Relationship Between Insulin Sensitivity and Maximal Forearm Blood Flow in Young Men

Eigil Fossum, Aud Høieggen, Andreas Moan, Morten Rostrup, Gudmund Nordby, Sverre E. Kjeldsen

Abstract—Insulin resistance is a part of the metabolic cardiovascular syndrome. We aimed to test the hemodynamic hypothesis of insulin resistance, which suggests that a decreased skeletal muscle blood supply with subsequent reduced nutritional flow causes insulin resistance in skeletal muscle. We assessed determinants of peripheral blood flow such as maximal forearm blood flow (MFBF), minimal forearm vascular resistance (MFVR), and whole blood viscosity (WBV) in 27 young men with borderline elevation of blood pressure. Insulin sensitivity measured as glucose disposal rate (GDR) correlated with MFBF (r=0.55, P=0.003), MFVR (r=−0.58, P=0.002), and WBV (r=−0.39, P=0.046 at shear rate 201 s⁻¹). There was no correlation between GDR and myocardial thickness or left ventricular mass. In a stepwise multiple regression analysis, MFVR and WBV explained 54% of the variation in GDR. The relative increase in mean arterial blood pressure during a mental stress test, as a marker of reactivity or an alert reaction, was correlated with MFVR (r=0.56, P=0.002) and inversely with GDR (r=−0.45, P=0.018) and MFBF (r=−0.49, P=0.01) but not with cardiac dimensions. In a stepwise multiple regression analysis, 48% of the increase in blood pressure during a mental stress test was explained by MFVR and WBV. Fasting insulin correlated with MFVR (r=0.41, P=0.036) and GDR (r=−0.62, P=0.001). These data show a positive association between the appearance of peripheral structural vascular changes as quantified through a hemodynamic technique and insulin resistance in young men with borderline elevation of blood pressure. The cause-effect relationship of this finding needs further evaluations. (Hypertension. 1998;32:838-843.)

Key Words: hypertension, borderline insulin blood flow blood vessels

Impaired sensitivity to insulin-stimulated glucose disposal, insulin resistance, was described as part of syndrome X by Reaven in 1988⁷ and was later proposed as the metabolic link between non–insulin-dependent diabetes mellitus, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease.² The primary site of insulin resistance, as measured by the glucose clamp technique, is skeletal muscle.³,⁴ Julius et al³ proposed a hemodynamic link between insulin resistance and hypertension, suggesting that a decreased skeletal muscle blood supply with subsequently reduced nutritional flow causes insulin resistance in skeletal muscle. This hypothesis is in part based on the hemodynamic studies of Folkow,⁶ who found increased peripheral resistance in structurally altered hypertensive vessels.

In support of the hemodynamic hypothesis⁵ of insulin resistance in skeletal muscle, we earlier showed an association between insulin sensitivity and calculated⁸ and directly measured⁷ whole blood viscosity (WBV) in young men with borderline elevation of blood pressure.¹⁰ In the present study we aimed to test the hypothesis that structural vascular changes, as a determinant of peripheral resistance and blood flow, are correlated with insulin sensitivity in these men. Structural vascular changes were assessed by postischemic maximal forearm blood flow (MFBF) with the Hokanson plethysmograph.¹¹ Cardiac dimensions, as a second model of cardiovascular structure, were assessed by echocardiography¹² and postulated not to correlate with nutritional supply to skeletal muscle tissue and insulin sensitivity.

Second, since we implemented cardiovascular reactivity in regulating insulin sensitivity,¹¹ we wanted to test whether cardiovascular structure was a determinant of hemodynamic responses to a mental stress test (MST).

