3. RESULTS

3.1. Experimental groups

The experiments were divided into four major groups. Experiments in the Group I deal with the analysis of the cardiovascular and the respiratory parameters with short term (2 - 3 min) distension of the urinary bladder and the electrical stimulation of the afferents from the bladder. Results of the experiments in Group II focus on the factors influencing these parameters studied with the bladder distension. Group III comprises the experiments dealing with the possible mechanisms contributing to the observed cardiovascular and respiratory changes during the bladder distension and also with the direct electrical stimulation of the afferents from the bladder. Results obtained with prolonged distension of the urinary bladder (30 - 120 min) are presented in the Group IV.

In general the results presented here are as follows: In most of the experiments a qualitative analysis of an individual experiment representing the experimental group has been presented. Then quantitative analysis was described with average values ($\bar{X}$) along with standard error of the mean (Sm). When there was no difference in the pretest values, for statical analysis the average values between the two groups were compared. When there was a great variation in the pretest values between the two groups, either the ratios i.e., test/control or the differences i.e., test - control along with the standard error of the mean were presented.

3.2. Effects of short term distension of the urinary bladder

3.2.1. Effects of pneumatic distension of the urinary bladder in dogs

In 23 dogs the urinary bladder was pneumatically distended with stepwise increase of the intraluminal pressure from 20 - 140 Torr for 1 to 2 min. Its effects on the mean arterial pressure, heart

frequency and respiratory frequency were analysed. The mean arterial pressure was approximated as follows:

$$\bar{P}a = 1/3 \text{ (Pa systol - Pa diastol)} + \text{Pa diastol.}$$

3.2.1.1. Changes in the arterial pressure

Figure 2 represents an example of an experiment in which an increase in the arterial pressure was seen as a consequence of gradually elevating the intraluminal pressure of the bladder. The quantitative analysis of these results were summarised in figure 3. As it can be seen in this figure (Fig. 3) gradual elevation of the intraluminal pressure from 20 to 140 Torr resulted in a small but a consistent increase of the mean arterial pressure from the control arterial pressure of 128 $\pm$ 4.7 Torr. Minimum increase to 132 $\pm$ 3 Torr (+ 2.5 %) was seen with intraluminal pressure of 20 Torr, while a maximum increase of 137 $\pm$ 4.9 Torr (+ 6.5 %) was obtained with 140 Torr of intraluminal pressure. After releasing the intraluminal pressure, the arterial pressure fell down to 120 $\pm$ 3.3 Torr which is - 6.5 % below the control value.

3.2.1.2. Changes in the heart frequency

The predistension heart frequency studied in 13 dogs was 129.7 $\pm$ 10.3 min^{-1} . From this control value of 129.7 $\pm$ 10.3 min^{-1}, the heart frequency increased to 139 $\pm$ 12.4 min^{-1} (+ 7 %) with 20 Torr of intraluminal pressure. The maximum increase of the heart frequency was 147 $\pm$ 13.3 min^{-1} (13 %) at an elevated intraluminal pressure of 120 Torr (Fig. 3). There was slight adaptation in the increase of the heart frequency with further elevation of the intraluminal pressure. Thus, at 140 Torr of intraluminal pressure the frequency was 142 $\pm$ 12.6 min^{-1}, which is about 5 beats.min^{-1} (- 2 %) less than the maximal tachycardic response. There was a marked bradycardia of 118 $\pm$ 16.3 min^{-1}

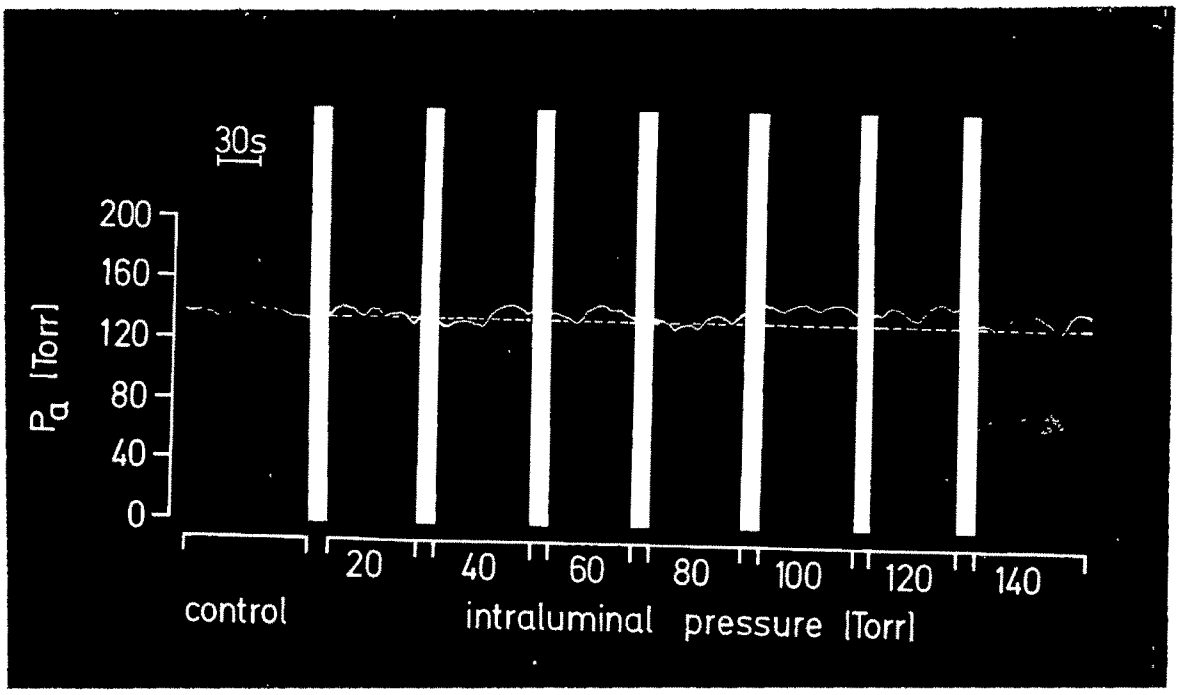


Figure 2: A kymograph record of the arterial pressure during the pneumatic distension of the urinary bladder varying from 20 to 140 Torr of intraluminal pressure. The continuous dotted line indicates an approximate control mean arterial pressure.

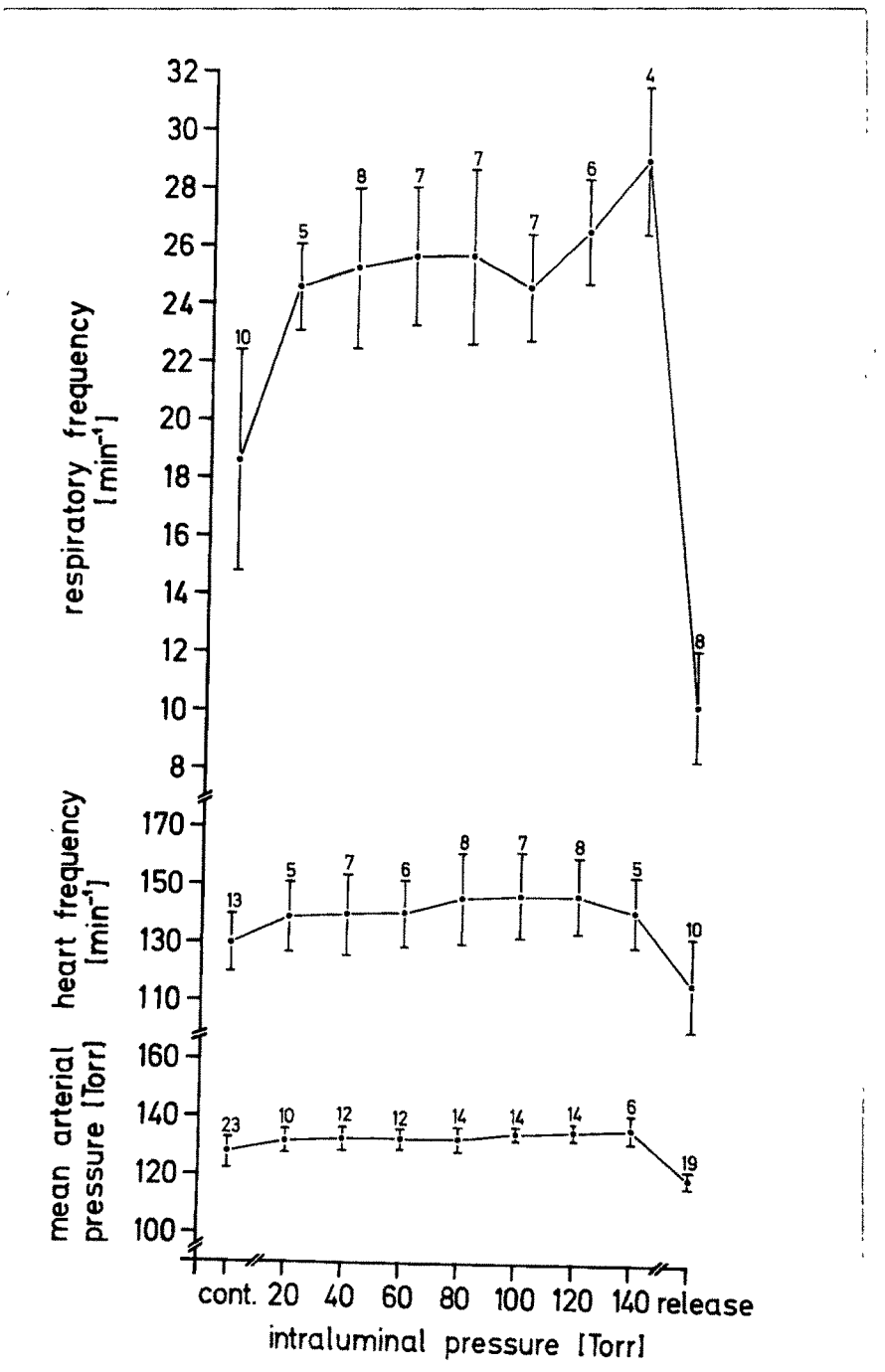


Figure 3: Quantitative analysis of the changes in the mean arterial pressure (Torr), the heart frequency (HF min^{-1}) and the respiratory frequency ($f.min^{-1}$) during the pneumatic distension of the urinary bladder in chloralose anaesthetized dogs. The data presented are the mean values ($\bar{X}$) with standard error of the mean (Sm) obtained from 10 - 23 dogs. The numbers above the points indicate the number of observations.

(- 9.5 %) after releasing the intraluminal pressure.

3.2.1.3. Changes in the respiratory frequency

In 10 dogs, the changes in the respiratory frequency were analysed after the pneumatic distension of the urinary bladder. As a result of elevating the intraluminal pressure to 20 Torr, the respiratory frequency increased to 25 $\pm$ 1.6 min^{-1} (+ 32 %) from the control value of 19 $\pm$ 3.8 min^{-1}. The increase in the respiratory frequency reached a maximum value of 29 $\pm$ 2.6 min^{-1}. This maximum increase of the respiratory frequency was seen with an intraluminal pressure of 140 Torr. After releasing the intraluminal pressure, the respiratory frequency showed an undershoot.

Though, in general the cardiovascular and respiratory parameters showed an increase as a result of bladder distension, occasionally a small decrease or no change in these parameters was also seen especially at high intraluminal pressures i.e., above 120 Torr. No change in these parameters was encountered when there was a massive haematoma of the bladder.

3.2.2. Effects of distension of the bladder by saline

In another group of 5 dogs, the distension of the urinary bladder was achieved by urethral infusion of saline solution for a period of two minutes. In these experiments the rate of the bladder filling was kept between 40 - 45 $ml \cdot min^{-1}$, with a pressure head of 90 Torr. The intravesical pressure and the mean arterial pressure were analysed for every 30 s.

As a result of gradual inflow of the saline into the bladder, within 30 s the intravesical pressure rose to 41 $\pm$ 3.9 Torr. Correspondingly, the arterial pressure increased from 136 $\pm$ 4.8 Torr to 145 $\pm$ 4.8 Torr (Fig. 4). The increase of the arterial pressure reached to its maximum at 0 - 60 s of distension.

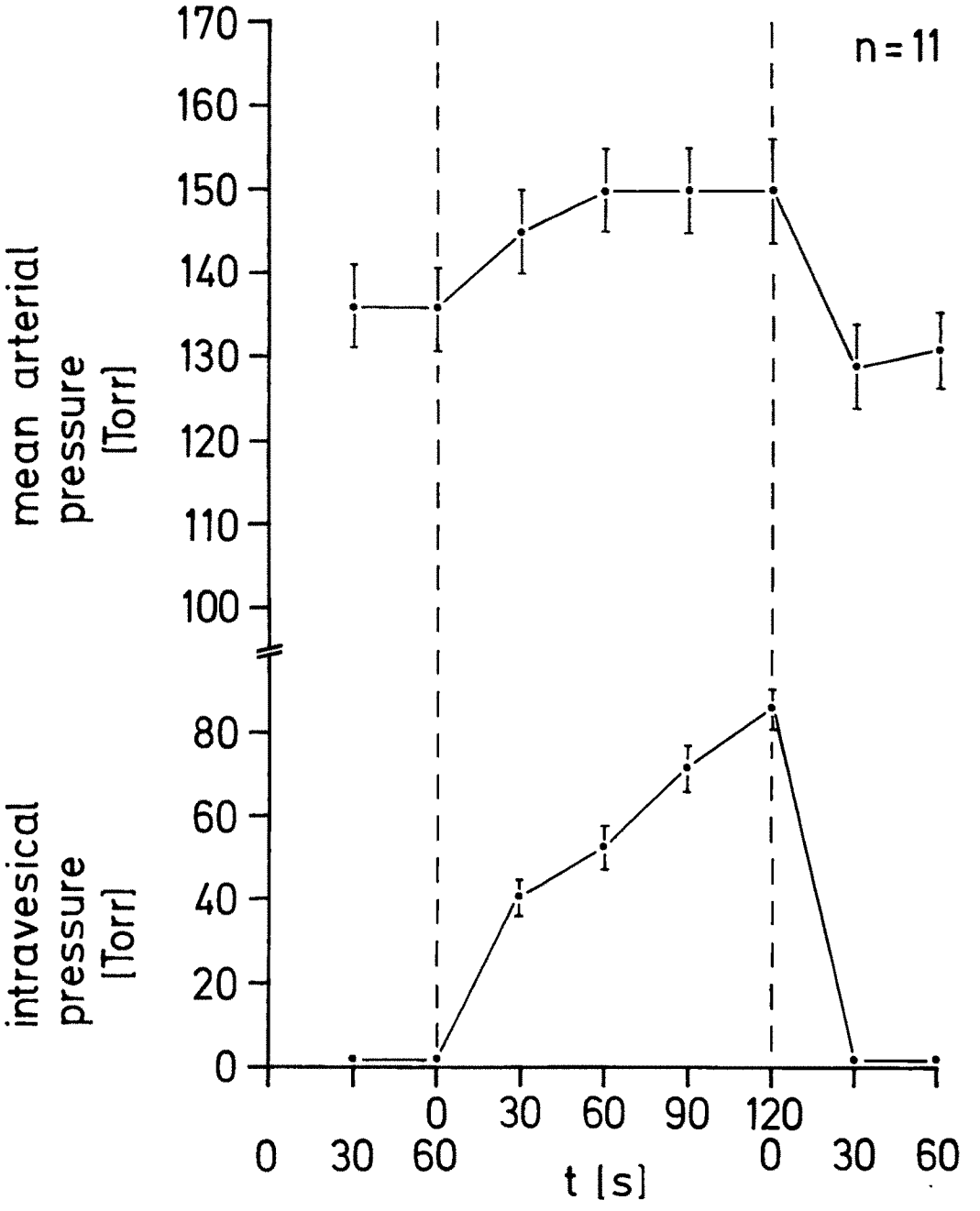


Figure 4: Effect of increasing the intravesical pressure with urethral infusion of saline at a rate of 40 - 45 $ml \cdot min^{-1}$ on mean arterial pressure in anaesthetized dogs. The dotted vertical lines indicate the beginning and the end of distension of the bladder. No relation between the increase of intravesical pressure and arterial pressure was seen. The data presented were obtained from 11 distensions performed on 5 dogs, mean values ($\bar{X}$) with standard error of the mean (Sm).

