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Sympathoadrenal Reactivity to Stress as a Predictor of Cardiovascular Risk Factors*

A. Flaa, M. Rostrup, S. E. Kjeldsen

Abstract: There is much uncertainty about the pathophysiology of essential hypertension. One possible cause may be alterations in the autonomic nervous system, which plays an important role in the normal physiological regulation of pressure. Therefore, we studied the relationship between resting blood pressure and arterial plasma catecholamines, cardiovascular and sympathetic reactivities, and cardiovascular risk factors in young men (aged 19 years) with low, normal, and high blood pressures, who were unaware of their blood pressure status.

In the initial cross-sectional study, lower blood pressure was associated with a better lipoprotein profile, lower fructosamine concentration, and waist-hip-ratio. Mental stress test was the only test that induced differential responses between the 3 blood pressure groups, where the high blood pressure group showed the most and the low blood pressure group the least pronounced response in blood pressure, heart rate, and plasma catecholamines.

Adrenaline and noradrenaline concentrations during mental stress test were significant predictors of future systolic blood pressure in a follow-up study over 18 years, while plasma catecholamine levels at rest and during the cold pressor test did not show significant associations with later blood pressure. Noradrenaline response to mental stress was a weak positive predictor for future waist circumference. None of the other parameters during rest or cold pressor test were significantly related to changes in Body Mass Index, waist circumference, or triceps skinfold thickness. Noradrenaline response to the cold pressor test was positively related to fasting plasma glucose and HOMA-IR at follow-up in univariate analyses. In the multiple regression analyses, noradrenaline response was an independent positive predictor of HOMA-IR. There were no significant associations with plasma catecholamines at rest or during mental stress test.

Thus, reactivity of the sympathetic nervous system is related not only to blood pressure but also to a number of metabolic risk factors. The responses to the cold pressor test and the mental stress test seemed to have different predictive impact on the development of these risk factors.

Key words: sympathetic nervous system, stress reactivity, blood pressure, insulin resistance, obesity

Kurzfassung: Sympathoadrenale Reaktivität auf Stress als Prädiktor kardiovaskulärer Risikofaktoren. Es besteht erhebliche Unsicherheit über die Pathophysiologie der primären Hypertonie. Eine mögliche Ursache könnten Alterationen im autonomen Nervensystem sein, das eine wichtige Rolle in der normalen physiologischen Regulation des Blutdrucks spielt. Wir untersuchten deshalb die Beziehungen zwischen Ruheblutdruck und arteriellen Plasmakatecholaminen sowie die kardiovaskuläre und sympathische Reaktivität auf Stresstests und kardiovaskuläre Risikofaktoren bei jungen Männern (19 Jahre alt) mit niedrigem, normalem und hohem Blutdruck.

In einer initialen Querschnittsuntersuchung war niedriger Blutdruck mit einem besseren Lipoproteinprofil, niedrigerer Fruktosaminkonzentration und geringerer Bauch-Hüft-Relation assoziiert als hoher. Der mentale Stresstest war der einzige Test, der unterschiedliche Reaktionen zwischen den 3 Blutdruckgruppen hervorrief. Die Gruppe mit hohem Blutdruck zeigte die ausgeprägtesten, die Gruppe mit niedrigem Blutdruck die geringsten Anstiege von Druck, Herzfrequenz und Plasma-Katecholaminen. Die Adrenalin- und Noradrenalin-Spiegel während eines mentalen Stresstests erwiesen sich als signifikante Prädiktoren des zukünftigen Blutdrucks nach einem Follow-up von 18 Jahren, während Plasmakatecholamine in Ruhe und während eines „Cold-pressor"-Tests keine signifikante Beziehung zur Blutdruckentwicklung zeigten. Die Reaktion von Noradrenalin auf den mentalen Stresstest war ein schwacher positiver Prädiktor für die Entwicklung des Bauchumfangs. Keiner der anderen Parameter in Ruhe oder im „Cold-pressor"-Test zeigte eine signifikante Beziehung zu Änderungen des Body-Mass-Index, Taillenumfangs oder der Hautfaltendicke über dem Trizeps. Die Reaktion von Noradrenalin im „Cold-pressor"-Test war in einer univariaten Analyse positiv mit der Nüchtern-Plasmaglukose und HOMA-IR im Follow-up assoziiert. In der multiplen Regressionsanalyse erwies sich die Reaktion des Noradrenalins als ein unabhängiger positiver Prädiktor der HOMA-IR. Mit den Plasmakatecholaminen in Ruhe oder während des mentalen Stresstests ergaben sich keine Korrelationen.

