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Baroreceptor-heart rate reflex sensitivity enhancement after urinary bladder distention in essential hypertensives

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Abstract Our objective was to determine if urinary bladder distention modifies the sensitivity of the baroreceptor-heart rate reflex in hypertensive and control subjects. The baroreceptor-heart rate reflex sensitivity was measured in 15 male patients (mean age 37 ± 8 years) with mild untreated hypertension (mean 163 ± 8/95 ± 12 mmHg) and 17 age- and sex-matched control subjects before and after urinary bladder distention. Bladder filling was performed infusing saline heated to 37°C via a urinary catheter; the volume infused in each patient corresponded to that which caused the urge to void without reaching the pain threshold. The baroreceptor-heart rate reflex sensitivity was determined correlating the variations of the systolic pressure and of the peak blood flow velocity in the common carotid artery with the variations of the ECG RR′ interval of the following heart beat, both during spontaneous and phenylephrine-induced fluctuations of the haemodynamic variables. After bladder distention the diastolic pressure of the hypertensive subjects increased significantly (95 ± 12 vs. 100 ± 12 mmHg; $P < 0.02$), whereas the heart rate decreased (RR = 873 ± 70 vs. 926 ± 80 ms; $P < 0.005$). These parameters were unchanged in the normotensive subjects (84 ± 9 vs. 83 ± 8 mmHg and 914 ± 158 vs. 913 ± 140 ms, respectively). The baroreceptor-heart rate reflex sensitivity, measured on the basis of spontaneous pressure and carotid blood flow velocity fluctuations in relationship to RR changes, decreased in the normotensive subjects after bladder distention (10.7 ± 4.6 vs. 9.4 ± 2.7 ms/mmHg; $P < 0.05$ and 423 ± 99 vs. 356 ± 102 ms/kHz; $P < 0.01$, respectively), whereas it increased in the hypertensive patients (6.9 ± 3.6 vs. 8.3 ± 2.8 ms/mmHg; $P < 0.03$, and 332 ± 86 vs. 381 ± 97 ms/kHz; $P < 0.03$ respectively). After bladder distention and phenylephrine administration the baroreceptor-heart rate reflex sensitivity, measured by the correlation between systolic pressure and RR interval, increased only in the hypertensive group (10.2 ± 5.4 vs. 15.2 ± 7.7 ms/mmHg; $P < 0.005$). In conclusion urinary bladder distention provokes in hypertensives but not normotensive controls a brisk parasympathetic response of the component of the baroreceptor-heart rate reflex which controls heart rate.

Key words Baroreceptor-heart reflex · Hypertension · Systolic pressure · Diastolic pressure · Bladder distention · EKG · Phenylephrine

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Introduction

Distention of the hollow viscera such as the stomach [8], the small intestine [12], the rectum [11], the gall bladder [10], and the urinary bladder [18] decreases the sensitivity of the baroreceptor reflex in experimental animals. To our knowledge the effect of hollow organ distention on baroreceptor reflex sensitivity in humans is unknown. We conjectured that hypertensive patients, who have a diminished baroreceptor reflex sensitivity at rest [7], may demonstrate altered baroreflex function compared with normotensive controls after bladder distention.

The objective of the present investigation was to determine if bladder distention produced during routine urodynamic studies modified the sensitivity of the baroreceptor-heart rate reflex in hypertensive patients compared with sex- and age-matched normotensive controls.

Patients and methods

The study population consisted of two groups of male subjects, 15 patients (mean age 37 ± 8 years) with mild untreated hypertension

and 17 normotensive subjects matched for sex and age, who had undergone negative urodynamic studies for suspected bladder abnormalities and had given informed consent. The initial diagnostic test served to establish the bladder filling volume at which the patient reported the urge to urinate without, however, reaching the pain threshold. The clinical history was obtained and the blood pressure measured on the same occasion. The patients with elevated pressures and a history of hypertension underwent the haemodynamic studies. During the following period the blood pressure was again measured in the clinic; if the values were consistently elevated, the patient was included in the analysis as a hypertensive. Fifteen minutes after completion of the diagnostic urodynamic examination the haemodynamic study was begun with measurement of the blood pressure, heart rate and baroreceptor reflex sensitivity with the bladder empty. The sensitivity was determined from the slope of the regression line of the correlation both between peak systolic pressure and the RR interval (the Oxford method, [15]) and between peak carotid blood flow velocity and the RR interval of the next cardiac cycle, as described by Carretta et al. [2]. However, as described by Ferrari et al. [4], if the correlation between pressure or velocity and the next RR interval was weak the following RR intervals ranging from the second to the ninth beats of the sequence were used, with the intention of achieving the best correlation function. In the present study an RR interval shift different from 1 resulted in a greater correlation in about 10% of the cases. The parameters were measured both during spontaneous pressure and blood velocity fluctuations and during rapid and transitory increments of these parameters induced by intravenous bolus [100 μg) injections of phenylephrine.

Blood pressure was measured in the middle finger with the plethysmographic method (Finapress Ohmeda); common carotid blood flow velocity was measured by a CW-Doppler (Medasonics, Mountain View, Calif.). The haemodynamic variables were recorded on-line and stored on computer (IBM TS SISTEMI) for later evaluation.