		PREDISTENSION		DISTENSION				POSTDISTENSION	
	time (s)	0-30	30-60	0-30	30-60	60-90	90-120	0-30	30-60
Mean arterial pressure [Torr]	$\bar{X}$	136.4	136.6	144.9	149.5	150.0	150.2	129.1	131.1
	Sm	4.77	4.81	4.81	5.0	4.95	5.64	5.04	4.72
	n	11	11	11	11	11	11	11	11
predistension vs distension	t			4.1	4.4	5.1	4.8	3.2	4.2
	p			0.0005	0.0003	>0.0002	>0.0002	0.005	0.0005
intravesical pressure [Torr]	$\bar{X}$	-	-	41.1	53.5	72.2	86.7	-	-
	Sm	-	-	3.99	5.10	6.02	5.35	-	-
	n	-	-	11	11	11	11	-	-

Table 1: Average arterial pressure changes during the distension of the urinary bladder with saline in anaesthetized dogs. $\bar{X}$ is the arithmetic mean, Sm is the standard error of the mean, n is the number of observations obtained from 5 dogs. Statistical comparison of the distension values with the predistension were made using the paired 't' test.

This maximum increase of the arterial pressure was 149.5 ± 5.0 Torr, which is +9.5 % above the control value. At the time of the maximal increase of the arterial pressure, the value of the intravesical pressure was 54.5 ± 5.1 Torr. Compared to the control value the arterial pressure increase during the distension was significant (Table 1). After attaining the maximal value the arterial pressure maintained a plateau, inspite of the further increase in the intravesical pressure to about 86.7 ± 5.4 Torr. Within one minute after releasing the bladder pressure the arterial pressure fell to 131 ± 4.7 Torr, which is about 4 % below the control value.

3.2.3. Effects of saline distension of the urinary bladder in cats

Figures 5 and 6 show examples of the experiments in which the heart frequency, arterial pressure, tidal volume, and end expiratory $P_{E\ CO_2}$, intravesical pressure, and rectal temperatures were measured in anaesthetized cats. The urinary bladder was distended for a period of 2 minutes with 35 ml of saline (Fig. 5) and 55 ml (Fig. 6) infused through the urethra. The rate of urethral infusion of saline was about 80 $ml \cdot min^{-1}$. The cardiovascular and the respiratory parameters were analysed. for every 30 s.

3.2.3.1. Arterial pressure

In the example shown in Fig. 5 the arterial pressure began to increase in response to bladder distension. The elevation in the systolic and diastolic pressures reached their maximum value at 0-90 s of the distension period - where the intravesical pressure was 59 Torr. The maximal increases were to 187.8 Torr (+21.9 %) and 146 Torr (12.7 %) for systolic and diastolic pressures from the control values of 154 and 129.7 Torr respectively. Followed by this maximal increase, the arterial

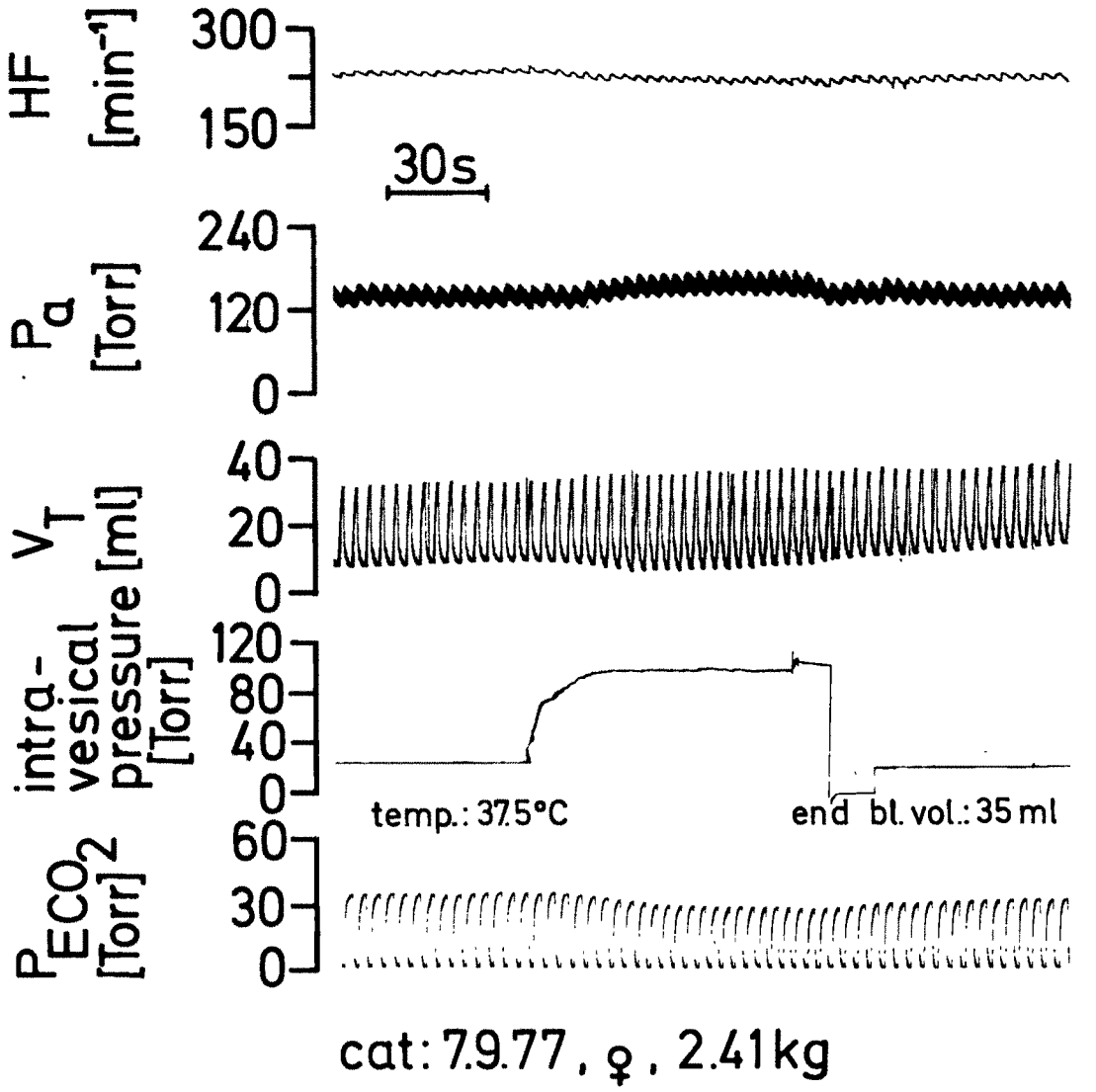


Figure 5: Continuous record of the heart frequency (HF min^{-1}), arterial pressure (Pa Torr), tidal volume (V_T ml), intravesical pressure (Torr) and end-expiratory CO_2 (Torr) in spontaneously breathing anaesthetized cat. As the intravesical pressure was increased by urethral infusion of 35 ml saline, an increase in the arterial pressure, bradycardia and an increase in ventilation were seen. As the bladder pressure was released all these changes returned to the predistension level.

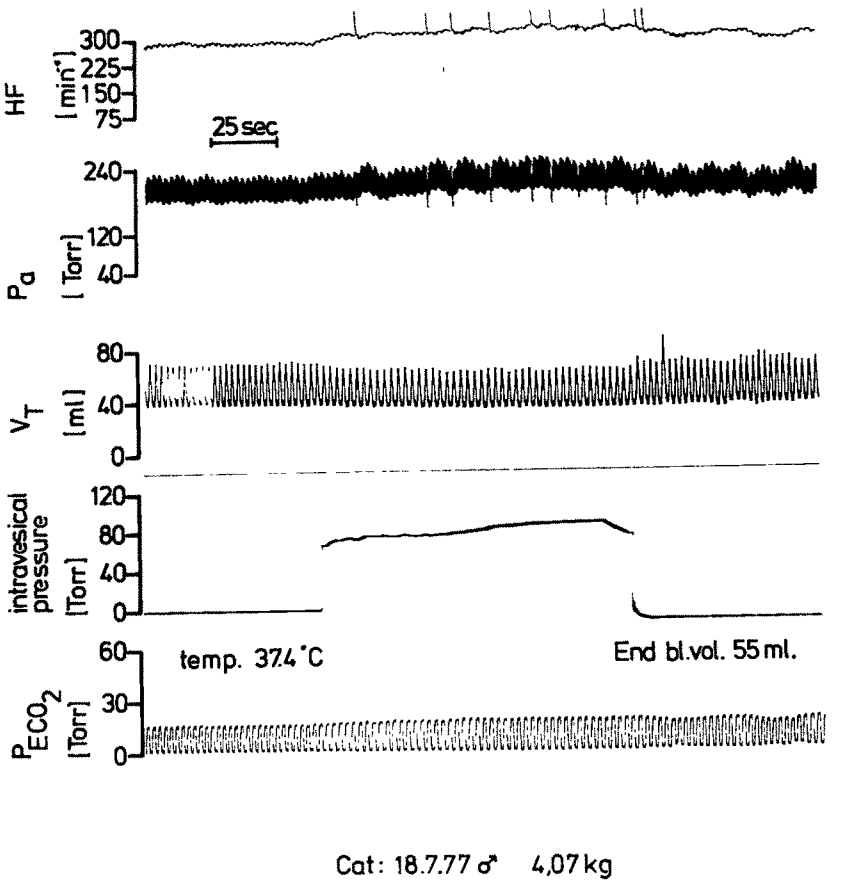


Figure 6: Continuous record of heart frequency ($HF \cdot min^{-1}$), arterial pressure (Pa Torr), tidal volume (V_T ml), intravesical pressure (Torr) and expiratory P_{CO_2} (P_E CO_2 Torr) in spontaneously breathing anaesthetised cat. The urinary bladder was distended with urethral infusion of 55 ml of saline. During the distension of the bladder an increase of arterial pressure, tachycardia with extrasystoles and a decrease of tidal volume were seen. As soon as the bladder pressure was released the arterial pressure showed an undershoot and extrasystoles were no longer seen. There was an increase in ventilation in the post distension period.

pressure slightly decreased, although the bladder pressure was still increasing. After emptying the bladder within one minute, the systolic and the diastolic pressures almost returned to the predistension values. Such an increase of the arterial pressure resulting from the bladder distension can also be seen in the experiment shown in figure 6.

The response of the increase in arterial pressure, during the distension of the urinary bladder was highly reproducible, provided there was no haematoma of the bladder.

Figure 7 and Table 2 represent the quantitative analysis of the systolic and diastolic pressure changes during 11 distensions of the bladder carried out on six cats. As the intravesical pressure started to increase there were increases in the systolic and diastolic pressures. Average latency for the increase of the arterial pressure was 11.3 $\pm$ 1.9 s. The increase in the arterial pressure started when the intravesical pressure was about 58.1 $\pm$ 1.3 Torr. The maximum elevation of the systolic pressure was to 188 $\pm$ 4.6 Torr from the control value of 160 $\pm$ 2.6 Torr. The maximum increase in the diastolic pressure was to 152 $\pm$ 3.9 Torr from 129 $\pm$ 2.7 Torr. These maximal increases were obtained at 0-120 s of distension. During the later phases of distension, the arterial pressure slightly decreased from the maximal value, but remained elevated above the control value. The increase in the systolic and the diastolic pressures were statistically significant (Table 2). As the bladder was emptied within one minute the arterial pressure fell about 2 % (156.7 $\pm$ 2.4 systolic; 126.6 $\pm$ 3.8 diastolic) below the control value. During the distension phase, the relative increases in the systolic and diastolic pressures were almost of the same magnitude as can be seen from the calculated ratios (test/control) of these parameters (Table 2).

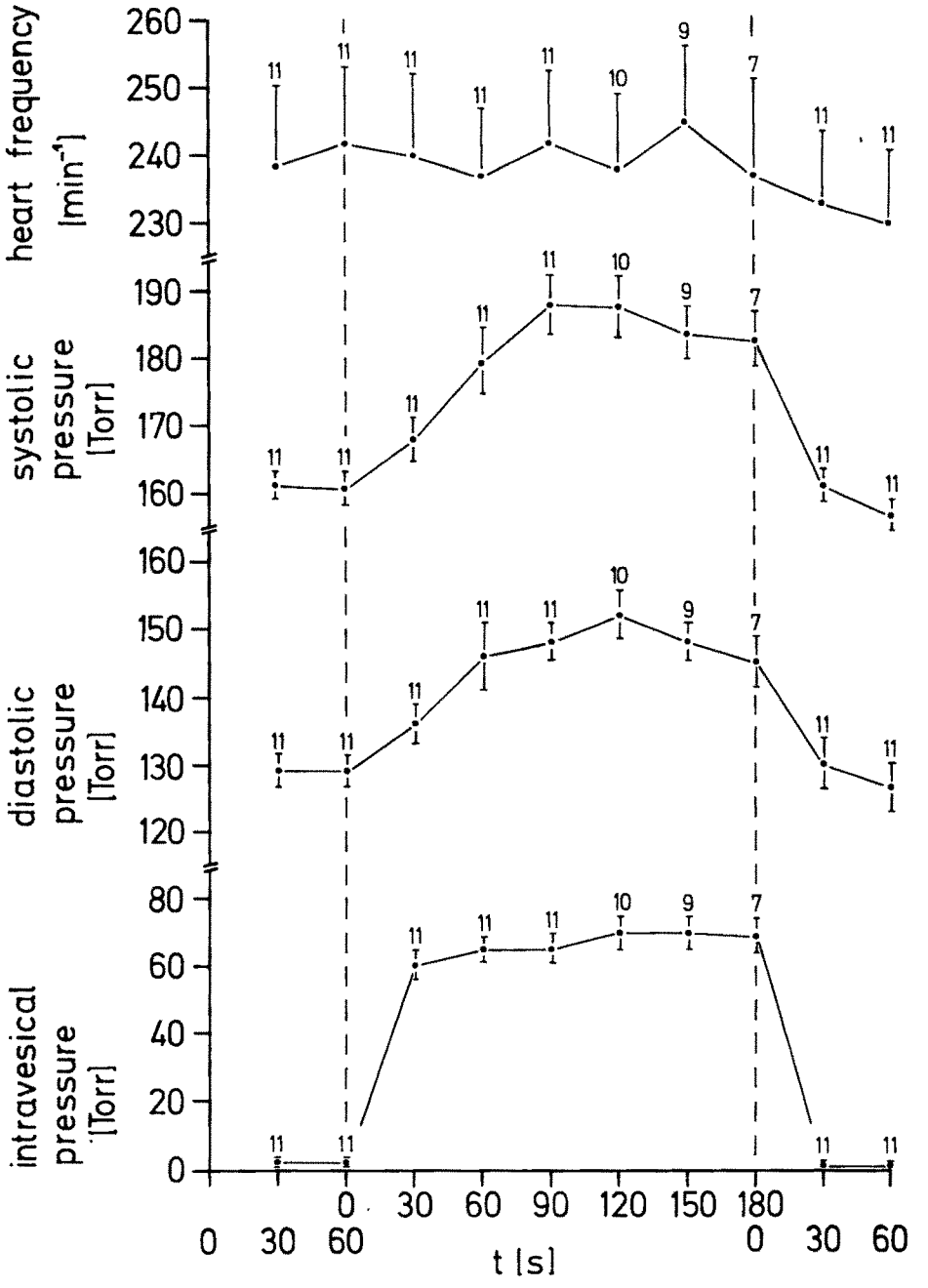


Figure 7: Averages of the systolic pressure, the diastolic pressure (Torr) and the heart frequency (min^{-1}) during distension of the urinary bladder with urethral infusion of saline in anaesthetized cats. The dotted vertical lines indicate the beginning and the end of the distension. The data presented were the average values ($\bar{X}$) with the standard error of the mean (Sm). The numbers above the data indicate the number of observations obtained from six cats. There was no relation between the increase of the arterial pressure and the intravesical pressure. A slight adaptation of the pressor response can be seen from 0 - 120 s of distension period.

	time (s)	PREDISTENSION 0-30	PREDISTENSION 30-60	DISTENSION 0-30	DISTENSION 30-60	DISTENSION 60-90	DISTENSION 90-120	DISTENSION 120-150	DISTENSION 150-180	POSTDISTENSION 0-30	POSTDISTENSION 30-60
systolic pressure [Torr]	$\bar{X}$	161.3	160.4	168.2	179.6	187.6	188.2	184.3	183.1	161.5	156.7
	Sm	2.42	2.59	3.59	4.98	4.47	4.68	4.09	4.05	2.77	2.38
	n	11	11	11	11	11	10	9	7	11	11
predistension vs distension	t			1.8	3.4	5.3	5.2	4.9	4.3	0.3	1.0
	P			0.1	0.0027	<0.0002	<0.0002	<0.0002	0.00054	> 0.5	0.34
diastolic pressure [Torr]	$\bar{X}$	129.1	129.2	136.2	146.2	147.9	151.9	148.3	145.4	130.0	126.6
	Sm	2.72	2.72	3.28	5.03	3.06	3.99	3.24	4.19	3.93	3.87
	n	11	11	11	11	11	10	9	7	11	11
predistension vs distension	t			1.6	2.9	4.6	4.7	4.5	3.2	0.2	0.6
	P			0.15	0.012	<0.0002	<0.0002	0.00024	0.005	> 0.5	> 0.5
test/control diastolic systolic pressure pressure	$\bar{X}/\bar{X}$ control	-	-	1.04	1.11	1.16	1.17	1.14	1.12	0.99	0.97
	Sm	-	-	0.01	0.01	0.02	0.02	0.02	0.01	0.01	0.01
	n	-	-	11	11	11	10	9	7	11	11
	$\bar{X}/\bar{X}$ control	-	-	1.05	1.13	1.14	1.18	1.16	1.13	0.99	0.97
	Sm	-	-	0.01	0.02	0.01	0.01	0.02	0.02	0.01	0.01
	n	-	-	11	11	11	10	9	7	11	11

Table 2: The systolic and the diastolic pressure changes during the distension of the urinary bladder in anaesthetized cats. $\bar{X}$ is the arithmetic mean, Sm is the standard error of the mean, n is the number of observations obtained form 6 cats, t is the t value calculated according to Fischer's t-test, P is the probability according to null hypothesis. The P values which were underlined indicate that they are statistically significant. Ratios (test/control) of the systolic and the diastolic pressure changes were also presented with the standard error of the mean (Sm) to show that both the systolic and diastolic pressures were increased to the same extent during the urinary bladder distension.

