulin profile seen after a high carbohydrate meal was commenced. This infusion was facilitated by adding 10 U of insulin (Human Actrapid Novo) mixed with 2 ml of the subject's own blood to 58 ml of 150 mmol/liter NaCl, which was infused (Treonic IP4 syringe pump Vickers England) over the 2-h postprandial period. The infusion did not use a priming bolus of insulin and was calculated according to the subject's weight to reproduce the insulin profile seen after a 2.5-MJ high carbohydrate meal (1). The insulin infusion rate was 1.25 mU/kg per min for the first 30 min; 1.00 mU/kg per min for 30 to 45 min; 0.76 mU/kg per min for 45 to 60 min; 0.62 mU/kg per min for 60 to 90 min; and 0.45 mU/kg per min for 90 to 120 min. Twenty percent glucose was infused (IVAC 591 volumetric pump) at a variable rate according to the arterialized blood glucose determinations in an endeavor to maintain glucose within the range seen after a high fat meal. On the other two occasions, measurements were made after high fat and high carbohydrate meals with a saline placebo infusion into the antecubital vein.

Hemodynamic measurements. Heart rate and blood pressure were measured using a semiautomated oscillometric device (Accutorr 1A, Datascope) with the cuff placed around the right upper arm. Cardiac output was calculated from measurements of aortic blood velocity and aortic diameter. Pulsed wave Doppler ultrasound (Scimed Digidop 220) was used to measure blood velocity in the ascending aorta, with the transducer placed in the suprasternal notch. The aortic outflow tract diameter was measured using two-dimensional echocardiography (Diasonics Sonotron) from the left sternal edge in the long-axis view, with a mean of three measurements taken for each subject. This method of measuring cardiac output has been validated against thermodilution (19) with a correlation coefficient of 0.96 (which is similar to our own). In addition, we have shown in our laboratory a correlation coefficient of 0.93 between cardiac output measured using Doppler ultrasound and the indirect Fick method. A number of studies have shown

Table 1. Baseline Hemodynamic and Neurohumoral Data

Meal	CO	HR	MAP	CBF	CVR	SVR	SMABF	SMAVR	NE	EPI
HF	4.3 ± 0.2	62 ± 3	96.4 ± 3.9	3.0 ± 0.2	33.3 ± 2.5	22.1 ± 1.1	408 ± 22	241 ± 16	1.2 ± 0.1	0.2 ± 0.04
HC	4.4 ± 0.3	63 ± 2	97.4 ± 4.7	2.9 ± 0.3	34.8 ± 2.8	22.3 ± 1.6	405 ± 16	244 ± 17	1.5 ± 0.1	0.2 ± 0.03
HFI	4.4 ± 0.2	62 ± 2	100 ± 3.6	3.1 ± 0.3	34.4 ± 2.2	22.9 ± 1.3	392 ± 16	259 ± 17	1.3 ± 0.1	0.2 ± 0.03

Data presented are mean value ± SEM. CBF = calf blood flow (ml/100 ml per min); CO = cardiac output (liters/min); CVR = calf vascular resistance (mm Hg/[ml/100 ml per min]); EPI = plasma epinephrine (nmol/liter); HR = heart rate (beats/min); MAP = mean arterial pressure; NE = plasma norepinephrine (nmol/liter); SMABF = superior mesenteric artery blood flow (ml/min); SMAVR = superior mesenteric artery vascular resistance (mm Hg/[ml/min]); SVR = systemic vascular resistance (mm Hg/liter per min).

a short-term coefficient variation of $<10\%$ (20), which is similar to our own. All measurements were carried out by an operator experienced (T.A.S.) in echocardiographic techniques.

Calf blood flow in the right leg was measured using venous occlusion plethysmography (21) with mercury in rubber strain gauges (22). An occlusion cuff around the upper thigh was inflated to 40 mm Hg to prevent venous return from the leg. Inflation took place in a cyclic manner, with the change in calf circumference measured with a strain gauge. Flow both in and out of the foot was prevented during measurements using a cuff placed around the ankle and inflated to 200 mm Hg. At each time point at least four measurements were made, and the mean of these measurements used in subsequent analysis. The coefficient of variation for measurement of calf blood flow by venous occlusion plethysmography on different days is 11.5%.

