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Sympathetic Efferent Activity in the Viscerovascular Reflexes Induced by Urinary Bladder Distension

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Abstract In chloralose-anesthetized cats, rapid distension of the urinary bladder with warm (37°C) normal saline (50–60 ml) causes an increase in blood pressure and contraction of the spleen. This response is due to peripheral vasoconstriction. In this experiment, the evidence of direct involvement of the spleen, as well as splenic and splanchnic sympathetic efferent activity on the viscerovascular reflexes, was investigated by pharmacological and electrophysiological (single unit preparation) means and analysis. The viscerovascular reflexes induced by urinary bladder distension remained unaffected by propranolol, but phentolamine, guanethidine sulfate, and hexamethonium completely antagonized the reflex vasopressor response. All these results with these blocking agents show that sympathetic nerves are actively involved in the reflex responses to distension of the urinary bladder with activation at the postganglionic level involving α-adrenoceptors and thereby the release of catecholamines. It is thus evident that the same mechanisms operate in the case of reflex elevation of blood pressure and contraction of the spleen. After bilateral denervation of the splanchnic sympathetic nerves, bladder distension failed to produce a reflex response. The efferent activity from the splanchnic and splenic sympathetic nerves in producing a reflex rise in blood pressure was recorded for direct evidence. The significant increase of asynchronous spontaneous discharge rate in the splanchnic and splenic sympathetic nerves was found along with a rise in blood pressure during bladder distension. On the basis of this study, it may be suggested that the spleen as well as splenic and splanchnic sympathetic nerves play an important role in the control of viscerovascular reflexes.

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Stress in any form can significantly alter the cardiovascular functions. The association of the elevation of blood pressure with the distension of the urinary bladder has attracted the attention of a number of investigators, yet great difficulties are still encountered in the analysis of the effects of bladder distension. Sherrington [1] was the first to show that the stretching of certain hollow viscera viz., ureter, bile duct, causes reflex vascular responses. In the clinical field, cardiovascular disturbances associated with gastrointestinal obstructions or retention of urine, become unmanageable episodes. Cardiovascular disturbances have been reported in paraplegics, associated with distension of the urinary bladder [2, 3], with the rise of blood pressure being considered to be due to peripheral vasoconstriction [4, 5], and under a supraspinal inhibitory influence [6]. It has also been indicated that the tension to which the bladder wall is subjected is the effective stimulus for such effect [5]. Several studies indicated that the rise of blood pressure is highest in patients with spinal cord transection [1, 2, 4]. Wurster and Randall [7] reported that elevation of blood pressure was more marked and characterized by greater systolic elevation in patients with lesions above T_5 than in patients with lower lesions (below T_5). Direct experimental evidence as well as pharmacological and single fiber recording are still lacking as regards the role of splenic and splanchnic sympathetic nerves in modulation of viscerovascular responses induced by urinary bladder distension. The present experiment will give us a comprehensive understanding of the involvement and behavior of the particular sympathetic nerves in a condition of urinary bladder distension where hypertension is the most notable manifestation.

MATERIALS AND METHODS

Investigations were performed on 35 adult cats (2–3 kg) of both sexes. The animals were anesthetized with α-chloralose (60–70 mg/kg, I.V.) after initial induction with anesthetic ether. A "T" shaped tracheal tube was inserted into the trachea after a low tracheotomy for free breathing and also for artificial ventilation with a Starling-Ideal-Respiratory pump, if required. A thermistor was connected with the tracheal T tube for monitoring respiration through a Beckman RM Dynograph (Beckman Instruments). Variations in the temperature of the inspired and expired air recorded on a Beckman RM Dynograph via the thermistor indicated the respiratory rate. The left femoral vein was also cannulated. To maintain body fluid balance, the animals were infused with lactated Ringer's solution containing 5% dextrose ($\sim$15 ml/h) through the left femoral vein. The body temperature was maintained by a circulating hot water heating pad underneath the animals and by an infrared heating lamp. The core temperature was maintained at 37–38°C by

means of a thermoprobe (Yellow Spring Instrument, Model 401) inserted into the rectum and connected to a thermoregulator (Yellow Spring Instrument, Model 74) that automatically controlled the infrared heating lamp.