Die Reaktivität des sympathischen Nervensystems zeigt nicht nur eine Beziehung zum Blutdruck, sondern auch zu einer Reihe von metabolischen Risikofaktoren. Die Reaktionen auf den „Cold-pressor"-Test und den mentalen Stresstest scheinen einen unterschiedlichen Aussagewert für die Entwicklung dieser Risikofaktoren zu haben. **J Hypertonie 2012; 16 (2): 13–8.**

Schlüsselwörter: sympathisches Nervensystem, Stressreaktivität, Blutdruck, Insulinresistenz, Adipositas

Introduction

There is much uncertainty about the pathophysiology of essential hypertension, and there is probably a large number of factors contributing to elevated blood pressure [1]. One possible cause may be alterations in the autonomic nervous system, which plays an important role in the normal physiological regulation of blood pressure. Based on our previous observations, we hypothesized that resting blood pressure was related to arterial plasma catecholamines, cardiovascular and sympathetic reactivities, and cardiovascular risk factors in a cross-sectional study in young men with low, normal, and high blood pressures, who were unaware of their blood pressure status (part 1).

In a follow-up study over 18 years (part 2), we hypothesized that initial sympathoadrenal reactivity to stress at 19 years of age was related to the development of future cardiovascular risk factors, such as high blood pressure, obesity, and insulin resistance.

Furthermore, we examined whether reactivity to the cold pressor test and the mental stress test differed in predictive power.

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Subjects and Methods

Subjects

The data for the cross-sectional study was collected from 1986–1989. All subjects were initially selected from the military draft procedures in 1986 and 1987. In 1986, the number of screened subjects was 3861, while 4123 were screened in 1987. Blood pressure measurements on all subjects attending in Oslo were performed once after 5 minutes of sitting. Mean blood pressure was thereafter calculated as (diastolic blood pressure + pulse pressure)/3. None of the subjects were informed about the results of the blood pressure recordings at this stage to avoid effects of hypertension labelling on responses to the forthcoming stress tests [2, 3]. In part 1, subjects were reexamined in our laboratory on a separate day before final inclusion. Subjects belonging to the 98th–99th percentile of the military screening blood pressure distribution were included if mean blood pressure at reexamination exceeded the population blood pressure + 1 SD. Subjects of the 50th percentile were included if their mean blood pressure was within mean screening blood pressure ± 1 SD. Subjects of the 1st percentile were included if their mean blood pressure was lower than mean screening blood pressure –1 SD.

In the follow-up study performed from 2005–2006 (part 2), we selected subjects from the 1st, 50th, and 95th–99th percentiles of the mean blood pressure distribution of the initial military screening. All were previously healthy and of Caucasian origin except for one who was half Asian and half Caucasian. 99 of the subjects from entry had satisfactory examinations and were suitable for follow-up. Out of these, 81 (82 %) subjects were available for examination at follow-up, a total of 18 were not reexamined. Subjects not eligible for follow-up did not differ from eligible subjects in resting blood pressure, heart rate, BMI, waist circumference, or catecholamine stress responses at entry. One subject undergoing reexamination had ulcerative colitis and had to be excluded from further analyses due to a previous colectomy and excessive intake of water and salt. At follow-up, 21 subjects (25.9 %) reported having one or more of the following diseases: hypertension (9 subjects), hypercholesterolemia (12), diabetes mellitus (3), and previous myocardial infarction (1). Eight of these subjects used one or more of the following medications regularly: angiotensin receptor blockers (3), beta-blockers (3), ACE inhibitors (1), statins (2), anti-diabetics (3), and acetylsalicylic acid (1).