Superior mesenteric artery blood flow (SMABF) was measured using transcutaneous Doppler ultrasound (Diasonics Ltd.) with a 3.5-MHz transducer. The superior mesenteric artery (SMA) was visualized with a sagittal scan of the abdomen. The midrange frequency of the imaging system allows scanning to depths of up to 10 cm without compromising the quality of the B-mode images of the vessel. Care was taken to ensure that the entire vessel was insonated and the sample volume placed in the proximal part of the artery away from the bifurcation of the SMA from the aorta, thus avoiding an error in flow measurements as a result of the turbulent flow at the junction of the two arteries. The angle of insonation was recorded and used to convert the Doppler shift values (kHz) into blood flow velocity (cm/s), and care was taken to ensure that wherever possible the same angle of insonation was used in each subject (mean angle of insonation 28.5 ± 0.2°), which would introduce an error $<4\%$ into flow calculations (23). A comparison of SMA flow measurement by Duplex ultrasound and electromagnetic flowmetry showed a strong correlation between the two techniques (24). The same study reported a coefficient of variation of 11% in the measurement of flow, which is very similar to our own value.

Vascular resistance for the calf and SMA were calculated from flow values and mean arterial blood pressure obtained from [Systolic blood pressure + 2 (Diastolic blood pressure)]/3, the units thus being mm Hg/(ml/100 ml per min) and mm Hg/(ml/min), respectively. For these calculations it was assumed that brachial artery pressure was a reliable index of calf and mesenteric artery perfusion pressures, although disparity

between central and peripheral blood pressure measurements has been noted (25). However, any differences were likely to be minimized in healthy subjects and be similar on the three visits.

Neurohumoral, glucose and insulin measurements. Arterialized blood samples were used to measure blood glucose (YSI 23 AM, Yellow Springs Instrument) every 5 min for 2 h postprandially. Every 20 min postprandially, arterialized blood was taken and centrifuged and the plasma separated. Three milliliters of plasma was mixed with 75 μl of ethylene glycol-bis (beta-aminoethyl ether)-*N, N, N', N'*-tetraacetic acid (EGTA)-glutathione (antioxidant) and stored at $-80°C$ for later determination of norepinephrine and epinephrine concentrations using high performance liquid chromatography with electrochemical detection (26). All samples for one subject were run on the same day, and operators had no knowledge of the experimental protocol. The intraassay coefficients of variation were 6% for norepinephrine and 8% for epinephrine, the interassay values being 8% and 10%, respectively, at the levels of catecholamine present in these samples. Plasma was also stored for later determination of insulin concentration by radioimmunoassay using a double-antibody technique developed in-house. The intraassay coefficient of variation is 8% and the interassay value is 12%.

Statistical analysis. To correct for any difference in baseline values for hemodynamic and neurohumoral responses, change from baseline was calculated, and the responses were compared using analysis of variance with repeated measures (27) using the package MINITAB (Minitab Inc.) on a Macintosh LCIII computer. Where analysis of variance (ANOVA) indicated a significant effect, paired t tests with application of a Bonferroni correction were used to locate the differences. Similarly, paired t tests with application of a Bonferroni correction were used to assess significant changes from baseline. Data are expressed as mean value ± SEM. Statistical significance was taken as $p < 0.05$.

Results

The profiles of insulin and glucose are given as absolute values because they represent the primary manipulated variables. To clearly show the effect of insulin on the neurohumoral and hemodynamic responses to the high fat meal, these values are shown as change from baseline. Baseline values are shown in Table 1; there were no significant differences between visits.

Autonomic function. Subjects showed normal responses to standard tests of cardiac autonomic function for this age group.