3.2.3.2. Heart frequency

In the example shown in the figure 5 bladder distension resulted in a decrease of the heart frequency. The maximum decrease of the heart frequency was about 15 min^{-1} (248 min^{-1}) from the control heart rate of 263 min^{-1}. After releasing the bladder pressure the heart rate returned to the predistension value.

Another example of the heart frequency response with bladder distension is presented in the figure 6. In this experiment an increase of the heart frequency of about +37 min^{-1} (322 min^{-1}) from the control value of 285 min^{-1} was seen during the bladder distension. This increase in the heart frequency was accompanied with extrasystoles. After releasing the bladder pressure the heart rate returned to the control value and the extrasystoles also disappeared. Thus there was a great variation of the heart rate response during the bladder distension in the experiments studied in this group. Analysis of the data collected from six cats have shown a slight bradycardia during the initial phases (at 0 - 60 s) of the bladder distension. This bradycardia was quickly adapted in the later phases of distension (Fig. 7).

3.2.3.3. Respiratory parameters

In the example shown in the figure 5, as the bladder was distended, the tidal volume increased from 24 to 29 ml (+5 ml) and the respiratory frequency increased from 15 to 18 min^{-1} (+3 min^{-1}). The minute ventilation increased from the predistension value of 362 $ml \cdot min^{-1}$ to 526 $ml \cdot min^{-1}$ (+164 $ml.min^{-1}$). After releasing the bladder pressure the respiratory parameters returned to the control value.

Although in majority of the experiments there was an increase in the ventilation, occasionally a decrease of ventilation was also encountered.An example of such a decrease in the ventilation is

depicted in the figure 6. In this experiment as the bladder was distended the tidal volume decreased from 31 ml to 28 ml and the respiratory frequency from 28 min^{-1} to 22 min^{-1}. Similarly the minute ventilation decreased from the control value of 870 $ml \cdot min^{-1}$ to 605 ml·min-^{1} (-265 $ml \cdot min^{-1}$). After releasing the bladder pressure the respiratory parameters returned to the predistension values.

Averaging the data obtained from eleven distensions performed in six individual experiments has shown that bladder distension resulted in a maximum increase of the tidal volume from 20 $\pm$ 1.6 ml to 23.6 $\pm$ 1.4 ml (+17.4 %) at 0-90 s of distension (Fig. 8). But the full increase in the tidal volume was not maintained throughout the distension phase. It almost returned to the control value at 0-180 s of distension. Respiratory frequency responded with a maximum increase from 17.3 $\pm$ 1.4 min^{-1} to 19.5 $\pm$ 2.2 min^{-1} at 0 - 180 s of distension.

It can be seen from figure 8 that with elevated intravesical pressure there was an increase of the minute ventilation from the control value of 339.6 $\pm$ 27.6 $ml \cdot min^{-1}$ to a maximum of 431 $\pm$ 36.7 $ml \cdot min^{-1}$ (+28.8 %) at 0 - 150 s of distension. At 0 - 180 s of distension the increase of the minute ventilation was adapted and stabilized at 393 $\pm$ 43.5 $ml \cdot min^{-1}$ which is 16 % above the predistension ventilation. The increase of the ventilation during the distension was statistically significant (Table 3). After one minute of releasing the bladder pressure the respiratory parameters almost returned to their predistension values.

Summarising this group of experiments it can be stated that pneumatic distension of the bladder in dogs resulted in an increase of the arterial pressure, the heart frequency and the respiratory frequency. Similarly distension of the bladder with saline for 2 - 3 min in both dogs and cats resulted in an increase of the arterial pressure. In the experiments on cats the ventilation increased during the distension.

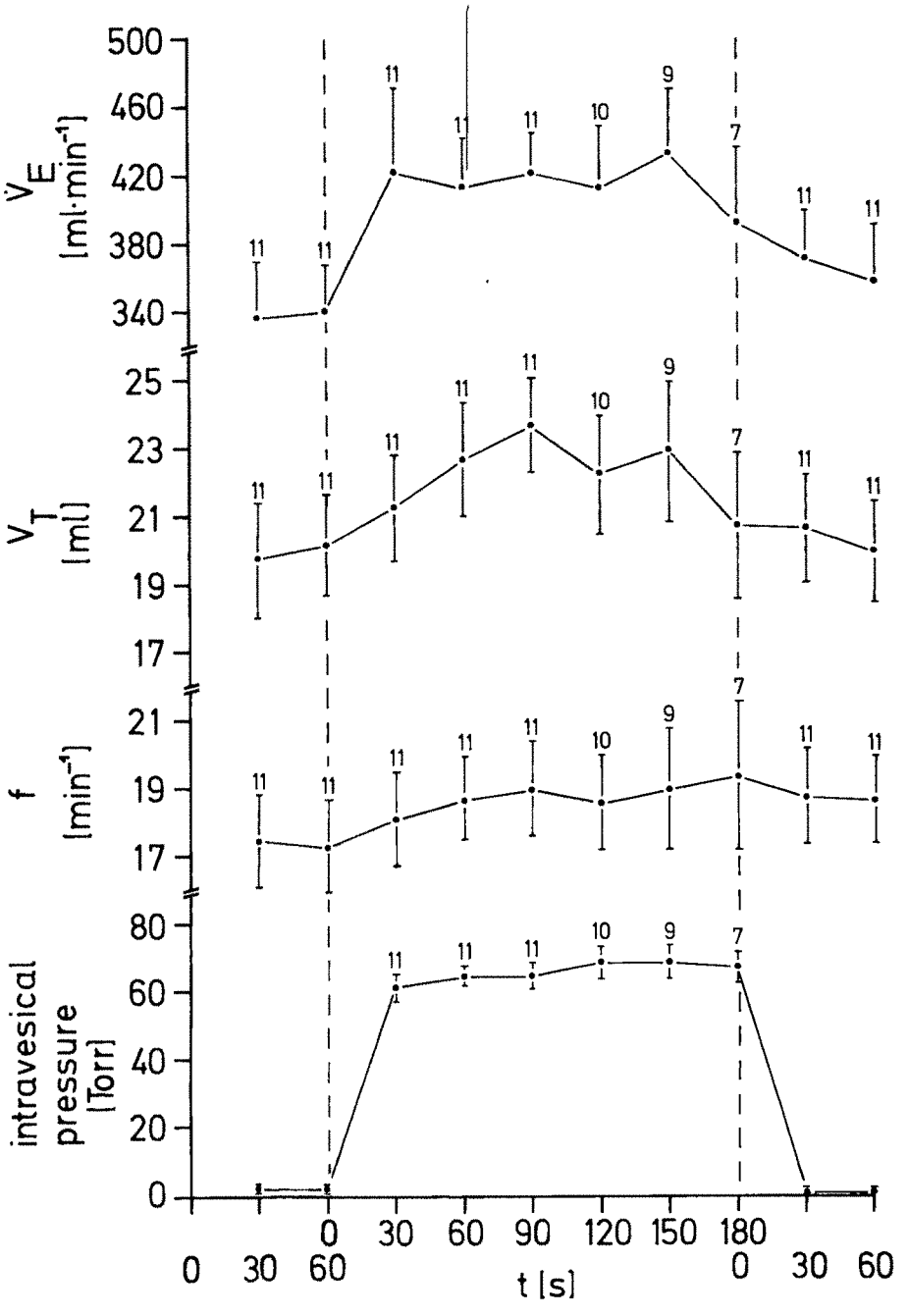


Figure 8: Averages of the respiratory frequency ($f \cdot min^{-1}$), the tidal volume (V_T ml) and the minute ventilation ($\dot{V}_E$ $ml \cdot min^{-1}$) during distension of the urinary bladder with saline in anaesthetized cats. The dotted vertical lines indicate the beginning and the end of the stimulation. The data presented were The mean values ($\bar{X}$) with standard error of the mean (Sm). the numbers above the data indicate the number of observations obtained from six cats.

		PREDISTENSION		DISTENSION						POSTDISTENSION	
	time (s)	0-30	30-60	0-30	30-60	60-90	90-120	120-150	150-180	0-30	30-60
Tidal volume [V_T ml] predistension vs distension	$\bar{X}$	19.8	20.3	21.3	22.7	23.6	22.4	23.1	20.8	20.8	20.1
	Sm	1.77	1.55	1.63	1.75	1.41	1.89	2.15	1.21	1.68	1.55
	n	11	11	11	11	11	10	9	7	11	11
	t			0.4	1.0	1.6	1.9	1.1	- 0.3	0.2	0.1
	P			>0.5	0.36	0.14	0.054	0.32	>0.5	>0.5	>0.5
frequency [$f\ min^{-1}$] predistension vs distension	$\bar{X}$	17.5	17.3	18.1	18.7	18.9	18.7	18.9	19.5	18.8	18.7
	Sm	1.40	1.44	1.42	1.28	1.48	1.46	1.83	2.20	1.40	1.35
	n	11	11	11	11	11	10	9	7	11	11
	t			0.4	0.7	0.8	0.7	0.7	0.8	0.8	0.7
	P			>0.5	>0.5	>0.5	>0.5	>0.5	>0.5	>0.5	>0.5
Minute ventilation [$\dot{V}_E$ ml·min^{-1}] predistension vs distension	$\bar{X}$	335.2	339.6	422.1	413.3	421.4	414.4	431.4	393.3	371.7	359.6
	Sm	33.4	27.6	51.0	26.8	28.7	35.6	36.7	43.5	28.6	32.2
	n	11	11	11	11	11	10	9	7	11	11
	t			0.9	5.5	4.8	5.4	5.2	2.3	2.5	1.2
	P			>0.5	0.0003	0.00054	0.0005	0.00054	0.04	0.03	0.26

Table 3: Changes in the tidal volume ($V_T$ml), respiratory frequency ($f.min^{-1}$) and minute ventilation ($\dot{V}_E$ $ml \cdot min^{-1}$) during the distension of the urinary bladder in anesthetized cats. $\bar{X}$ is the arithmetic mean; Sm is the standard error of the mean, n is the number of observations obtained from 6 cats. t is the t value calculated according to the paired t-test. P values which were underlined indicate that they are statistically significant.

3.2.4. Effects of electrical stimulation of the afferents from the urinary bladder

This group of experiments is dealing with the experiments performed on cats, where the activity of the bladder receptors has been mimicked by electrical stimulation of the afferents from the bladder, namely the pelvic and the hypogastric nerves.

Electrical stimulation for about 30 s was carried out on one (either the right or the left) cut central end of the pelvic and the hypogastric nerves. The contralateral bladder nerves were cut so as to avoid efferent influences on the bladder (DE GROAT and LALLY 1972), which might modify the observed responses. The stimulus parameters used were usually 4 - 5V; 10 - 20 imp·s^{-1}, 2 ms. Cardiovascular and respiratory parameters were analysed for every 5 s.

3.2.4.1. Arterial pressure

Electrical stimulation of the pelvic as well as the hypogastric nerve led to an increase of the arterial pressure. An example of this group of experiments is shown in figure 9 a and b. In this experiment with the pelvic nerve stimulation, the maximum increase in the systolic pressure was from 183.4 to 235.2 Torr (+28.2 %) and the diastolic pressure was from 143 to 177.6 Torr (+24 %). In the same experiment with identical stimulus parameters a more marked increase of the arterial pressure was seen with stimulation of the hypogastric nerve (Fig. 9b). The increase in the systolic pressure was from 186.2 to 264 Torr (+41.8 %) and the diastolic pressure was from 147.8 to 196.8 Torr (+ 33.2 %). With both the pelvic and the hypogastric nerves after the maximum increase there was some adaptation in the increase of the arterial pressure; but throughout the stimulation period the arterial pressure remained elevated above the control value. As the electrical stimulation was stopped

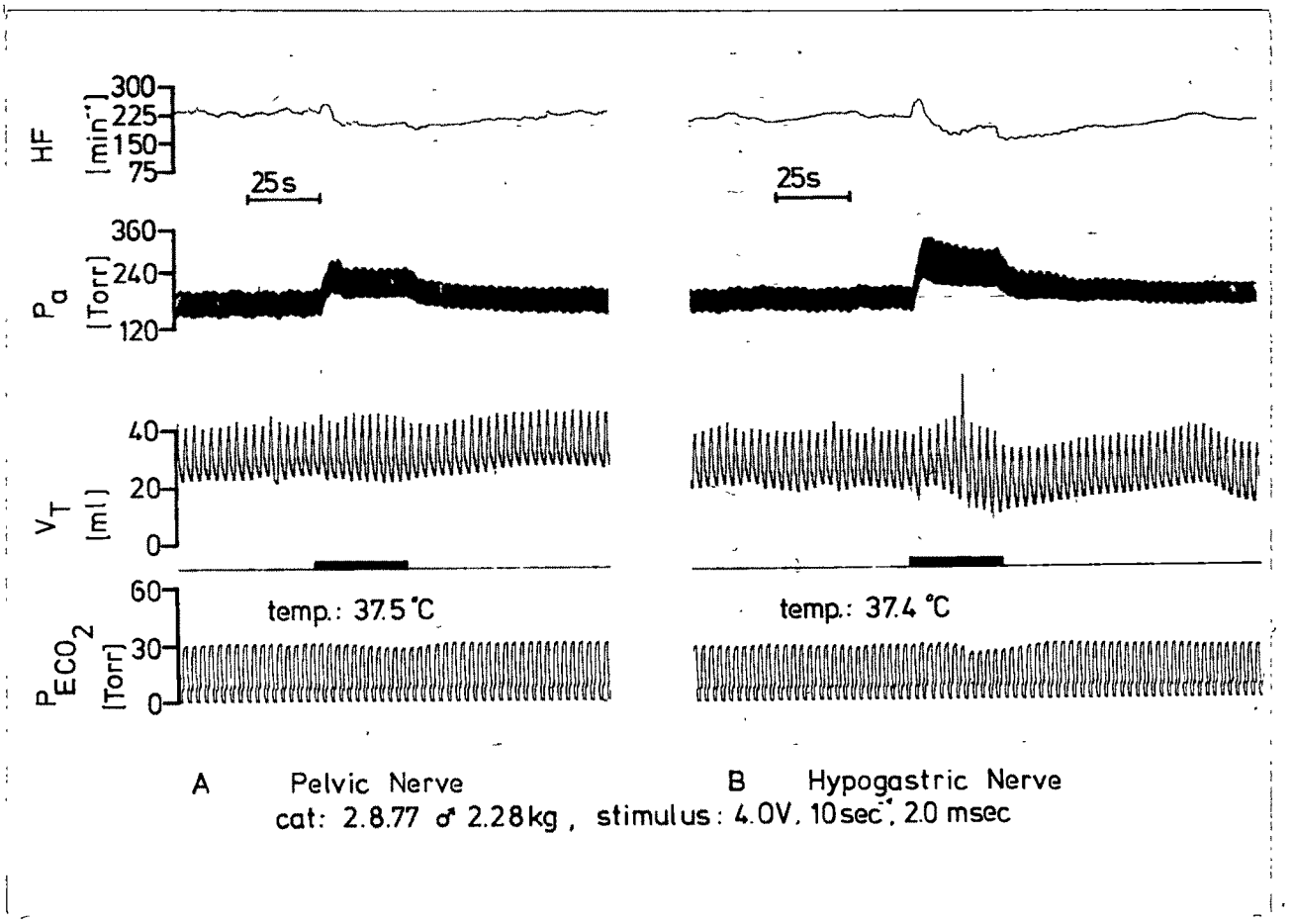


Figure 9 (a and b): Continuous record of the heart frequency (HF·min^{-1}), the arterial pressure (Pa Torr), the tidal volume (V_T ml) and the end tidal CO_2 (P_{ECO_2} Torr) during the electrical stimulation of the cut central ends of the pelvic and the hypogastric nerves in an anaesthetised cat. The black bars indicate the period of stimulation. Note that with the same stimulation parameters the arterial pressure increase in hypogastric nerve stimulation was more marked in comparison to pelvic nerve stimulation. After stopping the stimulus with both the nerves there was a slow return of the arterial pressure to the prestimulus value.

with the pelvic as well with the hypogastric nerve, there was a slow return of the arterial pressure to the control value.