Methods

Blood Pressure Measurements

Screening measurements at military draft procedures in 1986 and resting measurements in the laboratory were recorded by an automatic auscultatory device (Boso-digital II S, Bosch & Sohn, Jungingen, Germany) validated against a sphygmomanometer, and a hidden printer, to serve as an unbiased measurement. However, diastolic blood pressure distribution of the 3861 men at screening was skewed to the left, suggesting underestimation in some subjects. Thus, in 1987, we decided to use a standard sphygmomanometer.

Blood pressures during stress tests in the laboratory at entry were monitored directly by a canula in the brachial artery of the non-dominant arm. All subjects were unaware of their blood pressure status, previously shown to be a confounding factor [2–4].

At follow-up, resting blood pressure was measured 3× with a mercury sphygmomanometer on the left arm after at least 15 minutes of sitting and was calculated as mean of the last 2 measurements.

Plasma Catecholamines

Arterial plasma catecholamines were measured by a radioenzymatic technique according to Peuler and Johnsen [5], as previously reported [3, 6]. All blood samples were analyzed by the same technician at entry and at follow-up. The assay has been used for > 20 years in our laboratory and is also precise at low-plasma concentrations.

Insulin Resistance

Insulin resistance at follow-up was quantified using the homeostasis model assessment for insulin resistance (HOMA-IR). HOMA-IR was calculated in fasting conditions as serum glucose (mmol/l) multiplied by serum insulin (pmol/l) and divided with 135, as described by Matthews et al [7].

Stress Tests

We used 3 stress tests in the present work to activate the sympathoadrenal system. We sampled plasma catecholamines and measured blood pressure and heart rate before, during, and after stress tests. The response to stress was defined as the mean values during the tests minus the baseline value or the absolute value during the tests.

Mental Stress Test

The mental arithmetic stress test has been widely used. In our studies, the subjects were asked to subtract the number "13" repetitively starting from "1079" for 5 min, while a metronome made noise at a frequency of 2 Hz. The subjects had to calculate loudly, and feedback was given at any miscalculation. Mental stress test is known to elicit a fight-and-flight reaction and is a classic example of a β-adrenergic response, where the increased blood pressure is mediated primarily via an increase of cardiac output [8, 9]. Total peripheral resistance shows little change during the test.

Cold Pressor Test

One hand is completely immersed in ice water (0–2 °C) for 1–6 minutes. We used 1 minute in our studies. In contrast to the mental stress test, the cold pressor test elicits a response that is predominantly mediated by α-adrenergic vasoconstriction [9]. This means that the observed increase in blood pressure is mainly due to an increased total peripheral resistance.

Orthostatic Test

Subjects were asked to stand up for 2 minutes from the supine position. After standing up, pooling of the blood takes place in the legs. A transient reduction in cardiac output elicits a reflex increase in sympathetic activity [10].

Statistics

Data were analyzed using the statistical package SPSS version 12.0 (part 1) and 14.0 (part 2) for Windows (SPSS Inc, Chicago, IL). Parametric tests were used for normally distributed, non-parametric data when normality was not achieved by natural log transformation.

One-way analysis of variance (ANOVA) with trend analysis or the Kruskal-Wallis test was used to compare differences between the initial screening groups (part 1). Subsequent Student's t-tests without adjustments were carried out if there was any significant group interaction. The effect of stress tests on blood pressure and plasma catecholamines was additionally analyzed by repeated-measure ANOVA, and group differences were analyzed by effect*group interaction, with subsequent t-tests.

Associations between continuous variables were assessed using Pearson's correlations or Spearman's rank correlation, while Chi-Square testing with linear-by-linear association was used for dichotomous variables. To adjust for possible confounders, linear regression analysis was performed. Due to a large number of univariate correlation analyses in part 2, the Bonferroni correction was used to reduce the risk of type-1 errors.

Paired sample T-tests or the Wilcoxon test were used to analyze possible changes in normally distributed continuous variables from entry to follow-up (part 2), while categorical variables were analyzed by sign test.