Insulin and glucose. Fasting plasma insulin concentrations were 7.5 ± 0.9 mU/liter before the high fat meal, 7.2 ± 0.7 mU/liter before the high carbohydrate meal and 8.1 ± 2.0 mU/liter before the high fat meal with insulin, and these values did not significantly differ from each other. After the high fat meal, insulin reached a peak concentration at 35 min of 23.9 ± 3.9 mU/liter, and this declined over the postprandial period (Fig. 1). After the high carbohydrate meal, insulin reached a peak concentration at 55 min of 80.3 ± 14.1 mU/liter and remained significantly above basal throughout the postprandial period. After the high fat meal with insulin, the insulin infusion achieved a very similar profile to the high carbohydrate meal, with a peak insulin concentration of 89.6 ± 12.1 mU/liter at 35 min.

Fasting blood glucose concentrations were 4.8 ± 0.1 mmol/liter before the high fat meal, the high carbohydrate meal and the high fat meal with insulin (Fig. 1). After the high fat meal and the high fat meal with insulin, there was no difference in blood glucose profile, with peak values being <6 mmol/liter. After the high carbohydrate meal, blood glucose reached a peak concentration of 8.9 ± 0.3 mmol/liter at 35 min and remained above baseline levels throughout the postprandial period.

Plasma norepinephrine and epinephrine. There was no difference in the responses after the three meals. Norepinephrine tended to increase after the three meals but did not reach statistical significance. Epinephrine did not change significantly over the 2-h postprandial period after any of the meals.

Cardiac output and heart rate. After all the meals, cardiac output and heart rate increased significantly. After the high fat meal, cardiac output increased by 0.7 ± 0.27 liter/min over the 2-h period, whereas after the high carbohydrate meal, cardiac output increased by 0.95 ± 0.27 liter/min and after the high fat meal with insulin by 0.97 ± 0.29 liter/min (Fig. 2). After the high fat meal, heart rate increased by 3.8 ± 1.4 beats/min over the 2-h period, after the high carbohydrate meal by 4.5 ± 1.3 beats/min and after the high fat meal with insulin by 5.9 ± 1.3 beats/min. During each experimental condition, the peak heart rate response occurred between minute 15 and minute 35, with increases after the high fat meal of ~5 beats/min, after the high carbohydrate meal ~7 beats/min and after the high fat meal with insulin ~9 beats/min. There was no difference in the heart rate response between meals. Cardiac output and heart rate tended to increase by greater amounts after the high carbohydrate meal and the high fat meal with insulin, but this did not reach statistical significance.