Recording of blood pressure. The femoral artery was cannulated for continuous recording of systemic blood pressure which was measured with a Bell & Howell (Type 4-327-0129) pressure transducer coupled with the Beckman RM Dynograph. The pressure transducer was initially filled with heparin-saline solution (100–150 IU/ml). Blood pressure was recorded on the Beckman RM Dynograph after initial amplification through the Beckman V/P/Pressure coupler (Type 9853A).

Intravesicular pressure recording. The urinary bladder cannulation was performed as described by Koley *et al.* [8]. The urethra was exposed by a midline suprapublic incision of the lower abdomen and cleared of surrounding tissues. A polyethylene catheter was inserted into the urinary bladder via the urethra to record intravesicular pressure. The bladder was first emptied and then filled with 10 ml of physiological saline introduced through the catheter. The cannula was connected to a T tube, one arm of which was attached to a Bell & Howell (Type 4-327-0129) pressure transducer for recording intravesicular pressure on the Beckman RM Dynograph and the other arm was used for rapid distension of the urinary bladder with 50–60 ml of warm (37°C) normal saline. During the filling phase of the bladder, the intravesicular pressure rose sharply to attain a height of 50–60 mmHg, but this was immediately followed by a fall to a level of 30–40 mmHg at the completion of filling, and it remained at that level as long as the bladder was kept distended. The period of distension of the urinary bladder with warm normal saline was 90 s. The bladder was evacuated just after 90 s.

Measurement of spleen volume changes. A laparotomy was performed on the lateral side of the left abdominal wall of the anesthetized cat to expose the spleen and its vasculature for plethysmography. The spleen was carefully cleared from each attachment to the stomach and replaced in its natural position in the abdominal cavity. The spleen was carefully and gently (avoiding any bleeding) pushed through the longitudinal slit of the fine membrane of the plethysmograph which was then secured by a clamp close to the cat so as to avoid traction on the splenic vessels and nerves. The plethysmograph was then connected with a pressure transducer to record the spleen volume changes on the Beckman RM Dynograph.

The absolute volume of the spleen of the cat before stimulation was 15–20 ml. This volume was considered as zero (resting volume) after placing the spleen inside the plethysmograph. The change in volume (Δ) of the spleen was measured by water displacement in the plethysmograph.

Denervations, isolation of sympathetic nerves, electrical stimulation, single fiber preparation, and recording. The respective sympathetic nerves were cleared and isolated from the surrounding tissues carefully. A fine loop was made around each of the nerves and left as such. The nerve was raised by pulling the loop and was sectioned when necessary. The separation of nerves and bilateral denervation were performed under a stereoscopic dissecting microscope (Vicker's, UK) after placing

a small ice cube over the nerves to prevent cardiac shock. The experiments performed in animals with bilateral splanchnic nerve denervation utilized the same techniques of operation as described by Mukherjee [5] and Floyd *et al.* [9, 10]. The nerves were stimulated with rectangular pulses from a Grass S48 stimulator delivered through a stimulus isolation unit (SIU5). The stimulation was applied at the peripheral end of the splanchnic nerves at the rate of 20 Hz, at a duration of 1 ms and at 10 V. The blood pressure changes by nerve stimulation, with or without bladder distension, were recorded on the Beckman RM Dynograph. After their careful exposure, the splanchnic and splenic sympathetic nerves were isolated from the surrounding connective tissues using a dissecting microscope and then emerged in paraffin. The central cut end of the splanchnic and splenic sympathetic nerves were placed on a black ebonite dissecting plate and kept emerged in a warm (37°C) paraffin pool. A small length of the nerve was desheathed and split into fine filaments under a stereoscopic dissecting microscope. A fine filament of the central cut end was placed on a pair of silver-silver chloride recording electrodes for studying single unit activities [11–13]. The single unit activity was displayed on a Tektronix dual beam oscilloscope (Model 5112), after amplification through a differential preamplifier (Tektronix AM502). Parallel connections were made to an audio-amplifier for monitoring the sound and to a thermionic 4FM tape recorder (Recal-Thermionic Ltd., UK) for recording the activity when necessary and played back to a storage oscilloscope (Model 5113, Tektronix Inc., USA) for further analysis and photography [14].

