Sympathetic Activity and Blood Pressure Increases With Bladder Distension in Humans

Jan Fagius and Sakari Karhuvaara

Microneurographic recordings of muscle nerve sympathetic activity, which is governed by baroreceptors and involved in blood pressure regulation, were made in the peroneal nerve in 16 healthy volunteers during physiological bladder distension. When the urge to urinate was pronounced, sympathetic outflow increased from a baseline level of 16.3±1.7 to 23.2±1.9 bursts/min (mean±SEM, p<0.01). There was a concomitant significant rise in both systolic and diastolic blood pressure, from 125±2/74±2 to 140±4/84±3 mm Hg. After micturition, sympathetic activity and blood pressure returned toward initial values. It is concluded that 1) increased sympathetic outflow contributed to the rise in blood pressure, 2) there is a vesicovascular response mediated by sympathetic vasoconstrictor neurons in humans corresponding to mechanisms observed in animals, and 3) the described functional relation between bladder distension and sympathetic vasoconstrictor activity probably plays a role in clinical conditions such as autonomic dysreflexia in humans with cervical spinal cord lesions and nocturnal micturition syncope. (Hypertension 1989;14:511–517)

Well-known clinical conditions, such as autonomic dysreflexia with hypertensive spells in patients with cervical spinal cord lesions1-2 and nocturnal micturition syncope in apparently healthy subjects,3 indicate the existence of a functional relation between urinary bladder distension and blood pressure regulation. In animal experiments, reflex increase in arterial pressure and peripheral vascular resistance can be elicited by bladder filling,4-9 and this pressor effect coincides with increased outflow in sympathetic nerves.10,11 Little is known, however, about the influence of bladder filling on the sympathetic vasoconstrictor outflow to resistance vessels in normal humans.

Microneurography allows direct recording of sympathetic nerve traffic in nerves in the extremities in humans12 and has shown sympathetic impulses in muscle nerves to be vasoconstrictor signals governed by baroreceptor reflexes and involved in cardiovascular homeostasis.13 Occasional observations in our laboratory of simultaneous increases in sympathetic activity and blood pressure in subjects with a desire to void prompted a study of the effect of increasing physiological distension of the urinary bladder on muscle nerve sympathetic outflow and blood pressure.

Subjects and Methods

Sixteen healthy, normotensive subjects, seven women and nine men, 21–39 years old (mean 26 years) participated in the study after informed consent was obtained. The nerve recordings were approved by the Ethics Committee of the Medical Faculty of Uppsala University.

Nerve Recordings

A tungsten microelectrode, with a diameter of about 5 μm at the uninsulated tip, was inserted manually through the intact skin into the right peroneal nerve at the fibular head. A low impedance reference electrode was placed subcutaneously 2 cm away. The nerve was localized by means of electrical stimuli delivered through the recording electrode. A position within a muscle nerve fascicle is characterized by muscle twitches after electrical stimuli with no concomitant skin paresthesia and by afferent activity from muscle spindles occurring when the appropriate muscle is stretched or tapped. When the nerve fascicle had been identified, minor adjustments of the electrode were made until the characteristic multiunit bursts of muscle nerve sympathetic activity (see Figure 1) were encountered. The search for an acceptable recording position took from 5 to 50 minutes. The criteria for the
sympathetic origin of the signal recorded have been summarized previously.\textsuperscript{13}

Minor discomfort may have been experienced by the subject during the search for the recording position, but once this was found, there was no discomfort during the continuous recording. Transient slight paresthesia in the innervation zone of the nerve may occur a few days after the experiment, but none of the present subjects reported any side effects on a letter follow-up.

The nerve signal was amplified in two steps, with a total gain of $\times 50,000$, and fed through a 700–2,000 Hz bandpass filter and an amplitude discriminator for optimal signal-to-noise ratio. A resistance-capacitance integrating network with time constant of 0.1 second delivered a mean voltage neurogram, which was used for display and analysis of the nerve activity (the relation between discriminated original and the mean voltage neurogram is illustrated in Figure 1).

Electrocardiogram (ECG) was recorded by chest electrodes and respiratory movement by a strain gauge strapped around the chest with an elasticized band.

All recorded signals were displayed on a storage oscilloscope during the experiment, and the nerve signal was also fed through a loudspeaker. The signals were stored on tape (FM tape recorder, Sangamo Weston-Schlumberger, Sarasota, Florida) for subsequent analysis.