Once the baseline measurements were performed, the bladder was filled with saline warmed to 37°C at a rate of 50 ml/min through a urinary catheter until the volume was reached which caused the urge to void, as established during the initial diagnostic urodynamic study. At that point the haemodynamic variables were again measured as described above. The bladder was then emptied, and after a 10-min interval to recover basal conditions the haemodynamic variables were measured again. This sequence was repeated five times.

The slope of the regression line between peak pressures and/or carotid blood flow velocity and the RR interval was used as the index of baroreceptor-heart rate reflex sensitivity only if the correlation coefficient exceeded 0.75 and at least nine pairs of values were obtained per subject for each trial. These criteria were fulfilled in all subjects in at least three of the five trials when the correlation between peak pressure and the RR interval was used to calculate the sensitivity. However, when the correlation between peak carotid blood flow velocity and RR interval was used during bladder distention, the correlation coefficient exceeded 0.75 on only two occasions in five hypertensive patients, probably due to technical difficulties in obtaining an adequate ultrasound signal during all the phases in which phenylephrine exerted its effect.

Baseline and bladder distention haemodynamic values were expressed as mean ± standard deviation. Statistical significance of the various parameters before and after bladder distention was evaluated with the paired *t*-test, and the statistical analysis between the two groups of subjects was carried out with the unpaired *t*-test.

Results

After bladder distention blood pressure increased in the hypertensive patients, although the difference was statistically significant only in relation to the diastolic pressure. The intrapatient coefficient of variation (CV) was 10% for the systolic blood pressure and 7% for the diastolic. The heart rate, on the other hand, decreased significantly in the hypertensive group (intrapatient CV 8%) but remained unchanged among the control subjects (Table 1). The baroreceptor-heart rate reflex sensitivity, measured from spontaneous variations of pressure and carotid blood flow velocity in respect to variations of the RR interval, was significantly increased in the hypertensive patients after bladder distention but decreased in the normotensive subjects (Table 1). The baroreceptor-heart rate reflex sensitivity, measured with the same techniques after phenylephrine administration, was unchanged in the normotensive subjects but was significantly increased in the hypertensive patients, although only when the Oxford method was utilized to measure this parameter (Table 1).

Discussion

Distention of the hollow organs such as the stomach, gall bladder, small intestine and urinary bladder reduces the sensitivity of the baroreceptor reflex and activates

Table 1 Correlation between bladder distention and sensitivity of the baroreceptor-heart reflex in hypertensive patients compared with sex- and age-matched normotensive controls

		SAP (mmHg)	DAP (mmHg)	RR′ (ms)	VEL (Hz)	S O-BRS (ms/mmHg)	S V-BRS (ms/kHz)	Ph O-BRS (ms/mmHg)	Ph V-BRS (ms/kHz)
	B	141 ± 12	84 ± 9	914 ± 158	915 ± 207	10.7 ± 4.6	423 ± 99	17.9 ± 7.1	713 ± 196
NORMOTENSIVES	§	n.s.	n.s.	n.s.	n.s.	$P < 0.05$	$P < 0.01$	n.s.	n.s.
	V	142 ± 13	83 ± 8	913 ± 140	931 ± 211	9.4 ± 2.7	356 ± 102	16.3 ± 7.2	672 ± 184
**		$P < 0.01$	$P < 0.005$	n.s.	n.s.	$P < 0.01$	$P < 0.01$	$P < 0.02$	$P = 0.05$
	B	163 ± 8	95 ± 12	873 ± 70	969 ± 180	6.9 ± 3.6	332 ± 86	10.2 ± 5.4	603 ± 82
HYPERTENSIVES	§	n.s.	$P < 0.02$	$P < 0.005$	n.s.	$P < 0.035$	$P < 0.03$	$P < 0.005$	n.s.
	V	168 ± 11	100 ± 12	926 ± 80	974 ± 254	8.3 ± 2.8	381 ± 97	15.2 ± 7.7	592 ± 149

SAP systolic arterial pressure, *DAP* diastolic arterial pressure, *VEL* carotid blood flow velocity

** At rest: hypertensives vs. normotensives (Student's *t*-test for unpaired data)

§ Rest (B) vs. submaximal urinary bladder distention (V) (Student's *t*-test for paired data)

Baroreflex sensitivity measured by the correlation between systolic pressure and RR′ interval during spontaneous variations of the blood pressure (S O-BRS) and after phenylephrine injections (Ph O-BRS)

Baroreflex sensitivity measured by the correlation between carotid blood velocity and RR′ interval during spontaneous variations of the blood velocity (S V-BRS) and after phenylephrine injections (Ph V-BRS)

the sympathetic nervous system in experimental animals [8, 10–12, 18].

To our knowledge there are no human studies which evaluate the sensitivity of the baroreceptor reflex after urinary bladder distention. The hypertensive patient, from the point of view of reflex nervous blood pressure control, is a particularly interesting study subject, since alterations of the baroreflex sensitivity are already present during baseline conditions. Therefore, the most provocative, and in part paradoxical, finding that emerges from the present study is that the baroreceptor-heart rate reflex sensitivity during bladder distention decreases in normotensive subjects but increases in hypertensive subjects.

