Comparison of Sympathetic Nerve Activity in Normotensive and Hypertensive Subjects

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ABSTRACT

A microneurographic technique was used to record multiunit sympathetic activity in skin and muscle nerves of 24 healthy subjects and 21 hypertensive subjects. In both groups, the sympathetic activity recorded during rest appeared in bursts following one of two highly different temporal patterns—one characteristic for muscle nerves and the other characteristic for skin nerves. Muscle nerve sympathetic activity probably consisting of vasoconstrictor impulses, occurred in bursts that followed the pulse rhythm and waxed and waned in inverse relation to spontaneous blood pressure fluctuations. Transient random elevations of blood pressure above a certain level caused total suppression of the sympathetic bursts. This inhibitory blood pressure level was higher in hypertensive subjects than it was in normotensive subjects, suggesting an elevated baroreflex working range in hypertension. No other important differences in muscle nerve sympathetic activity were noted between the two groups. Skin nerve sympathetic activity, probably consisting of both vasoconstrictor and sudomotor impulses, had a similar temporal pattern in normotensive and hypertensive subjects at rest: bursts of variable duration occurred randomly or were loosely related to the respiratory rhythm. In both groups of subjects, the strength of this activity increased in response to arousal stimuli, mental stress, and body cooling. These findings emphasize the necessity of having highly standardized experimental conditions in future studies aimed at a quantitative comparison of the absolute strength of sympathetic activity in normotensive and hypertensive subjects.

KEY WORDS  pathophysiology of hypertension  microneurography  vasoconstrictor impulses  muscle and skin nerves  baroreflex control

In 1968 Vallbo and Hagbarth (1) introduced a microneurographic technique for recording action potentials in peripheral nerves of awake humans. Although the method was primarily intended for studying afferent inflow from various receptors, it has also proved useful for recording efferent sympathetic activity (2). Recently the characteristics of multiunit sympathetic activity in muscle and skin nerves was investigated using this technique in a group of healthy adult subjects (3-6), and distinct differences were found between the two nerve types in both the pattern of their spontaneous activity and their response to various maneuvers.

Although a proper regulation of the sympathetic vasoconstrictor outflow is of major importance for normal blood pressure control, it is still uncertain to what extent disturbances in the neural regulatory mechanisms are responsible for the development and the maintenance of the high blood pressure levels found in subjects with arterial hypertension. Thus, it would be of interest to compare "sympathicograms" (SPGs) from muscle and skin nerves of hypertensive subjects with those of normotensive control subjects. An SPG does not provide a reliable measure of the absolute strength of the sympathetic outflow in any particular nerve bundle, but as long as the electrode position remains constant it does clearly show spontaneous temporal variations and reflexly induced changes in this outflow. Muscle nerve SPGs combined with simultaneous recordings of systemic blood pressure fluctuations give a clear picture of the continuous baroreflex modulation of the sympathetic vasoconstrictor outflow to the muscles.

In the present study major attention was paid to the following questions. (1) Do hypertensive subjects differ from normotensive subjects with respect to the temporal patterns—the profiles—of their SPGs recorded from skin and muscle nerves during resting conditions? (2) Is the normal correlation between blood pressure and muscle nerve SPG preserved in hypertensive subjects? (3) Do maneuvers of different types, some resulting in blood pressure changes and some not, give SPG...
responses of similar sign in hypertensive and normotensive subjects?

It must be emphasized that no serious attempts were made to measure the absolute strength of the resting sympathetic activity or the strength of the sympathetic responses to different maneuvers. To be valid such measurements require more standardized external conditions than those established in the present study. In addition, the absolute strength of the nerve activity is, to a large extent, determined by the location of the electrode tip in relation to the active fibers; therefore, interindividual quantitative comparisons must be based on recordings from more electrode positions than were used in the present work. The only quantitative observations reported in this paper are assessments of the amount of intraneural probing required to obtain multunit SPGs with a good signal-to-noise ratio.

Methods

Normotensive Subjects.—Recordings of sympathetic activity were made in 33 experimental sessions on a total of 24 normotensive subjects, 12 men and 12 women, ranging in age from 24 to 54 years (mean 35.5 years). They were all clinically healthy without signs or symptoms of any cardiovascular or neurological disorder. SPGs were obtained from 32 muscle nerve and 36 skin nerve fascicles in the following nerve trunks: the median nerve at the wrist or the elbow, the superficial radial nerve at the wrist, the peroneal and posterior tibial nerves at the knee, and the saphenous nerve below the knee. Part of this material (14 subjects) has been reported on in previous studies dealing with the normal characteristics of sympathetic activity (3—6).