Mean arterial blood pressure. There was a significantly different blood pressure response between meals ($p < 0.001$, ANOVA) (Fig. 3). Over the postprandial period, blood pressure did not change after the high fat meal. However, after the high carbohydrate meal, blood pressure fell by 8.0 ± 1.8 mm Hg and after the high fat meal with insulin by 9.6 ± 1.9 mm Hg.
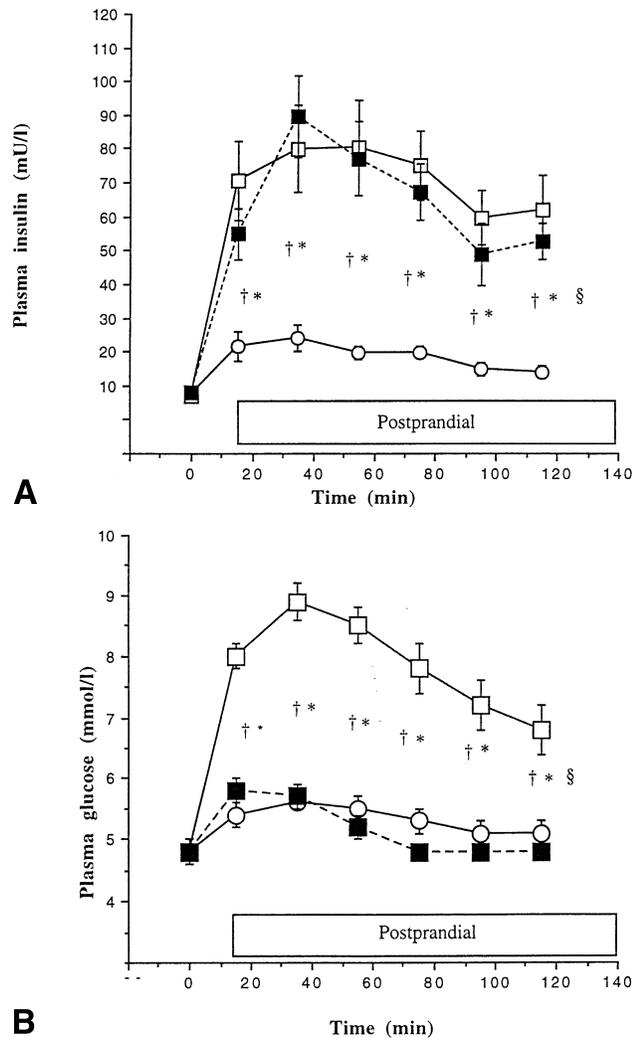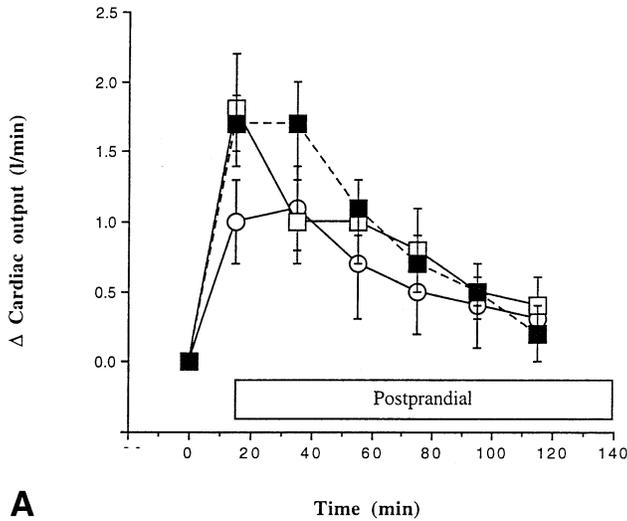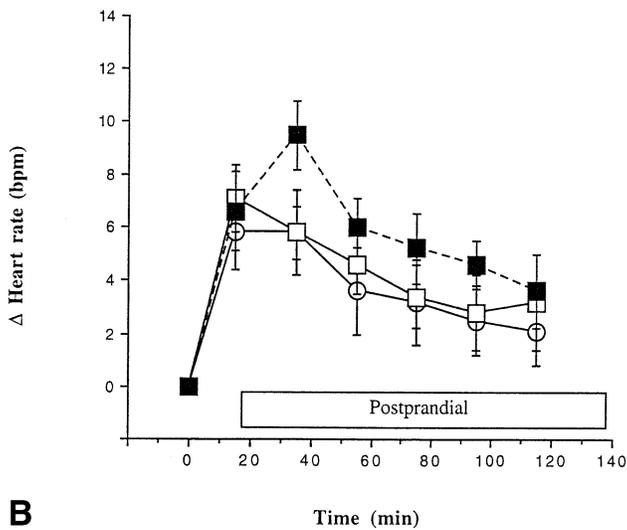

Figure 1. A, Plasma insulin profiles after high fat meal (**circles**), high carbohydrate meal (**open squares**) and high fat meal with insulin infusion (**solid squares**). After high carbohydrate meal, the maximal insulin concentration occurred at 55 min. As planned, the profile accompanying the high fat meal with insulin reproduces this pattern of plasma insulin. Both the high carbohydrate meal and the high fat meal accompanied by insulin had markedly greater insulin responses than the high fat meal alone. **B,** Blood glucose responses to high fat meal, high carbohydrate meal and high fat meal with insulin. As planned, blood glucose levels after the high fat meal with insulin were held at the same levels as those after high fat alone. After the high carbohydrate meal, there was a substantially greater blood glucose response than after the other meals. §Significant difference ($p < 0.001$) between meals: †high fat meal versus high fat meal with insulin; *high fat meal versus high carbohydrate meal.

