

Insulin Sensitivity Is Related to Physical Fitness and Exercise Blood Pressure to Structural Vascular Properties in Young Men

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Abstract—Insulin resistance is related to physical inactivity, which is a risk factor for cardiovascular disease and death. Moreover, blood pressure responses during the first 6 minutes of an exercise test (600 kilo/pound/meter [kpm] per min) are more predictive for cardiovascular morbidity and mortality than blood pressure at rest, which could reflect that exercise blood pressure correlates more closely to peripheral structural vascular changes than casual blood pressure. We have recently shown a correlation between insulin resistance and minimal forearm vascular resistance (MFVR) in young men recruited from the highest blood pressure percentiles during a military draft session. In the present study, we tested the hypotheses that insulin sensitivity relates to physical fitness and that blood pressure responses during an exercise test relate to peripheral structural vascular changes in these men; we also tested whether these findings were interrelated. We assessed insulin sensitivity and physical fitness in 27 young men randomly selected from the cohort having a blood pressure of 140/90 mm Hg or higher during the compulsory military draft session in Oslo. Insulin sensitivity correlated with physical fitness ($r=0.58$, $P=0.002$). Systolic blood pressure after 6 minutes of exercise (600 kpm/min) correlated with MFVR ($r=0.46$, $P=0.015$). MFVR and physical fitness independently explained 60% of the variation in insulin sensitivity, and MFVR independently explained 19% of the variation of systolic blood pressure after 6 minutes of exercise. In conclusion, insulin sensitivity is related to physical fitness and exercise blood pressure to structural vascular properties in these young men. (*Hypertension*. 1999;33:781-786.)

Key Words: insulin resistance ■ exercise ■ blood pressure ■ physical fitness ■ vascular structure

Insulin resistance¹ has been proposed as the metabolic link between non-insulin-dependent diabetes mellitus, hypertension, and atherosclerotic cardiovascular disease.² In our earlier studies of young men, recruited from the highest blood pressure (BP) percentiles during the compulsory military draft session in Oslo, we showed a positive correlation between insulin resistance and cardiovascular risk factors such as lipids³ and body weight.⁴ Physical fitness is a determinant of insulin sensitivity,⁵⁻⁷ which we previously have not included in our studies of these apparently healthy 18-year-old men. In the present study, we therefore aimed to relate physical fitness to glucose disposal rate (GDR) in this well-described population of young men and to assess a possible mechanism for a relationship; ie, whether there is a direct relationship or whether it is influenced or determined by other correlates of GDR, such as lipids, body weight, minimal forearm vascular resistance (MFVR),⁸ or whole blood viscosity (WBV).^{3,4} We assessed physical fitness as the total work performed during an ergometer bicycle exercise test divided by body weight because this technique for assessing physical fitness rather strongly predicts cardiovascular mortality in healthy, middle-aged Norwegian men.⁹

The hemodynamic hypothesis of insulin resistance¹⁰ suggests peripheral structural vascular changes and rarefaction to be determinants of insulin resistance. In support of this hypothesis, we have previously shown a positive correlation between insulin resistance and determinants of peripheral blood flow, such as calculated⁴ and directly measured³ WBV and structural vascular changes as assessed by MFVR.⁸ Furthermore, in these young men, insulin resistance is closely and positively related to sympathetic activity and BP responses during mental stress,^{8,11} and BP responses during mental stress correlate closely and positively with MFVR.⁸

Systolic BP (SBP), taken after 6 minutes on the first load of 600 kilo/pound/meter [kpm] per min (≈ 100 W) during an ergometer bicycle exercise test in middle-aged healthy Norwegian men,⁹ was a strong independent risk factor for cardiovascular death¹² and death from myocardial infarction.¹³ In fact, the predictive power of SBP after 6 minutes of exercise was so strong that the predictive value of casual BP became nonsignificant when the two values were analyzed together. On the basis of hemodynamic studies of Folkow,¹⁴ who found increased peripheral resistance in structurally altered hypertensive vessels, Mundal et al¹³ hypothesized that

Received August 14, 1998; first decision September 8, 1998; revision accepted November 6, 1998.