Methods

Subjects

The subjects were recruited from the ~3500 18-year-old men who underwent medical examinations during the military draft procedure in Oslo, Norway, in 1993. Because attendance is compulsory, these subjects constitute all 18-year-old men without severe medical disorders in the Oslo area. No follow-up evaluation of the subjects was performed until the present study. Of 74 subjects, randomly assigned from the 350 with blood pressure ≥140/90 mm Hg in 1993, 27 subjects were willing to participate in the present study in 1995 and 1996. The participating subjects did not differ from the invited group except for willingness. Characteristics of the study population are shown in the Table. Except for borderline blood pressure elevation, they were all healthy, and none used regular medication. Five subjects were smokers. All subjects fasted and refrained from smoking for the preceding 8 hours and abstained from alcohol for the preceding 24 hours before the study. The study was approved by the
The forearm was supported at the wrist and elbow slightly above heart level. A pediatric cuff was inflated at the wrist to suprasystolic pressure to occlude hand blood flow. The occlusive cuff placed around the proximal end of the arm was then rapidly inflated to supravenous pressure (50 mm Hg) with the Hokanson rapid cuff inflator E 20. The volume of the arm begins to expand as arterial blood continues to flow into the arm, while the cuff prevents venous return. The strain gauge attached distally will stretch as the volume increases, and this increase can be recorded and measured. Flow measurements are expressed in terms of milliliters flow per 100 mL of tissue per minute.

MFBF was measured after 10 minutes of ischemic forearm exercise. The proximal occlusive cuff was inflated to suprasystolic pressure for 10 minutes while the subjects were asked to contract the hand. One minute before MFMB measurement, the pediatric cuff was inflated at the wrist to suprasystolic pressure. After 10 minutes the proximal occlusive cuff was rapidly deflated and then inflated to supravenous pressure to measure MFMB as described above. MFMB was then calculated as the average of ≥3 readings. With >3 acceptable readings (maximum of 6 readings), the highest and lowest values were excluded from the analysis. This technique for measuring MFMB has a CV of 13% in our laboratory. Blood pressure was measured with a mercury sphygmomanometer at the right arm as an average of 3 readings at the end of the 10-minute ischemic period, directly before measurement of MFMB. Mean arterial pressure was calculated from these readings as the sum of diastolic pressure and one third of the pulse pressure. Minimal forearm vascular resistance (MFVR) was measured as mean arterial pressure divided by MFMB.

Mental Stress Test
A standardized MST was performed directly after the 2-hour clamp period. The infusions of insulin and glucose were kept unchanged. The subjects were asked to subtract 13 from 1079 and downward for 5 minutes. They were not informed of the MST until just before it was started. A metronome with a frequency of 2 Hz further increased the stress. Blood pressure and heart rate were measured at baseline before information, 2 and 3 minutes after the announcement but before the arithmetic task, after 2 minutes of arithmetic, and during recovery after 10 minutes, ie, a total of 6 measurements. The change in mean arterial pressure during MST was calculated by subtracting the last measurement before the announcement from the highest recorded value during MST, irrespective of time to reach maximum, and then dividing by the last measurement before the announcement, thus giving the value as Δ%. Systolic and diastolic blood pressure and heart rate measurements during MST have a test/retest CV of <7% in our laboratory.

Echocardiography
Echocardiographic measurements were performed with Wing-Med CFM-750 equipment. The thickness of the interventricular and posterior walls was measured 3 times in M-mode. Measurements were standardized to diastole. We used the average of the interventricular and posterior wall thickness measurements for the calculations. This measurement has a CV of 7% in our laboratory. Left ventricular mass (LVM) was calculated with the equation16

\[
LVM = 1.04[(IVST + PWT)^2 - LVID^2] + 13.6 \text{ g}
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where IVST is interventricular septal thickness, LVID is left ventricular internal dimension, and PWT is posterior wall thickness.

Biochemical and Blood Pressure Measurements
WBV was measured at shear rates of 0.5, 1.1, 5.8, and 201 s⁻¹ in EDTA-anticoagulated blood with a Bohlin CS 10 rheometer (Bohlin Instruments Ltd) with a double-gap technique. We have earlier described and validated this technique in detail.9,11 Glucose, cholesterol, and triglycerides were measured with Cobas Integra (Roche). Insulin levels were measured by radioimmunoassay with the use of a specific antibody from Linco Research, with an intra-assay CV <9% at all levels. Blood pressure and heart rate were measured after 20 minutes of supine rest, during the clamp, and during MST with an Omega 1000 Adult/Pediatric Blood Pressure Recorder (INVIVO

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Forearm blood flow was measured by mercury-in-Silastic strain-gauge venous occlusion plethysmography (ECSR Plethysmograph, D.E. Hokanson, Inc17 with the patient in a supine position and room temperature kept constant by thermostatic control. An occlusive cuff was placed around the proximal end of the left arm, and the strain gauge was placed around the largest diameter of the forearm. The

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Research Laboratories Inc), which has previously been validated in our laboratory. A mercury sphygmomanometer was used to measure sitting blood pressure before the clamp procedure and during MFBE studies.