Results

Cross-Sectional Associations Between Resting Blood Pressure and Sympathoadrenal Activity and Stress Reactivity

Differences in resting blood pressure among the 19-year-old men were reflected by a similar pattern in both arterial adrenaline and noradrenaline concentrations at rest. Mental stress test, cold pressor test, and orthostatic test evoked significant cardiovascular and catecholamine responses in all blood pressure groups. However, the mental stress test was the only test that induced differential responses between the 3 blood pressure groups (Figure 1), where the high-blood pressure group showed the most, and the low-blood pressure group the least pronounced response in blood pressure, heart rate, and plasma catecholamines. The study also showed that lower blood pressure was associated with a better lipoprotein profile, a lower fructosamine concentration, and lower waist-hip-ratio.

Sympathoadrenal Reactivity as a Predictor of Future Blood Pressure

Adrenaline and noradrenaline concentrations during the mental stress test were significant predictors of future systolic blood pressure, while the plasma catecholamine levels at rest and during the cold pressor test did not show significant associations with later blood pressure. Together, in the multiple regression model, adrenaline and noradrenaline levels during mental stress explained 12.7 % of the variation of future systolic blood pressure, after adjusting for resting blood pressure, family history, Body Mass Index (BMI) at entry, and systolic blood pressure during stress (adjusted R^2 for the whole model: 0.65).

Sympathoadrenal Reactivity as a Predictor of Future Body Fat

Adrenaline response to mental stress was negatively related to changes in BMI and waist circumference during follow-up in univariate analyses. In supplementary multiple regression analyses, adrenaline response was a highly consistent negative predictor of future BMI, waist circumference, and triceps skinfold thickness after adjusting for exercise level and initial BMI, waist circumference, or triceps skinfold. Noradrenaline response to mental stress was a weak positive predictor for future waist circumference and did not significantly predict BMI and triceps skinfold thickness. None of the other adrenaline and noradrenaline parameters during rest or cold pressor test were significantly related to changes in BMI, waist circumference, or triceps skinfold thickness.