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a sudden rise in SBP during exercise was caused by a failure to reduce total peripheral resistance during exercise, ie, that SBP during exercise may be a marker for structural vascular changes. Therefore, the second aim of the present study was to investigate a possible association between exercise BP taken as SBP after 6 minutes of exercise at 600 kpm/min and peripheral vascular structure assessed by MFVR in the young men and also to relate exercise SBP after 6 minutes to other BP values.

Methods

Subjects

Subjects were recruited from the approximately 3500 18-year-old men examined during the military medical 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. Approximately 350 of these young men had a sitting BP $\geq 140/90$ mm Hg in 1993. In 1995 and 1996, 27 of these subjects, selected at random, participated in the present study. They were all healthy and none used regular medication. Baseline characteristics of this cohort have been published previously⁸; main demographics are (mean \pm SD) age, 20.7 \pm 0.5 years; body mass index, 23.8 \pm 3.0 kg/m²; SBP, 134 \pm 15 mm Hg; diastolic BP, 86 \pm 12 mm Hg; heart rate, 64 \pm 11 beats/min; cholesterol, 4.0 \pm 0.8 mmol/L; triglycerides, 1.1 \pm 0.4 mmol/L; glucose, 5.0 \pm 0.4 mmol/L; insulin, 107 \pm 28 pmol/L; GDR, 7.0 \pm 1.9 (mg/kg)/min; MFVR, 3.1 \pm 1.1 AU; interventricular septal thickness, 11 \pm 1 mm; left ventricular posterior wall thickness, 10 \pm 1 mm; and left ventricular mass, 232 \pm 48 g. BP and heart rate were measured at baseline, with subjects sitting in the laboratory (office BP). Blood tests were made with fasting samples taken during baseline. Daytime BP, as specified below, averaged 115 \pm 8 mm Hg for SBP, 82 \pm 6 mm Hg for mean arterial BP, and 67 \pm 6 mm Hg for diastolic BP. Subjects underwent a thorough physical examination and blood biochemistry to exclude illness. Five subjects were smokers. None was a high-performance athlete, ie, competed on a national level; 17 exercised twice a week or more; 10 were physically inactive. All subjects fasted and refrained from smoking for the 8 hours before the study and abstained from alcohol for the 24 hours before the study. The study was approved by the Regional Ethical Committee, and informed consent was obtained from each subject.

Hyperinsulinemic, Isoglycemic Glucose Clamp

We performed a hyperinsulinemic, isoglycemic glucose clamp procedure, as previously described⁴ and validated in detail.¹⁵ The procedure clamps glucose level at the fasting level (isoglycemic) and not at a predetermined (euglycemic) level, ie, 5.0 mmol/L. By using the euglycemic clamp, one would tend to underestimate insulin sensitivity in individuals with elevated fasting glucose. Also, in individuals with elevated fasting glucose, one would have to lower glucose levels with a subsequent risk of hypoglycemic counterregulation, including hepatic glucose production and activation of the sympathetic nervous system. The clamp procedure was performed for 2 hours using the glucose infusion during the last 60 minutes as the basis for the calculation of insulin sensitivity. With this technique, insulin sensitivity can be measured with a day-to-day coefficient of variation (CV) of 5% in our laboratory, as previously discussed.^{4,15}

Physical Fitness

Physical fitness was assessed with a bicycle test according to the protocol of previous authors^{9,12,13} with an EM 369/1 bicycle (Elema-Schoenander) as described. The initial work load was 600 kpm/min (≈ 100 W), which was increased by 300 kpm/min every 6 minutes. Subjects were encouraged to exercise until exhaustion. BP and heart rate were measured at baseline and every second minute throughout the test and the first 6 minutes of recovery. In the analysis, we used SBP at baseline (preexercise) and after 6 minutes of exercise, as well

as the difference between these two measurements calculated as the percentage increase. As originally described,⁹ we assessed three models of physical fitness: (1) The total work load as the sum of the work during each of the work load levels; (2) physical fitness calculated as total work load divided by body weight; and (3) according to self-reported physical activity at home (physically active men were defined as those who exercised at least twice a week to the level of sweating and becoming short of breath).⁹

