Preserved Relative Dispersion but Blunted Stimulation of Mean Flow, Absolute Dispersion, and Blood Volume by Insulin in Skeletal Muscle of Patients With Essential Hypertension

Hanna Laine, MD; M. Juhani Knuuti, MD; Ulla Ruotsalainen, PhD; Tapio Utriainen, MD; Vesa Oikonen, MSc; Maria Raitakari, MD; Matti Luotolahti, MD; Olli Kirvelä, MD; Paolo Vicini, MSc; Claudio Cobelli, PhD; Pirjo Nuutila, MD; Hannele Yki-Järvinen, MD

Background—We examined the integrity of the effects of insulin on mean muscle blood flow, flow heterogeneity, and blood volume in essential hypertension.

Methods and Results—Positron emission tomography, combined with \([^{15}\text{O}]\text{H}_2\text{O}\) and \([^{15}\text{O}]\text{CO}\) as tracers for direct measurement of blood flow and volume in skeletal muscle, and a new bayesian iterative reconstruction algorithm allowing pixel-by-pixel quantitation of blood flow and flow dispersion, were used. Measurements were performed basally after an overnight fast and under normoglycemic hyperinsulinemic conditions in 11 newly diagnosed, untreated mildly hypertensive men (age, 35 ± 1 years; body mass index, 25.2 ± 0.4 kg/m²; blood pressure 141 ± 4/96 ± 2 mm Hg, mean ± SE) and 11 matched normotensive men. Insulin-stimulated whole body glucose uptake was significantly decreased in the hypertensive men (41 ± 4 μmol/kg per minute) compared with the normotensive (59 ± 4 μmol/kg per minute, \(P<0.005\)) men. Mean blood flow in skeletal muscle was significantly lower in the hypertensive than the normal subjects basally (1.7 ± 0.2 versus 2.7 ± 0.4 mL/0.1 kg per minute, \(P<0.05\)) and during hyperinsulinemia (2.3 ± 0.2 versus 4.2 ± 0.8, \(P<0.05\)). The flow response to insulin (0.6 ± 0.2 versus 1.9 ± 0.5 mL/0.1 kg per minute, hypertensive versus normal subjects, \(P<0.05\)) was also significantly blunted. Muscle blood volume was significantly lower in the hypertensive than in the normal subjects, both basally (3.0 ± 0.2 versus 3.5 ± 0.2 mL/0.1 kg, \(P<0.05\)) and during hyperinsulinemia (3.1 ± 0.2 versus 4.0 ± 0.2 mL/0.1 kg muscle, \(P<0.02\)). The increase in muscle blood volume by insulin was significant in the normal subjects (\(P<0.05\)) but not the hypertensive subjects. Regional pixel-by-pixel analysis within femoral muscles revealed significant spatial heterogeneity of blood flow. Insulin increased absolute dispersion of blood flow significantly more in the normal subjects than in the hypertensive subjects (\(P<0.05\)).

Conclusions—True flow heterogeneity, as judged from the coefficients of variation (relative dispersion), was comparable between the groups basally and during hyperinsulinemia. We conclude that mean flow, its absolute dispersion, and blood volume exhibit insulin resistance in patients with essential hypertension. (Circulation. 1998;97:2146-2153.)

Key Words: blood pressure ■ insulin ■ glucose ■ tomography

Insulin has dual effects on skeletal muscle blood flow. It increases blood flow in a time- and concentration-dependent fashion through a mechanism that can be abolished by inhibiting nitric oxide synthesis. Insulin also stimulates, at physiological concentrations, sympathetic nerve activity, an effect counteracting insulin-induced vasodilatation. In normal subjects, the vasodilatory effect of insulin predominates. In patients with essential hypertension, blunted nitric oxide–dependent vasodilatory responses have been reported in some but not all studies. This possible defect, vascular rarefaction in biopsies of skeletal muscle, lack of attenuation of vasoconstrictive responses to angiotensin II by insulin, and data demonstrating overactivation of the sympathetic nervous system by insulin, raise the possibility that the vascular effects of insulin also are impaired in these patients.