Such changes in the arterial pressure obtained with electrical stimulation of the afferents from the urinary bladder (i.e., the pelvic and the hypogastric nerves) were highly reproducible in all the six cats studied. The average changes in the cardiovascular parameters were analysed for every 5 s and were presented in figure 10 a and b. Electrical stimulation of the cut central end of one pelvic nerve (4 - 5 V; 10 - 20 imp$\cdot s^{-1}$, 2 ms) resulted in an increase of the arterial pressure. The average maximum increase of the systolic pressure was to 214.8 ± 5.3 Torr (+20.5 %) from the control value of 178 ± 4.2 Torr and of the diastolic pressure was 152.9 ± 6.9 Torr (+26 %) from the prestimulation value of 121 ± 5.1 Torr (Fig. 10a). Also, the hypogastric nerve stimulation with the same stimulus parameters was followed by an increase in the systolic pressure from 178.0 ± 4.1 to 234.8 ± 9.4 Torr (+32 %) and the diastolic pressure from 122.5 ± 5.5 to 164 ± 7.4 Torr (+33.8 %) (Fig. 10b). Followed by this maximal elevation, from 15 s of stimulation onwards there was an adaptation in the arterial pressure increase. Thus the systolic and the diastolic pressures with the pelvic nerve stimulation were stabilized at +17.7 % (209.9 ± 5.5 Torr) and +21 % (147.2 ± 7.1 Torr) respectively above the control values. As with the hypogastric nerve stimulation they were +26 % (224 ± 7.9 Torr systolic) and +25 % (153 ± 6.4 Torr diastolic) above the prestimulus value.

For the purpose of statistical comparison the arterial pressure values were averaged over a period of 30 s (12 experiments) in the control period and during the stimulation. Such average values of the systolic and diastolic pressures during the stimulation were compared with the prestimulus values. The increase in the systolic and diastolic pressures during the pelvic nerve stimulation were significant at P values less than 0.0002 for $n = 70$, while with the hypogastric nerve stimulation they were significant at P values less than 0.0002 for $n = 70$.

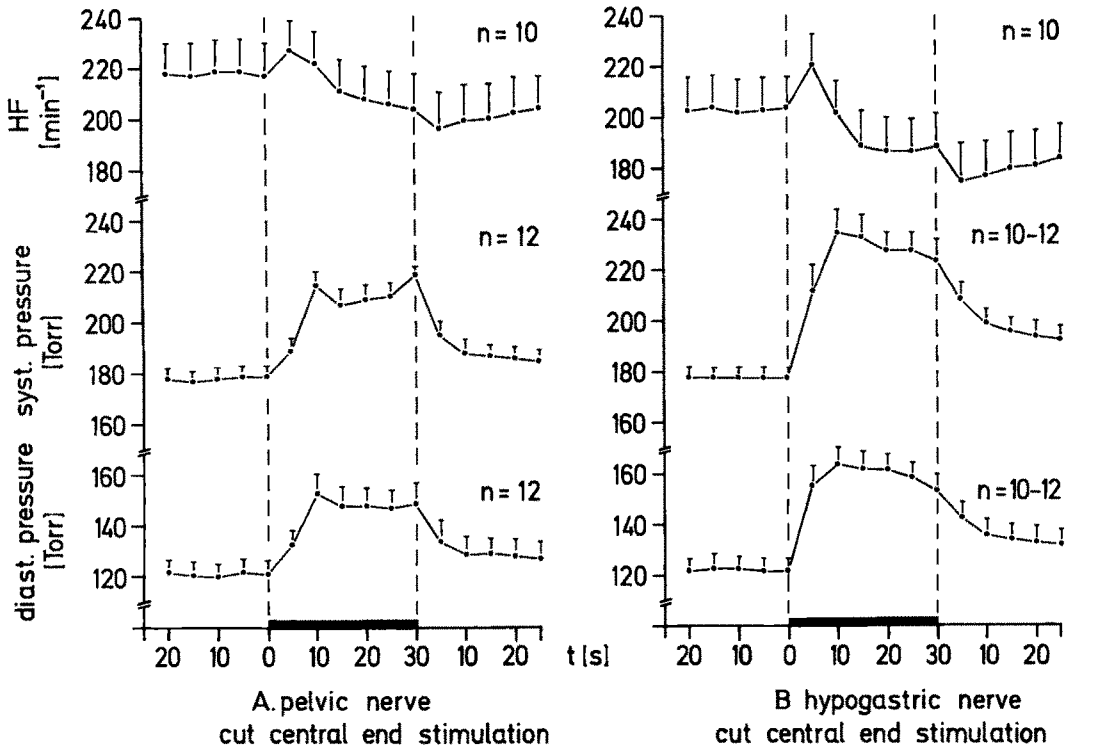


Figure 10 (a and b): Averages of the systolic pressure, the diastolic pressure (Torr) and the heart frequency ($HF \cdot min^{-1}$) during electrical stimulation of the pelvic and the hypogastric nerves with 4 - 5 V; 10 - 20 $imp.sec^{-1}$, 2 ms. The black horizontal bars on the abscissa indicate the period of stimulation. The data presented are the mean values ($\bar{X}$) with standard error of the mean (Sm). n is the number of observations obtained from six cats. With identical stimulus parameters the cardiovascular changes were more marked with the hypogastric nerve stimulation than with the pelvic nerve stimulation.

In this group of experiments it was observed that with identical stimulus parameters the increase in the arterial pressure was more pronounced with hypogastric nerve stimulation than with the pelvic nerve stimulation. In order to test the statistical validity, the pressor responses obtained with the hypogastric nerve stimulation were compared with the responses of pelvic nerve. As it can be seen from Table 4 with identical stimulus parameters both the systolic and the diastolic pressure increases resulting from the hypogastric nerve stimulation were significantly higher as compared with pelvic nerve stimulation (P values less than 0.0002).

As the stimulation was stopped, the systolic and the diastolic pressures tended to reach the control value, but remained elevated by about +5 % to +8 % above the control value.

3.2.4.2. Heart frequency

Pelvic and hypogastric nerve stimulation resulted in an initial tachycardia followed by a bradycardia (Fig. 9 a and b). In pelvic nerve stimulation, the average increase in the heart frequency was to 227 ± 12.4 min^{-1} (+4 %) from the control value of 218 ± 12.7 min^{-1} (Fig. 10a). The tachycardic response obtained with hypogastric stimulation was 220 ± 12 min^{-1} (+8.5 %) from the prestimulus frequency of 204 ± 12.9 min^{-1} (Fig. 10b). This increase in the heart frequency lasted for about 5 to 7 s. After 10 s of the stimulation there appeared a progressive bradycardia which reached its maximum after about 30 s of stimulation. The maximum bradycardia obtained with pelvic nerve stimulation was 204 ± 13.9 min^{-1} (-6 %), while the corresponding value with stimulation of the hypogastric nerve was 187 ± 13.8 min^{-1} (-7.9 %).

As soon as the stimulation was stopped the bradycardia became more pronounced for about 5 s. Even after 25 s of the poststimu-

			PRESTIM.	STIM.	POSTSTIM.
systolic Pa [Torr]	Pelvic nerve	$\bar{X}$	178.3	207.9	186.6
		Sm	1.9	2.4	2.4
		n	60	70	60
	Hypogastric nerve	$\bar{X}$	179.5	227.0	195.8
		Sm	2.2	3.6	4.0
		n	60	70	60
	Pelvic vs hypogastric	t	0.410	4.42	1.97
		P	> 0.5	< 0.0002	0.05
diastolic Pa [Torr]	Pelvic nerve	$\bar{X}$	121.3	146.6	129.4
		Sm	2.2	2.9	2.9
		n	60	70	60
	Hypogastric nerve	$\bar{X}$	122.5	160.6	135.5
		Sm	2.4	2.9	2.8
		n	60	70	60
	Pelvic vs hypogastric	t	0.43	5.24	2.83
		P	> 0.5	< 0.0002	0.005

Table 4: Comparison of the systolic and the diastolic pressure changes with the electrical stimulation of the pelvic nerve with the hypogastric nerve stimulation. The stimulating parameters were 4 - 5 V; 10 - 20 imp·sec^{-1}; 2 ms. Prestim. is the prestimulus period. n is the number of the points in 25 s prestimulus and 30 s stimulus period obtained from 12 stimulations performed on six cats. $\bar{X}$ is the arithmetic mean; Sm is the standard error of the mean. t is t value according to Fischer's t-test; P is the probability according to null hypothesis. P values which were underlined indicate that they are statistically significant.

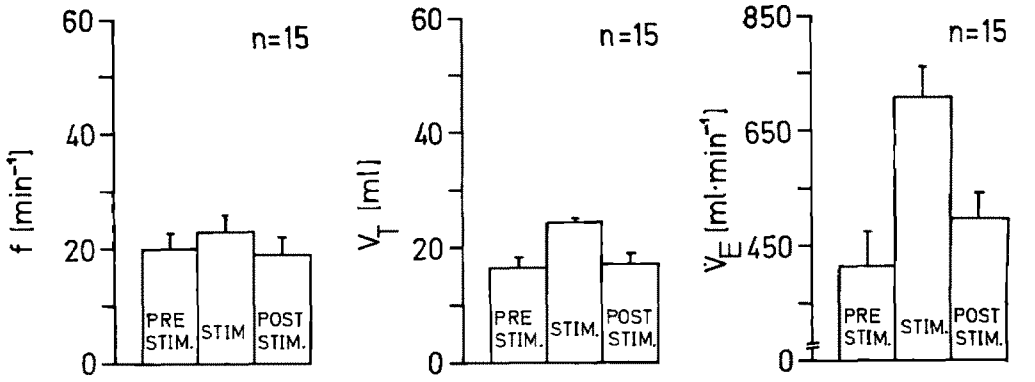
lation period the heart frequency was -6 % to 9.5 % below the control value in stimulation experiments on the pelvic and the hypogastric nerves respectively.

3.2.4.3. Respiratory parameters

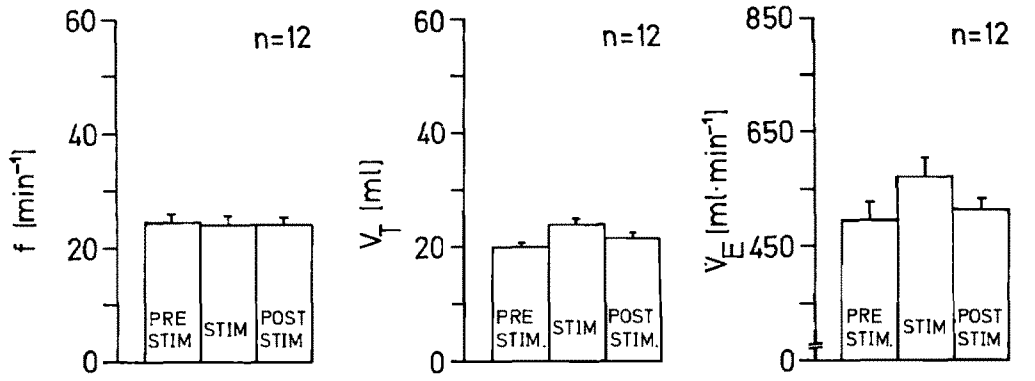
In the experiment shown in the figure 9a, electrical stimulation of the pelvic nerve resulted in an increase of the tidal volume from 19 to 21.2 ml (+10.5 %) without an appreciable alteration in the respiratory frequency. The increase in the minute ventilation was only from 437 to 469.8 $ml.min^{-1}$ (+ 7.5 %). In the same experiment (Fig. 9b), the hypogastric nerve stimulation resulted in an increase of the tidal volume from 19 to 25.8 ml (+33.7 %) without much change in the respiratory frequency. The minute ventilation responded with an increase from 463 to 593 $ml \cdot min^{-1}$ (28 %). All the respiratory parameters returned almost to the control values, after stopping the electrical stimulus.

In the type of experiment described it appears that ventilatory responses to the pelvic nerve stimulation were not so much pronounced. But the data obtained from 15 observations in six cats have shown that the pelvic nerve stimulation results in a considerable increase in the ventilation (Fig. 11a). Electrical stimulation of the cut central end of the pelvic nerve increased the tidal volume from 17 ± 1.8 to 25 ± 0.4 ml and the respiratory frequency from 20 ± 1.6 to 23 ± 3.1 min^{-1}. Increase in the tidal volume was highly significant (P is less than 0.0002 for n = 15; Table 5a). The minute ventilation responded with an increase from 415 ± 59.4 to 708.2 ± 54.4 $ml \cdot min^{-1}$ which is +70.6 % above the control value. This increase in the minute ventilation was significant at a P value of 0.0027 for n = 15.

Electrical stimulation of the hypogastric nerve resulted an increase of the tidal volume from 20 ± 0.4 to 24 ± 0.8 ml (P = 0.0010, n = 12). But no change in the respiratory frequency



A. pelvic nerve stimulation



B. hypogastric nerve stimulation

Figure 11 (a and b): Ventilatory changes with electrical stimulation of the pelvic nerve and the hypogastric nerve (4 - 5 V, 10 - 20 imp·sec^{-1} and 2 ms). The data presented are the average values ($\bar{X}$) with the standard error of the mean (Sm), n is the number of observations obtained from six cats.

		A. PRESTIM.	B. STIM.	C. POSTSTIM.
V_T ml	$\bar{X}$	16.6	24.8	17.3
	Sm	1.8	0.48	1.8
	n	15	15	15
A vs B	t		4.40	
	P		<0.0002	
$f \cdot min^{-1}$	$\bar{X}$	20.2	23.2	18.8
	Sm	1.64	3.11	1.88
	n	15	15	15
A vs B	t		0.73	
	P		>0.5	
$\dot{V}_E$ $ml \cdot min^{-1}$	$\bar{X}$	415.1	708.2	498.7
	Sm	59.4	54.4	42.6
	n	15	15	15
A vs B	t		3.64	
	P		0.0027	

Table 5a: Ventilatory changes during the electrical stimulation of the cut central end of the pelvic nerve with 4 - 5 V; 10 - 20 imp·sec^{-1} and 2 ms. PRESTIM. is the prestimulus period; STIM. is the stimulation period; POSTSTIM. is the poststimulation period; V_T ml is the tidal volume; f·min^{-1} is the respiratory frequency; $\dot{V}_E$ ml·min^{-1} is the minute ventilation; $\bar{X}$ is the arithmetic mean; Sm is the standard error of the mean; n is the number of observations obtained from 6 cats. P values which were underlined indicate that they are statistically significant.

		A. PRESTIM.	B. STIM.	C. POSTSTIM.
V_T ml	$\bar{X}$	20.3	24.0	21.5
	Sm	0.46	0.83	0.66
	n	12	12	12
	t		3.93	
A vs B	P		0.0027	
$f \cdot min^{-1}$	$\bar{X}$	24.5	24.0	24.1
	Sm	1.30	1.52	1.18
	n	12	12	12
	t		0.25	
A vs B	P		> 0.5	
$\dot{V}_E ml \cdot min^{-1}$	$\bar{X}$	497	573.9	513.1
	Sm	27.4	31.2	16.2
	n	12	12	12
	t		2.9	
A vs B	P		0.016	

Table 5b: Ventilatory changes during the electrical stimulation of the cut central end of the hypogastric nerve with 4 - 5 V; 10 - 20 imp·sec^{-1} and 2 ms. PRESTIM. is the prestimulation period, STIM. is the stimulation period, POSTSTIM. is the poststimulation period; V_T ml is the tidal volume, f·min^{-1} is the respiratory frequency; $\dot{V}_E$ ml·min^{-1} is the minute ventilation; $\bar{X}$ is the arithmetic mean; Sm is the standard error of the mean; n is the number of observations obtained from 6 cats. Paired t-test was used for calculating t values. P values which were underlined indicate that they are statistically significant.

was seen. The increase in the minute ventilation was to 573.9 ± 31.2 $ml \cdot min^{-1}$ from the control value of 497 ± 27.4 $ml \cdot min^{-1}$ ($P = 0.016$, $n = 12$, Table 5b).