Minimal Forearm Vascular Resistance

Forearm blood flow was measured by mercury-in-Silastic strain-gauge venous occlusion plethysmography (EC5R Plethysmograph; DE Hokanson, Inc)¹⁶ with the subject in a supine position and room temperature kept constant by thermostatic control. Maximal forearm blood flow (MFBF) was measured after 10 minutes of ischemic forearm exercise. This technique for measuring MFBF, previously described in detail,⁸ has a CV of 13% in our laboratory. BP was measured with a mercury sphygmomanometer on the right arm as an average of 3 readings at the end of the 10-minute ischemic period, directly before measurement of MFBF. Mean arterial pressure was calculated from these readings as the sum of diastolic BP and one third pulse pressure. MFVR was calculated as mean arterial pressure divided by MFBF. As discussed and validated by Pedrinelli et al^{17,18} and Agabiti Rosei et al,¹⁹ this method is able to detect peripheral structural vascular changes.

Echocardiography

Echocardiographic measurements were performed with a Wing-Med CFM-750 echocardiograph. Interventricular and posterior wall thicknesses were measured 3 times in M-mode. Measurements were standardized to diastole. For calculations, we used the average of interventricular and posterior wall thicknesses as mean myocardial thickness. This measurement has a CV of 7% in our laboratory. Left ventricular mass was calculated with the equation $LVM = 1.04[(IVST + LVID + PWT)^2 - LVID^2] - 13.6$ g, where IVST is interventricular septal thickness, LVID is left ventricular internal dimension, and PWT is posterior wall thickness. Mean myocardial thickness and left ventricular mass are referred to as cardiac dimensions.

BP and Biochemical Measurements

Office BP, the first BP measured, was calculated as the average of the last 2 out of 3 measurements after subjects had rested 5 minutes in the sitting position. Daytime versus clinic BP was defined as the difference between daytime SBP and office SBP. Office BP and BP during the exercise test were measured with a mercury sphygmomanometer. BP during the clamp was measured with an Omega 1000 adult/pediatric blood pressure recorder (INVIVO Research Laboratories Inc). Daytime BP was measured with a Medilog ABP (Oxford Medical Inc). The BP monitoring machine was fitted between 2 and 2:30 PM and removed at 11 PM; the average of 32 measurements from 3 to 11 PM was used in the calculations. Subjects were instructed to attend to their usual activities during the recording period. The reason for choosing this interval was to maintain optimal compliance among the young subjects. In a pilot study, nighttime recordings were of reduced quality in these young subjects, as they had problems adapting to the equipment during sleep.

Glucose, cholesterol, and triglyceride levels were measured with a Cobas Integra (Roche). WBV was measured at shear rates of 0.5, 1.1, 5.8, and 201 s⁻¹ in EDTA anticoagulated blood with a rheometer (CS 10, Bohlin Instruments Ltd) using a double-gap technique, which we have previously described and validated in detail.^{3,20}

Statistical Analysis

Data were analyzed using the statistical package SPSS Version 8.0. A 2-tailed *P* value ≤ 0.05 was considered statistically significant. Results are given as mean \pm SD. We used Pearson's correlation coefficients and Student's *t* test for normally distributed variables, and Spearman correlation coefficients, the Mann-Whitney test, and the Wilcoxon test for not normally distributed variables. Stepwise multiple regression analysis was applied to determine independent