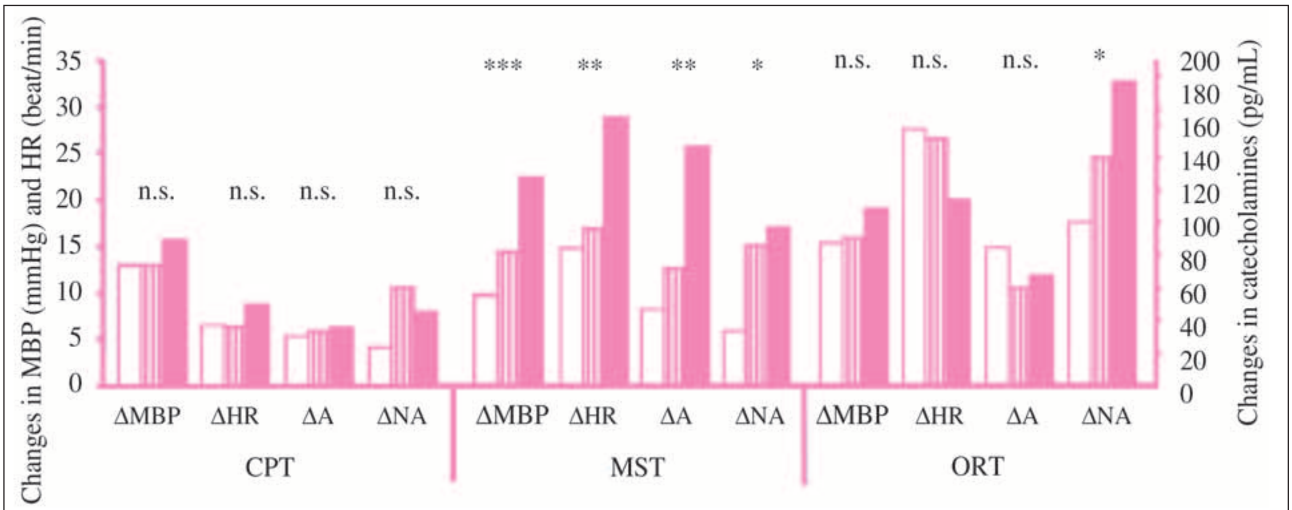

Figure 1. Comparison of group differences in cardiovascular and catecholamine response (Δ) to cold pressor test (CPT), mental stress test (MST), and orthostatic test (ORT) for group 1 (white), group 2 (white and black lines), and group 3 (black). *p < 0.05; ** p < 0.01; *** p < 0.001 (for linear trend). Reprinted from [Flaa A, Mundal HH, Eide I, Kjeldsen S, Rostrup M. Sympathetic activity and cardiovascular risk factors in young men in the low, normal, and high blood pressure ranges. Hypertension 2006; 47 (3): 396–402] with permission from Wolters Kluwer Health.

Sympathoadrenal Reactivity as a Predictor of Future Insulin Resistance

Noradrenaline response to the cold pressor test was positively related to fasting plasma glucose and HOMA-IR at follow-up in univariate analyses. In multiple regression analyses, noradrenaline response was an independent positive predictor of HOMA-IR. There were no significant associations with plasma catecholamines at rest or during mental stress.

Discussion

Participants were recruited from the military draft procedures in Oslo, securing a homogenous sample of subjects of the same age, race, and gender, thus reducing statistical variance. However, this advantage also implies a limited ability to generalize the present results to older subjects, other ethnicities, and women.

We did not include a randomized sample from military screening, but rather a stratified selection which leads to an overrepresentation of subjects with extremely low and high blood pressures. However, we had a moderate sample size due to our resource-demanding invasive examinations, and blood pressure criteria ensured a satisfactory dispersion of the blood pressure range, which makes it easier to demonstrate relationships.

Military blood pressure screening was based on one blood pressure recording in the sitting position after 5 minutes of rest. These measurements involve elements of both rest and stress and do not meet the criteria of normal guidelines for blood pressure measurement. It may be questioned whether a single blood pressure screening value is representative for the subject's true blood pressure level, as current guidelines recommend several measurements taken on various occasions over a certain period of time, due to spontaneous variations both during daytime and between days [11]. However, blood pressure was determined according to the guidelines later in the laboratory for selected individuals, ensuring resting conditions.

We compared the 3 blood pressure groups with regard to their response to the 3 different stress tests in a cross-sectional study. The selection procedure (military enlistment) may be regarded as a psychological stress situation, raising the question of whether subjects with high blood pressure were partly preselected to respond vigorously to the mental stress test. However, there is evidence that hypertension and high-normal blood pressure are associated with increased cardiovascular and sympathoadrenal reactivities to mental stress compared to physical stress, such as orthostatic and cold pressor test [12]. In this study, sample groups were rather small (low-blood pressure group [group 1]: n = 15, normal-blood pressure group [group 2]:15, high-blood pressure group [group 3]: 13), and the lack of significant findings during the cold pressor and orthostatic tests could be due to insufficient power. However, the statistical power to detect a similar difference during cold pressor and orthostatic tests as during mental stress test was > 80 % for adrenaline, noradrenaline, mean blood pressure, and heart rate between groups 1 and 3, indicating sufficient sample sizes.

At follow-up, we were able to analyze 80 subjects of the original 99 men at entry. This is a remarkably high attendance rate after so many years, and the fact that subjects not eligible for follow-up had similar resting blood pressures, heart rates, BMI, waist circumferences, and catecholamine stress responses at entry as the 80 eligible subjects decreases the risk of sample bias. Due to certain diseases among the subjects at follow-up, analyses and interpretations were performed with precaution. When examining blood pressure development, we excluded 5 subjects due to their blood pressure-lowering treatment. Beta-blockers may affect body weight, but including this parameter in the analysis of weight development did not alter the results and we chose to remove the variable from the final analyses as there were only 3 subjects using them. Regarding development of insulin resistance, some would possibly argue that the 3 subjects with type-2 diabetes should be excluded from the analyses. However, they represent a true and important part of blood glucose distribution in the population. Furthermore, they took oral anti-diabetics, and as none of them administered insulin, HOMA-IR was a suitable measure of insulin resistance in these subjects.