In the case of hypogastric nerve the respiratory parameters returned nearly to the control values as soon as the stimulus was stopped, whereas with the pelvic nerve the minute ventilation remained about 20 % (498 ± 42.6 $ml \cdot min^{-1}$) above the control value.

In summary, it can be stated that with identical stimulus parameters electrical stimulation of the cut central end of the hypogastric nerve resulted in a more pronounced change in the cardiovascular parameters than of the pelvic nerve. Whereas the increase in the ventilation was more marked with the pelvic nerve stimulation than with that of the hypogastric nerve.

3.3. Factors influencing the cardiovascular and the respiratory responses with the urinary bladder distension

So far the cardiovascular and the respiratory responses after the bladder distension have been established. Factors such as

1. Intraabdominal pressure
2. ureteral pressure
3. the role of the sino-aortic nerves influencing these responses will be evaluated in the following experiments.

3.3.1. Role of the intraabdominal pressure

This group of experiments were performed on seven cats. These experiments were aimed to study the role of the mechanical factors like increased intraabdominal pressure affecting the cardiovascular and respiratory changes observed during the distension of the urinary bladder. In order to minimize the possible interference

of the mechanical factors resulting from the distension of the bladder in situ, the bladder was exteriorized from the abdomen keeping the nervous and the vascular supply intact. Then the intravesical pressure was increased by urethral infusion of saline solution. The cardiovascular and the respiratory responses were analysed and were compared with the results obtained with distension of the bladder in situ. In four experiments (n = 10), venous pressure distal to the bladder was measured by placing a catheter in the iliac veins.

An example from this group of experiments is shown in the figure 12 a and b, where the arterial pressure, tidal volume, intravesical pressure, end tidal P_{CO_2} and the peripheral venous pressure (distal of the bladder) were measured with distension in situ as well as with the exteriorized distension of the bladder.

In this experiment at 0-30 s of the distension of the bladder in situ, the increase in the systolic and the diastolic pressures were from 124.8 to 134.4 Torr (+7.7 %) and 100.8 to 110.4 Torr (+9.5 %) respectively. Distension of the exteriorized bladder in the same cat resulted in an increase of the systolic pressure from 129.6 to 148.8 Torr (+14.8 %) and the diastolic pressure from 105.6 to 120 Torr (+13.6 %). Otherwise, from 0 - 60 s of the distension onwards, the increase in the arterial pressure and also the return of it to the control value after releasing the intravesical pressure were the same in both the situations of the bladder distension. In otherwards, the arterial pressure responses resulting from the bladder distension in situ were not appreciably different from the changes with exteriorized distension.

The quantitative analysis of the arterial pressure responses in this group of experiments is as follows: After the distension of the bladder in situ, the average maximum increase in the systolic pressure was from 161 ± 5.8 Torr to 179.7 ± 7 Torr (+11 %) and the diastolic pressure was from 125.3 ± 3.1 to 141.3 ± 4.6 Torr (+12.5 %). With comparable degree of bladder

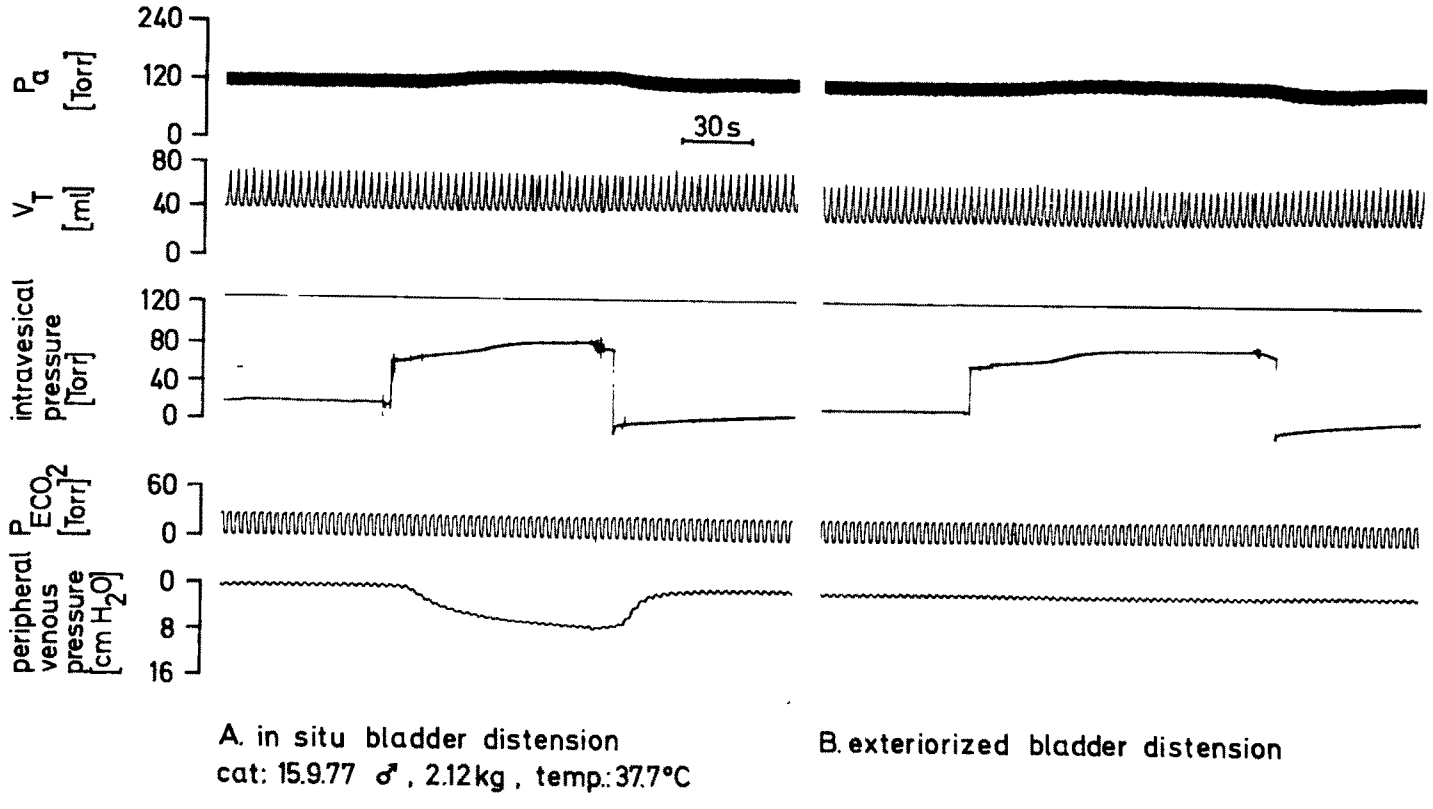


Figure 12 (a and b): Continuous recording of the arterial pressure (Pa Torr), the tidal volume (V_T ml), the intravesical pressure (Torr), the expiratory P_{CO2} (P_{ECO_2} Torr), and the peripheral venous pressure (Cm H_2O) below the bladder with in situ and exteriorized urinary bladder distension in an anesthetized cat. During the in situ bladder distension there is an increase of the peripheral venous pressure distal of the bladder, and no change in the distal venous pressure was seen during exteriorised bladder distension.

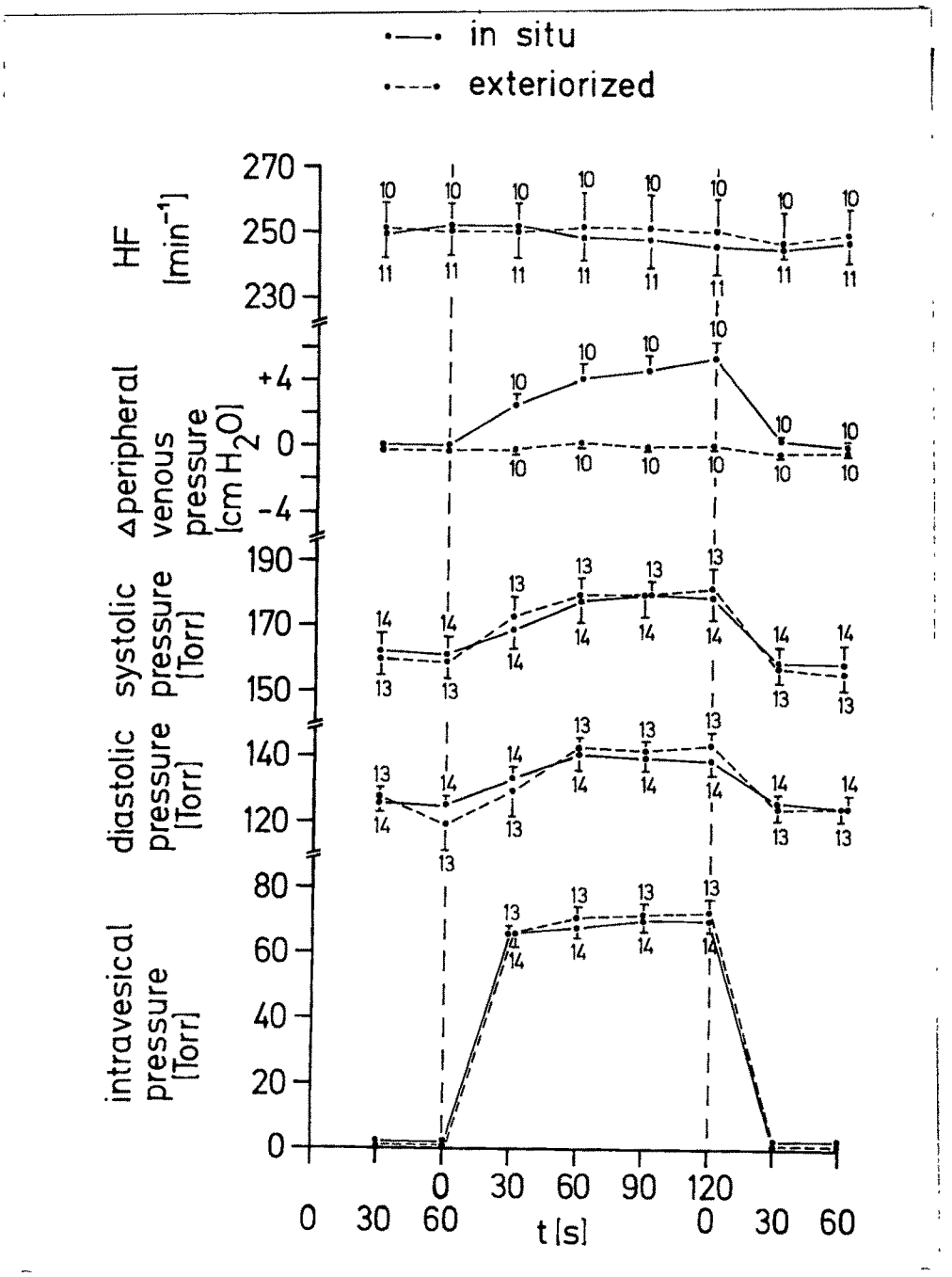


Figure 13: Comparison of the average cardiovascular changes during the bladder distension in situ with the exteriorized bladder distension. The peripheral venous pressure distal of the bladder increased during the distension in situ, whereas no such change was seen with the exteriorized distension. The data presented are the average values ($\bar{X}$) with the standard error of the mean (Sm). The numbers above the points indicate the number of observations obtained from seven cats. Vertical dotted lines indicate the beginning and the end of the bladder distension.

distension in the exteriorized condition the increase in the systolic and diastolic pressures were from 158.7 ± 5.2 to 182 ± 5.7 Torr (+14 %) and 127.2 ± 3.5 to 144 ± 3.7 Torr (+17.4 %) respectively. As it can be seen from figure 13 the magnitude of the systolic and the diastolic pressure increases was almost the same in both groups. Releasing the bladder pressure in both sets of experiments resulted in the return of the arterial pressure to the control value.

In the example shown in the figure 12a increasing the intravesical pressure of the bladder in situ resulted in a progressive elevation of the venous pressure distal of the bladder. This increase in the venous pressure was from 0.8 to 7.2 cm H_2O. Such an increase in the venous pressure was not seen with distending the bladder in the exteriorized situation (Fig. 12b). The increase in the venous pressure distal to the bladder was consitently seen with bladder distension in situ. The average maximum increase of the venous pressure was +5.3 ± 1.1 cm H_2O. On the other hand, these increases in the venous pressure were totally absent with the exteriorized distension (Fig. 13). As result of the in situ distension of the bladder the heart frequency responded with an average bradycardia of about 7 beats.min^{-1} (245.7 ± 7.8 min^{-1}) from the control value of 252.4 ± 7.5 min^{-1}, whereas no change was seen in exteriorized distension. Otherwise, no apparent difference in the response of the heart frequency was seen between the two groups of experiments (Fig. 13).

In the experiment shown in the figure 12 a and b the respiratory changes resulting from bladder distension were not appreciably different between the two situations of bladder distension. Due to the large variations in the absolute values of the respiratory parameters in this group of experiments, the ratios of test/control were analysed. Though in the figure 14 it appears that there was a reduction in the respiratory parameters with the exteriorized distension in comparison with the distension in situ, but the P values were always above 0.05.

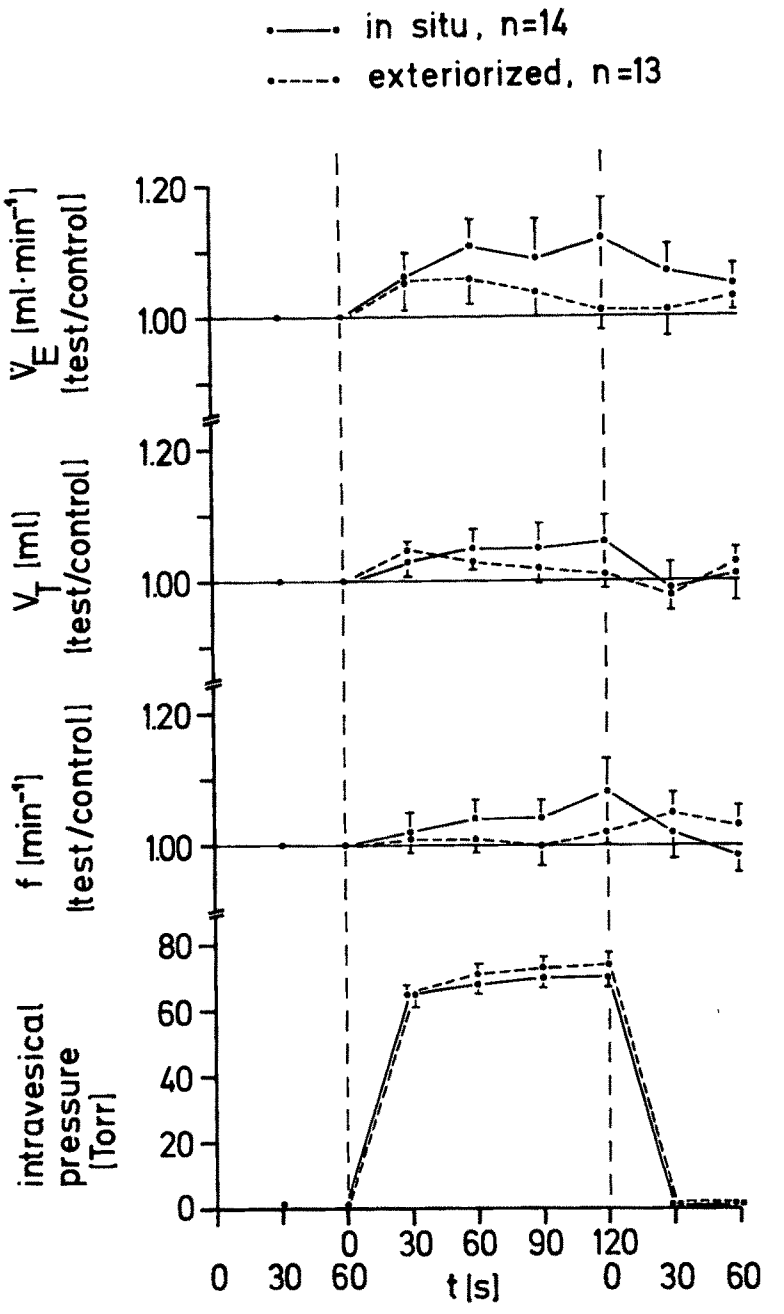


Figure 14: Comparison of the ratios (test/control) of the ventilatory parameters during the bladder distension in situ with that of the exteriorized distension. Though, it appears that the ventilatory changes were not so much pronounced with the exteriorized distension but these differences were not statistically significant ($P > 0.05$) in comparison with the distension in situ. n is the number of observations obtained from seven cats.