Surprisingly, however, with the exception of the subgroup of hypertensive patients with high Na/Li countertransport activity in erythrocytes, insulin-stimulated blood flow has been found to be unaltered in essential hypertension in all seven studies hitherto performed. In normal subjects, however, inverse relations have been found in two studies between mean arterial blood pressure and insulin-stimulated blood flow. In the latter studies, the insulin concentra-
tions were high enough to clearly (on the average by 80% to 117%) increase blood flow above basal values, whereas in the studies performed in hypertensive subjects, insulin either did not increase blood flow significantly or the increase was modest (10% to 30%). We hypothesized that if defects in insulin-stimulated blood flow do indeed characterize patients with essential hypertension, the stimulus, that is, the dose of insulin or duration of the insulin infusion, must be high enough to clearly increase blood flow in normal subjects.

Even if a defect did exist in insulin-stimulated blood flow, its significance for insulin-stimulated nutrient delivery would remain unclear. If flow increased because of an increase in linear blood flow velocity through functional arteriovenous shunts, both blood volume and substrate availability in nutritive capillaries remain unchanged. However, insulin recently has been shown to increase capillary recruitment in hindleg muscles of anesthetized rats. These new data combined with our previous data showing that insulin increases not only blood flow but also blood volume in normal subjects classifies insulin as a true vasodilatory hormone. A defect in the ability of insulin to increase blood volume in patients with essential hypertension would therefore be consistent with diminished capillary recruitment. The effect of insulin on muscle blood volume has not yet been studied in essential hypertension.

Capillary exchange of nutrients is also dependent on the distribution of flow among vessels, which can be defined as some vessels receiving more and some less of their appropriate fraction of total has been invoked to explain phenomena such as flow-limited muscular performance and suboptimal capillary transport of small solutes. In animals, various experimental maneuvers have opposite effects on flow and capillary exchange. For example, infusion of vasodilators may increase flow but reduce capillary transport of diffusible indicators in skeletal muscle. Currently no data are available regarding the effect of insulin on blood flow heterogeneity in patients with essential hypertension.

Use of positron emission tomography (PET), labeled water, and carbon monoxide enables the quantitation of skeletal muscle blood flow and volume in vivo in humans. Recent refinements in reconstruction methods of PET images enabled us to accurately perform pixel-by-pixel quantitation of regional muscle blood flow and analyze the absolute and relative dispersion of blood flow and the shape of its frequency distribution as indexes of flow heterogeneity. In our study, we used this technique to compare effects of insulin on mean muscle blood flow and volume in normal subjects and patients with essential hypertension. We also examined whether insulin changes the absolute or relative distribution of flow in normal subjects and whether these actions of insulin are preserved in essential hypertension. Our results demonstrate defects in the vascular actions of insulin in the stimulation of mean flow, absolute flow dispersion, and blood volume but preserved relative dispersion in patients with essential hypertension.

**Methods**

**Subjects**

Eleven men with newly diagnosed, untreated essential hypertension and 11 normotensive men were studied (Table). The hypertensive subjects were recruited among clients of an occupational health service on the basis of the following criteria: (1) age 20 to 50 years, (2) diastolic blood pressure >95 mm Hg on at least three separate occasions, (3) no signs of other cardiovascular disease, and (4) no regular medication. Secondary forms of hypertension were excluded by history and physical examination and standard laboratory tests. All subjects had normal electrocardiograms. At least 3 days before the study, the subjects consumed a weight-maintaining diet containing 200 g carbohydrate per day. The nature, purpose, and potential risks of the study were explained to all subjects before they gave their voluntary consent to participate. The study protocol was approved by the Ethical Committee of the Turku University Hospital.

**Study Design**

The subjects were studied in the supine position after an overnight 10- to 12-hour fast. Two catheters were inserted: one in an antecubital vein for infusion of glucose and insulin and injection of labeled water and one in the opposite radial artery for blood sampling. Each study consisted of a 40-minute basal period (~40 to 0 minutes) and a 100-minute (0 to 100 minutes) hyperinsulinemic period (Figure 1). Blood volume and flow were measured in cross sections of the femoral region during the basal period as described in detail below. Serum insulin was thereafter increased with a primed, continuous infusion of insulin at a rate of 5 mU/kg per minute (Velosulin, Novo Nordisk A/S). Normoglycemia was maintained with an infusion of 20% glucose on the basis of arterial plasma glucose concentration measurements, which were performed every 5 to 10 minutes. After 50 to 60 minutes of hyperinsulinemia, measurements of blood flow and capillary exchange were performed as described in detail below.
volume and flow were repeated (Figure 1). Whole body glucose uptake was calculated from the glucose infusion rate (during 60 to 100 minutes) after correction for changes in the glucose pool size. 13 Arterial blood samples for measurement of the concentrations of serum insulin were taken at 30-minute intervals. 36 Blood [15O]H2O and [15O]CO radioactivities were measured as described below.