**General Procedure**

The experiments took place at 8:00 AM. The subjects were instructed not to smoke after midnight, to empty the bladder as usual on awakening, and to eat no breakfast but to drink 3–4 dl tea. In a first series of experiments ($n=11$), subjects were lying comfortably supine on a bed in a laboratory with an ambient temperature of 22–24° C. When an intraneural electrode position with acceptable signal-to-noise ratio was found (accounting for 10–60 minutes), the basal level of nerve activity was followed during 15 minutes of rest. Thereafter, the subjects were given water to drink (through a straw in the supine position), 2 dl at a time with intervals of 5–10 minutes until a moderate degree of bladder filling was felt; the amount of water given ranged from 2 to 20 dl, mean 9.5 dl. The recording then went on during supine rest until the urge to empty the bladder was irresistible, and the experiment was discontinued. A second series of experiments comprised five male subjects who sat in a semirecumbent position during the recording and who had a condom catheter applied before the recording; the
same procedure took place as in the first experiment. Thus, the subjects were able to void without interruption of the nerve recording, and thereafter the recording was continued at rest for about 10 minutes.

Blood pressure was measured noninvasively with an automatic blood pressure recorder (EME Ltd, Brighton, U.K.) every third minute throughout the experiment and every minute during the final phase. In the five male subjects who emptied the bladder during ongoing recording, noninvasive continuous finger arterial blood pressure monitoring (Finapres, Ohmeda, Englewood, Colorado) was also used.

In seven subjects of the first series, blood samples for plasma norepinephrine analysis were drawn during initial rest and when the subject assessed that he could wait only another 5 minutes before emptying the bladder; an intravenous cannula was inserted into an antecubital vein for this purpose before the nerve recording was initiated.

The subjects were instructed to relax and to indicate the increasing degree of the sensation of bladder filling on an analogue scale, with 0 representing a complete lack of this sensation and 10 representing an irresistible desire to void.

**Plasma Norepinephrine Assay**

Blood samples were collected into prechilled EDTA tubes, placed on ice immediately, and centrifuged promptly at +4°C. Plasma samples were stored at −70°C until analyzed. Plasma norepinephrine was determined with high-performance liquid chromatography (HPLC) with colorimetric detection. The method has an intra-assay coefficient of variation of 2% in the physiological concentration range.

**Result Analysis**

The mean voltage neurogram, ECG, respiratory movements, and finger arterial pressure were written out on paper, 2.5 mm/sec, with an ink-jet recorder (Siemens-Elema, Stockholm, Sweden). The bursts of muscle nerve sympathetic activity, time-locked in the cardiac rhythm (see Figure 1), were counted during 10 minutes of initial rest, during the last 6 minutes before micturition, and during 6 minutes at rest after micturition in the five experiments where the recording continued. Thus, a mean value of sympathetic outflow, expressed in bursts per minute, was calculated during the periods under study for each subject. Heart rate and respiratory rate were obtained from the same paper display. Because the two experimental series provided the same result, they were analyzed together (n=16); a separate analysis of the second series (n=5) was made only for assessment of final rest after micturition.

The burst amplitude in the mean voltage neurogram, reflecting the strength of individual bursts of sympathetic activity, is critically dependent on the electrode position intraneurally, and cannot be compared between different recordings. Within a given recording, however, burst amplitude can be compared between different parts of the recording, provided the intraneural electrode site remains unchanged. Therefore, mean burst amplitude for the periods of initial rest and during strong urge to urinate was calculated as the mean of 50 consecutive bursts during that period for each subject. The measurement was made, in arbitrary units, on a digitizing board (Hipad, Houston Instruments, Austin, Texas) connected to a computer (Digital MicroVAX II, Digital Equipment, Maynard, Massachusetts). The product of this mean amplitude and the number of bursts per minute was used as a measure of “total” muscle nerve sympathetic outflow (expressed as arbitrary units/min) for the period.

Blood pressure for each subject was calculated as the mean of five to six consecutive individual measurements during the period under analysis.

Results are expressed as mean±SEM. Statistical analyses applied were Student’s t test for paired and unpaired samples, analysis of variance (ANOVA) with multiple comparisons, linear regression analysis, and the nonparametrical Spearman correlation test.

**Results**

The observed changes in sympathetic outflow and blood pressure are exemplified in Figure 1 and summarized in Figure 2.