Calf blood flow and vascular resistance (Fig. 4A). There were significant differences in calf blood flow responses between meals ($p < 0.01$, ANOVA) (Fig. 4). After the high fat meal, calf blood flow fell by a mean value over the postprandial period of 0.8 ± 0.3 ml/100 ml per min, with a peak fall of 1.1 ± 0.3 ml/100 ml per min at 95 min. After the high carbohydrate meal and the high fat meal with insulin, there was no significant change in calf blood flow. There was a significant differ-

Figure 2. Change (Δ) in cardiac output **(A)** and heart rate **(B)** after high fat meal **(circles)**, high carbohydrate meal **(open squares)** and high fat meal accompanied by insulin infusion reproducing the insulin profile seen after the high carbohydrate meal **(solid squares)**. There was no difference in cardiac output or heart rate response between the three meals. bpm = beats/min.

Figure 3. Change (Δ) in mean arterial blood pressure after high fat meal **(circles)**, high carbohydrate meal **(open squares)** and high fat meal accompanied by insulin infusion reproducing the insulin profile seen after the high carbohydrate meal **(solid squares)**. After both the high carbohydrate and high fat meal accompanied by insulin, there was a significant fall in mean arterial blood pressure, which differed significantly from the high fat meal ($p < 0.01$). §Significant difference between meals: †high fat meal versus high fat meal with insulin; *high fat meal versus high carbohydrate meal.

ence in the calf vascular resistance (CVR) responses between meals ($p < 0.01$, ANOVA). After the high fat meal, CVR increased over the postprandial period by a mean value of 15.5 ± 4.4 U, with a peak increase of $\sim$20 U at 115 min, whereas after the high carbohydrate meal and the high fat meal with insulin, CVR did not change significantly.

SMABF and vascular resistance (Fig. 4, B and C). There was no difference in the SMABF responses to the three meals. SMABF increased after the high fat meal by a mean value of 58 ± 12 ml/min, after the high carbohydrate meal by a mean value of 70 ± 10 ml/min and after the high fat meal with insulin by a mean value of 61 ± 11 ml/min. There was a significant difference in the superior mesenteric artery vascular resistance (SMAVR) responses between meals ($p < 0.01$, ANOVA). After the high fat meal, SMAVR fell by 31 ± 7.2 U, whereas
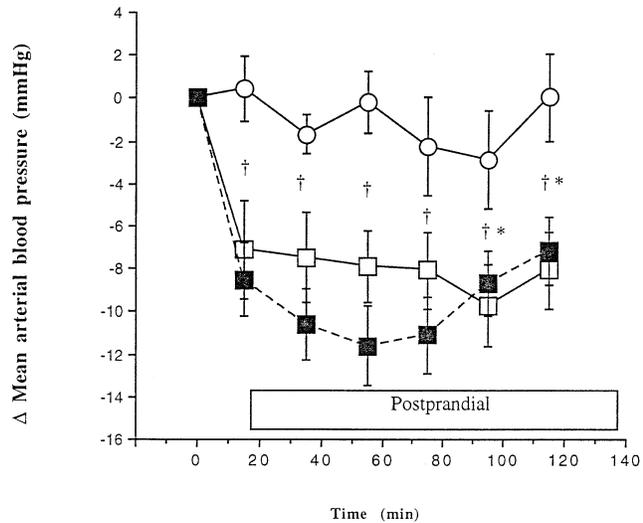
after the high carbohydrate meal and the high fat meal with insulin, SMAVR fell by 52 ± 25 and 55 ± 26 U, respectively, with maximal falls occurring 35 min after each meal.

Systemic vascular resistance (Fig. 4D). There was a significantly different systemic vascular resistance response between meals ($p < 0.01$, ANOVA). After the high fat meal systemic vascular resistance fell by a mean value of 2.6 ± 1.1 U over the postprandial period, with a maximal fall of $\sim$4 U at 35 min, whereas after the high carbohydrate meal and the high fat meal with insulin, systemic vascular resistance fell by a mean value of 5.3 ± 1.2 and 5.2 ± 1.1 U, respectively, over the postprandial period, with a maximal fall of $\sim$7 U at 35 min.