Drug used. Drugs, dissolved in physiological saline, were injected intravenously through a catheter in the femoral vein; doses refer to the salt. Drugs used were propranolol hydrochloride (ICI), phentolamine mesylate (Rogitine, Ciba-Geigy), guanethidine sulfate (Ciba-Geigy), hexamethonium bromide (Koch-Light Lab), reserpine (Serpasil, Ciba-Geigy), and tyramine (Aldrich Chemical).

Statistical analysis of data. Results are expressed as mean±standard error of mean (mean±SE). Each mean value was the average of 10 animals. The significance of the differences between groups was estimated using Student's *t*-test. The level of significance was taken as $p < 0.05$. In the text, whenever any change in results is mentioned, it is taken into account that the difference is significant at the level of <0.05, 0.01, or 0.001.

RESULTS

Effect of distension of urinary bladder on blood pressure and spleen volume

It was observed that the spleen of the anesthetized cats underwent contraction along with the rise of blood pressure caused by urinary bladder distension. The spleen volume contraction was gradual and reached the maximum level at 60 s of distension; this magnitude of contraction continued up to 90 s of distension. With the evacuation of the bladder, the spleen volume gradually increased towards the initial level (Fig. 1).

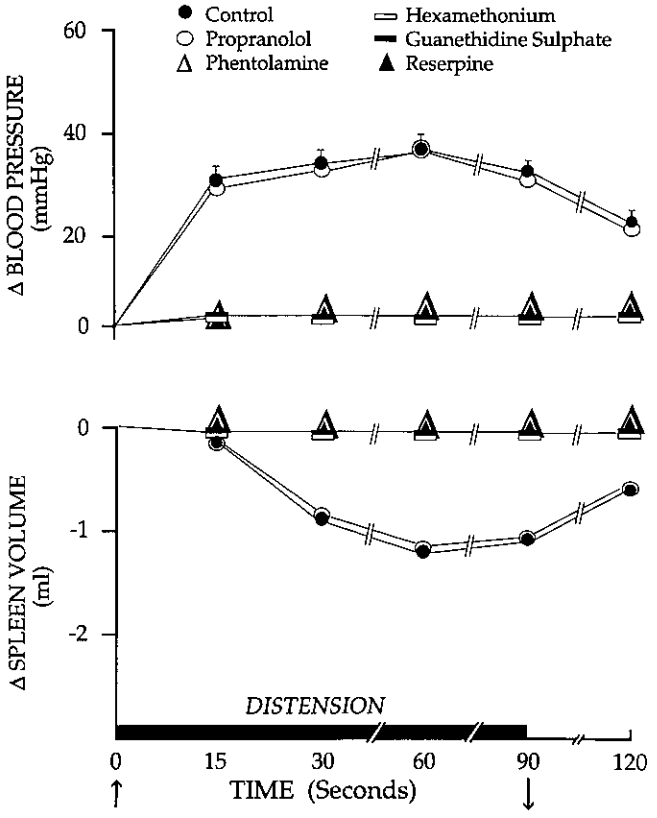

Fig. 1. Graphs illustrating the response pattern of mean blood pressure (upper tracing) and spleen volume (lower tracing) to bladder distension in cat, intact (control), and pretreated with propranolol (1 mg/kg), phentolamine (2.5 mg/kg), hexamethonium (1 mg/kg), guanethidine sulfate (20 mg/kg), and reserpine (2.5 mg/kg). Results are expressed as means±SEM ($n = 10$) in each treatment. The total distension period was 90 s, as indicated by the arrows (↑ ↓).

Effect of propranolol and phentolamine on blood pressure and spleen volume following distension of urinary bladder

Administration of propranolol (1 mg/kg) 15 min before bladder distension was found to be ineffective in altering the rise of blood pressure and spleen volume following urinary bladder disatension (Fig. 1), but administration of phentolamine (2.5 mg/kg) 15 min before distension significantly ($p < 0.001$) antagonized the vasopressor response to distension of the urinary bladder and also the contraction of spleen volume following bladder distension (Fig. 1).