Hypertensive Subjects.—Sympathetic activity was recorded in 30 experimental sessions on a total of 21 hypertensive subjects, 11 men and 10 women, ranging in age from 25 to 63 years (mean 42.6 years). SPGs were obtained from 22 muscle nerve and 21 skin nerve fascicles in either the peroneal nerve at the knee or the median nerve at the elbow or the wrist. One subject (no. 10) was investigated three times, once before and twice after the initiation of antihypertensive treatment. Ten subjects had taken antihypertensive drugs at some previous time, but with the exception of the last two investigations on subject 10 all had been drug free for at least 2 weeks prior to the study. The most important clinical data concerning the hypertensive subjects are presented in Table 1. All subjects underwent a thorough physical examination with repeated measurements of blood pressure. The routine examination included an electrocardiogram (ECC) and measurements of serum creatinine, electrolytes, and urine catecholamine excretion. The ECC showed left ventricular hypertrophy in 3 subjects and suspected hypertrophy in another 3 subjects. The heart volume was determined by chest x-ray and was moderately increased in 2 subjects (nos. 10 and 18) and normal in all others. Intravenous pyelography was performed in all subjects with normal results. Renal arteriography was carried out in 18 of the 21 subjects, and signs of renal arteriosclerosis were noted in 3 subjects, but only one (no. 18) was considered to have a significant stenosis of a renal artery. On the basis of these investigations, 19 subjects were considered to have essential hypertension. The 2 subjects in which secondary hypertension could not be excluded were nos. 10 and 18. Subject 18 had stenosis of one renal artery, and subject 10 had had a severe attack of porphyria with confusion and polyneuritis 16 years prior to the discovery of the hypertension. On that occasion, however, her blood pressure was normal; therefore, a causal relationship between the porphyria and the hypertension is very questionable.

Electrodes and Recording Systems.—Nerve electrodes, recording and display systems, and techniques used for recording sympathetic nerve activity, intraarterial blood pressure, respiratory movements, ECG, heart rate, blood flow in the forearm, calf, hand, or foot, changes in skin resistance, and pulse plethysmograms have been described in detail previously (3—6). The nerve recording method used in the present investigation was not selective for sympathetic impulses. On the contrary, action potentials could be picked up from several different types of axons within an impaled fascicle but not from neighboring fascicles (7). This circumstance was used in every experiment to decide whether the impaled fascicle innervated a skin area or a skeletal muscle. In a high proportion of all fascicles impaled, it was possible to find electrode sites at which multunit sympathetic activity could be recorded with an acceptable signal-to-noise ratio and without an appreciable admixture of afferent or efferent somatic impulses. The reasons for this condition and the evidence for the sympathetic origin of the impulses studied have been discussed in previous publications (3, 5) and will not be reiterated in this paper. In the illustrations, the nerve signals are shown as mean voltage neurograms obtained by electronic integration of the original nerve record (time constant 0.11 seconds). Since no attempts were made to quantify the strength of the nerve activity, amplitude calibrations of the nerve signals are omitted.

General Procedures.—The subjects lay comfortably in the horizontal position with their feet resting against a footplate, which provided support when the experimental table was temporarily tilted. They were instructed to relax and to avoid all movements except on request. Uncontrolled environmental influences were avoided. The room temperature was 20—25°C. Most subjects adjusted quickly to the experimental situation and did not regard the investigation as alarming or very unpleasant. As a rule the blood pressure values of the hypertensive subjects recorded at rest during the experiments were lower than those found at the time when they were admitted to the hospital.

Pure muscle or skin nerve fascicles were impaled percutaneously with tungsten microelectrodes and identified from the type and the site of peripheral
These fascicles were considered to be mixed, and data once the double recording was made in two muscle maneuvers used to induce changes in the sympathetic once in one skin and one muscle nerve fascicle. The stable recording for 1-2 hours. Four times simultaneous and warming, and cigarette smoking. These maneuvers identified, minute electrode adjustments were made site had been found, it was often possible to maintain a recording from two different leg nerves: twice in two skin nerve fascicles, and from them was discarded. When the fascicle had been ty appeared in the neurogram. Once such a recording impulses were evoked both by muscle and skin stimuli. For skin nerve fascicles, the receptive fields from them was discarded. When the fascicle had been were mapped by light touch stimuli. Sometimes afferent responses were evoked both by muscle and skin stimuli. These fascicles were considered to be mixed, and data from them was discarded. When the fascicle had been identified, minute electrode adjustments were made until the characteristic spontaneous sympathetic activity appeared in the neurogram. Once such a recording site had been found, it was often possible to maintain a stable recording for 1-2 hours. Four times simultaneous recordings were made from two different leg nerves: once the double recording was made in two muscle nerve fascicles, twice in two skin nerve fascicles, and once in one skin and one muscle nerve fascicle. The maneuvers used to induce changes in the sympathetic activity included passive changes in body position, Valsalva's maneuver, muscle work, emotional stress (mental arithmetic), hyperventilation, body cooling and warming, and cigarette smoking. These maneuvers have been described in detail previously (4).