**Production of Positron Emitting Tracers, Scanning**

[15O]H2O 32,37 and [15O]CO 27 were produced as previously described. The subject was positioned in the tomograph with the femoral region within the gantry. Before emission scanning, a transmission scan for correction of photon attenuation in the body was performed for 15 minutes with a removable ring source containing 66Ge (total counts, 15 to 30×106 in a plane). Before the images were reconstructed, the data were corrected for decay of [15O]. Dead time was corrected for in each plane and frame separately, and correction for photon attenuation was done with the use of data obtained from a transmission scan. The data were then reconstructed into a 128×128 matrix with the use of a recently developed bayesian iterative reconstruction algorithm with median root prior (the MRP method) with 150 iterations and a bayesian coefficient of 0.3 in the flow studies and 0.9 in the blood volume studies. The pixel-by-pixel inhomogeneity and reconstruction artifacts were defined with a cylindrical phantom in which the relative radioactivity concentrations were chosen to represent the levels in muscle and blood vessels. Inhomogeneity, as estimated from the coefficient of variation (%), averaged ≈10% using the former reconstruction method (filtered back-projection, the FBP method) and ≈6% using the newly developed iterative algorithm. 36

**Measurement of Muscle Blood Flow**

[15O]H2O (30 to 45 mCi) was infused intravenously (30 seconds), and a dynamic scan for 6 minutes was started simultaneously. In three subjects, insulin-stimulated blood flow could not be measured because of technical problems. To obtain the input function, arterial blood was withdrawn with a pump at a speed of 6 mL/min from the radial artery, and the radioactivity concentration was measured with a two-channel detector system (Scanditronix), which was calibrated to the well counter (Bicron 3MW3/3, Bicron Inc) and the PET scanner. The delay between the input curve and the tissue curve was solved by fitting. Blood flow was quantitated with a single compartment model and an autoradiographic method as previously described in detail. We have recently validated this method for quantitation of low blood flows in skeletal muscle by using [15O]H2O, PET, and plethysmography. Blood flow was calculated pixel by pixel into parametric flow images with a 250-second tissue integration time as previously described. 32,37 The size of a pixel in the parametric flow image was 9 mm2 (∼3×3 mm).

**Measurement of Muscle Blood Volume**

The subjects inhaled [15O]CO (0.14% CO mixed with room air) (95 to 135 mCi) for 2 minutes. A static scan was started 2 minutes after the end of the inhalation, as previously described. 27 The inhaled CO combines with hemoglobin to form carboxyhemoglobin, which becomes distributed in the volume of red blood cells. During the scan period, three blood samples were taken and their radioactivity concentration was measured with a well counter (Bicron 3MW3/3). Regional muscle blood volume was calculated under steady-state conditions by dividing the concentration of tissue [15O]CO radioactivity by the concentration of [15O]CO in the blood, as previously described. 37 This ratio was then divided by the regional tissue–to–large vessel hematocrit, which was assumed to equal 0.91 on the basis of studies of Chaplin et al, who showed the ratio of total body hematocrit to venous hematocrit to be constant over a wide range of peripheral venous hematocrits. There are no published data on the effect of insulin on the hematocrit in a deep vein draining muscle tissue. However, hematocrits were determined and remained unaffected by insulin or glucose in a large study in which forearm glucose uptake was measured over a range of insulin concentrations from basal to 1800 mU/L and glucose of 5 to 22 mmol/L. 43 We have previously shown the reproducibility of two repeated measurements of blood volume in the same subject to be 3.0±1.8%. 27

**Regions of Interest**

Regions of interest (ROIs) were drawn in the posterior, anterolateral, and anteromedial muscular compartments of the femoral region in four transaxial slices in both legs, carefully avoiding the great vessels. The localization of the muscle compartments was verified by comparing the CO images with the transmission image, which provides a topographic distribution of tissue density. The ROIs outlined in the CO images were copied to the flow images to quantitate flow and volume in identical regions.