According to the selection procedure at entry, we could have assessed the prevalence of various risk factors at follow-up in the 3 original blood pressure groups. Even though there are close cross-sectional relationships between these groups and catecholamine levels, as demonstrated in part 1, we chose to focus on the cardiovascular and catecholamine parameters independently of the initial blood pressure groups, making it possible to study various components of the sympathoadrenal system during rest and stress tests in more detail. Moreover, even though they originally represented 3 different groups of blood pressure at screening, their blood pressures showed a normal distribution when reexamined in the laboratory due to the regression to the mean.

In a previous study of ours there was a tendency that subjects with high screening blood pressure came close to normal when reexamined in the laboratory [13]. To ensure differences in resting blood pressure, subjects underwent a second blood pressure examination, where we selected only the ones with extremely low and high blood pressures in addition to subjects with normal levels. Among these subjects, we found a clear relationship between resting blood pressure and arterial plasma catecholamine levels. Even though there are several reports of increased catecholamine levels in subjects with high blood pressure [3, 14–16], this is the first study demonstrating an association between plasma catecholamines and blood pressure within the whole range of resting blood pressure, by showing that subjects with low blood pressure have decreased sympathetic tone compared to normotensives. The original 3 screening groups showed a clear differentiation in cardiovascular and catecholamine responses to the mental stress test, in contrast to the cold pressor and orthostatic tests that showed no such differences. There are several possible mechanisms explaining hyperreactivity to mental stress [9]:

- Structural changes in the vascular wall or increased receptor sensitivity may amplify the pressor effect of catecholamines. However, one would have expected a similar hyperreactivity to the orthostatic and cold pressor tests if

vascular wall or receptor properties were the only explanation.
- Hyperreactivity may be initiated in subcortical structures (hypothalamus and brain stem). The fact that we found differences not only in blood pressure and heart rate responses, but also in catecholamine responses, indicates a central origin.
- The third option is mechanisms located in the cortical areas, as each subject has a different perception and reaction pattern. Some have described a “hypertensive personality”, with a tendency to be submissive, to avoid confrontations, and to suppress anger. We have previously demonstrated that stress reactivity is related to certain personality traits like muscular tension, irritability, and detachment [17].

The significant relationships between blood pressure and the cardiovascular risk factors triglycerides, HDL, HDL-total cholesterol ratio, fructosamine, and waist-hip-ratio in our study demonstrate how blood pressure may represent a marker of other risk factors, even in young subjects < 20. Likewise, the Tecumseh study showed clear evidence of a worse cardiometabolic profile in young subjects with borderline hypertension compared to normotensives [18].

Thus, our findings suggest that resting blood pressure reflects both sympathetic activity and other cardiovascular risk factors. Furthermore, as high screening blood pressure also relates to mental stress responses, it is reasonable to question whether sympathoadrenal responses to mental stress are related to the development of cardiovascular risk factors.

Previous longitudinal studies have mainly examined resting plasma catecholamines [19–21] or urinary catecholamines [22] as predictors of future blood pressure, obesity, and insulin resistance. However, we did not find any significant associations during rest. One reason could be insufficient power, even though we had a larger sample size than 2 of the aforementioned studies [19, 22]. Another possible explanation could be the different ethnicities represented in the various studies.

However, in contrast to these earlier studies, we found that catecholamines during stress were better predictors than the variables recorded at rest. Blood pressure at follow-up were markedly stronger related not only to catecholamine levels but also to blood pressure and heart rate during stress (especially mental stress) compared to rest. Earlier findings showed that casual office [23, 24] and ambulatory blood pressures [11, 25] are stronger predictors than the recommended standardized office measurements after several minutes of rest [26, 27], and measurements performed during situations involving elements of stress activation may be more useful as predictors of future blood pressure than standardized resting measurements [28, 29]. As for the prediction of weight gain and insulin resistance, the strongest predictors were adrenaline response during mental stress and noradrenaline during the cold pressor test, respectively.