Results

MUSCLE NERVE SYMPATHETIC ACTIVITY IN NORMOTENSIVE SUBJECTS

General Characteristics of Resting Activity.—As previously described by Delius et al. (3), the typical sympathetic mass activity recorded from muscle nerve fascicles in relaxed normotensive subjects consisted of pulse-synchronous bursts of impulses occurring in short sequences separated by periods of relative neural silence (Fig. 1). The periodicity was sometimes quite regular, but on other occasions the burst sequences had varying durations and appeared in an irregular fashion. No typical differences in pattern were found between activity in different nerves or different extremities. There were great variations in the amount of nerve probing required before muscle nerve SPGs with an acceptable signal-to-noise ratio were obtained. Thus, the time required to find a stable intrafascicular recording site of this sort varied from about 1

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minute to 2–3 hours. In some experiments sympathetic signals of comparatively high amplitude were obtained from several recording sites in different muscle nerve fascicles, whereas in other experiments only low-voltage SPGs were obtained in spite of extensive probing. Undoubtedly a large element of luck was involved in finding a good recording site. However, it appeared to be somewhat easier to find recording sites with a good signal-to-noise ratio in subjects above the age of 40 (3).

Resting Activity Related to Spontaneous Blood Pressure Fluctuations.—It is generally accepted that pulse-synchronous grouping of sympathetic impulses is brought about by inhibitory influences from arterial baroreceptors elicited by each systolic blood pressure wave (8–11). In agreement with this assumption, we found, for each particular recording site, a constant reflex delay between each short pause between succeeding neural bursts and a preceding systolic pressure wave. Furthermore, simultaneous recordings of nerve activity and intra-arterial blood pressure showed that the waxing and the waning of the sympathetic bursts correlated closely with the spontaneous fluctuations in blood pressure. Thus, the periods of enhanced pulsatile neural activity were preceded by temporary blood pressure reductions, whereas the periods of neural silence were preceded by blood pressure elevations. When the reflex delay (1–1.5 seconds) was compensated for, it was clear that the profile of the muscle SPG reflected the systemic blood pressure variations like an inverse mirror image. A temporal correlation was also observed between the sympathetic burst sequences and the succeeding blood pressure elevations: after compensation for a delay of 3–5 seconds, a definite similarity in the profile of the two curves was noted (Figs. 1 and 3). These findings illustrate how during resting conditions the sympathetic outflow to skeletal muscles participates in the systemic blood pressure control via a closed negative feedback loop. In recordings of this type lasting for several hours, we occasionally observed transient changes in neural outflow that were not correlated with preceding blood pressure fluctuations, but, on the whole, for each individual the correlation was stable enough to permit an approximate evaluation of the blood pressure level required to cause a complete suppression of the sympathetic bursts. This blood pressure level varied slightly during the course of an experiment, but, as judged from records with an optimal signal-to-noise ratio, values within the range of 120 to 150/70 to 90 mm Hg were common.

The results agree with the notion that the bursts were composed mainly of vasoconstrictor impulses. This idea was confirmed by the finding that maneuvers causing changes in muscle nerve sympathetic activity generally caused parallel changes in vascular resistance.

Maneuvers Causing Changes in Muscle Nerve Sympathetic Activity.—The muscle nerve sympathetic activity was affected by several different maneuvers (4). During Valsalva’s maneuver and mental stress the changes in sympathetic outflow were inversely related to the changes in blood pressure, i.e., the changes in neural activity appeared to be brought about by baroreflex effects (such reactions are illustrated in Figs. 5 [left] and 6A, which show the outcome of Valsalva’s maneuver and mental stress, respectively). During Valsalva’s maneuver, systolic blood pressure always decreased and a concomitant increase in sympathetic outflow occurred. Mental stress usually was associated with an increase in blood pressure and a concomitant decrease in pulsatory nerve activity.

In contrast, during muscle work and hyperventilation parallel changes in blood pressure and sympathetic outflow were observed. During muscle work, there was an increase in both blood pressure and sympathetic activity in nerves to muscles not engaged in the work, and at the same time a reduction in forearm blood flow occurred. However, superimposed on these parallel changes, the usual
inverse relationship between the spontaneous rhythmic fluctuations in the SPG and the blood pressure curve persisted. Therefore, although the general increase in sympathetic activity during muscle work could not be explained as a baroreflex response, the results suggest that the baroreflex nevertheless operated during the maneuver. Hyper-ventilation was performed only twice in normal subjects; in both cases a simultaneous reduction in blood pressure and muscle nerve sympathetic activity occurred.

MUSCLE NERVE SYMPATHETIC ACTIVITY IN HYPERTENSIVE SUBJECTS

General Characteristics of Resting Activity.—In 21 of 22 muscle nerve fascicles in 14 hypertensive subjects the sympathetic impulses appeared in sequences of pulse-synchronous bursts similar to those in normal subjects. It was impossible to decide from the muscle nerve SPG whether the subject was hypertensive or not. In one fascicle the pulse-synchronous bursts were intermingled with other bursts that appeared to be unrelated to the pulse rhythm. However, a similar aberrant pattern was seen in a healthy subject, and it probably only signified that the impaled muscle nerve fascicle was not “pure” but also contained sympathetic fibers destined for the skin.