**Heterogeneity Analysis of Blood Flow**

Distributions of blood flow were constructed from the pixel-by-pixel images. ROIs were drawn onto the muscle areas as described above and used for heterogeneity analysis. Each ROI comprised the average 23.3±1.5 cm3. The standard deviation (SD) of flow values was used to characterize the absolute dispersion of flow. The coefficient of variation (CV) for blood flow was calculated by dividing the SD by its respective mean value (SD/mean flow). The CV is a measure of relative dispersion or true flow heterogeneity. However, it is possible that the coefficient of variation remains constant in response to an intervention, whereas the shape of the distribution changes. The latter would also indicate redistribution of blood flow. This possibility was evaluated by visually analyzing the shape of the histograms depicting relative flow.

**Other Measurements**

Maximal aerobic power (VO2,max) was determined by use of an electrically braked cycle ergometer (Ergoline 800 S, Mijnhardt). The criteria used to establish the VO2,max were a plateau in VO2 with increasing intensity and a respiratory quotient of >1.10. Blood pressure and heart rate were followed every 15 minutes during the study.

**Statistical Methods**

Comparison of normotensive and hypertensive subjects and differences between basal and insulin-stimulated measurements was performed with two-way ANOVA for repeated measures. Analysis of frequency histograms has been described above. Correlation analysis was calculated with Spearman’s rank correlation coefficient. The abbreviation “kg” after muscle flow and volume measurements refers to kilograms of muscle. Probability values of <.05 were considered statistically significant. All data are shown as mean±SEM.

**Results**

**Whole Body Glucose Uptake**

Fasting plasma glucose and insulin concentrations are given in the Table. During the insulin infusion, serum-free insulin (394±22 versus 453±28 mU/L, normotensive versus hypertensive subjects, NS) and plasma glucose (5.5±0.1 versus 5.4±0.1 mmol/L, respectively) concentrations were comparable. Insulin-stimulated whole body glucose uptake was 32% lower in the hypertensive men (41±4 μmol/kg body wt per minute) than in the normotensive men (59±4 μmol/kg body wt per minute, P<0.05).

During insulin infusion, systolic blood pressure (Table) remained unchanged in both groups, whereas diastolic blood pressure decreased from 79±3 to 66±7 mm Hg (P<0.05) in the normal subjects and from 96±2 to 87±2 mm Hg (P<0.05) in the hypertensive subjects. Basal heart rate was significantly higher in the hypertensive subjects (68±2 bpm) than in the normal (58±3 bpm) subjects. During hyperinsu-
linemia, heart rate increased to 62±3 bpm in the normal subjects (P<0.05) and to 70±3 bpm in the hypertensive subjects (NS).

Muscle Blood Flow
Basal muscle blood flow was significantly lower in the hypertensive men than in the normotensive men (Figure 2). Insulin increased mean muscle blood flow significantly in both groups, by 55%, from 2.7±0.4 to 4.2±0.8 mL/0.1 kg per minute in the normal subjects (P<0.01), and by 35%, from 1.7±0.2 to 2.3±0.2 mL/0.1 kg per minute in the hypertensive subjects (P<0.01). Both basal (P<0.05) and insulin-stimulated flow (P<0.05) and the increments in blood flow by insulin (0.6±0.2 versus 1.9±0.5 mL/0.1 kg per minute, P<0.05) were significantly lower in the hypertensive than the normotensive subjects.

Heterogeneity of Blood Flow
Examples of frequency distributions of absolute flows from one hypertensive and one normal subject are shown in Figure 3. In response to insulin, absolute dispersion of flow increased significantly in the normal subjects from 1.11±0.25 to 1.47±0.35 mL/0.1 kg per minute (P<0.03) but not in the hypertensive subjects (0.63±0.06 versus 0.75±0.05, basal versus insulin, NS). Relative dispersion was not significantly different between the groups either basally (0.355±0.03 versus 0.373±0.01, normal versus hypertensive subjects) or during hyperinsulinemia (0.332±0.03 versus 0.336±0.01, respectively, Figure 4). Also, the responses to insulin did not differ significantly between the groups (−0.037±0.01 versus −0.022±0.02, respectively, NS).