Effect of hexamethonium and guanethidine sulfate on blood pressure and spleen volume following distension of urinary bladder

The responses following urinary bladder distension were significantly ($p<0.001$) antagonized by the administration of hexamethonium (1 mg/kg) and guanethidine sulfate (20 mg/kg) given intravenously 15 min before bladder distension (Fig. 1).

Responses after reserpine treatment

Intraperitoneal injection of reserpine (2.5 mg/kg) 24 h before the start of distension of the urinary bladder significantly ($p<0.001$) counteracted the effect of bladder distension on the changes in blood pressure and spleen volume (Fig. 1). The effect of reserpine was checked by intravenous administration of tyramine (20 μg/kg) when the antagonistic effect of reserpine, with respect to the inhibition of the rise of blood pressure and spleen volume after bladder distension, remained unaffected.

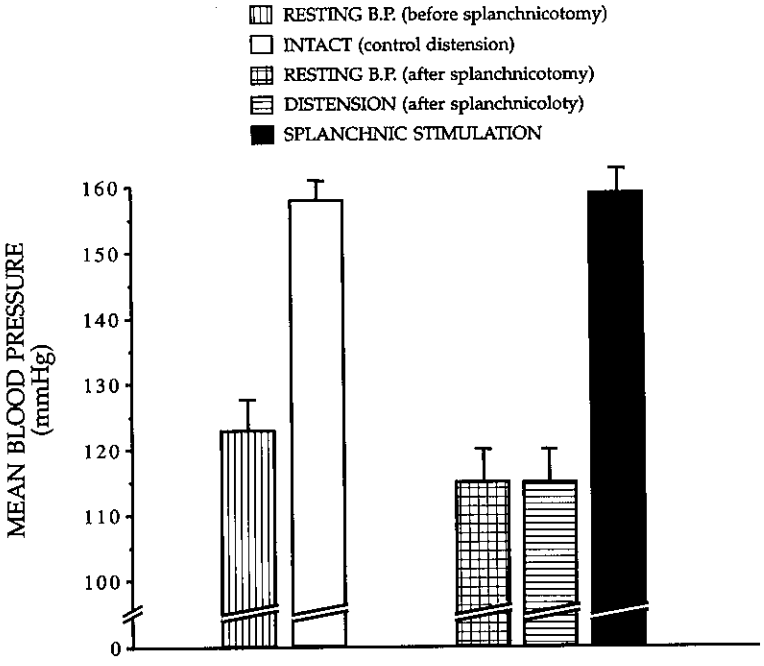

Fig. 2. Histogram represents the response pattern of mean blood pressure changes in intact (before splanchnicotomy), after splanchnicotomy and stimulation of splanchnic nerves. Each column shows the blood pressure as mean±SEM ($n=10$). The vertical bars on the columns represent the standard error of the mean ($n=10$). No significant differences were found ($p=0.273$, $t=1.131$) in a comparison between before and after splanchnicotomy resting blood pressure using Student's t-test for unpaired data.

Responses after bilateral splanchnicotomy and stimulation

The resting mean blood pressure before and after splanchnicotomy was 123±5 and 115±5 mmHg, respectively. After splanchnicotomy, bladder distension did not produce any change ($p < 0.001$) in blood pressure (Fig. 2). In the intact animal where blood pressure rose (158±3 mmHg) with the distension of the bladder, bilateral splanchnicotomy abolished this response (115±5 mmHg). It was further observed that the stimulation (20 Hz, 1 ms, 10 V) of the peripheral cut ends of the splanchnic nerves of the same animals increased the blood pressure (159±3 mmHg) to a similar extent as found after bladder distension.

Activity of splanchnic sympathetic nerve following urinary bladder distension

The involvement of splanchnic sympathetic nerve in altering the systemic blood pressure during bladder distension was examined by recording its single unit electrical activity from the central cut end. The asynchronous spontaneous resting firing rate of the splanchnic nerve was 0–2 spikes/s (Fig. 3A). An increase in splanchnic nerve activity with the elevation of blood pressure was observed during bladder distension. The firing rate was enhanced to 9–12 spikes/s ($p < 0.001$) during bladder distension (Fig. 3B and C). A total of 32 fibers were recorded from the splanchnic sympathetic efferents of the cat. Out of these, 29 units were active and 3 were silent (no response).