Discussion

It is well established that the elderly can suffer a fall in blood pressure after eating, particularly meals rich in carbohydrates (7,8). A number of pathophysiologic mechanisms for this phenomenon have been suggested, including age-related impairment of baroreflex function (28), inadequate compensatory sympathoactivation (14), inadequate chronotropic and inotropic responses to the fall in splanchnic vascular resistance (8), excessive splanchnic blood pooling during digestion (29) and insulin-induced vasodilation or baroreflex impairment (30). However, until now a pathophysiologic mechanism of postprandial hypotension and, in particular, the role of insulin in this phenomenon has not been clearly defined.
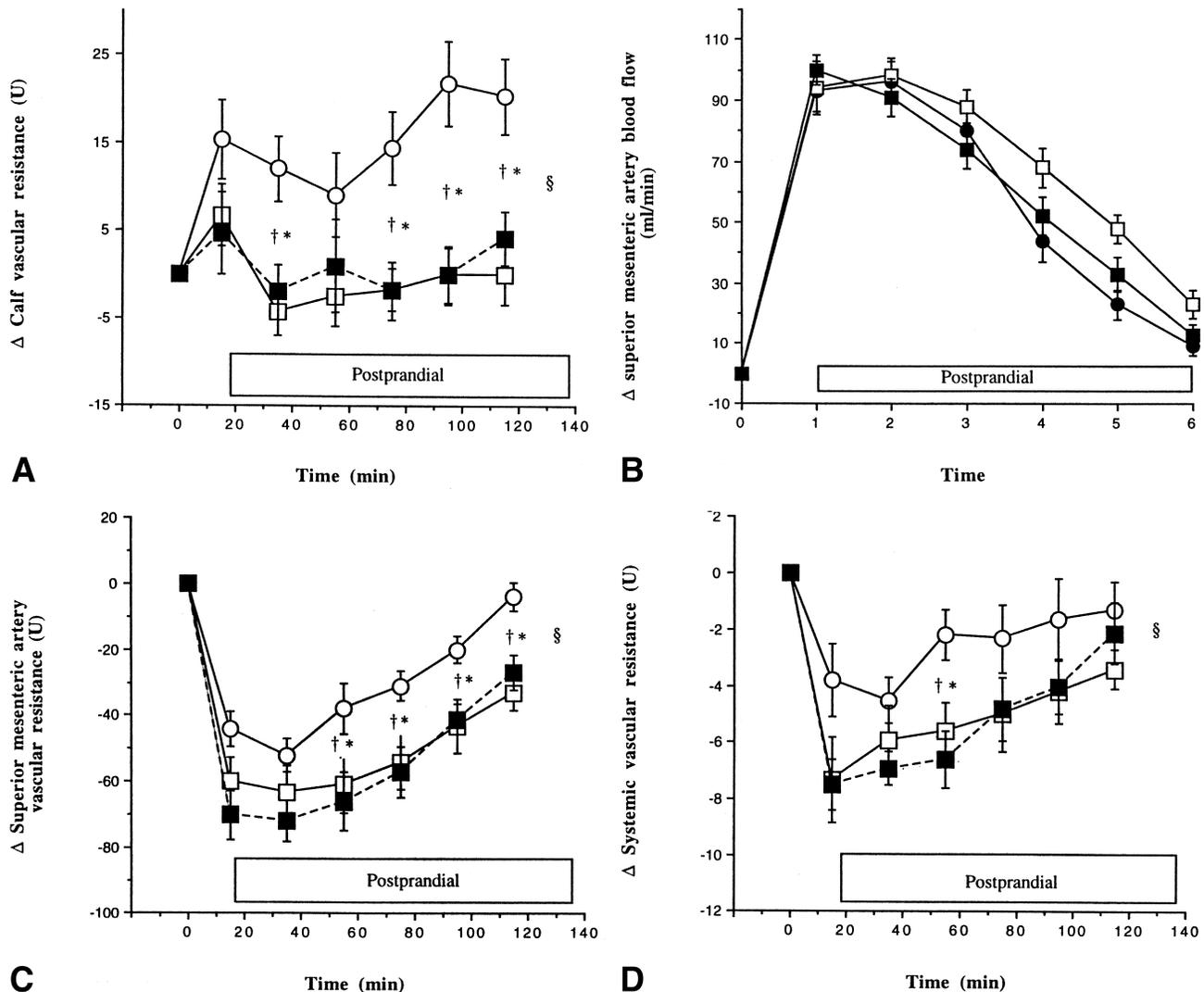
Figure 4. Change (Δ) in SMABF and vascular resistance in different vascular beds after high fat meal (**circles**), high carbohydrate meal (**open squares**) and high fat meal accompanied by insulin infusion reproducing the insulin profile seen after the high carbohydrate meal (**solid squares**). **A,** Change in CVR. The responses were significantly different ($p < 0.01$). After both the high carbohydrate meal and the high fat meal accompanied by insulin, there was no change in CVR, whereas after the high fat meal, there was a significant increase in CVR. **B,** Change in SMABF. After the three meals, SMABF increased significantly, but there was no difference in response between meals. **C,** Change in SMAVR. After both the high carbohydrate and the high fat meal accompanied by insulin, there was a similar fall in SMAVR, which was greater than and differed significantly from that after the high fat meal ($p < 0.01$). **D,** Change in SVR. After both the high carbohydrate meal and the high fat meal accompanied by insulin, there was a similar fall in SVR, which was significantly greater than that after the high fat meal ($p < 0.01$). §Significant difference between meals: †high fat meal versus high fat meal accompanied by the insulin infusion; *high fat meal versus high carbohydrate meal.