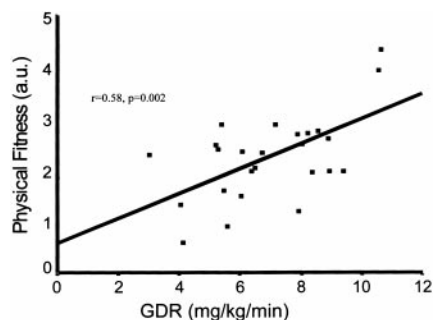


Figure 1. Correlation between insulin sensitivity assessed as GDR and physical fitness measured as total exercise work load divided by body weight. a.u. indicates arbitrary units.

explanatory variables of GDR and SBP after 6 minutes of exercise. One-way ANOVA was used to detect different levels of MFVR and different levels of other BP values between tertiles of exercise SBP. The Kruskal-Wallis test was used to detect different levels of other BP values between tertiles of daytime versus clinic BP.

Results

Total Work Load, Physical Fitness, and Physical Activity in Relation to Metabolic and Structural Variables

GDR correlated with total workload ($r=0.49$, $P=0.014$) and physical fitness ($r=0.58$, $P=0.002$) (Figure 1). Total work load or physical fitness did not correlate significantly with MFVR; WBV; metabolic variables, such as fasting insulin or lipids; or cardiac dimensions, except for a correlation between total work load and left ventricular mass ($r=0.43$, $P=0.032$). Total work load correlated significantly with body weight ($r=0.40$, $P=0.050$).

Physically active men ($n=17$) had a significantly higher GDR ($P=0.029$) and a tendency to lower WBV at shear rates of 201, 5.8, 1.1 and 0.5 s^{-1} ($P=0.014$, $P=0.033$, $P=0.056$, and $P=0.071$, respectively). The physically active men achieved a significantly higher total work load ($P=0.017$) and showed a borderline significantly better physical fitness ($P=0.057$). MFVR and cardiac dimensions did not differ significantly between the groups.

We performed a multiple regression analysis with GDR as dependent variable and MFVR, cardiac dimensions, physical fitness, cholesterol, body mass index, WBV, and mean arterial BP as independent variables. Only MFVR and physical fitness independently explained variation in GDR ($R^2=0.42$ for MFVR and $R^2=0.60$ for both).

Exercise BP in Relation to Other BP Values, Heart Rate, and Structural Properties

SBP after 6 minutes of exercise correlated with MFVR ($r=0.46$, $P=0.015$) but not with GDR, WBV, or cardiac dimensions. SBP after 6 minutes of exercise correlated significantly with office SBP, supine preclamp SBP, and preexercise SBP ($r=0.45$, $P=0.020$; $r=0.42$, $P=0.028$; and $r=0.49$, $P=0.010$, respectively) but not with daytime SBP ($r=-0.10$, $P=0.96$).

We performed a multiple regression analysis with SBP after 6 minutes of exercise as dependent variable and MFVR, the SBP used in the calculation of MFVR, cardiac dimen-

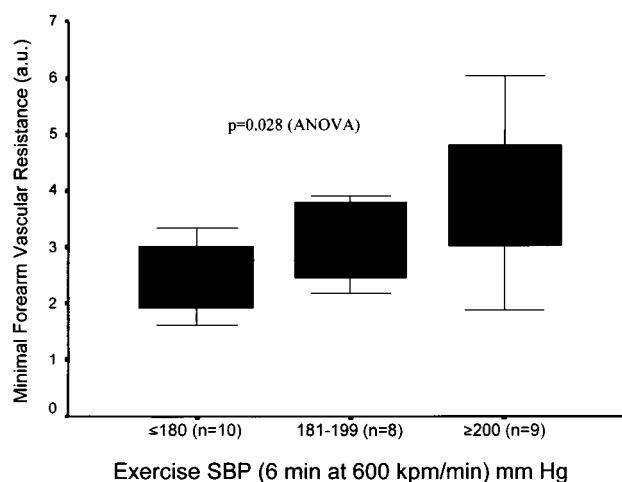


Figure 2. Highest and lowest quartiles of MFVR shown as lines and 2 interquartiles shown as boxes according to tertiles of SBP after 6 minutes of exercise. a.u. indicates arbitrary units.

sions, GDR, physical fitness, WBV, and the percentage increase in heart rate as independent variables. Only MFVR independently explained variation in SBP after 6 minutes of exercise ($R^2=0.19$).