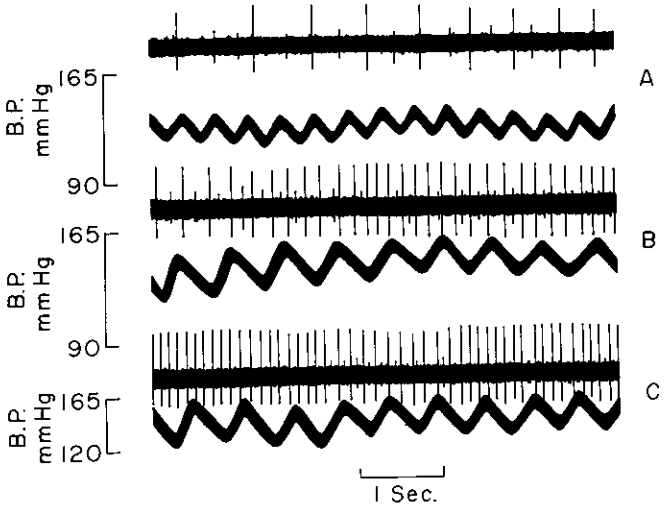

Fig. 3. Splanchnic sympathetic efferent asynchronous spontaneous discharge pattern to gradual rise of systemic pressure induced by urinary bladder distension. Tracing A shows the normal resting discharge of single unit and tracings B and C show the significant ($p < 0.001$) increased frequency of discharge during the rise in blood pressure after bladder distension. In A, B, and C, the upper tracing represents neural activity and the lower tracing represents blood pressure.

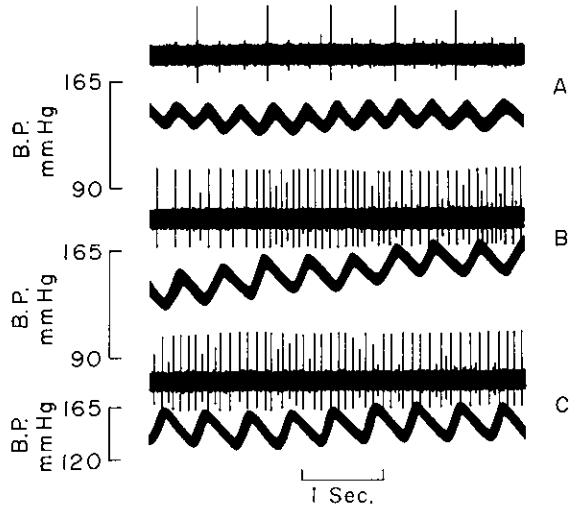

Fig. 4. The response pattern of one asynchronous efferent single unit in the splenic sympathetic nerve to distension of the urinary bladder. A: the spontaneous activity (control), B and C: increased discharge rate significantly ($p < 0.001$) with the rise in blood pressure during bladder distension. In all parts of the figure, the upper tracing represents neural activity and the lower tracing represents blood pressure.

Activity of splenic sympathetic nerve during urinary bladder distension

The single unit activity from the central cut end of the splenic sympathetic nerve was recorded during bladder distension. The resting firing rate of the asynchronous efferent splenic sympathetic nerve arising from the celiac ganglion was 0–1 spikes/s (Fig. 4A). After distension of the urinary bladder, this resting discharge rate was significantly ($p < 0.001$) increased along with the rise of blood pressure (Fig. 4B and C) and attained a maximum of 8–14 spikes/s during sustained rise of blood pressure. Thirty-nine active unit and 5 silent (no response) were found out of 44 fibers.

