Muscle and Skin Sympathetic Nerve Traffic During the “White-Coat” Effect

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**Background**—Sphygmomanometric blood pressure measurements induce an alerting reaction and thus an increase in the patient’s blood pressure and heart rate. Whether and to what extent this “white-coat” effect is accompanied by detectable changes in sympathetic nerve traffic has never been investigated.

**Methods and Results**—In 10 mild untreated essential hypertensives (age 37.9 ± 3.8 years, mean ± SEM), we measured arterial blood pressure (by Finapres), heart rate (by ECG), and postganglionic muscle and skin sympathetic nerve activity via microneurography. Measurements were performed with the subject supine during (1) a 15-minute control period, (2) a 10-minute visit by a doctor unfamiliar to the patient who was in charge of measuring his or her blood pressure by sphygmomanometry, and (3) a 15-minute recovery period after the doctor’s departure. The entire procedure was performed twice at a 45-minute interval to obtain, in separate periods, muscle or skin sympathetic nerve traffic recordings, whose sequence was randomized. The doctor’s visit induced a sudden, marked, and prolonged pressor and tachycardic response, accompanied by a significant increase in skin sympathetic nerve traffic (138.6 ± 6.7%, P < 0.01). In contrast, muscle sympathetic nerve traffic was significantly inhibited (225.5 ± 4.1%, P < 0.01). All changes persisted throughout the doctor’s visit and, with the exception of skin sympathetic nerve traffic, showed a slow rate of disappearance after the doctor’s departure.

**Conclusions**—Thus, the pressor and tachycardic responses to the alerting reaction that accompanies sphygmomanometric blood pressure measurement is characterized by a behavior of the adrenergic nervous system that causes muscle sympathoinhibition and skin sympathoexcitation. (*Circulation*. 1999;100:222-225.)

**Key Words:** blood pressure • nervous system • reflex • hypertension

Blood pressure (BP) measurements by a doctor are accompanied by an often marked increase in BP and heart rate (HR). It is believed that this increase (referred to as the “white-coat” effect) originates from an alerting reaction and is thus largely mediated by a sympathetic activation. No assessment of sympathetic nerve activity during BP measurements by a doctor has ever been obtained, however. In the present study, we addressed this issue by quantifying the white-coat effect on BP and HR together with quantification of sympathetic outflow to muscle and skin by microneurography.

**Methods**

Our study involved 16 patients with newly discovered hypertension, ie, with the novel finding of a diastolic BP > 90 mm Hg at 3 medical visits performed in outpatient clinics over a 3-month period. Because of instability and/or loss of nerve recording (see below) in 6 subjects, the study was successfully completed in 10 patients. These patients (8 men, 2 women) had a mean age of 37.9 ± 3.8 years, and their hypertensive condition was defined as being of a mild essential nature by the absence of clinical complications, major end-organ damage, and signs of a secondary cause for the BP elevation. Patients were untreated and gave their written consent to participate in the study after an explanation of its nature and purpose. The study was approved by the ethics committees of the institutions involved.

**Measurements**

BP was measured by (1) a mercury sphygmomanometer, taking the first and fifth Korotkoff sounds to identify systolic and diastolic values, respectively, and (2) a finger photoplethysmographic device (Finapres 2300) capable of providing accurate and reproducible beat-to-beat systolic and diastolic values and thus to calculate mean BP (diastolic plus one third of pulse pressure). HR was monitored continuously by an ECG, and respiration rate by a strain-gauge pneumograph positioned at mid-chest level. Multiunit recordings of efferent postganglionic sympathetic nerve activity to skeletal muscle (MSNA) or skin (SSNA) districts were obtained through a tungsten microelectrode inserted into the right or left peroneal nerve, as previously described, and displayed with BP, HR, and respiration rate on thermic paper by an ink polygraph (Gould 3800). The MSNA or SSNA nature was assessed by the criteria outlined in previous studies. Neurograms were accepted only if they did not show simultaneous SSNA and MSNA and if the quality of the microneurographic recordings was acceptable.

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signal-to-noise ratio was $>3.34$ Both MSNA and SSNA were quantified over each minute as number of bursts and as total activity (number of bursts per minute times mean burst amplitude, expressed in arbitrary units).

Protocol and Data Analysis

All patients were studied 1 to 2 weeks after the third medical visit and thus when mild hypertension had been conclusively identified. The protocol of the study was as follows: (1) the patient was asked to come in the morning to the outpatient clinics, was brought to the laboratory, placed in the supine position, and fitted with the various measuring devices; (2) the microelectrode was manipulated until MSNA (5 patients) or SSNA (5 patients) was obtained; (3) the patient was left undisturbed for 15 minutes with only the technician in charge of checking the continuing adequacy of the hemodynamic and sympathetic signals present; (4) a doctor unfamiliar to the patient entered the room and performed 3 sphygmomanometric BP measurements within a 10-minute period; (5) the doctor left the room and the patient remained in the conditions described under step 3 for another 15 minutes; (6) the microelectrode was repositioned to obtain the sympathetic nerve activity not obtained in the previous recording period; and (7) after 45 minutes, steps 3 through 5 were repeated.

Calculations were made by a single observer unaware of the experimental design to obtain values during each minute of the 15 minutes preceding the doctor’s visit, the 10 minutes of the visit, and the 15 minutes thereafter. Changes induced by the doctor’s visit were quantified (1) in relation to the value 4 minutes before the doctor’s visit and (2) as average values during the doctor’s visit versus average values in the 15 minutes before and after the visit. Values from individual subjects were averaged for the group as a whole and expressed as mean±SEM, differences in mean values being assessed by 2-way ANOVA. Student’s $t$ test for paired observations was used to locate the statistical significance of the difference, after Bonferroni correction. Changes in mean BP and sympathetic activity were also analyzed as linear correlations. A value of $P<0.05$ was taken as the level of statistical significance.