The increase in SBP after 6 minutes of exercise ranged from 10 to 80 mm Hg. The percentage increase in SBP after 6 minutes of exercise correlated with MFVR ($r=0.38$, $P=0.048$) but not significantly with the increase in heart rate, GDR, WBV, or cardiac dimensions. The percentage increase in SBP after 6 minutes did not correlate significantly with total work load or physical fitness.

We divided the study group into tertiles according to SBP responses after 6 minutes of exercise (men with exercise SBP at 600 kpm/min ≤ 180 mm Hg [$n=10$], with SBP between 181 and 199 mm Hg [$n=8$], and with SBP ≥ 200 mm Hg [$n=9$]). There was a significant difference between the groups regarding MFVR ($P=0.028$) (Figure 2) but not regarding GDR, WBV, or cardiac dimensions. Daytime SBP was not significantly different between the groups ($P=0.34$), whereas office SBP ($P=0.032$) and preexercise SBP ($P=0.005$) were significantly different between the groups (Figure 3). Supine preclamp SBP showed a similar tendency ($P=0.057$). Heart rate was not significantly different between the groups at baseline (office), preexercise, or after 6 minutes of exercise ($P=0.23$, $P=0.37$, and $P=0.71$, respectively).

Daytime Versus Clinic BP in Relation to Other BP Values, Heart Rate, and Structural Properties

The percentage increase between daytime SBP and office SBP correlated with the percentage increase between daytime SBP and SBP after 6 minutes of exercise ($r=0.52$, $P=0.006$). We divided the study group according to differences between daytime and office SBP (men with a difference ≤ 10 mm Hg [$n=6$], with a difference between 11 and 20 mm Hg [$n=9$], and with a difference >20 mm Hg [$n=12$]). There was a significant, stepwise increase regarding preclamp SBP, preexercise SBP, and SBP after 6 minutes of exercise ($P=0.002$, $P=0.032$, and $P=0.026$, respectively). Heart rate before the clamp, before exercise, and after 6 minutes of exercise; the

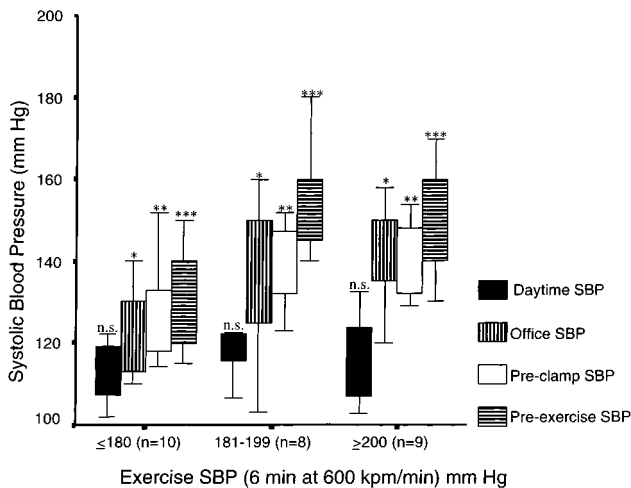


Figure 3. Highest and lowest quartiles of daytime SBP, office SBP (sitting), preclamp SBP (after 20 minutes of supine rest), and preexercise SBP (sitting before start of the test) shown as lines and 2 interquartiles shown as boxes according to tertiles of SBP after 6 minutes of exercise at 600 kpm/min. Probability values express intragroup differences. * $P=0.032$ (ANOVA), ** $P=0.057$ (ANOVA), *** $P=0.005$ (ANOVA).

percentage increase in heart rate during exercise; MFVR; and cardiac dimensions did not differ significantly among the groups.