DISCUSSION

The hollow viscera and the blood vessels serve the physiological needs of the body by pushing the contents forwards. Some hollow structures like the stomach, intestine, urinary bladder, gall bladder, etc., are generally accustomed to accommodate the contents and thereby to a certain amount of stretch. Others, however, are functionally mere conduits, but when movement of the contents of the hollow viscera is restricted due to obstruction it may become the causative factor for cardiovascular abnormality. Since the pioneering demonstration of reflex vascular responses to stretching of certain hollow viscera, viz., ureter, bile duct, urinary

bladder, etc. [1], a number of researchers have investigated the viscerovascular reflexes induced by urinary bladder distension and the possible pathways and mechanisms of the reflexes [2, 4, 5, 7, 15–20]. However, the exact mechanisms and pathways of the viscerovascular reflexes by urinary bladder distension and also the behavior and reactivities of the different sympathetic nerves during bladder distension are still not properly elucidated. Many studies [6, 13, 21, 22] have indicated the involvement of splanchnic sympathetic outflow in the adjustment of cardiovascular function, but confirming evidence as regards to single fibers is still lacking. Hence, this study was designed to study the role of splanchnic and splenic sympathetic activity in initiating cardiovascular changes during bladder distension.

Blood pressure response due to urinary bladder distension is minimal when the sino-aortic baroreceptors are functioning and the connection between the spinal and supraspinal centers are intact. Aortic baroreceptors exert an inhibitory influence over the spinal cord vasomotor center as evidenced by the higher viscerovasopressor response due to bladder distension following denervation of the sino-aortic baroreceptors [5]. Its inhibitory role over the spinal cord vasomotor center was further confirmed when the viscerovascular responses were minimal or absent following stimulation of the central cut end of the sinus or aortic nerve. In spinal (C_7–C_8) animals where the spinal cord vasomotor center is separated from the supraspinal center, viscerovascular responses are still possible and even exaggerated, indicating that the center for such reflexes lies in the spinal cord [23].

The viscerovasopressor response to distension of the urinary bladder is presumably associated with increased sympathetic activity, as evidenced by contraction of the nictitating membrane, and that this response was antagonized by α-adrenoceptor antagonists [13, 14]. In the present study, it was observed in intact anesthetized animals that the rise of blood pressure is always associated with the decrease of spleen volume, during rapid distension of the urinary bladder at a pressure head of 30–40 mmHg (50–60 ml normal saline), indicating an overall excitation of sympathetic nerves. These responses to rapid distension are thought to be due to increased sympathetic activity during bladder distension. Slow evacuation of the bladder was always accompanied by a gradual return of the blood pressure and spleen volume to the resting level. The involvement of the sympathetic nervous system for reflex vasopressor response has been indicated by Thompson and Witham [22] and Kurnick [24]. A similar indication has also been put forward by Mukherjee [5] who has suggested that the reflex vasopressor responses are due to splanchnic vasoconstriction. We have performed several experiments in the course of the present investigations to explore the possible involvement of the sympathetic nervous system and particularly the participation of the adrenoceptors in the viscerovascular reflexes during bladder distension. It was found that the reflex rise of blood pressure and change in spleen volume during bladder distension were not affected by the administration of propranolol (β-adrenoceptor antagonist), indicating that the β-adrenoceptors were not involved in such reflex response. The failure of propranolol to modify their effects on viscerovascular response (in

the present study) suggests that it is likely that the effects of this drug are mediated via the stimulation of β-adrenergic fibers on ganglion cells. Phentolamine (α-blocker), hexamethonium (ganglion blocker), and guanethidine sulfate (sympatholytic agent) completely prevented the reflex rise of blood pressure and contraction of the spleen (Fig. 1). The inhibitory effect of phentolamine on the reflex vasopressor response suggests the participation of α-adrenoceptors (sympathomimetic effect). In reserpinized cats, distension of the bladder produced no vasopressor response. Moreover, the effects of hexamethonium, guanethidine sulfate, and reserpine, as observed in the present experiments, on the reflex rise of blood pressure and contraction of the spleen volume not only exclude the involvement of cholinergic nerves, but also indicates the postganglionic activation of the sympathetic nerves including the release of catecholamines from different peripheral sympathetic nerves and also from the catecholamine stores, produce peripheral vasoconstriction. It is possible that the released catecholamines act on the α-adrenoceptors to produce peripheral vasoconstriction during bladder distension. It has been suggested that hexamethonium blocks the release of catecholamines from the sympathetic nerve endings [8, 25, 26]. The systolic and diastolic blood pressure changes during bladder distension in pre- and post-treated condition as found in our experiment are summarized in Table 1.