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Graphs showing changes of (from top to bottom) systolic and diastolic blood pressure (BP), heart rate, and muscle nerve sympathetic activity (MSA) from control period (A) to bladder distension period (B). Mean±SEM. *p<0.05; **p<0.01; ***p<0.001.
As expected, the individual level of sympathetic outflow showed a wide range at rest, from 4 to 35 bursts/min, with a mean of 16.3±1.7 bursts/min. With increasing sensation of bladder distension, there was an increase in sympathetic outflow in all subjects but three; mean outflow was 23.2±1.9 bursts/min during the last phase of the recording (p<0.01). Individual changes in sympathetic activity ranged from -3 through +22 bursts/min. The burst amplitude increased in eight subjects (see Figure 1) and remained virtually unchanged in eight. Total sympathetic outflow (i.e., with the effect of burst amplitude included) increased from 167±18 at rest to a final level of 283±34 arbitrary units/min (p<0.01).

In those subjects exhibiting an increase in sympathetic outflow, this was not observed until a sensation of bladder filling corresponding to 7–8 on the analogue scale was reported. The increase was not associated with any symptom other than that of bladder distension.

During the late phase of the recordings, a few subjects had brief periods of muscle tension that were detected as electromyographic artifacts in the nerve recordings and were easily controlled by the subjects when requested to relax. Such periods were not included in the analysis; the total time of analysis of the late phase was always 6 minutes. The episodes of muscle tension did not change the intraneural electrode position in any instance.

Both systolic and diastolic blood pressure were elevated, from a resting level of 125±2/74±2 to 140±4/84±3 mm Hg with urge to urinate (p<0.001 for both). Neither blood pressure increase was observed until the sensation of bladder filling was relatively pronounced, 7–8 on the analogue scale. Mean heart rate increased slightly but significantly from 66 to 70 beats/min (p<0.05; Figure 2). Mean respiratory rate did not change. However, one subject exhibited a considerable increase and another a decrease in respiratory rate when the urge to void was felt (from 9 to 16 and from 14 to 7 breaths/min, respectively); in both these subjects there was an increase in muscle nerve sympathetic activity.

One subject exhibited short-lasting increases (30–50 seconds) in sympathetic activity immediately after each intake of 2 dl water (Figure 3), whereas no change was observed in the nerve recording that coincided with the drinking in all other subjects.

Venous plasma norepinephrine (n=7) rose from an initial value of 1.25±0.19 to a final concentration of 1.50±0.26 nmol/l (NS). Linear regression analysis of individual changes in muscle nerve sympathetic activity and plasma norepinephrine revealed an r value of 0.63 (n=7, NS).

There was no correlation between the increases in sympathetic activity and blood pressure (Figure 4).

After micturition, sympathetic activity and blood pressure returned toward initial levels (Figure 5). All five subjects who urinated during ongoing sympathetic recording had to strain to a minor degree to initiate micturition in the semirecumbent position. The duration of micturition ranged from 1 to 2.5 minutes, and the urine volume ranged from 400 to

---

**Figure 3.** Tracings showing temporary increase in muscle nerve sympathetic activity (MSA) after water intake (indicated by horizontal bar) in one subject. Respiration (Resp), electrocardiogram (ECG), and mean voltage neurogram of MSA.

**Figure 4.** Scatter plots showing change in muscle nerve sympathetic activity (MSA) (abscissa) plotted against changes in systolic and diastolic blood pressure (BP) (ordinate).
FIGURE 5. Recordings from one subject at initial rest (Panel A), 2 minutes before micturition (Panel B), and after micturition (Panel C). Tracings are: from above, electrocardiogram (ECG), finger arterial blood pressure (BP), and mean voltage neurogram of muscle nerve sympathetic activity (MSA). Same time-scale in all panels.

1,100 ml. Sympathetic activity started to decrease in three of these five subjects during ongoing micturition and remained unchanged in two (one of whom had displayed no increase with desire to void). Two subjects exhibited a short-lasting further increase in sympathetic activity while initiating micturition before the decrease was observed. In the five subjects, sympathetic outflow at initial rest, before micturition, and at final rest was 16.7±1.9, 24.4±3.7, and 20.0±2.4 bursts/min, respectively (p<0.01, ANOVA; individual differences: first vs. second p<0.01; second vs. third p<0.05; first vs. third NS). Blood pressure was successively lowered during micturition. Mean blood pressures at initial rest, before micturition, and at final rest were 132±4/81±2, 155±8/96±4, and 135±5/81±2 mm Hg, respectively (p<0.001 for courses of both systolic and diastolic pressures, ANOVA; individual differences: first vs. second and second vs. third p<0.01; first vs. third NS).