As in normotensive subjects, the strength of the sympathetic bursts varied with the intrafascicular recording site. On the whole, muscle nerve sympathetic activity with an acceptable signal-to-noise ratio was obtained about as easily in the hypertensive subjects as it was in the controls. As in the healthy subjects, less probing seemed to be required to find sympathetic activity with a good signal-to-noise ratio in the subjects over 40 years old.

One of the tests employed to prove the sympathetic origin of the nerve signals in the normotensive subjects was to show that the activity was reversibly blocked by a sympathetic ganglionic blocking agent. Such tests were carried out on two hypertensive subjects while recording from muscle nerves, and in both cases the pulse-synchronous bursts of impulses were almost totally abolished during intravenous infusion of Trimetaphan but returned a few minutes after the end of the infusion.

In one subject a simultaneous recording was made from muscle nerve fascicles in both the left and the right peroneal nerves. For technical reasons the double recording lasted only 10 minutes, but during this time there was a remarkable similarity between the two records. As shown in Figure 2 almost every single sympathetic burst could be identified in both nerves. Even the profiles of the two curves were remarkably similar, i.e., the variations in amplitude of successive bursts were in parallel in the two nerves.

Resting Activity in Relation to Spontaneous Blood Pressure Fluctuations.—Simultaneous recordings of muscle nerve SPGs and intra-arterial blood pressure were made in nine experiments on seven hypertensive subjects. The profiles of the SPGs were related to the profiles of the blood pressure curves in a way similar to that for the normotensive subjects. Thus, most sympathetic bursts appeared during temporary blood pressure reductions, whereas transient increases in blood pressure inhibited the sympathetic outflow. There was, however, a clear difference between the two groups with respect to the blood pressure level required to cause a complete suppression of the outflow. In normal subjects this inhibition usually took place when the blood pressure exceeded 120-150/70-90 mm Hg, but the corresponding figures for hypertensive subjects were 150-200/100-120 mm Hg. This finding is clearly shown in Figure 3 where the inhibition occurred at approximately 145/80 mm Hg in the normotensive subject and 190/115 mm Hg in the hypertensive subject. The figure also illustrates that in spite of the difference in the inhibitory blood pressure level there was no major difference in the magnitude or the speed of the transient spontaneous blood pressure elevations necessary to inhibit the sympathetic bursts. Consequently, the results indicate that in subjects with hypertension the static systolic blood pressure level may be increased by 70-80 mm Hg without causing an appreciable long-lasting inhibition of baroreflex-controlled sympathetic outflow but that the outflow is nevertheless effectively inhibited by dynamic blood pressure changes of 10-20 mm Hg.

FIGURE 2

Examples of records from simultaneous recordings of muscle nerve sympathetic activity at rest from the left and the right peroneal nerves in subject 14, who had essential hypertension.
Representative examples of the relationship between muscle nerve sympathetic activity and blood pressure in a normotensive and a hypertensive subject (no. 18). Top: Respiratory movements (inspiration upwards). Middle: Integrated muscle nerve sympathetic activity recorded in the right peroneal nerves in both cases. Bottom: Blood pressure. Note that blood pressure calibrations are identical in the normotensive and the hypertensive case, whereas the neurograms are uncalibrated and have been aligned in an arbitrary way (also applies to Figs. 5 and 8).

As in normotensive subjects, the inhibitory blood pressure level varied somewhat during each experiment. In addition, some sympathetic bursts were seen which were not preceded by clear blood pressure reductions. The variations and aberrations were particularly common in some of the recordings in which the sympathetic activity was unusually strong and persistent. In the example shown in Figure 4, it is rather difficult to observe a clear-cut inverse relationship between blood pressure variations and sympathetic activity. However, in other parts of the recordings from the same subjects, especially when the blood pressure variations were more distinct than those in Figure 4, the usual inverse relationship was easy to distinguish. Further work would be required to make a quantitative analysis of the variability and to decide whether the variability is more pronounced in the hypertensive subjects than it is in the normotensive subjects.

One hypertensive subject (no. 10) was investigated three times, once before therapy and twice (2 weeks and 10 months) after treatment with propranolol had been initiated. The first two investigations were made when the subject was hospitalized, but on the last occasion she had been out of the hospital for 9 months and had resumed her normal work. During the first recording session resting blood pressure was 215/140 mm Hg, during the second 160/85 mm Hg (drug dose 400 mg/day), and during the last 185/100 mm Hg (drug dose 640 mg/day). In spite of the marked differences in blood pressure before and after therapy and the rather large doses of propranolol used, no significant changes in the character of the sympathetic activity were noted. In all three investigations it was comparatively easy to get SPGs with a high signal-to-noise ratio.