In summary this group of experiments has shown that peripheral venous pressure distal of the bladder increased after distending the bladder in situ, while this change was absent with similar distension of the exteriorized bladder. Except this difference, the cardiovascular and the respiratory responses were almost the same in both groups.

3.3.2. Role of the ureters

Increased ureteral pressure could be regarded as another possible factor influencing the cardiovascular and the respiratory responses after the bladder distension. In order to clarify this point, cats were divided into two groups. In the first control group of cats (n = 7) the ureters were intact, while in the second group of another five cats, the ureters were cannulated so as to avoid the increase of pressure and the accumulation of urine in the ureter itself.

3.3.2.1. Arterial pressure

The predistension systolic and diastolic pressures were about -2.9 % (171.3 ± 5.4 Torr) and -6 % (132.9 ± 4.4 Torr) respectively less in the animals with ureters cannulated in comparison to the control group (Fig. 15). Increasing the intravesical pressure resulted in an elevation of the arterial pressure in both groups. In the initial phase of the bladder distension (i.e., at 0 - 30 to 0 - 60 s) the elevation of the arterial pressure was almost the same in both groups (Fig. 15). But from 0 - 90 s of distension onwards compared to the controls the increase in the systolic pressure was about -10 % (196.2 ± 5.5 Torr) less and the diastolic pressure was -9 % (148.4 ± 4.3 Torr) less in the ureter cannulated group ($P=0.04 - 0.02$, n = 11). After releasing the bladder pressure the arterial pressure returned to the predistension value in both groups. As it can be seen from the

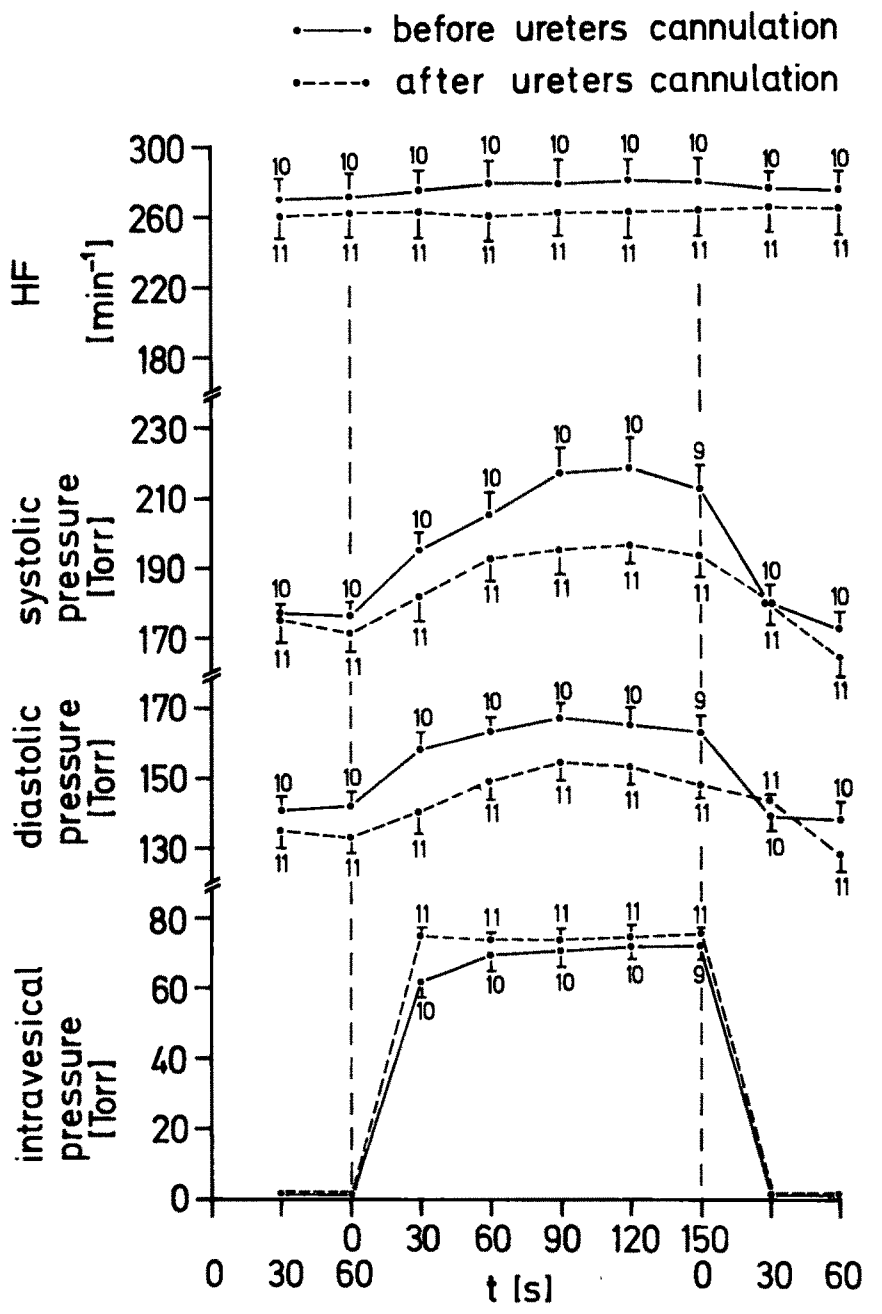


Figure 15: Average changes in the systolic pressure, diastolic pressure and the heart frequency during the bladder distension with intact and after cannulating the ureters. From 0 - 90 s of the distension the systolic and the diastolic pressures were significantly less in the ureter cannulated animals compared to controls with intact ureters ($P = 0.04$ to 0.02 for $n = 11$). The data presented were the average values ($\bar{X}$) with standard error of the mean (Sm). Numbers above the data are the number of observations obtained from 7 cats with intact ureters and 5 cats with cannulated ureters. The vertical dotted lines indicate the beginning and the end of distension.

figure 15 the change in the heart frequency was not appreciably different in the ureter cannulated group as compared to controls.

3.3.2.2. Respiratory parameters

Due to the large variation in the predistension ventilatory parameters for the sake of comparison between the two groups the test/control ratios were analysed. Figure 16 represents the analysis of the respiratory parameters with distension of the bladder in control as well as in the ureter cannulated animals. Respiratory changes observed with bladder distension in the ureter cannulated group were not significantly different from the changes observed in the control group(P is above 0.05 for n = 11).

Thus this group of experiments shows that the increase in the arterial pressure resulting from the later phases of the bladder distension (i.e.,0 - 90 s onwards) was considerably less in the ureter cannulated animals. Differences in the reactions of ventilation were not significant.

3.3.3. Role of the sino-aortic nerves

3.3.3.1. Cardiovascular and respiratory changes during the distension of the bladder after sino-aortic denervation

In order to evaluate the influence of the sino-aortic nerves on the cardiovascular and respiratory responses after the bladder distension, cats were divided into two groups. In the first control group (6 cats) the sino-aortic nerves were intact, while in the second group (7 cats), the responses were recorded after the bilateral sino-aortic denervation. The vagus nerves (except the aortic nerve) were left intact because their denervation might modify the heart frequency response.

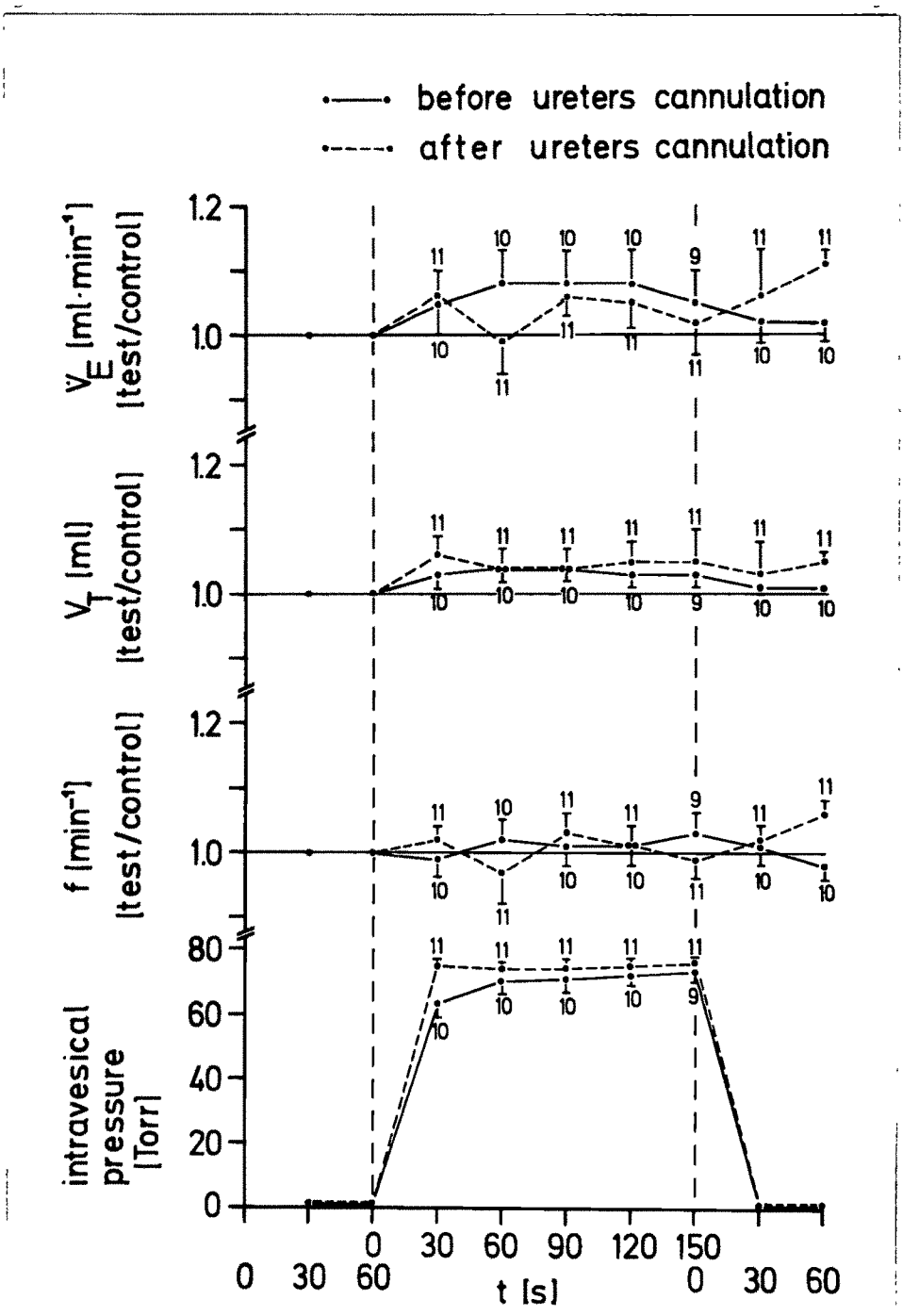


Figure 16: Ventilatory changes during the distension of the urinary bladder before and after cannulating the ureters. f·min^{-1} is the respiratory frequency; V_T ml the tidal volume; $\dot{V}_E$ml·min^{-1} is the minute ventilation. The data presented are the mean values of the ratios (distension/predistension) with their standard error of the mean (Sm). Numbers above the data are the number of observations obtained from 7 cats before cannulating the ureters and 5 cats after cannulating the ureters. The vertical dotted lines indicate the beginning and the end of the distension. Ventilatory changes during bladder distension in the ureter cannulated group were not significantly different from the changes observed with intact ureters group (P values above 0.05).

An example of this group of experiments is shown in figure 17, where the cardiovascular and respiratory parameters were measured with identical degree of bladder distension before and after sino-aortic denervation.

3.3.3.1.1. Arterial pressure

In the example shown in figure 17 already before the distension of the bladder, as a result of sino-aortic denervation the systolic and the diastolic pressures were increased by about +48 and +24 Torr respectively. In response to the distension of the bladder, the increase in the systolic pressure was about +9.6 Torr more in the sino-aortic denervated situation than in the control (Fig. 17). But the response of the diastolic pressure was almost the same. Release of the bladder from its pressure load resulted in the complete return of the arterial pressure to the predistension value.

Similar results were obtained in all the cats studied in this group. As a result of the sino-aortic denervation the predistension systolic and diastolic pressures were significantly more elevated by about +15 and +12 Torr respectively than in the control group ($P = 0.0009$ for systolic $P = 0.021$ for diastolic $n = 10$). During the bladder distension the systolic and the diastolic pressures showed a higher increase of about +30 to +15 Torr respectively than the controls (Fig. 18). Since the control arterial pressure was already elevated in the denervated group, the ratios (distension/predistension) of the systolic as well as the diastolic pressures were compared between the two groups (Table 6). Throughout the distension period of the bladder the systolic pressure was significantly more increased in the buffer denervated group than in the controls (P values ranged between 0.05 to 0.009, $n = 10$, details Table 6). Also the increase in the diastolic pressure was significantly higher till 0 - 120 s of the distension period (range of the P values were between 0.05 to 0.002, $n = 10$) than in the animals with intact buffer nerves. Upon releasing the intravesical pressure, the arterial pressure returned almost to

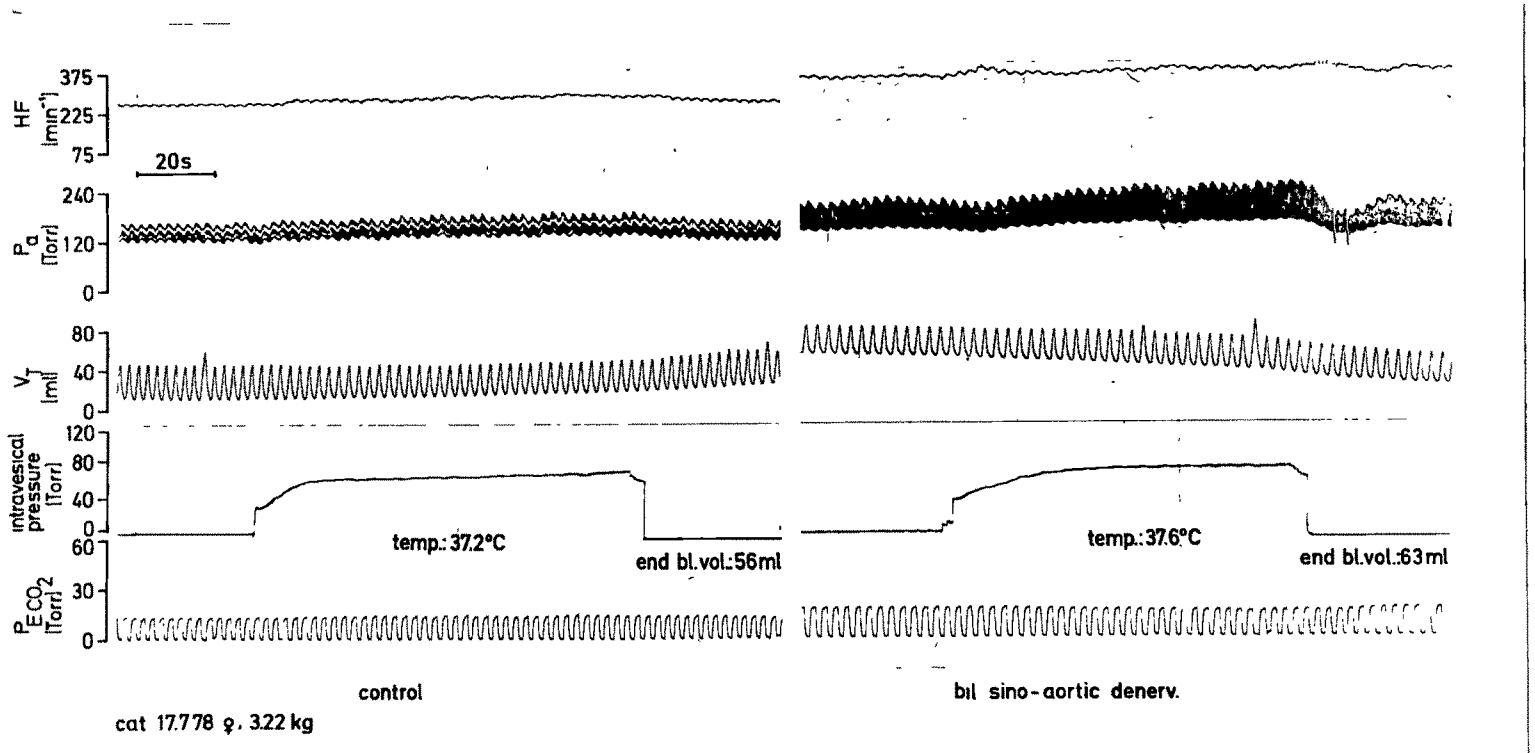


Figure 17: Comparison of the effects of distension of the urinary bladder before and after bilateral denervation of the sino-aortic nerves in an anaesthetized cat. Continuous record showing the registration of the heart frequency (HF. min^{-1}), arterial pressure (Pa Torr), tidal volume (V_T ml), intravesical pressure (Torr) and expiratory P_{CO_2} (P_{ECO_2} Torr). After denervation of the bilateral sino-aortic nerves with comparable increase of the intravesical pressure there was a marked increase in the arterial pressure response associated with trachycardia.