The absolute volume of spleen before stimulation was found to be 15–20 ml. The contraction of the spleen volume during bladder distension is also thought to be due to peripheral vasoconstriction caused by sympathetic nerve stimulation. The splanchnic region is considered to play a major role in the reflex control of the circulation and thus in the maintenance of blood pressure [27]. It has been suggested in some cases that a splanchnic vasoconstriction mediated by the sympathetic nervous system may be the cause of decrease in splanchnic blood volume [28]. There are reports that epinephrine appears to cause splanchnic vasoconstriction [28–30]. In support of splanchnic vasoconstriction as the cause of contraction of the spleen volume and the rise in blood pressure during bladder distension, we also found that bilateral splanchnicotomy abolished that reflex response (Fig. 2).

Table 1. Blood pressure changes in pre- and post-treated condition during bladder distension.

	Systolic pressure (mmHg)	Distolic pressure (mmHg)
Normal pressure (resting)	140±5	115±3
50–60 ml distension (control)	173±3*	151±3*
Propranolol	172±3	151±3
Phentolamine	146±2*	115±2*
Hexamethonium	142±2*	118±2*
Guanethidine sulfate	142±2*	116±2*

We compared the control distension effect with resting pressure, and the effect of blockers response was compared with control distension. *$p<0.001$.

As a result, no evidence was found of splenic vasoconstriction. The change of resting blood pressure after splanchnicotomy was not significant ($p=0.273$). Splanchnic vasoconstriction is therefore the main cause of the rise of blood pressure that occurs with the distension of bladder in chloralosed cats. The sympathetic nature of the splanchnic nerves and their involvement in the reflex hypertension on bladder distension are strongly indicated. This was further documented by the observed restoration of blood pressure (159 ± 3 mmHg) to a level as found during bladder distension by stimulation of the peripheral cut ends of the splanchnic nerves (Fig. 2). The splanchnic vasoconstriction may be the main cause or one of the causes of the reflex hypertension during bladder distension, as suggested earlier [5].

All these observations prompted us to study the bioelectric activity of the splanchnic sympathetic nerve following urinary bladder distension. The single unit activity from the central cut end was recorded. The resting firing rate from the splanchnic nerve was significantly increased from 0–2 spikes/s to 9–12 spikes/s with the rise in blood pressure during bladder distension (Fig. 3A–C). These increased discharges are sufficient direct indications of the increased activity of the splanchnic sympathetic nerve leading to a rise of blood pressure during bladder distension. Therefore, splanchnic nerves have a marked contribution to the reflex hypertension after bladder distension.

Since the splanchnic bed has a major role in altering the blood pressure and since there was splenic contraction during bladder distension, the splenic sympathetic nerve was recorded with single unit preparation. In our experiments, we observed that marked reduction in the spleen volume occurred with the rise in blood pressure during bladder distension. This observation might suggest the involvement of splenic sympathetic nerve in the splenic vasoconstriction and thereby in the contraction of the spleen along with the rise in blood pressure during urinary bladder distension. The splenic sympathetic nerves arise from the celiac plexus and the nerve to the spleen from the splenic plexus of nerves entwines the splenic artery. The asynchronous spontaneous efferent single unit activity from a branch of the central cut end of the splenic sympathetic nerve was recorded during bladder distension. The single unit activity increased from the resting firing rate of 0–1 spikes/s to 8–14 spikes/s along with the rise in blood pressure during bladder distension (Fig. 4A–C). It is apparent, therefore, that the increase in splenic sympathetic nerve activity was a contributory factor to splenic contraction and blood pressure rise when the bladder was distended.

In conclusion, we found that active involvement and participation of the associated sympathetic nerve, postganglionic sympathetic stimulation, α-adrenoceptor activity, and catecholamine secretion appear to contribute to the reflex viscerovascular responses. Sympathetic over-activity is another cause of increased blood pressure response during bladder distension. The observation that the single unit efferent sympathetic nerve activity was greatly increased along with a rise of blood pressure after bladder distension is direct evidence regarding the involvement of peripheral sympathetic nerves in viscerovascular reflexes.

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