Discussion

The present study demonstrates a positive correlation between insulin sensitivity and physical fitness as assessed both by an exercise test and by self-reported physical activity at home. Furthermore, SBP after 6 minutes of exercise and the increase in SBP during the first 6 minutes of exercise correlated with MFVR. The young men who increased their SBP to 200 mm Hg or higher after 6 minutes of exercise had a significantly higher MFVR than those with a lower BP response. These men also had significantly higher office and preexercise BP values, whereas daytime BP was unchanged between the groups. MFVR and physical fitness were the only factors that independently explained the variation in insulin sensitivity, and MFVR was the only factor independently explaining the variation in BP 6 minutes after exercise.

Physical fitness has been shown to be a graded, independent, long-term predictor of mortality from cardiovascular causes in healthy middle-aged men.⁹ Moreover, physical fitness correlates positively with insulin sensitivity in normotensive men with a family history of hypertension,⁵ in healthy nonobese subjects,⁶ and in older men.⁷ The present study shows this correlation also in young men recruited from the highest BP percentiles during a military draft session.

SBP and the percentage increase in SBP during the first 6 minutes of the exercise test correlated with peripheral structural vascular changes assessed as MFVR. Mundal et al^{12,13} have shown that SBP after 6 minutes of an exercise test predicts cardiovascular mortality and morbidity better than BP at rest in healthy middle-aged men, as also shown by Filipovsky et al.²¹ Mundal et al^{12,13} questioned whether a steep rise in exercise SBP in some individuals signifies a pressure response in subjects with peripheral structural vas-

cular changes. If so, they argued, a rapid rise in exercise SBP during the first 6 minutes may be a marker of a disease rather than a risk factor for the development of a disease. In support of this hypothesis, Rostrup et al²² recently studied acute hemodynamic changes in healthy young men during exercise. They found a steep rise in intra-arterial SBP, heart rate, and arterial catecholamines during the first 4 minutes of exercise, after which the response either was significantly blunted or showed no further increase. As shown by Folkow,¹⁴ this response would increase SBP more in men with structural vascular changes than in those with normal vessels. Accordingly, we have shown that insulin-resistant young men with peripheral structural vascular changes have a greater BP response during mental stress than those with normal vessels.⁸

The present study population consisted of young men recruited from the highest BP percentiles during the compulsory military draft session in the Oslo area. As reported previously,¹¹ men recruited this way are normotensive as documented through normal home BP readings. However, they are hyperreactive to mental stress¹¹; BP values recorded during the draft procedure could be considered as office BP or BP during an alert reaction. In the present study, the men in the tertile with the highest exercise SBP also had significantly higher office and preexercise BP values than the men in the lowest tertile. There was a borderline significant difference between the groups in supine preclamp SBP. These 3 measurements could be considered as different stress situations and show results similar to those previously shown with a mental stress test.^{8,11} In accordance, daytime BP did not differ significantly between the groups.

Structural vascular changes and elevated peripheral resistance are hallmarks of established essential hypertension.¹⁴ Moreover, insulin resistance is described as the metabolic link between hypertension and other cardiovascular risk factors.² In the present study, MFVR was the only factor that independently explained variation in both insulin sensitivity and BP responses after 6 minutes of an exercise test. As these men are young and have normal daytime BP values, they are not likely to have alterations in target organs, as documented through normal cardiac dimensions and renal analysis,⁸ or advanced structural vascular alterations. MFVR explained about 20% of the variation in exercise SBP, indicating that other explanatory factors not included in this study are involved. Figure 3 suggests a hyperreactive response in the men with the highest exercise SBP, indicating that some of the elevation in exercise SBP in this tertile was due to mental stress before the test. On the basis of the data in Figure 3, we analyzed the data according to tertiles of increasing hyperreactive response. These data supported the observation of a possible hyperreactive response or anticipation effect also included in other BP values, ie, preclamp, preexercise, and after 6 minutes of exercise. The lack of an association with heart rate does not exclude involvement of the sympathetic nervous system, as this also affects targets other than heart rate, ie, cardiac output and vascular wall tension, which both affect the BP response during exercise. A possible limitation of this observation lies in the quality of repeated out-of-clinic BP measurements as the true baseline BP, as discussed by

Parati et al^{23,24} and below. Moreover, we measured ambulatory BP during 8 hours in the afternoon, which does not reflect true daytime BP.