The apparent importance of stress tests may be explained by the excellent ability to detect certain characteristics among subjects at risk, due to the special properties of the various tests. For example, regarding weight development, mental stress is known to induce a more pronounced adrenaline release than the cold pressor test [9] and exerts its effects mainly through activation of β-receptors [30]. Thus, the association between mental stress reactivity and prediction of weight gain may indicate that reduced stimulation of β-adrenergic receptors plays an important role in the development of obesity. Low adrenaline response to mental stress in the laboratory possibly also reflects lower adrenaline reactivity during everyday life, including stressful daily activities, thus favoring less β-receptor stimulation, a lower metabolic turnover, and subsequent weight gain. The cold pressor test, on the other hand, seems more appropriate in predicting future insulin resistance, as this test predominantly acts by increasing the sympathetic activity to peripheral arterioles in skeletal muscles and skin. Thus, subjects characterized be elevated sympathetic activity to these organs with subsequent vasoconstriction may develop insulin resistance through reduced glucose uptake in skeletal muscles [31].

The choice of stress test may also be important in predicting hypertension. A large proportion of young subjects prone to develop hypertension are characterized by hyperkinetic circulation [32, 33]. Later, there is a transition from this early stage of hypertension development with increased cardiac output and nearly normal total peripheral resistance to the later stage characterized by normalization of cardiac output and increased total peripheral resistance [9, 13]. We found that responses to mental stress, which are predominantly β-mediated, may be better predictors than responses to the cold pressor test in our young cohort. Thus, using the cold pressor test in longitudinal hypertension studies may be suboptimal in young subjects, as it elicits an α-adrenergic vascular response more than a β-adrenergically mediated myocardial response [34, 35], and many of these young subjects prone to develop hypertension are characterized by hyperkinetic circulation mediated by β-adrenergic receptors.

Apparently, some of the present findings may represent a paradox. Increased sympathoadrenal activity predisposes to insulin resistance. On the other hand, development of obesity seems to be related to reduced activity in the adrenal medulla. However, the association between obesity and insulin resistance has been known for many years, and these 2 cardiovas-

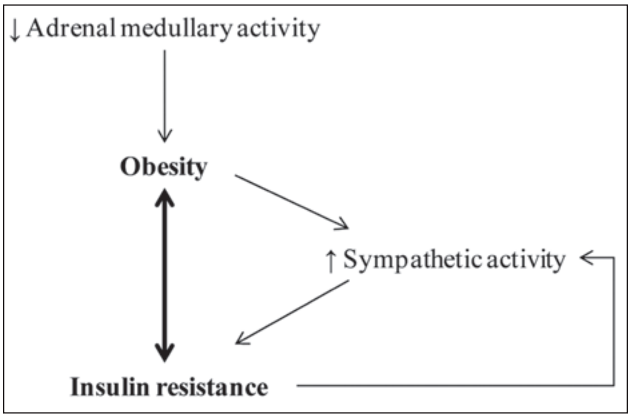

Figure 2. Possible relationships between adrenal medullary and sympathetic activity and development of obesity and insulin resistance.

cular risk factors are probably reinforcing each other [36]. Wouldn't it then be plausible that increased sympathoadrenal activity leads to both insulin resistance and obesity? It is important to note that adrenal medullary activity and overall sympathetic activity may show reciprocal alterations [37], and we believe that our findings are compatible with prior knowledge: reduced activity in the adrenal medulla may predict the development of obesity, with subsequent increase in sympathetic activity and development of insulin resistance (Figure 2). It should be mentioned that noradrenaline tended to be a positive predictor of weight gain in our study's multiple regression analyses, perhaps suggesting an earlier role of obesity development than suggested in Figure 2.

The positive relationship in the present long-term study between plasma noradrenaline concentration during mental stress at entry and systolic blood pressure at follow-up independent of the initial blood pressure level strongly supports an important role of increased sympathetic nervous activity in early development of hypertension [32].

Practical Relevance

The present study shows that resting blood pressure among young men reflects sympathoadrenal activity. Moreover, sympathoadrenal reactivity during stress at a young age seems to predict a future risk of developing hypertension and insulin resistance, thus supporting the theory that sympathoadrenal activity may play an important role in the development of these diseases.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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