Muscle Blood Volume
Insulin increased muscle blood volume by 14%, from 3.5±0.2 to 4.0±0.2 mL/0.1 kg in the normal subjects (P<0.01), but did not change blood volume significantly in the hypertensive subjects (3.0±0.2 versus 3.1±0.2 mL/0.1 kg, NS, Figure 2). Muscle blood volume was lower both basally (P<0.05) and during hyperinsulinemia (P<0.02) in the hypertensive subjects compared with the normal subjects (Figure 2).

Discussion
Insulin and Mean Muscle Blood Flow in Essential Hypertension
The primary aim of this study was to establish whether blood flow responses to insulin are abnormal in patients with essential hypertension and if so, whether a defect in blood flow is associated with a blunted increase in blood volume or abnormal distribution of blood flow in skeletal muscle. Insulin is known to be a slow-acting vasodilator in human skeletal muscle. In contrast to glucose extraction, which is maximally and by 10- to 20-fold stimulated within 30 minutes of insulin exposure in vivo, blood flow increases continuously over several hours in a time-dependent and insulin concentration–dependent fashion. These data imply that defects in the vascular effects of insulin cannot be found if studies are performed under conditions in which insulin
Use of PET and [15 O]H₂O enables quantitation of low flow.

Flow Heterogeneity

Insulin and Vascular Responses in Essential Hypertension

Figure 4. Frequency histograms of mean relative muscle blood flow values in normal (○, CONT) and hypertensive (●, HTN) subjects after an overnight fast (BASAL) and under normoglycemic hyperinsulinemic conditions (INSULIN). Relative flow (x-axis) was calculated by dividing the standard deviation of flow by mean flow, and this value was plotted against its frequency of all relative flows (y-axis).

does not increase flow or flow increases only marginally even in normal subjects. This may explain why defects in blood flow have not been observed in previous studies performed in patients with essential hypertension. Consistent with this hypothesis, Baron et al and Utriainen et al, who used 8 to 35 times higher doses of insulin than those used to study patients with essential hypertension, did find correlations between mean arterial pressure and leg blood flow in normal subjects. Our finding of a defect in mean blood flow in patients with essential hypertension at an insulin concentration of 450 mU/L is in line with the latter observations and provides the first evidence of a defect in the vasodilatory effect of insulin in these patients. Because blood flow was quantitated directly in skeletal muscle, artifically low blood flow values caused by possible differences in limb fat content between the groups were avoided. Large differences in body composition are also unlikely because of comparable body mass indexes between the groups. It should be emphasized, however, that studies performed with high doses or prolonged infusions of insulin should be viewed merely as attempts to unravel vascular abnormalities in hypertension in a manner analogous to the studies measuring blood flow responses to other vasoactive agents.

Flow Heterogeneity

Use of PET and [15 O]H₂O enables quantitation of low flow rates in tissues such as resting skeletal muscle. It enables presentation of blood flows in pixel-by-pixel parametric images. In resting skeletal muscle, the relation between tissue radioactivity after a bolus injection of [15 O]H₂O and blood flow is linear. Therefore, the calculated flow in the volume of measurement represents true average flow. The MRP method is a new reconstruction algorithm that reduces noise and improves image quality. In our study, statistical noise was reduced by use of a long integration time (250 seconds) and the MRP method. The better image quality enabled construction of absolute and relative blood flow distributions and made it possible to examine, for the first time in vivo in humans, blood flow heterogeneity in skeletal muscle of patients with essential hypertension.