Study findings. 1) In a group of healthy elderly subjects, a high carbohydrate meal and an isoenergetic high fat meal accompanied by an insulin infusion reproducing the plasma insulin profile seen after the high carbohydrate meal result in a fall in blood pressure, unlike the high fat meal alone. 2) A high fat meal leads to a significant increase in CVR, whereas after the high carbohydrate and high fat meal with the insulin infusion, this vasoconstrictor reflex was absent. 3) The primary event in the cardiovascular response to meal ingestion seems most likely to be the fall in splanchnic vascular resistance, which is most likely to be predominantly a result of metabolic autoregulation of vascular tone. Indeed, it has been demonstrated in vitro that jejunal blood flow is directly proportional to its oxygen consumption (31). The results of the present study show that insulin augments this vasodilation after a high fat meal, reproducing the pattern of change in SMAVR seen after a high carbohydrate meal. 4) Interestingly, unlike in the young (16), this insulin infusion did not lead to greater cardiac output and heart rate responses. However, there was a tendency for cardiac output and heart rate responses after the high carbohydrate and high fat meal with insulin to be greater than that after the high fat meal alone, thus demonstrating the inadequate cardiac response to a postprandial decline in blood pressure previously noted.

Postprandial stimuli for calf vasoconstriction. After meal ingestion there are a number of reflexes by which vasoconstriction in different vascular territories may be produced. The presence of food in the gut may stimulate visceral receptors, leading to sympathoactivation in different vascular territories; this has been demonstrated in animals (32) and warrants investigation in humans. It has also been demonstrated in animals (33) that there is an inverse relation between splanchnic blood flow and leg blood flow, suggesting the presence of a baroreflex that would increase CVR after eating. After the three meals there was a fall in splanchnic vascular resistance, which, in diverting blood to that particular vascular bed, would lead to unloading of cardiopulmonary baroreflexes and to a reflex rise in CVR (34). In addition, the fall in arterial blood pressure after the high carbohydrate meal and the high fat meal with insulin will have unloaded high pressure baroreceptors, leading to increased vasoconstrictor traffic to the calf. Accompanying these reflex stimuli leading to sympathoactivation after the high carbohydrate meal and high fat meal with insulin is the increase in insulin concentration itself. A number of studies have shown that insulin significantly increases sympathetic nerve traffic to the calf (for review see Baron [10]).