Parati et al²³ recently challenged the definition of white coat BP as the difference between clinic and daytime BPs. In their study of middle-aged, untreated subjects with hypertension, the increase in BP between daytime and clinic measurements was only one third of the increase obtained through continuous measurements made directly before and during the visit to the physician. As discussed by Parati et al,²³ differences in daily life activities during ambulatory or daytime BP recordings and the effect of regression to the mean through repeated measurements may cause the daytime-clinic BP difference to be less suitable for detecting the stress or alert reaction than a continuous recording. As we have previously shown, however, the young men with elevated screening BP have a more generalized hyperreactive response than that covered by the strict definition of the white coat effect. They react to awareness of high BP,²⁵⁻²⁷ to the anticipation of a forthcoming arithmetic challenge¹¹ (announcement), and to the military draft procedure per se. We therefore used the term "hyperreactivity" or "anticipation" rather than "white coat effect."

The primary site of insulin resistance, as measured by the glucose clamp technique, is skeletal muscle.^{28,29} The hemodynamic hypothesis of insulin resistance¹⁰ suggests peripheral structural vascular changes and rarefaction to be major determinants of insulin resistance in skeletal muscle. This may reduce delivery of substrate, ie, insulin and glucose, to the target cells, thus causing reduced glucose metabolism and hyperinsulinemia. We have previously reported a positive correlation between MFVR and insulin resistance.⁸ In the present study, peripheral structural changes, measured as MFVR, also explained variation in BP responses during exercise. As discussed by Mundal et al,¹² an increased BP response to a moderate exercise load, such as practiced in everyday life or during mental stress as previously shown,^{8,11} may increase the pressure burden on the cardiovascular system, thus further enhancing structural vascular remodeling.

SBP is included in the formula for the calculation of MFVR. Thus, one could argue that the correlation between MFVR and SBP during exercise is caused by the interrelationship between these 2 factors. In the regression analysis of SBP after 6 minutes of exercise, we therefore included as an explanatory factor the SBP used to calculate MFVR. The analysis showed that MFVR is a better predictor of SBP after 6 minutes of exercise than SBP alone.

Mundal et al³⁰ found high exercise BP to be associated with a number of coronary risk factors included in the cardiovascular metabolic syndrome. These associations were not significantly present in the present study. Most likely this is due to a lack of statistical power, as our study was designed primarily to detect structural differences. Another possibility would be that structural vascular changes precede metabolic changes, thus making these associations detectable in middle-aged but not in young men. The study population of Mundal et al³⁰ was older and selected in another way than the present study population, which must be considered when the data are

compared, especially regarding the age effect on vascular structure and hyperreactivity in the present study population.

We did not find any correlation between maximal SBP (data not shown) and cardiovascular risk factors. This is in accordance with the studies of Mundal et al,^{12,13} in which maximal SBP during an exercise test did not add prognostic information to the risk of future cardiovascular morbidity or mortality. We can only speculate on the reasons for this lack of correlation, but it could be due to less accurate BP measurements at peak physical performance.³¹

As a second model of cardiovascular structure, we measured cardiac dimensions, as described previously.⁸ These measurements were not related to the objectives of the present study. As the subjects are young and have normal home BP readings,¹¹ they are not likely to have alterations in target organs.

Many of the variables measured in the present study are directly or indirectly intercorrelated. Therefore, we did not make any adjustments for multiple comparisons, as discussed by Bland and Altman,³² but considered the results with some caution.

In conclusion, insulin sensitivity is related to physical fitness and peripheral structural vascular changes are related to both exercise BP responses and insulin sensitivity in healthy young men with high screening BP values. The relationship between these factors remains to be elucidated.

Acknowledgment

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

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