Maneuvers Causing Changes in Muscle Nerve Sympathetic Activity.—Because of technical difficulties head-up tilting was performed only occasionally, and in these cases the results were similar to those found in normotensive subjects. The sympathetic activity in peroneal muscle nerve fascicles increased in strength when the subject was tilted from horizontal to a more upright position. Valsalva’s maneuver was performed 19 times, and 13 times the intra-arterial blood pressure was monitored simultaneously. In all cases the sympathetic responses had the same highly characteristic pattern seen in normal subjects (Fig. 5); after an initial inhibition usually lasting 5-7 seconds, the sympathetic activity increased considerably until it was inhibited again a few seconds after the end of the maneuver. As shown in Figure 5, the increase in the activity corresponded to the period of decreased systolic blood pressure. Usually, the increased activity during the maneuver was of the common pulse-synchronous type. However, as in normotensive subjects, a few cases were seen in which the pulsatory inhibitions became less marked so that the sympathetic activity during the maneuvers appeared as a more continuous irregular discharge.

The effect of mental stress was studied 15 times in nine experiments while recording from a muscle nerve. Blood pressure was monitored during 13 of the tests. The results were rather variable. During
four periods of mental stress in three experiments the sympathetic activity decreased at the same time that the blood pressure increased; this same type of reaction occurred in most of the normotensive subjects. This type of reaction is shown in Figure 6B. During four stress periods in two experiments the sympathetic activity increased slightly in parallel with a slight increase in blood pressure (Fig. 6C). However, two of these tests were associated with alterations in heart rhythm which might have affected the results (Wallin and Delius, unpublished observation). In the remaining seven cases no significant change in muscle nerve sympathetic activity was observed. Blood pressure increased slightly in one case, did not change in another case, showed a slight decrease in three cases (one subject), and was not monitored during the last two stress periods.

Muscle work was performed on 14 occasions in seven subjects while recording from a muscle nerve innervating a muscle not engaged in the work. The results agreed with those seen in normotensive subjects: the sympathetic activity increased in 11 cases, no change occurred in 2 cases, and a decrease in activity was seen in the remaining case. Blood pressure was monitored during 13 of the work periods and increased in all cases. The increase in sympathetic activity was rather weak in some cases and quite pronounced in others. In one case the strength of the contraction was suddenly increased in the middle of the work period; at the same time the strength of the bursts increased.

Changes in the respiratory rhythm often affected the muscle nerve sympathetic activity. Deep slow breathing could initiate large blood pressure fluctuations, and, since each transient reduction in blood pressure was associated with an increase in nerve activity, this type of breathing sometimes seemed to cause an overall increase in the sympathetic outflow to the vascular bed of skeletal muscle. True hyperventilation was performed in three cases. Blood pressure was recorded during two of these periods. In both cases the blood pressure was reduced, but in one the sympathetic activity increased and in the other it remained unchanged. In the third case, a slight reduction in the sympathetic bursts was noted.

**SKIN NERVE SYMPATHETIC ACTIVITY IN NORMOTENSIVE SUBJECTS**

Resting Activity.—The spontaneous multiunit sympathetic activity recorded in skin nerves dif-
fered in several respects from muscle nerve sympa-
thetic activity (5). The nerve impulses were
集团 in synchronized bursts, but these barrages
had a longer, more varied duration than that
characteristic of muscle nerves and they occurred
more randomly without correlation with the heart
rhythm. During rest the occurrence of the bursts
was not correlated with spontaneous blood pressure
variations, but it was common to find some
correlation with the respiratory rhythm. This
coupling to the respiratory rhythm was, however,
rather loose, and the burst sequences usually
continued uninterrupted during apneic periods. The
difference in pattern between muscle and skin nerve
SPGs is illustrated in Figure 1. The pattern of
activity was similar in skin nerves in upper and
lower extremities, and no difference was found
between fascicles innervating glabrous or hairy
skin. As with muscle nerves, the strength of the
activity varied widely between different recording
sites. In contrast to our experience from muscle
nerve recordings, there seemed to be no correlation
between the amount of probing required to find
skin nerve sympathetic activity with a good signal-
to-noise ratio and the age of the subject.

In two experiments (one normotensive and one
hypertensive subject) simultaneous recordings of
skin nerve sympathetic activity were made from
two leg nerves. The results were similar in both
experiments, and Figure 7 shows an example of the
results from the normotensive subject. The record
contains a mixture of spontaneously occurring and
triggered sympathetic bursts. On the whole, the
tracings from the two nerves were very similar.

Simultaneous recordings of skin nerve sympathet-
ic activity and skin electrical resistance, measured
within the receptive field of the impaled fascicle,
revealed that many of the spontaneous sympathetic
bursts after a latency of 1-1.5 seconds were
followed by transient decreases in skin electrical
resistance. In other experiments it was found that

some sympathetic bursts led to transient changes in
the pulse plethysmogram recorded from a finger
innervated by the impaled fascicle (5).

From these findings it was concluded that the
sympathetic activity recorded in skin nerves con-
isted of a mixture of sudomotor and vasoconstric-
tor impulses. The lack of pulse synchrony in the
neurogram and the poor correlation between blood
pressure variations and sympathetic activity sug-
gested that the impulses were not subjected to
baroreflex control.