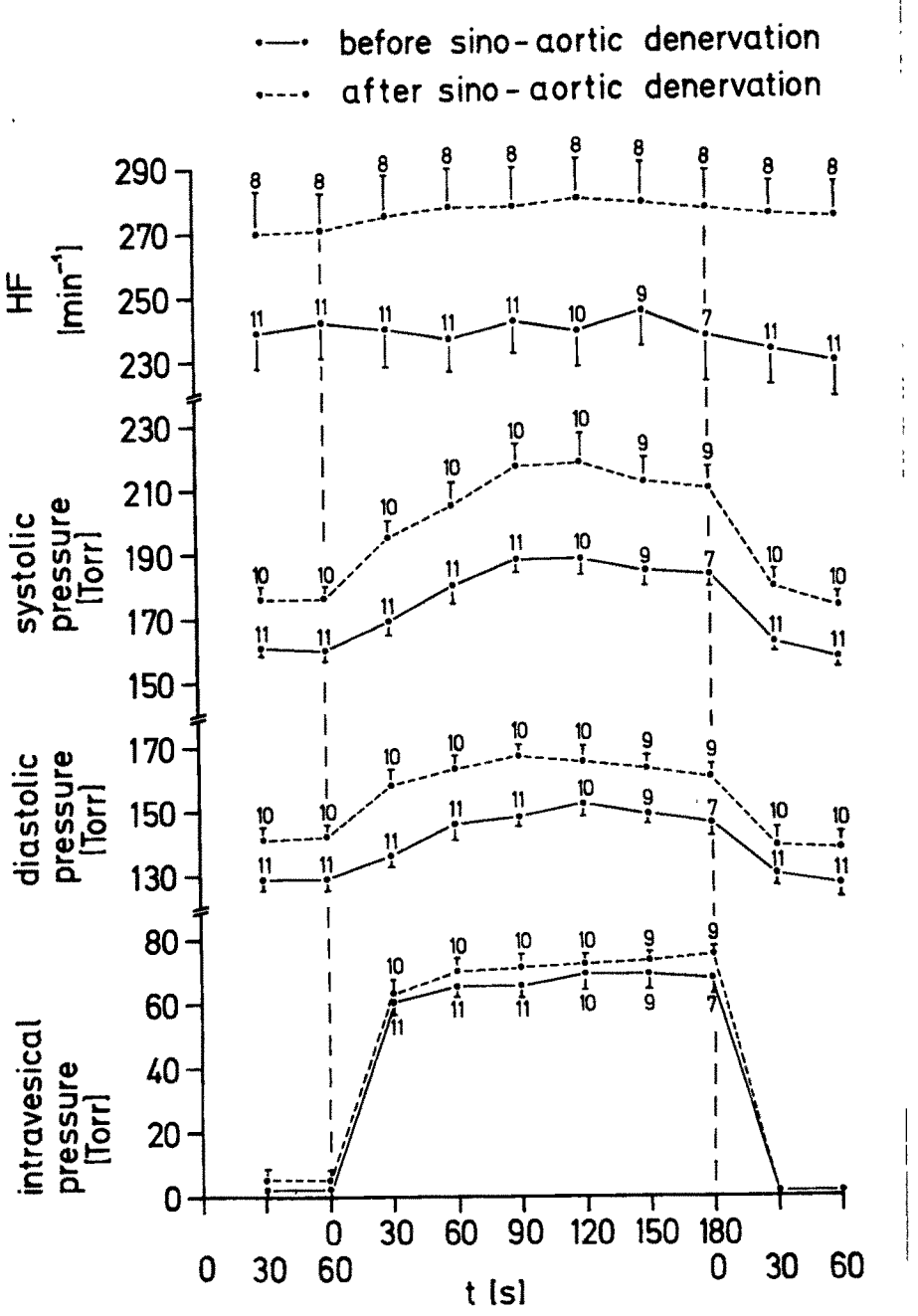


Figure 18: Comparison of the average changes in the systolic pressure, diastolic pressure (Torr) and the heart frequency (min^{-1}) during the distension of the urinary bladder before and after bilateral sino-aortic denervation. The data presented are the average values ($\bar{X}$) with standard error of the mean(Sm). Numbers above the points represent the number of observations. Vertical dotted lines indicate the beginning and the end of the distension.With identical degree of bladder distension the changes in the arterial pressure were more pronounced in the sino-aortic denervated group.

			time (s)	DISTENSION 0-30	30-60	60-90	90-120	120-150	150-180	POSTDISTENSION 0-30	30-60
Systolic Pa distension / predistension	A) intact buffer nerv.	$\bar{X}$		1.04	1.11	1.16	1.17	1.14	1.12	0.99	0.97
		Sm		0.01	0.01	0.02	0.02	0.02	0.01	0.01	0.01
		n		11	11	11	10	9	7	11	11
	B) bil. sino-aort. denerv.	$\bar{X}$		1.11	1.16	1.21	1.24	1.19	1.18	1.02	0.98
		Sm		0.01	0.02	0.02	0.02	0.01	0.02	0.01	0.01
		n		10	10	10	10	9	9	10	10
	A vs B	t		5.4	2.8	2.6	2.6	2.1	3.0	1.8	0.84
		P		<0.0002	0.012	0.018	0.018	0.05	0.009	0.09	> 0.5
Diastolic Pa distension / predistension	A) intact buffer nerv.	$\bar{X}$		1.05	1.12	1.14	1.18	1.16	1.13	0.99	0.97
		Sm		0.01	0.02	0.01	0.01	0.02	0.02	0.01	0.01
		n		11	11	11	10	9	7	11	11
	B) bil. sino-aort. denerv.	$\bar{X}$		1.12	1.18	1.19	1.23	1.20	1.17	0.99	0.98
		Sm		0.02	0.02	0.01	0.02	0.02	0.02	0.01	0.01
		n		10	10	10	10	9	9	10	10
	A vs B	t		3.5	2.1	3.3	2.3	1.6	1.4	-	0.71
		P		0.011	0.05	0.0027	0.03	0.12	0.2	-	> 0.5

Table 6: Comparison of the ratios (distension/predistension) of the systolic and the diastolic pressures during the distension of the bladder before and after bilateral sino-aortic denervation . $\bar{X}$ is the average value. Sm is the standard error of the mean. n is the number of the observations obtained form 6 cats (with intact buffer nerves) and 7 cats (after bilateral buffer denervation). t is value according to Fisher's t-test and P is the probability of the null hypothesis. The P values which were underlined indicate that they are statistically significant.

the control value in both groups.

3.3.3.1.2. Heart frequency

The predistension heart frequency after the sino-aortic denervation was about +22 min^{-1} (285 min^{-1}) higher than with the intact buffer nerves in the example shown in figure 17. The increase in the heart frequency in response to the bladder distension was about +7.5 min^{-1} higher in the denervated condition than with intact buffer nerves.

In seven cats studied after the buffer nerve denervation the average predistension heart frequency was 270.6 ± 13.3 min^{-1} which was about +30 min^{-1} higher than the controls (240.5 ± 10.9 min^{-1}, Fig. 18). In the denervated group the average heart frequency showed only tachycardia (increase of frequency from 270 ± 12.4 min^{-1} to 279 ± 12.1 min^{-1}) in response to increase in the intravesical pressure, while in average of the control group there was slight bradycardia during the initial phases of the bladder distension (at 0 - 60 s). After releasing the bladder pressure in the controls there was an undershoot of the heart frequency, whereas it in the sino-aortic denervated group almost returned to the predistension value.

3.3.3.1.3. Respiratory parameters

Averaging the results of the respiratory parameters in this group of experiments have shown that after bilateral sino-aortic denervation the predistension tidal volume was decreased by about 3 - 4 ml as compared to the controls. However, these reductions in the tidal volume were not of statistical significance (P values above 0.05 n = 10). In response to bladder distension in the buffer denervated group the increase in the tidal volume was about 6.0 ml (17.7 ± 2.1 ml) less than that of

		time (s)	PREDISTENSION 0-30	PREDISTENSION 30-60	DISTENSION 0-30	DISTENSION 30-60	DISTENSION 60-90	DISTENSION 90-120	DISTENSION 120-150	DISTENSION 150-180	POSTDISTENSION 0-30	POSTDISTENSION 30-60
V_T ml	A) intact buffer nerves	$\bar{X}$	19.8	20.3	21.3	22.7	23.6	22.4	23.1	20.8	20.8	20.1
		Sm	1.8	1.6	1.6	1.8	1.4	1.9	2.2	2.2	1.2	1.6
		n	11	11	11	11	11	10	9	7	11	11
	B) bil. sino-aort. denervation	$\bar{X}$	17.0	16.8	17.2	17.5	17.7	17.6	17.6	17.9	17.2	16.9
		Sm	1.9	1.9	1.6	1.7	2.1	2.2	2.2	2.3	1.9	1.8
		n	10	10	10	10	10	10	9	9	10	10
	A vs B	t	1.1	1.5	1.8	2.1	2.4	1.7	1.8	0.9	1.4	1.4
		P	0.28	0.15	0.058	0.05	0.023	0.12	0.059	> 0.5	0.15	0.15
$f \cdot min^{-1}$	A) intact buffer nerves	$\bar{X}$	17.5	17.3	18.1	18.7	18.9	18.7	18.9	19.5	18.8	18.7
		Sm	1.4	1.4	1.4	1.3	1.5	1.5	1.8	2.2	1.4	1.4
		n	11	11	11	11	11	10	9	7	11	11
	B) bil. sino-aort. denervation	$\bar{X}$	18.4	18.9	18.5	19.1	18.8	18.9	19.4	19.2	18.8	18.5
		Sm	1.0	1.1	1.4	1.3	1.1	1.3	1.5	1.6	1.1	1.0
		n	10	10	10	10	10	10	9	9	10	10
	A vs B	t	0.5	0.90	0.4	0.2	0.05	0.1	0.2	0.1	-	0.1
		P	> 0.5	> 0.5	> 0.5	> 0.5	> 0.5	> 0.5	> 0.5	> 0.5	-	> 0.5
$\dot{V}_E$ $ml \cdot min^{-1}$	A) intact buffer nerves	$\bar{X}$	335	339.6	422	413	421	414	434	393	371.7	359.6
		Sm	33.4	27.6	41.0	26.8	28.7	35.6	36.7	43.5	28.6	32.2
		n	11	11	11	11	11	10	9	7	11	11
	B) bil. sino-aort. denervation	$\bar{X}$	307	304	309.9	316	320.9	322	319.9	315	309	306.7
		Sm	31.1	31.9	20.5	20.4	23.7	25.8	26.0	31.1	28.8	28.5
		n	10	10	10	10	10	10	9	9	10	10
	A vs B	t	0.6	0.8	2.5	2.9	2.7	2.1	2.6	1.5	1.5	1.2
		P	> 0.5	> 0.5	0.02	0.01	0.014	0.045	0.018	0.15	0.15	0.23

Table 7: Comparison of the ventilatory changes during the distension of the urinary bladder before and after bilateral sino-aortic denervation. $\bar{X}$ is the mean value; Sm is the standard error of the mean; n is the number of the observations; t is value obtained from Fisher's t-test; P is the probability according to the null hypothesis. Underline P values indicated that they are statistically significant.

the controls ($P = 0.05$, $n = 10$). There was no difference in the response of the respiratory frequency between the two groups. With elevated intravesical pressure, the increase of the minute ventilation was about 97 $ml \cdot min^{-1}$ (316 $\pm$ 20.4 $ml \cdot min^{-1}$) less in the sino-aortic denervated group as compared to the controls (413.3 $\pm$ 26.8 $ml \cdot min^{-1}$). This reduced response of the ventilation in the denervated group was statistically significant (details Table 7). Release of the bladder pressure brought the ventilatory parameters almost back to the predistension values in both groups.

3.3.3.2. Electrical stimulation of the pelvic and the hypogastric nerves after sino-aortic denervation

3.3.3.2.1. Arterial pressure responses

In general electrical stimulation of the afferents from the bladder after the bilateral sino-aortic denervation resulted in a higher increase of the arterial pressure when compared with the responses obtained with intact buffer nerves. Figure 19a illustrates an example of the electrical stimulation of the pelvic nerve before and after sino-aortic denervation. With intact sino-aortic nerves, stimulation of the pelvic nerve resulted in an increase of the systolic pressure from 153.6 to 177.6 Torr (+15.6 %) and the diastolic pressure from 124.8 to 139.2 Torr (+11.5 %). As it can be seen from figure 19a bilateral sino-aortic denervation itself resulted in an increase of the prestimulus arterial pressure. Repeating the stimulation after the sino-aortic denervation led to an elevation of the systolic pressure from 182.4 to 278.4 Torr (+52.6 %) and the diastolic pressure from 148.8 to 163.2 Torr (+9.7 %). After stopping the stimulus within 25 s the arterial pressure returned to the prestimulus value with intact as well as after buffer denervation.

In the same experiment, stimulation of the hypogastric nerve in presence of buffer nerves resulted in an elevation of the systolic pressure from 148.8 to 187.2 Torr (+25.8 %) and the diastolic

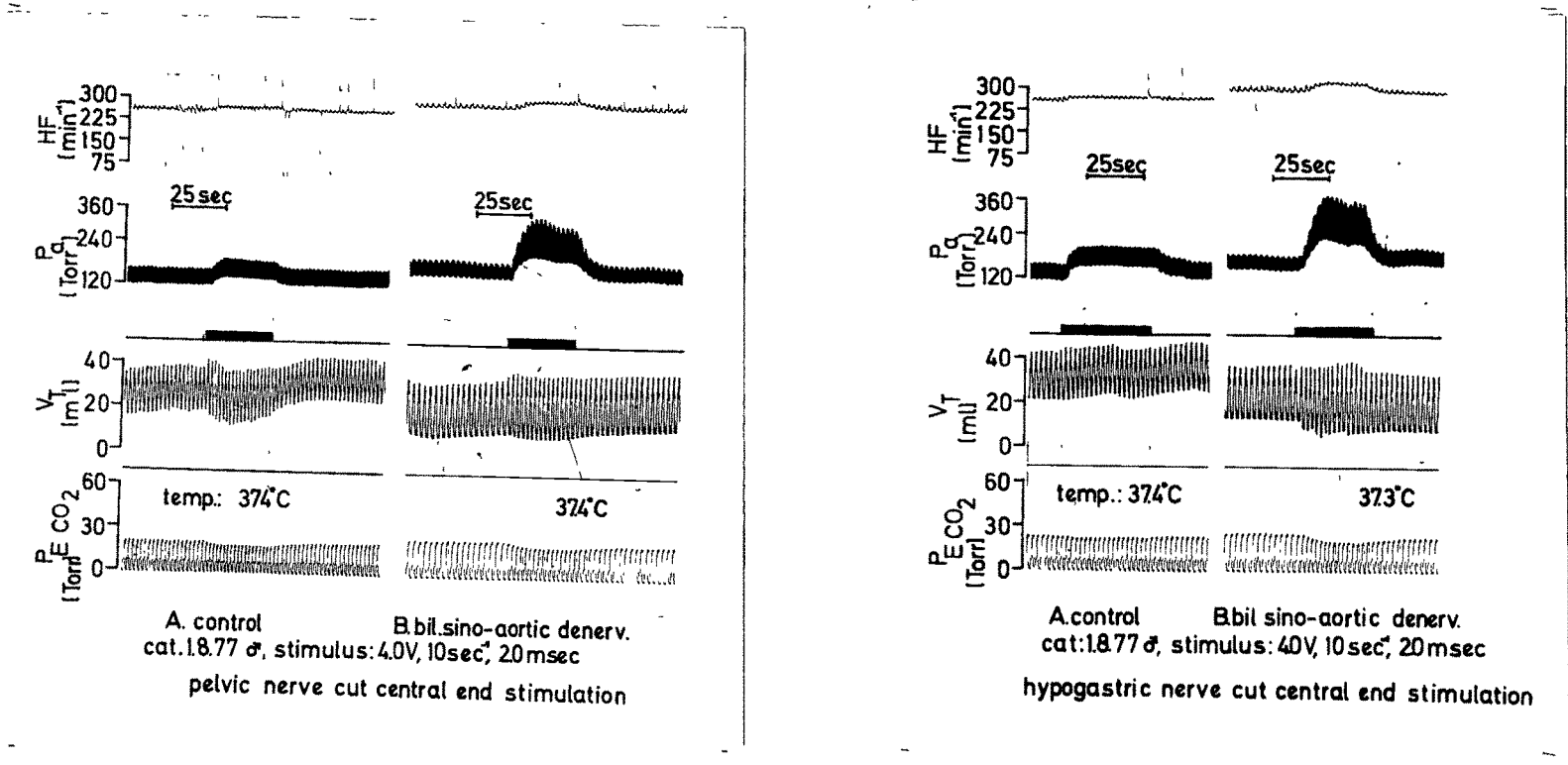


Figure 19 (a and b): Continuous record of the heart frequency (HF min^{-1}), arterial pressure (Pa Torr), tidal volume V_T ml and end tidal CO_2 (P_{ECO_2} Torr) during the electrical stimulation of the pelvic nerve and the hypogastric nerve before and after bilateral sino-aortic denervation. Increase in the arterial pressure during the stimulation was pronounced after bilateral sino-aortic denervation. In case of the hypogastric nerve respiratory changes during the stimulation were pronounced after buffer denervation. The black horizontal line indicate the period of stimulation.

pressure from 124.8 to 144 Torr (+15.4 %) (Fig. 19b). After buffer denervation with the same stimulus parameters a marked elevation of the systolic pressure of about +74.3 % (from 168 to 292.8 Torr) and the diastolic pressure of about +41.3 % (from 139.2 to 196.8 Torr) were seen. With intact as well as without buffer nerves, even after 25 s of the release of the stimulus the arterial pressure remained about 10 to 20 Torr above the prestimulus value.