Statistical Analysis
The data were analyzed with the statistical package SPSS version 7.0. A 2-tailed P-value <0.05 was considered statistically significant. Results are given as mean±SD. We used Pearson correlation coefficients and Student’s t test for normally distributed variables and Spearman correlation coefficients and Mann-Whitney and Wilcoxon tests for nonnormally distributed variables. Stepwise multiple regression analysis was applied to determine independent explanatory variables of GDR and change in blood pressure during MST. The Kruskal-Wallis test was used to detect differences between tertiles of GDR.

Results

Determinants of Insulin Sensitivity
Insulin sensitivity in the skeletal muscle tissue, measured as GDR, had a 3-fold range (Table). MFBE had a 4-fold range and correlated highly significantly and positively with GDR (r=0.55, P=0.003) (Figure 1). Mean arterial blood pressure during MFBE was 107.0±11.1 mm Hg. MFVR had an almost 4-fold range and correlated negatively with GDR (r=-0.58, P=0.002) (Figure 1). MFVR did not correlate significantly with WBV at any shear rate.

Cardiac dimensions had only a 2-fold range (Table) and were not related to GDR. Cardiac dimensions remained unrelated to GDR even when we averaged septum and posterior wall as mean myocardial thickness (Figure 1) or corrected left ventricular mass for body surface area. Myocardial thickness, left ventricular mass, and left ventricular mass/body surface area did not correlate significantly with MFBE, MFVR, WBV, or metabolic parameters such as fasting glucose, insulin, cholesterol, or triglycerides.

We performed a stepwise multiple regression analysis with GDR as dependent variable and body mass index, baseline mean arterial blood pressure, MFVR, mean myocardial thickness, and WBV as independent variables. Only MFVR and WBV at shear rate of 201 s⁻¹ independently explained variation in GDR. MFVR explained 41% of the variation, and together they explained 54% of the variation.

Fasting insulin correlated with waist/hip ratio (r=0.51, P=0.008) and MFVR (r=0.41, P=0.036) and negatively with GDR (r=-0.62, P=0.001).

We divided the group into tertiles and compared the men with the lowest GDR (<6.05, n=9), intermediate GDR (6.05 to 8.03, n=9), and the highest GDR (>8.03, n=9). The insulin-sensitive group (GDR>8.03) had the highest MFBE, lowest MFVR, lowest fasting glucose, and lowest fasting insulin (P=0.050, P=0.039, P=0.023, and P=0.001, respectively).

Blood Pressure Reactivity to MST
The increase in mean arterial blood pressure during MST was 18±10 mm Hg, with a range from 0 to 40 mm Hg. The relative increase in mean arterial blood pressure during MST correlated positively with MFVR (r=0.56, P=0.002) (Figure 2) and inversely with GDR (r=-0.45, P=0.018) (Figure 2) and MFBE (r=-0.49, P=0.01) but not with cardiac dimensions. We performed a stepwise multiple regression analysis with change in mean arterial pressure during MST as dependent variable and MFVR, GDR, mean myocardial thickness, change in heart rate, and change in forearm blood flow during MST and WBV as independent variables. Only MFVR and WBV at shear rate of 1.1 s⁻¹ independently explained variation in change in mean arterial pressure during MST. MFVR explained 37%, and together they explained 48% of the variation.

Effects of Smoking
There were no significant differences between the group of smokers (n=5) and nonsmokers regarding GDR, MFVR, cardiac dimensions, body weight, blood pressure, heart rate, and metabolic parameters except fasting triglycerides, which were significantly higher among the smokers (P=0.016).

Discussion
In the present study, indices of peripheral resistance, ie, MFVR and WBV, were the only independent explanatory
arterial inflow. Pedrinelli et al. re-assessed the method and applied it that only the structure of the vessels limits further studies. Venous occlusion plethysmography is used to study structural vascular changes assessed by MFBF after arterial occlusion. This model assumes that reactive hypoxemia is the most potent vasodilator stimulus that can be quantified with MFVR and inversely correlated with MFBF and insulin sensitivity, MFBF, MFVR, WBV, lipids, or insulin. The correlations described above did not change when we corrected GDR for measured insulin at 60 and 120 minutes as GDR/I.