Mechanisms for insulin-mediated failure of calf vasoconstriction after a high carbohydrate meal. Despite numerous stimuli for vasoconstriction after eating (as clearly demonstrated by the increase in CVR after the high fat meal), this did not occur after the high carbohydrate meal or the high fat meal with insulin. Although we can only speculate on the mechanism by which this occurred in the present study, it has been clearly demonstrated (12) that despite increasing calf sympathetic nerve activity, insulin has a vasodepressor action in that vascular bed. This is at least in part due to insulin-induced nitric oxide release mediating vascular smooth muscle relaxation (35,36). Allied to this is the effect of insulin to blunt the skeletal muscle vasoconstrictor response to norepinephrine and to increase its metabolic clearance by 20% (37).

Mechanisms underlying inadequate cardiac response to the fall in blood pressure after high carbohydrate meal. After each meal there was an increase in heart rate and cardiac output. Despite a significant fall in blood pressure after the high carbohydrate and the high fat meal with insulin, the chronotropic and inotropic responses did not differ to the response seen after the high fat meal alone. In contrast to this we have shown (16) in healthy young subjects that an identical insulin infusion after a high fat meal results in greater increments in heart rate and cardiac output than the high fat meal alone. There are a number of possible explanations for this inadequate cardiac response to meal ingestion in the elderly. It may be that the aging myocardium has a diminished response to the inotropic action of insulin similar to the diminished response to catecholamines (38). Another possibility is that the attenuated cardiac response to the postprandial decline in blood pressure is due to the decline in baroreceptor sensitivity seen in the elderly (30). In addition, high carbohydrate and

insulin may further reduce baroreceptor sensitivity (39). A further possibility is that an increase in heart rate and cardiac output occurring as a result of parasympathetic withdrawal (shown to occur in healthy young subjects [40]) is limited by an age-related decline in parasympathetic nervous system-mediated reflex responses to cardiac stressors.

Study limitations. The noninvasive nature of the present study means that we cannot provide a detailed explanation for the mechanisms underlying the failure of vasoconstriction and the inadequate cardiac responses to the fall in blood pressure. There were no direct measurements of augmented splanchnic vasodilation, so we cannot conclude that insulin definitely augments vasodilation. The fall in systemic vascular resistance could have been a reflex response to a rise in cardiac output. However, in the present experiment, blood pressure fell; thus, any reflex vasodilation is inappropriately large for the rise in cardiac output. Data supporting the vasodilatory effect of insulin are convincing (for review see Baron [10]); in addition the failure of vasoconstriction seen in our study is intimately linked to the "physiologic" plasma insulin profile that we reproduced, although other factors may also play a part. In view of this, our conclusions regarding the mechanisms underlying the insulin-augmented fall in systemic vascular resistance remain sound.

The plasma norepinephrine levels recorded in the present study showed only a tendency to rise; however, this simply illustrates no significant change in whole-body sympathetic tone. It does not provide information on regional sympathetic activity. Thus, in the skeletal muscle vascular bed, vasoconstrictor sympathoactivation would not necessarily produce an increase in plasma norepinephrine. Despite this, it is clear from our data that after the high fat meal there was a significant increase in CVR. This study was a pragmatic assessment of the role of insulin in postprandial blood pressure regulation in the elderly. Our hypothesis was that the insulin profile seen after a high carbohydrate meal would prevent compensatory vasoconstriction in the calf, or to all intents and purposes, the skeletal muscle vascular bed; our data confirm this hypothesis.

Conclusions. To our knowledge, this is the first study to critically assess the part played by insulin in postprandial blood pressure regulation in the elderly. Our data showed that the fall in blood pressure seen after a high carbohydrate meal in healthy elderly subjects is at least in part due to failure of vasoconstriction in skeletal muscle vasculature and augmented splanchnic vasodilation. These effects are modulated by the vasodepressor action of insulin, which, allied to an attenuated cardiac response to meal ingestion, leads to postprandial hypotension after a high carbohydrate meal. We now have evidence that insulin plays an important role in the genesis of postprandial hypotension in the elderly. In addition, this experiment provides a model for further studies assessing therapeutic intervention in this common problem, which may lead to significant morbidity and mortality (41).

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