Flow heterogeneity, as defined by Duling and Damon, can be defined simply as an uneven distribution of flow among perfused vessels. Relative dispersion serves as a true measure of flow heterogeneity and reflects the extent to which some vessels receive more and some less flow than their appropriate fraction of total. We quantitated relative blood flow dispersion in the basal state and under normoglycemic hyperinsulinemic conditions in normal and hypertensive subjects. Relative blood flow dispersions and normalized flow distribution histograms remained unchanged in both groups. This suggests that the fractional distribution of blood flow remained constant as the mean blood flow increased. These data are consistent with previous studies demonstrating that changes in mean blood flow by infusion of glucose-insulin-potassium in the dog heart, exercise, or sympathetic nerve activity in skeletal muscle of the rabbit do not change relative flow or the shape of flow distributions, whereas vasodilatation with adenosine increases both mean flow and its relative dispersion in the heart. The magnitude of relative dispersion, 0.38 in both the normal and hypertensive subjects basally, is within the range of values reported with the use of microspheres, number of ink-filled capillaries in histologic sections, and tritiated water in dog and rat. Insulin (0.56 mU/L, Reference 49), and rabbit skeletal muscle preparations. In contrast to relative dispersion, insulin did increase absolute dispersion (standard deviation of blood flow) significantly in the normal subjects. The increase in absolute dispersion by insulin was not statistically significant in the hypertensive subjects. Although one may predict absolute dispersion to change as a function of mean blood flow, the small standard error of blood flow and the relatively small number of hypertensive subjects studied could have contributed to the failure to observe a significant increase in absolute dispersion in the hypertensive subjects.

Variability of blood flow among vessels has been termed the spatial heterogeneity and the variability with time within each vessel as temporal heterogeneity. There are no perfect methods for measuring flow heterogeneity, and each method is subject to significant and different sampling errors as a result of temporal and spatial variations in flow. In our study, images were integrated from data collected over 4 minutes (250 seconds). In resting frog sartorius muscle, in which spatial and temporal heterogeneity have been separately quantitated, overall flow heterogeneity measured during a 10-second period was similar to spatial heterogeneity measured over 10 minutes, although temporal heterogeneity made a small contribution to overall heterogeneity. In the
dog heart, spatial heterogeneity of myocardial blood flow remains stable for hours. These data suggest that the heterogeneity measured in the present study predominantly reflects spatial heterogeneity.

Considering the diameter of a capillary (5 to 7 μm) relative to the width of a pixel (3 mm) or the smallest surface area that can be quantitated after the reconstruction process (5x5 mm²), values of flow heterogeneity in this study do not measure heterogeneity at the capillary level. Heterogeneity in capillaries, when measured with direct visualization techniques, have given higher coefficients of variation (mean, 0.61, see Reference 28 for review) than those observed in the present or in whole organ studies. From the view of microvessel organization, regions of groups of capillaries with dimensions of cubic millimeters are controlled by an arteriole, but it is unknown whether the present analysis of flow heterogeneity reflects heterogeneity at this level. Thus we can only conclude that flow heterogeneity, when measured in areas of ~5x5 mm² in size in the femoral region, is comparable between normal subjects and patients with essential hypertension. Despite this, the present methodology has advantages compared with some previous approaches. First, the method is suitable for use in humans. Second, it involves neither invasive manipulation of tissue nor its innervation, factors that profoundly affect flow heterogeneity.

Insulin and Skeletal Muscle Blood Volume

Theoretically, a defect in insulin-stimulated blood flow could be due to a defect in blood flow velocity or blood volume (capillary recruitment) or both. The former is thought to reflect nonnutritive flow (functional vascular shunting) and the latter nutritive flow. Capillary recruitment can lead to a large increase in the number of capillaries open at any given moment and thereby facilitate the access of nutrients to tissue. This mechanism of flow increase might be expected to be accompanied by an increase in muscle blood volume, whereas a simple increase in linear blood flow velocity through functional vascular shunts would not alter blood volume. In our study we found significant decreases in blood volume basally and during insulin stimulation in the hypertensive subjects. Furthermore, the insulin-induced increase in blood volume was blunted in the hypertensive subjects. The difference in blood volume between the hypertensive and normal subjects in this study (3.0 versus 3.5 mL/0.1 kg muscle) may appear small compared with our previous report of a blood volume of 3.3 mL/0.1 kg muscle in normal subjects. It should be considered, however, that (1) a small difference in blood volume translates into a much larger difference in blood flow because flow is proportional to the fourth power of the radius of a blood vessel, at least theoretically according to Poiseuille’s law, (2) a different reconstruction method was used in the present study compared with the previous study, and (3) although mean blood volume in the hypertensive subjects was within the previously found normal range (2.3 to 4.1 mL/0.1 kg), mean blood volumes were significantly different between the hypertensive and normal subjects in the present study. Previous data on muscle blood volume in hypertension are sparse because of methodological difficulties in accurately quantitating this parameter in humans. Schmieder et al measured total blood volume by using 125iodine-labeled albumin and hematocrit and central blood volume by indocyanine green dilution and found central blood volume to be 20% increased in 40 patients with borderline hypertension. In these patients, total blood volume was unchanged, implying that peripheral blood volume was subnormal. The data from this study provide direct support for the latter possibility.