Maneuvers Causing Changes in Skin Nerve
Sympathetic Activity.—In contrast to the findings in
muscle nerves, a burst of skin nerve sympathetic
activity could be triggered by stimuli such as a deep
breath, an electric shock against the skin (applied
anywhere on the body surface), a sudden sound, a
sudden touch of the skin of the subject, etc. The
triggered bursts, which often were stronger than the
spontaneous ones, appeared after a latency of about
0.5 seconds (when recording from the median
nerve at the elbow) and had a duration of 1-1.5
seconds. However, all stimuli were not equally
effective in all subjects. A deep breath or an electric
shock against the skin evoked strong reflex re-
sponses in most subjects, but only a few subjects
responded to skin taps. In addition, the strength of
the response could sometimes be affected by the
state of attention of the subject, the stimulus
repetition rate, etc. In general, the more unexpected
and novel a stimulus was, the more intense was the
response.

Related to this finding was the observation that
the intensity of the spontaneous sympathetic
activity often was correlated with the emotional
state of the subject. In general, the activity
decreased when the subject was relaxed and
comfortable but increased during periods of mental
stress. Figure 8 (left) shows an example of the
changes in sympathetic activity and blood pressure
when a resting subject suddenly was asked to
perform mental arithmetic. Simultaneous measure-
ments of hand blood flow showed that this type of
increased neural activity could be accompanied
either by an increase or a decrease in vascular
resistance. Similar nervous responses were also
elicited in other situations (the subject talking,
somebody entering the room, the subject being
offered a cup of coffee, etc.). In fact almost any
type of stimulus could lead to an increase in skin
nerve sympathetic activity. Usually the neural
reaction ended soon after the end of the stimulus,
but occasionally it lasted for several minutes.
Examples of the effects of mental stress on skin nerve sympathetic activity in a normotensive subject and in a hypertensive subject (no. 7). The stress situation was brought about by unexpectedly asking the subject to solve an arithmetic problem. The top three tracings are the same as in Figure 3, and the bottom trace is heart rate.

Room temperature also affected the intensity of the sympathetic outflow, and usually the activity increased when the subject was cooled and decreased when he was warmed. Cigarette smoking led to an increased skin nerve sympathetic activity which could last for several minutes after the end of the smoking period.

As mentioned above, changes in body position and Valsalva's maneuver were effective in changing muscle nerve sympathetic activity. In contrast, these maneuvers had no reproducible effect on skin nerve sympathetic activity, supporting the view that baroreflex control is of minor importance in the regulation of sympathetic outflow to the skin.

SKIN NERVE SYMPATHETIC ACTIVITY IN HYPERTENSIVE SUBJECTS

Resting Activity.—Skin nerve sympathetic activity was recorded in 21 fascicles in 14 hypertensive subjects. In all cases the pattern of activity was similar to that found in normal subjects and gave no indication that the hypertension was associated with a qualitatively altered sympathetic outflow to the skin. As in normal subjects, the strength of the activity varied considerably between different fascicles and between different subjects, but there was no obvious correlation between the age of the patient and the difficulty involved in finding skin nerve sympathetic activity of high amplitude. On the average, it seemed easier to find spontaneous skin nerve sympathetic activity with a good signal-to-noise ratio in hypertensive subjects than it was in normal subjects, but some exceptions did occur. In one hypertensive subject we were not able to find any skin nerve sympathetic activity at all. In two subjects, an intravenous infusion of a ganglionic blocking agent (Trimetaphan) was given, and as expected the sympathetic activity was markedly reduced during the infusion.

Intra-arterial blood pressure was monitored during recordings from seven skin nerve fascicles in four hypertensive subjects, and as in normal subjects there was no correlation between the spontaneous variations in blood pressure and the occurrence of the sympathetic bursts. In one case nerve activity was monitored in parallel with skin electrical resistance, measured in the receptive field of the impaled fascicle. The results did not differ from those for normal subjects; after a latency of about 1 second many spontaneous sympathetic bursts were followed by transient decreases in skin resistance lasting up to 5-10 seconds. When several bursts occurred with short intervals, the variations in skin resistance merged and the correlation to nerve activity became more difficult to observe.

Maneuvers Causing Changes in Skin Nerve Sympathetic Activity.—No qualitative differences were noted between the normotensive and the hypertensive subjects with regard to the reflex bursts of sympathetic impulses triggered by a deep breath or by various arousal stimuli. It was also evident that the strength of the sympathetic outflow in the hypertensive subjects increased during stress situations and decreased during mental relaxation. Fairly well-defined periods of mental stress were elicited 23 times in ten hypertensive subjects (usually by asking them to perform mental arithmetic). In all cases except one, an increase in the strength of the activity occurred. Figure 8 (right) shows an example from one of the ten tests made during continuous monitoring of the intra-arterial blood pressure. As in normotensive subjects, the increase in activity often ended when the subject was instructed to relax again after the test. In other cases, however, the increase did not recede completely until minutes later.