In the recording exemplified in Figure 5, a beat-to-beat analysis was made of diastolic blood pressure from the finger arterial pressure (Finapres, Ohmeda) recording during the heart beats associated with a sympathetic burst. Diastolic blood pressure was chosen as it has been shown to be the main determinant for appearance of a sympathetic burst in muscle nerve fascicles at rest. Mean diastolic blood pressure for the heart beats associated with 35 consecutive sympathetic bursts was 64±1 mm Hg at initial rest, 89±1 mm Hg before micturition (p<0.001), and 72±1 mm Hg at final rest (p<0.001 compared with both preceding levels).

Discussion

The main result of the present study is that there is an increase in sympathetic outflow in muscle nerves on distension of the urinary bladder with a concomitant elevation of blood pressure and a return toward initial values after micturition. The sympathetic response showed considerable variation, but the mean change was a significant increase in the number of sympathetic bursts per minute with half of the subjects also exhibiting increases in recorded burst amplitude (i.e., increased strength of individual bursts). The validity of the observed increase in sympathetic activity is reinforced by a slight increase in plasma norepinephrine and a tendency to a correlation between these changes, as a correlation between sympathetic activity in muscle nerves and venous plasma norepinephrine at rest and during certain maneuvers is well established.

It cannot be ruled out that the observed events represent in part an indirect effect of the discomfort from the distended bladder. Occasional observations indicate that physical stress because of an uncomfortable body position may cause an increase in muscle sympathetic activity, and such mechanisms have to date been poorly studied. However, the decrease in sympathetic activity after micturition rules out the hypothetical possibility that the change in sympathetic outflow is dependent on distress caused by a sustained recording session in an unchanged and hence increasingly uncomfortable body position. The short-lasting increase in sympathetic activity during the initial phase of micturition in two subjects does not allow any conclusion because the subjects were straining to some degree at this moment, that is, performing a Valsalva-like maneuver, which is known to exert a strong influence on muscle nerve sympathetic activity.

From animal experiments, there are observations supporting the suggestion that the increase in sympathetic outflow observed in the present study is directly related to the distension of the bladder via tension receptors in the bladder wall. In anesthetized animals, a pressor effect of graded or abrupt bladder distension is well documented, and recordings from sympathetic nerves to different vascular regions in animals have shown an increase in discharge with bladder distension. Moreover, blocking the innervation of the bladder by instillation of procaine before distension of the bladder abolished the sympathetic and blood pressure responses. In cats, the increase in sympathetic nerve traffic was not clear-cut until the increase in vesical pressure was pronounced, similar to our observation in the
present study that an increase in sympathetic outflow was not detected until the feeling of bladder distension was in the upper part of the analogue scale. Monitoring of the bladder pressure, which would have required urethral catheterization, was not considered for both medical and ethical reasons in these healthy volunteers.

In humans, digital vasoconstriction has been observed during distension of the urinary bladder and other visceral organs. This effect, however, is probably due to increased sympathetic outflow in skin nerves, which is not involved in blood pressure regulation. Consequently, the quoted results, taken in conjunction with ours, imply that the sympathetic response to bladder filling in humans involves more than one sympathetic subdivision, which is consistent with animal findings.

Thus, it seems reasonable to conclude that the observed sympathetic and blood pressure changes were related to the increasing bladder distension. However, other contributing mechanisms must also be considered.

Isometric muscle work evokes an increment in muscle nerve sympathetic outflow with blood pressure elevation probably mediated by ergoreceptors or chemoreceptors in the muscle. Although some of the subjects in the present study showed signs of muscle tension when the urge to void became prominent, a major contribution from muscle tension to the observed effects is unlikely as the muscle tension was brief and rapidly controlled by the subjects on request.

Muscle nerve sympathetic outflow is to some extent modulated by the respiratory pattern. However, nothing suggests that this was of importance for the events observed in the present study as mean respiratory rate did not change, and two subjects with opposite, relatively marked, changes of respiratory pattern displayed similar increases in sympathetic outflow.

Xanthines in the tea drunk by the subjects before the experiment may have exerted some influence on circulation and diuresis. Whether caffeine or theophylline directly affects muscle nerve sympathetic activity is not known. However, it is unlikely that the pharmacological action of xanthines contributed to the effects observed as the time relation between tea intake and increase in muscle nerve sympathetic activity varied strongly between the subjects.