Results

In our patients, sphygmomanometric systolic and diastolic BP were 137.3±3.1 and 97.9±2.4 mm Hg, respectively. Control finger mean BP (ie, the value obtained 4 minutes before the doctor’s entrance into the room) was 109.2±2.9 mm Hg, whereas control HR was 70.2±1.8 beats/min, control MSNA was 32.7±2.7 bursts/min, and control SSNA was 12.8±2.6 bursts/min. The corresponding values for MSNA and SSNA total activity were 224.7±21 and 107.8±14 arbitrary units, respectively. All values were relatively stable over the 15 minutes preceding the doctor’s visit that caused, in each subject, a sudden marked increase in mean BP and HR, a sudden marked increase in the number of SSNA bursts, but a sudden marked reduction in the number of MSNA bursts (Figures 1 and 2). SSNA and MSNA also showed an increase and a reduction, respectively, when expressed as total activity (peak change: SSNA $+75.1±11$ and MSNA $-58.7±9$ arbitrary units, $P<0.01$ for both). All changes persisted throughout the doctor’s visit and, with the exception of SSNA, showed a slow rate of disappearance.

The mean BP increase during the doctor’s visit was related to the MSNA reduction ($r=0.77$, $P<0.01$) but not to the SSNA increase ($r=0.12$, $P=NS$). The average increase in mean BP and HR seen during the first visit (in which 5 patients had MSNA and the remaining 5 SSNA measurements) was comparable (9.4±1.1 mm Hg and 7.9±0.8 beats/min, respectively) to that seen during the second visit, during which the sequence of sympathetic activity measurements was switched.

Discussion

In our patients, a visit by an unfamiliar doctor in charge of measuring BP caused the expected marked increase in BP and HR.12 The novel finding of our study, however, is that this pressor and tachycardic response was accompanied by profound changes in sympathetic nerve traffic. These changes, however, were not homogeneous, because whereas SSNA was markedly increased (average increase 38.6±6.7%, $P<0.01$), MSNA was concomitantly markedly reduced (average reduction 25.5±4.1%, $P<0.01$). Thus, the emotional reaction widely known as the white-coat effect is character-
ized by a behavior of the sympathetic nervous system that heterogeneously combines an activation with a deactivation.

Previous studies in humans have shown a variety of emotional behaviors to be characterized by a vasoconstriction in all regional districts except skeletal muscle, in which a vasodilatation has often been observed. This vasodilatation, however, has been ascribed to the activation of cholinergic sympathetic fibers, because these fibers have been shown to vasodilate skeletal muscle arterioles in the defense reaction of several animal species and to contribute to the muscle vasodilatation that accompanies isometric exercise in humans. It has also been ascribed to epinephrine, because its increase during emotion dilates skeletal muscle vessels through stimulation of β-adrenergic receptors. Our results, however, provide evidence that this phenomenon is probably not entirely accounted for by the above 2 mechanisms. A third mechanism definitely consists of a selective MSNA inhibition, making the heterogeneous hemodynamic changes that accompany emotional behavior at least in part due to a heterogeneous pattern of sympathetic activity. This heterogeneous pattern may have a central origin, ie, it may be inborn in the diencephalic areas integrating cardiovascular adjustments to emotional behavior, because when these areas are stimulated in animals, one can elicit the somato-motor components of a defense reaction together with a selective pattern of sympathetic stimulation, ie, activation to the heart and visceral areas with inhibition to skeletal muscle. In our patients, however, the degree of muscle sympathoinhibition was correlated with the degree of the BP increase, suggesting that it may be of a reflex nature, ie, that MSNA may be reduced during emotion because of the BP rise and baroreceptor stimulation. This is supported by the evidence that in humans, arterial baroreceptors modulate MSNA but not SSNA in several conditions and diseases.

Several further points deserve to be mentioned. (1) Both the hemodynamic and the sympathetic responses to the doctor’s visit lasted for several minutes after the end of the visit, thus showing a slow disappearance rate. (2) The BP and HR increases were superimposable in the first and second visits, indicating no attenuation of the cardiovascular responses to this emotional stimulus with its repetition. (3) Our study does not clarify whether sympathetic nerve traffic elsewhere in the body behaves like SSNA or MSNA. Visceral districts, however, have been shown to respond to emotional stimuli with vasoconstriction. Furthermore, these stimuli are usually accompanied by a plasma norepinephrine increase. In addition, the marked BP increase observed during the doctor’s visit can hardly be explained by a vasoconstriction in the skin, which accounts for only ~10% of total vascular resistance. This makes it likely that sympathetic nerve traffic to other districts of the body increases in a fashion similar to SSNA and different from MSNA. (4) Our study was conducted in mild hypertensives only, which did not allow us to establish whether the pattern of sympathetic changes that accompany a doctor’s visit is qualitatively and/or quantitatively similar in normotensive subjects and in patients with more severe hypertension. It should be mentioned, however, that in previous studies, we found that the BP increase to the doctor’s BP measurement occurs in patients with both normal and variably elevated 24-hour average pressures, suggesting that the pattern of sympathetic firing we described in the present study exists within a wide range of BP levels. This does not exclude the possibility that in patients with a particularly pronounced alerting response, the pattern of sympathetic responses may be quantitatively different. Microneurography might allow us to address all these issues because of its ability to determine the adrenergic reactivity to emotional stimuli (and the clinical implications) in a direct and precise dynamic fashion.
References