Cigarette smoking and body cooling were each tested in one subject, and the results were qualitatively similar to those observed in normotensive subjects.

Discussion

THE MATERIAL

Apart from two cases (hypertensive subjects 10 and 18) in which secondary hypertension could not be excluded, the hypertensive subjects in this study had essential hypertension. As evident from Table 1 the known duration of the hypertension varied widely. However, although many subjects showed slight hypertensive retinal changes, only a few of
them had roentgenological or other signs of cardiovascular complications. The majority was classified as hypertension stage I according to the criteria proposed by the World Health Organization. The age limits of the normotensive and the hypertensive groups were similar, but the mean age for the two groups was different. It is important to minimize such unequal age distributions in future quantitative studies of sympathetic activity in normotensive and hypertensive subjects, particularly since the present study gives some hints that age may well be a determinant for the amplitude of the SPGs led off from the peripheral nerves. Both in healthy subjects and in subjects with hypertension the functional characteristics of the cardiovascular system are known to change with age (12-15). If there are any neural correlates with some of these changes, they are presumably of a quantitative rather than a qualitative nature. In the present study no age differences were noted with respect to the temporal patterns of the resting sympathetic rhythms and the signs of the SPG responses to various maneuvers.

**SPG Patterns in Normotensive and Hypertensive Subjects**

Once a selective sympathetic activity recording site has been found in a skin or a muscle nerve fascicle, the integrated nerve record will give a semiquantitative measure of the consecutive variations in strength of the sympathetic activity within the pickup range of the electrode tip (16). In this connection it is of interest to note that there were great similarities between SPGs obtained simultaneously from two different skin nerves or two different muscle nerves. This finding clearly indicates than an SPG from one particular recording site in a peripheral nerve fascicle in quite a representative way illustrates how the sympathetic outflow fluctuates and changes not only in the fascicle impaled but also in other fascicles destined to the same type of effector organs.

The double nerve recordings illustrated that the recording technique was well suited for analysis of both fast and slow temporal variations in sympathetic activity. Thus, one might expect that an SPC pattern analysis would yield information about disturbances in the control mechanisms governing the sympathetic outflow. In the present study visual inspections of a great number of muscle and skin SPGs provided no evidence that the SPG patterns in hypertensive subjects were significantly different from those in normotensive subjects. In both groups of subjects, pulse-synchronous grouping of the impulses was a typical characteristic of muscle nerve sympathetic activity, whereas in skin nerves the impulses occurred in more irregular bursts of varying duration. The pulse-synchronous grouping of the sympathetic volleys was as distinct in the hypertensive subjects as it was in the control subjects, suggesting that in hypertension phasic, pulse-driven, baroreceptor volleys are potent inhibitors of the sympathetic outflow. Since both the pattern of activity at rest and the nerve responses to different maneuvers were qualitatively similar regardless of the subject's blood pressure, it seems likely that the multiunit sympathetic activity found in muscle and skin nerves of hypertensive subjects was made up of impulses from the same fiber population as it was in normotensive subjects and that the outflow of these impulses was controlled by similarly operating mechanisms in the two groups.

**Relationship between Blood Pressure and Muscle Nerve Sympathetic Activity during Rest**

In normotensive subjects both the pulse synchrony in the neurogram and the intimate relationship between variations in the strength of the sympathetic activity and the corresponding blood pressure fluctuations suggest that the sympathetic outflow to the vascular bed of skeletal muscle is controlled by arterial baroreflex mechanisms (3). In the present investigation, similar observations were made on hypertensive subjects. In both normotensive and hypertensive subjects transient blood pressure increases of 10-20 mm Hg were sufficient to cause complete suppression of the pulse-synchronous sympathetic volleys. These findings are in agreement with many previous observations that baroreceptive vasomotor responses can be elicited in subjects with hypertension (17-19). However, although baroreflex modulation of the sympathetic outflow to the vascular bed of skeletal muscle was present in hypertensive subjects, the working range of the baroreflex mechanisms seemed to be altered. In resting normotensive subjects, muscle nerve sympathetic activity was inhibited by random transient blood pressure increases above a level of about 120-150/70-90 mm Hg, whereas in hypertensive subjects the corresponding total inhibition occurred at a level of 150-200/100-120 mm Hg. This finding does not imply that in each subject muscle nerve sympathetic activity was inhibited at a certain well-defined, constant blood pressure level. Both in normotensive and hypertensive subjects we noted variations in the inhibitory blood pressure level both at rest and during various maneuvers. Further quantitative studies are needed.
to find out if such variations in the baroreflex working range are equally pronounced in normotensive and hypertensive individuals.