The temporary increase in sympathetic outflow immediately after drinking in one subject (Figure 3) might possibly have been evoked by afferent impulses from tension receptors in the stomach. Pressure changes in the neck, induced by sucking the straw, are not likely to be responsible as acute neck suction and pressure induce only transient changes in sympathetic outflow. This increase in sympathetic outflow after drinking was seen in only one subject of 11, was of short duration, and is therefore not believed to contribute to the change in sympathetic activity seen with the urge to urinate.

The precise mechanism behind the sympathetic activation is not clear from the present data. Because blood pressure increased, it seems unlikely that the response is mediated by baroreceptor reflexes; indeed, with an increased blood pressure, the baroreceptor influence would be expected to counteract an increase in sympathetic outflow, in accordance with the observation in animal experiments that the pressor response to bladder distension was accentuated after baroreceptor denervation. In humans, high pressure baroreceptors are responsible for the dynamic relation at rest between sympathetic bursts in muscle nerves and blood pressure with the bursts appearing during temporary reductions of (especially diastolic) blood pressure, and for the time-locking of the bursts in the cardiac rhythm. In the present study, the continuous finger arterial blood pressure monitoring revealed that release of sympathetic bursts occurred at a higher blood pressure level with the desire to urinate (see Figure 5) indicating that the level of baroreceptor inhibition was modified by some other input.

If the sympathetic response is evoked by physical stress and discomfort, it is presumed to be a central effect, facilitating the outflow. If a direct receptor input from the bladder wall is the explanation, a spinal reflex can be assumed as well. The existence of spinal sympathetic reflexes is exemplified by the digital vasoconstriction after a sudden deep inspiration, which is due to sympathetic impulses in skin nerves. A spinal reflex underlying the present pressor response to bladder distension would accord with the phenomenon of autonomic dysreflexia in traumatic tetraplegia, where marked blood pressure elevations may be induced by bladder manipulation. The relation between bladder filling, sympathetic nerve traffic, and autonomic dysreflexia is poorly understood, however, and microelectrode recordings of sympathetic activity below the lesion in such patients during controlled bladder distension via a urethral catheter revealed only a minor, albeit clear-cut, increase in sympathetic activity. It cannot be ruled out that the present observations and autonomic dysreflexia in humans with spinal cord lesions are related phenomena, although of very different intensity because of very different central control of sympathetic outflow in the two situations. The time course and duration of bladder distension in the present study and in that of humans with spinal cord lesions were not identical, and thus a more detailed comparison between the responses is not relevant.

The abolished arterial pressor response after sympathectomy and the abolished sympathetic and blood pressure responses after blocking vesical afferent nerve activity in animal experiments strongly suggest that the sympathetic activation is responsible for the elevation of blood pressure. Likewise, it is reasonable to assume that the increased vasoconstrictor sympathetic outflow in the present experiments contributed to the increment in blood pressure, despite the lack of a direct relation between individual sympathetic and pressor responses. The
interindividual variation in muscle nerve sympathetic response makes individually varying activation of vasoconstrictor outflow to other resistance vessel beds possible, and such a variation would blunt the relation with the only sympathetic subdivision under study in a limited number of subjects. Thus, in humans there also seems to be a vesico-vascular mechanism through which bladder distension may cause muscle nerve sympathetic activity to contribute to elevation of blood pressure. Such an elevating effect of muscle nerve sympathetic activity on the blood pressure level diverges from its primary counteraction of pressure reductions during resting, basal conditions. In this respect, bladder distension would be related to other conditions with an apparent nonbaroreceptor input inducing a pressor effect of muscle nerve sympathetic activity, such as isometric muscle work, the cold pressor test, and the diving response.

One practical implication of the present study is that patients should always be instructed to empty the bladder before having their blood pressures measured to avoid an erroneous diagnosis of hypertension.

The pathophysiology of nocturnal micturition syncope might be illustrated indirectly by the present findings: When a subject wakes up at night with an urge to void and walks, with orthostatic mechanisms operating, directly to the bathroom to empty the bladder, it seems reasonable to suggest that the sudden release of bladder distension can induce a marked reduction of sympathetic vasoconstrictor outflow (see Figure 5) with fainting as a consequence.

References


Key Words: microneurography • bladder distension • micturition • sympathetic nerve activity • blood pressure • clinical study
Sympathetic activity and blood pressure increases with bladder distension in humans.
J Fagius and S Karhuvaara

Hypertension. 1989;14:511-517
doi: 10.1161/01.HYP.14.5.511

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/14/5/511

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in
Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/