To discuss the present findings, it is important to address the reliability of the methods, the validity of the measurements, and the representativeness of the present study population. The glucose clamp technique is found to be highly reproducible and is regarded as the reference method for quantifying insulin resistance in skeletal muscle tissue. The human forearm is a well-established model for flow studies. Venous occlusion plethysmography is used to study structural vascular changes assessed by MFBF after arterial occlusion. This model assumes that reactive hypoxemia is the most potent vasodilator stimulus that can be applied and that only the structure of the vessels limits further arterial inflow. Pedrinelli et al. re-assessed the method and found the postischemic MFBF to be unaffected by concomitant infusion of vasodilators or vasoressors. This was in accordance with the findings of Takeshita and Mark in another experimental setting. Agabiti Rosei et al. found a strong correlation between structural vascular changes as assessed with postischemic forearm plethysmography and direct micromyographic measurements of media/lumen ratio in subcutaneous resistance vessels. An evaluation of intra-arterial blood pressure measurements versus sphygmomanometric measurements during occlusion showed a close correlation between the 2 calculated values of MFVR \( r=0.996, \ P<0.001 \), with only a slight overestimation when the sphygmomanometric measurements were used.

All groups found the method to be highly reproducible. However, it is fundamental for the interpretation of the present data to acknowledge that postischemic forearm plethysmography is a dynamic procedure that only allows an indirect estimation of the vascular structure. The method is not designed to discriminate between the different types of vascular changes, ie, hypertrophy of the media versus eutrophic remodeling, as discussed by Korsgaard et al. Furthermore, the distribution of muscle fibers seems to be important because the slow-twitch muscle fibers appear more insulin sensitive than the fast-twitch fibers. Direct correlations have been shown between insulin sensitivity and capillary density and the percentage of slow-twitch fibers in humans. Fever capillaries in a given tissue would result in a reduced diffusion surface and increased distance between capillaries and cell surface. The MFVR is a function of the integrated arteriolar lumen in a particular vascular region and cannot discern the relative contribution of an increased wall/lumen ratio versus arteriolar rarefaction. The present study was designed to investigate the precapillary resistance vessels as measured by the venous occlusion plethysmograph. Thus, we cannot quantify the relative contribution of vascular rarefaction versus media/lumen changes on insulin sensitivity or blood pressure changes during stress because this would have required muscle biopsies.

The values for MFVR show some variation from one study to another. Pedrinelli et al. found mean values of 2.5 to 3.9 arbitrary units in different settings in uncomplicated hypertensives, and Rocchini et al. found a mean of 2.9 and 3.0 arbitrary units in 2 groups of obese adolescents. Because Andersson et al. measured hand flow, which is more difficult to evaluate than forearm flow, the figures are not directly comparable. The MFVR data in our study (mean of 3.1 arbitrary units) seem to be in the range of several comparable populations.

The subjects in the present study were selected among the 10% of the subjects from the military draft procedure having a sitting blood pressure of \( 140/90 \text{ mm Hg} \). As reported earlier, young men recruited this way are hyperreactive to mental stress, and blood pressure values recorded during the blood pressure changes during stress because this would have required muscle biopsies.
with men from the lower screening blood pressure levels.\textsuperscript{10} Since they were selected through screening blood pressure alone, there was some range in the body mass index. Body mass index was therefore included as a possible pathophysiological factor in the regression analysis.

In the present study there was a 3-fold range in GDR and an almost 4-fold range in MFBF and MFVR. In previous studies of young men selected in the same way as in the present study, we found an even more impressive range in GDR, from 2 to 18 mg/kg per minute.\textsuperscript{7,13} However, we then included subjects from both the lower and higher blood pressure percentiles (2nd and 98th), while the subjects included in the present study were all in the higher blood pressure range. This could explain the somewhat lower range in GDR in this study compared with our earlier studies. On the other hand, the inclusion was based on only 1 blood pressure reading. This probably allows our subjects to be “diluted” with some nonhyperreactive subjects because of spontaneous variations of blood pressure measurement during the draft procedure, as shown by the wide range in blood pressure in the laboratory. This could in part explain the wide range in MFBF and MFVR.