The present results agree with previous hemodynamic studies in man which indicate that the baroreflex working range is elevated in hypertension (19, 20). The locus of this change may be at the baroreceptor level, since changes in baroreceptor threshold or sensitivity following a sustained increase in blood pressure are well known from animal experiments (21-23). In rats with experimental hypertension due to subdiaphragmatic aortic constriction, such an adaptation or resetting has been shown to develop within 24-48 hours after the blood pressure increase (24). However, a pressure receptor adaptation that involves dynamic and static sensitivity to an equal extent can hardly account for the present findings, since in the hypertensive subjects there was no apparent reduction in the dynamic sympathetic reactions to small transient blood pressure changes. To explain the present results in terms of changes in baroreceptor function, one has to assume that the static receptor sensitivity is comparatively more affected than the dynamic receptor sensitivity.

One could also account for the present findings by assuming that an increased inhibitory inflow from the baroreceptors in the hypertensive subjects was compensated for by central adjusting mechanisms that prevented a complete sympathetic silence, for instance by increasing the background level of the central excitatory drive on which the baroreflex inhibitions play.

The possibility should also be considered that, at least in some subjects, the elevated pressure was a consequence of a centrally induced resetting of the baroreflex working range. Such central resetting of arterial baroreflexes is known from animal experiments (25), and its possible relationship to essential hypertension has been discussed by Korner (26). That hypothalamic influences may cause blood pressure elevations is a well-documented fact (27), and in recent studies interaction between hypothalamic defense reactions and baroreflexes has been demonstrated (28, 29).

**THE MANEUVERS**

On the whole the sympathetic responses elicited by the maneuvers were qualitatively similar to those encountered in normotensive subjects. This finding is in agreement with previous hemodynamic data showing that various maneuvers give rise to qualitatively similar alterations in peripheral blood flow in normotensive and hypertensive individuals (30, 31). The only unusual effects noted in the present investigation were two cases in which mental arithmetic led to a slight increase in muscle nerve sympathetic activity (Fig. 6C) instead of the usual inhibition and one other case in which muscle work led to a decrease instead of an increase in muscle nerve sympathetic activity. These aberrations from the common pattern are interesting, but they are exceptional findings; a significant relationship to hypertension seems unlikely. Our experience from recordings on healthy subjects is still limited, and we cannot exclude the possibility that the unusual sympathetic reactions were normal variations brought about by some unknown circumstance, perhaps related to the fact that most maneuvers involve several different stimuli interacting in a complex fashion. In support of this view the inhibitory response during muscle work has recently been observed in a healthy normotensive subject.

**QUANTITATIVE EVALUATION OF THE SYMPATHETIC OUTFLOW**

It would obviously be of considerable interest to compare the absolute strength of the sympathetic outflow in the hypertensive and the normotensive groups, since such a comparison could give an indication of the strength of the vasoconstrictor drive to the peripheral blood vessels. It should be recalled, however, that with the present multunit recording technique the size of the signals in any particular neurogram does not provide a reliable measure of the absolute number of sympathetic impulses transmitted per unit time within the impaled fascicle (3). The signal size depends on the electrode characteristics and the distance between the electrode tip and the active sympathetic fibers. Therefore, standardized recordings from a large number of randomly chosen electrode sites are necessary to obtain a valid measure of the overall strength of the resting sympathetic outflow to skin and muscles in any particular individual. In view of these considerations our observations that skin nerve SPCs with a good signal-to-noise ratio were easier to find in hypertensive subjects than in normotensive subjects and that muscle nerve SPCs with a good signal-to-noise ratio were easier to find in subjects over the age of 40 must be considered as preliminary. Still these observations may serve as a guide for planning future studies aimed at a true quantitative evaluation of sympathetic activity in hypertensive and normotensive persons. In such studies the following two questions may be raised. If there really is an increased sympathetic outflow...
to the skin in hypertensive subjects, does this reflect an increased responsiveness in stress situations? Continuous monitoring of blood pressure has shown that many hypertensive subjects react with greater blood pressure elevations than do normotensive subjects to different stimuli encountered during normal daily activities (32, 33). Therefore, quantitative determinations of the magnitude of the sympathetic response in relation to the blood pressure changes during various maneuvers in normotensive and hypertensive individuals would be of great interest. The present recording technique seems suitable for studies of this sort, since for each individual the comparison would involve an evaluation of consecutive changes in strength of the sympathetic activity in an unchanged electrode position. Is there a decreasing baroreflex inhibition of muscle nerve sympathetic activity with increasing age? If so, are there any quantitative differences between hypertensive and normotensive individuals in this respect? Gribbin et al. (20) have found a decreased baroreflex sensitivity in man with increasing age, and histological investigations on man have shown degeneration of both baroreceptors and other wall elements in the carotid sinus with increasing age (34, 35). Hemodynamic data concerning skeletal muscle vascular resistance at different ages are few and somewhat inconclusive, but the tendency seems to be an increasing vascular resistance with increasing age both in normotensive and hypertensive subjects (13, 14). Although structural changes may be involved, an increased strength of sympathetic vasoconstrictor outflow could partly explain such findings.

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References


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