Possible Causes of Altered Blood Flow and Volume Responses to Insulin in Essential Hypertension

Previous studies have documented multiple abnormalities in neurohumoral control of blood flow as well as structural abnormalities such as capillary rarefaction in blood vessels in patients with essential hypertension. Such changes, if present in our study subjects, could contribute to the observed defects in insulin-stimulated blood flow and volume and to blunted responses of these parameters to insulin. Sympathetic overactivity is well documented, especially in young patients with borderline hypertension. In this study, basal heart rate was significantly higher in the hypertensive subjects than in the normal subjects, suggesting, in view of comparable physical fitness of the groups (Table), that sympathetic activity might have been increased in our study subjects. In patients with essential hypertension, insulin increases sympathetic activity more than in normotensive subjects. This activation and peripheral insulin resistance are observed when insulin is given systemically rather than locally, suggesting that central activation of the sympathetic nervous system is responsible for insulin resistance.

In this study, we did not compare the blood flow response to insulin with a response to another vasoactive agent. Thus the blunted vascular response could have been limited to insulin, or it might reflect other vascular abnormalities present in patients with mild essential hypertension. In addition to sympathetic overactivity, subnormal nitric oxide synthesis or action might underlie the defect in insulin-induced vasodilatation. A defect in nitric oxide production could explain blunted responses to several vasoactive agents including insulin, β-agonists, and classic endothelium-dependent agents such as acetylcholine. Studies specifically examining the integrity of nitric oxide–dependent vasodilatation, abnormal responses have been found in many but not all studies. It has also been recently demonstrated that forearm β-adrenergic receptor–mediated vasodilatation is impaired, without alteration in local forearm norepinephrine spillover, in borderline hypertension. The vasodilatory effect of β-stimulation in the human forearm can be reduced by inhibition of nitric oxide synthesis. Considering that insulin-induced vasodilatation also can be abolished by inhibition of nitric oxide synthesis and that insulin potentiates isoproterenol-induced vasodilatation, the flow defect in the hypertensive subjects could reflect impairment in endothelial synthesis of nitric oxide or resistance to nitric oxide action.

In conclusion, we examined multiple aspects of the vascular actions of insulin in skeletal muscle and found patients with essential hypertension to be resistant to stimulation of mean flow, its absolute dispersion, and blood volume. It is
presently unclear whether these abnormalities are specific for insulin or merely reflect some generalized defect in endothelial nitric oxide synthesis or sympathetic overactivation in these patients. It also remains to be established whether the resistance to insulin in blood vessels is a consequence of hypertension or a primary contributor to increased peripheral resistance.

Acknowledgments

This study was supported by grants from the Academy of Finland (H.Y.-J., P.N.), the Ahokas (H.Y.-J., P.N.), Nuevo Nordisk (H.Y.-J., P.N.), Turku University (H.L.), and the Maud Kuistila (H.L.) Foundations. We thank Mika Teräs, MSc, Hannu Sipilä, MSc, Tuula Tolvanen, MSc, and all the personnel in the Turku PET Center for help during the studies.

References


Preserved Relative Dispersion but Blunted Stimulation of Mean Flow, Absolute Dispersion, and Blood Volume by Insulin in Skeletal Muscle of Patients With Essential Hypertension

Hanna Laine, M. Juhani Knuuti, Ulla Ruotsalainen, Tapio Utriainen, Vesa Oikonen, Maria Raitakari, Matti Luotolahti, Olli Kirvelä, Paolo Vicini, Claudio Cobelli, Pirjo Nuutila and Hannele Yki-Järvinen

*Circulation*. 1998;97:2146-2153
doi: 10.1161/01.CIR.97.21.2146

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/97/21/2146

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/