Although this observational study was not designed to establish the mechanisms of the differences between the two groups of subjects, some pathophysiological mechanisms can be inferred. First, however, it should be emphasized that the study design strictly adhered to standard measurement conditions to enhance reproducibility. For this reason the bladder was filled via catheter, always using the same volume of saline and the same infusion rate for each patient. Thus, factors confounding the measurement of the reflex sensitivity, such as stomach distention, were avoided, and time intervals between trials were shortened, allowing a greater number of measurements. Nevertheless, repeating the determinations for five trials per subject was insufficient to have at least three regression lines between carotid blood flow velocity and RR interval with a correlation coefficient greater than 0.75 in all the hypertensive subjects. A correlation coefficient of 0.75 was considered the minimum value because the slope of the regression line was used as the index of baroreceptor-heart rate reflex sensitivity [15]. The low value of the correlation coefficient obtained in some patients was probably due to difficulty obtain an adequate recording of the ultrasound signal during all phases of haemodynamic perturbations induced by phenylephrine. For this reason, in our opinion, the differences between baroreceptor-heart rate reflex sensitivity, measured using carotid blood flow velocity and RR interval correlation after phenylephrine injections before and during bladder distention, did not attain statistical significance in the hypertensive group. Under the same conditions these differences were statistically significant when the correlation between peak systolic pressure and RR interval (the Oxford method, [15] was used to determine the baroreceptor-heart rate reflex sensitivity.

Maximal urinary bladder distention evokes, via a reflex mechanism activation of the sympathetic nervous system and inhibition of the vagal system [3, 17] and, in consequence, an increase in heart rate and systemic blood pressure. Nevertheless, the interactions between the activation of the autonomic nervous system induced by bladder distention and those induced by other reflex mechanisms, such as distention of the atria, the pulmonary veins or the carotid sinus, are very complex in that the same nerve contains different groups of fibres with opposing actions, depending on whether they are stimulated by carotid or bladder receptors. For example, Hassan et al. [6] have demonstrated in dogs baroreceptor and carotid chemoreceptor stimuli that reduce the activity of the sympathetic fibres which, however, are activated by bladder receptor stimuli. On the other hand, efferent vagal fibres to the heart in dogs exist that increase their electrical activity in relation to increasing pressure within the carotid sinus; the activity of the same fibres is reduced when the bladder is stretched. As a result, when the bladder is filled, the activation of the vagal fibres produced by distention of the carotid sinus decreases as the intracarotid pressure is increased [14].

Although the design of our study did not take into account the activity of the autonomic nervous system, the results suggest possible mechanisms involved in the origin of the haemodynamic alterations we observed. First of all, we cannot exclude the possibility that in the hypertensive patients the baroreceptor stimulus was more intense than in the control subjects, given that after bladder distention the blood pressure increased only in the hypertensive group. On the other hand, in animals [5, 17] and in humans [3] bladder distention increases the activity of the sympathetic nervous system, and hypertensive patients demonstrate greater vascular reactivity to a number of stimuli that activate the sympathetic nervous system [1], explain the increased pressure observed in this group of patients in the present study. Recently Seitzbergen et al. [16] have observed an increased nerve activity of the bladder smooth muscle of spontaneously hypertensive rats compared with Wistar-Kyoto rats, probably mediated by a high rate of secretion of nerve growth factor, with an increased response of both the afferent sympathetic and efferent parasympathetic urinary bladder pathways, resulting in hyperactive voiding.

Therefore, to explain the increased sensitivity of the baroreceptor reflex-heart rate, one could hypothesize that besides an important stimulus of the carotid and aortic baroreceptors, central interference in the baroreceptor-heart rate reflex function by impulses coming from bladder mechanoreceptors may exist in hypertensive subjects. Since the Oxford method of measuring the reflex sensitivity provides information primarily on the vagal efferent component of the reflex arc [13], the present results imply increased vagal tone in hypertensives when the bladder is distended and blood pressure is increased in the carotid sinus. This effect may be attributed to diminished vagal inhibition exerted by those parasympathetic fibres coming from the bladder, the stimulation of which reduces activity of the baroreceptor reflex in dogs [14]. This selective downregulation of the nerve pathways of the baroreflex may explain why in baseline conditions, when baroreceptor-heart rate reflex sensitivity is increased, only bradycardia is observed while blood pressure is allowed to increase during submaximal bladder distention in hypertensives.

The activation of mechanoreceptors during bladder distention represents only one phase of micturition. Although the bladder refilling was performed artificially by catheter, the consistent reproducibility of the haemodynamic events with each refilling suggests that the experimental conditions were representative of the preliminary phase of micturition, i.e. the bladder distention.

In conclusion, the increased parasympathetic response of the heart to urinary bladder distention in the hypertensive may potentially predispose this group of subjects to micturition syncope. Epidemiological studies would be useful to determine if the prevalence of this disorder is elevated in hypertensive compared with normotensive subjects.

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