The pathophysiological abnormalities causing insulin resistance in skeletal muscle are multifocal, taking place at both the receptor (insulin) and postreceptor levels. However, in this study we tested the hemodynamic hypothesis of insulin resistance,\textsuperscript{3} which could be regarded as a prereceptor abnormality. Julius et al\textsuperscript{12} suggested that structural vascular changes and rarefaction would decrease skeletal muscle blood supply with a subsequent reduced nutritional flow limiting the diffusion of insulin and substrates from the intravascular space to the target cell surface, thus causing insulin resistance in skeletal muscle. Since skeletal muscle constitutes 30% to 40% of body mass, skeletal muscle insulin resistance is a major determinant of whole body insulin resistance.\textsuperscript{33}

As hypothesized, we found rather impressive correlations between MFBF, MFVR, WBV, and insulin sensitivity, supporting the hemodynamic hypothesis of insulin resistance. However, MFBF and MFVR mainly describe the structure and not the dynamic properties of the vessel. The question remains regarding to what extent these structural alterations affect the dynamic properties of the vessel during activities of daily life. Vascular changes have been shown in both borderline and established hypertensives.\textsuperscript{20,25} Takeshita and Mark\textsuperscript{20} found a 40% higher MFVR in young borderline hypertensives compared with normotensives. Folkow\textsuperscript{3} has shown that an identical decrease in vascular lumen diameter would give a significantly higher blood pressure response in a structurally altered vessel compared with a normal vessel. In our subjects blood pressure responses to MST correlated positively with MFVR and inversely with insulin sensitivity and MFBF. There was a wide range in blood pressure responses to the strictly standardized MST. In established essential hypertension there is evidence of an increased pressor response to vasoconstrictors\textsuperscript{34}; however, sensitivity to vasoconstrictors seems to be unchanged.\textsuperscript{35} Eliasson et al\textsuperscript{16} found borderline hypertension to be associated with enhanced cardiovascular reactivity revealed by MST but not by orthostatic testing or cold pressor test in their comparison of groups of established and borderline hypertensives with normotensives. Jern\textsuperscript{22} found a correlation between stress-induced increase in forearm blood flow and increased forearm glucose extraction during MST in nonobese normotensive men. Furthermore, Baron et al\textsuperscript{17} found skeletal muscle blood flow to be a possible link between insulin resistance and blood pressure in lean normotensives, suggesting that attenuated insulin-induced skeletal muscle vasodilatation may be a major cause of insulin resistance.

Hypertension and insulin resistance contribute independently and synergistically to left ventricular hypertrophy and peripheral vascular changes. Left ventricular hypertrophy and peripheral vascular changes may, however, not develop in parallel, as shown in patients with essential hypertension by Lucarini et al.\textsuperscript{36} Our young subjects were not established hypertensives, as documented through normal home blood pressure readings.\textsuperscript{13} Furthermore, since they were studied in a very early stage, they were not likely to have target organ affection. Thus, as hypothesized, cardiac dimensions were unrelated to forearm vascular structure, insulin sensitivity, fasting insulin, and blood pressure.

There was no difference between the group of smokers and nonsmokers. This is probably a result of the small number of smokers in this study.

In contrast to our study, Andersson et al\textsuperscript{39} found body mass index to be associated with minimal vascular resistance in the hand in young lean men. Their subjects had established mild hypertension, in contrast to our group. Moreover, minimal vascular resistance was measured in the hand and not in the forearm. The hand and the forearm represent 2 different vascular beds, especially with regard to vascular density, which is an important factor of minimal vascular resistance.\textsuperscript{24,27} Since we, in accordance with recommendations from several authors,\textsuperscript{11,20,21,23,24} arrested hand flow with a pediatric cuff, these data are not directly comparable.

Many of the variables measured in the present study are directly or indirectly dependent of each other. Therefore, we have not performed any adjustments for multiple comparisons according to Bland and Altman.\textsuperscript{39}

In conclusion, these data show a positive association between the appearance of peripheral structural vascular changes (as quantified through a hemodynamic technique) and insulin resistance in young men with borderline elevation of blood pressure. The cause-effect relationship of this finding needs further evaluation.

Acknowledgment

We thank the Norwegian Council on Cardiovascular Diseases for financial support of the study.

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