Figure 20 a and b represent the analysis of the average changes in the arterial pressure analysed for every 5 s with electrical stimulation of the afferents from the bladder before and after sino-aortic denervation.

After the bilateral buffer denervation, the prestimulus arterial pressure itself was increased by about 15 to 17 Torr. In presence of the sino-aortic nerves electrical stimulation of the pelvic nerve resulted in a maximum increase of the arterial pressure at 10 s of the stimulation. The maximum average increase of the systolic pressure was +35.9 Torr (from 178.9 ± 4.3 to 214.8 ± 5.3 Torr) and of the diastolic pressure was +31.3 Torr (from 121.6 ± 5.0 to 152.9 ± 6.9 Torr). After the bilateral sino-aortic denervation repeating the stimulus procedure resulted in a higher increase of the arterial pressure (Fig. 20a). At 10 s of stimulation the maximum average increase of the systolic pressure was +51 Torr (from 194.2 ± 3.1 to 254.2 ± 8.0 Torr) and the diastolic pressure was +30.5 Torr (from 137.1 ± 6.8 to 167.6 ± 5.9 Torr). These maximal increases obtained after the sino-aortic denervation were +14.1 % (systolic) and 9.6 % (diastolic) higher compared to the control group. In control as well as in the sino-aortic denervated groups following the maximal increase the systolic and the diastolic pressures were adapted but remained still above the prestimulus values. After stopping the stimulus within 25 s in both groups the arterial pressure almost returned to the prestimulus value.

The direction of the arterial pressure changes during hypogastric

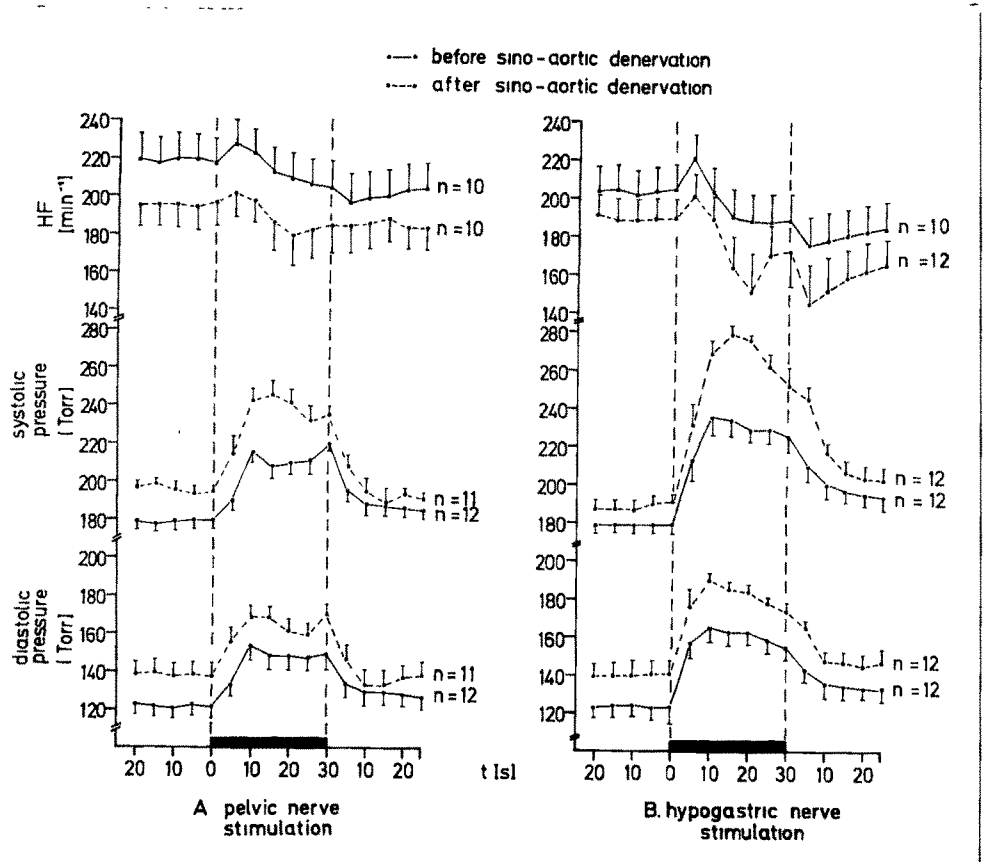


Figure 20 (a and b): Quantitative analysis of the heart frequency (HF min^{-1}), the systolic and the diastolic pressure changes with electrical stimulation of the pelvic (a) and the hypogastric nerve (b) before and after bilateral sino-aortic denervation. The data presented are the average values ($\bar{X}$) with standard error of the mean (Sm). n is the number of observations. Vertical dotted lines indicate the beginning and the end of the stimulation. The stimulus parameters were 4-5 V, 10-20 imp.sec^{-1} and 2 ms.

nerve stimulation was the same as that of the pelvic nerve. But the magnitude of the increases was always higher. With intact sino-aortic nerves the average maximum increase of the systolic pressure at 10 s of stimulation was +57.2 Torr (from 177.6 ± 4.1 to 234.8 ± 9.4 Torr) and the diastolic pressure was + 42.4 Torr (from 121.6 ± 5.5 to 164 ± 7.4 Torr). After the sino-aortic denervation the average maximal increase of the systolic pressure was +88 Torr (from 189.6 ± 4.1 to 277.6 ± 3.8 Torr) and the diastolic pressure was +48 Torr (from 140.8 ± 6.6 to 188.8 ± 4.4 Torr). These maximal increases after sino-aortic denervation were + 53.8% (systolic) and +14.3 % (diastolic) higher when compared with the corresponding increases obtained in the control group (intact sino-aortic group).

Following the maximal elevation the arterial pressure showed an adaptation in the sino-aortic denervated group as well as in controls.

Even after 25 s of releasing the stimulus the arterial pressure did not return completely to the prestimulus value, but remained about 10 to 15 Torr above the control values in both groups.

3.3.3.2.2. Heart frequency

Analysis of experiments on six cats have shown that electrical stimulation of afferents from the bladder (the pelvic and the hypogastric nerves) resulted in an initial tachycardia followed by a bradycardia with intact as well as with denervated sino-aortic nerves (Fig. 20 a and b).

Bilateral sino-aortic denervation itself resulted in a decrease of the prestimulus heart frequency by about -10.9 % in comparison to the controls.

Electrical stimulation of the cut central end of the pelvic nerve with intact buffer nerves resulted in an initial increase of the

heart frequency of about + 4 % (from 218 ± 12.7 to 227.3 ± 12.4 min^{-1}). Repeating the stimulation after buffer denervation led to a tachycardic response of about +3 % (from the control value of 195 ± 11.8 min^{-1}) (Fig. 20a). With identical stimulus parameters the tachycardic response obtained with the hypogastric nerve stimulation in the control group was +8.5 % (from the prestimulus value of 204 ± 12.9 to 220.5 ± 12 min^{-1}). The increase in the heart frequency after buffer nerve denervation was about +6 % (from 188.9 ± 11.3 min^{-1} to 200 ± 11.3 min^{-1}) (Fig. 20b). Thus, the tachycardic response was not appreciably altered after the sino-aortic denervation with the pelvic as well as with the hypogastric nerve stimulations.

In both groups (control as well as denervated) the tachycardia lasted for about 5 to 7 s. After 10 s of stimulation there appeared a progressive bradycardia. In case of the pelvic nerve stimulation the average maximum bradycardia in the denervated group was -8.6 % (from 195 ± 11.8 to 178.9 ± 15.6 min^{-1}). On the other hand, the bradycardia in response to the hypogastric nerve stimulation was more pronounced after sino-aortic denervation. The average maximum bradycardia was -20.6 % (from 188.9 ± 11.3 to 15o ± 19.8 min^{-1}) in the denervated group, while with intact buffer nerves it was only -7.9 % (from 204 ± 12.9 to 187 ± 13.8 min^{-1}).

With both the pelvic and the hypogastric nerves even after 25 s of post stimulation the heart frequency remained about -5 to -12 % below the control value in the denervated as well in the control group.

3.3.3.2.3. Respiratory parameters

In the example shown in figure 19a electrical stimulation of the pelvic nerve with intact buffer nerves led to an increase of the tidal volume from 20 to 25 ml and the respiratory frequency from 35 to 37.5 min^{-1}. Minute ventilation responded with an increase of about 937.5 $ml \cdot min^{-1}$ from the prestimulus value

of 705.9 ml·min^{-1}. A similar increase in these parameters was also seen after the sino-aortic denervation. The increase in the tidal volume and the respiratory frequency were 24 to 28 ml and 25 to 31.5 min^{-1} respectively. The increase in the minute ventilation was from 600 to 882 ml·min^{-1}.

In the same experiment in presence of the buffer nerves, electrical stimulation of the hypogastric nerve resulted in an increase of the tidal volume from 21 to 23 ml and the minute ventilation from 630 to 690 ml·min^{-1} (+ 60 ml·min^{-1}), without any change in the respiratory frequency. Whereas stimulation of the same nerve after buffer denervation brought about an increase of the tidal volume from 24 to 31 ml and the respiratory frequency from 30 to 33 min^{-1}. The minute ventilation increased from the control value of 720 ml·min^{-1} to 1032 ml·min^{-1}, which is +312 ml·min^{-1} more than the prestimulus value (Fig. 19b). After the release of the stimulus, with intact as well as without buffer nerves, the respiratory parameters returned almost to the control value, after stimulation of both the pelvic and the hypogastric nerves.

Respiratory responses resulting from the electrical stimulation of the pelvic and the hypogastric nerves described in the above example were reproducible in all the six cats studied. The increase in the tidal volume, respiratory frequency and the minute ventilation resulting from the pelvic nerve stimulation were by the same order of magnitude both in the control and in the sino-aortic denervated situation (Table 8).

In presence of the sino-aortic nerves the respiratory frequency was not altered by hypogastric nerve stimulation. But after the sino-aortic denervation, stimulation of the same nerve led to an increase of the respiratory frequency from 25 ± 1.6 to 27 ± 1.7 min^{-1} (+2 min^{-1}) with a simulataneous increase of the tidal volume from 21.9 ± 0.4 to 29.2 ± 0.9 ml (+7.3 ml). Similarly the minute ventilation increased by about +221.6 ml·min^{-1} (from 556.8 ± 42:7 to 778.4 ± 46.4 ml.min^{-1}). By comparison of these ventilatory changes with the control group the differences were found to be statistically significant (Table 9). After stopping

			PRESTIM.	STIM.	POSTSTIM.
V_T ml	A) Before sino-aortic denervation	$\bar{X}$	16.6	24.8	17.3
		Sm	1.8	0.5	1.8
		n	15	15	15
	B) After sino-aortic denervation	$\bar{X}$	21.8	26.5	21.6
		Sm	0.6	0.6	0.9
		n	12	12	12
	A vs B	t	2.8	2.1	2.1
		P	0.01	0.05	0.05
$f \cdot min^{-1}$	A) Before sino-aortic denervation	$\bar{X}$	20.2	23.2	18.8
		Sm	2.6	3.1	2.9
		n	15	15	15
	B) After sino-aortic denervation	$\bar{X}$	22.9	25.2	23.1
		Sm	0.6	1.3	0.9
		n	12	12	12
	A vs B	t	1.0	0.6	1.4
		P	0.32	> 0.5	0.2
$\dot{V}_E$ ml $\cdot$ min^{-1}	A) Before sino-aortic denervation	$\bar{X}$	415.1	708.2	498.7
		Sm	59.4	54.4	42.6
		n	15	15	15
	B) After sino-aortic denervation	$\bar{X}$	503.5	678.1	504.2
		Sm	24.7	54.6	36.1
		n	12	12	12
	A vs B	t	1.4	0.4	0.1
		P	0.2	> 0.5	> 0.5

Table 8: Comparison of the ventilatory parameters to electrical stimulation of the pelvic nerve before and after bilateral sino-aortic denervation. The stimulus parameters were 4 - 5 V, 10 - 20 imp.sec^{-1} and 2 ms. $\bar{X}$ is the average value and Sm is the standard error of the mean. n is the number of observations obtained from six cats. t values were calculated with Fisher's t-test. P is the probability of the null hypothesis.

			PRESTIM.	STIM.	POSTSTIM.
$f \cdot min^{-1}$	A) Before sino-aortic denervation	$\bar{X}$	24.5	24	24.1
		Sm	1.3	1.5	1.2
		n	12	12	12
	B) After sino-aortic denervation	$\bar{X}$	25.0	27.0	25.4
		Sm	1.6	1.7	1.6
		n	17	17	17
	A vs B	t	0.20	1.3	1.3
		P	> 0.5	0.22	0.22
V_T ml	A) Before sino-aortic denervation	$\bar{X}$	20.4	24.0	21.5
		Sm	0.5	0.8	0.7
		n	12	12	12
	B) After sino-aortic denervation	$\bar{X}$	21.9	29.2	24.2
		Sm	0.4	0.9	0.7
		n	17	17	17
	A vs B	t	2.5	4.3	2.8
		P	0.02	> 0.0002	0.009
$\dot{V}_E$ $ml \cdot min^{-1}$	A) Before sino-aortic denervation	$\bar{X}$	497.0	573.9	513.1
		Sm	27.4	31.2	16.2
		n	12	12	12
	B) After sino-aortic denervation	$\bar{X}$	556.8	778.4	613.4
		Sm	42.7	46.4	39.6
		n	17	17	17
	A vs B	t	1.2	3.7	2.3
		P	0.28	0.0010	0.03

Table 9: Comparison of the ventilatory responses to hypogastric nerve stimulation before and after buffer den. The stimulus parameters were 4 - 5 V; 10 - 20 imp.sec^{-1}, 2 ms; $\bar{X}$ is the average value, Sm is the standard error of the mean, n is the number of observations obtained from six cats. t values were calculated according to Fisher's t-test and P is the probability of the null hypothesis. Underlined P values indicate that they are statistically significant.

the stimulus the respiratory parameters nearly returned to the prestimulus values.

This group of experiments shows that after bilateral sino-aortic denervation, the increase in the arterial pressure was more pronounced during stimulation of the pelvic and hypogastric nerves. Respiratory changes were almost the same in both groups with pelvic nerve stimulation, whereas after buffer denervation hypogastric nerve stimulation led to a marked increase of the ventilation. The bradycardia resulting from the stimulation of the hypogastric nerve was more pronounced in the buffer denervated group than the controls.

3.4. Mechanisms contributing to the cardiovascular and respiratory changes during the urinary bladder distension in cats

This group of experiments deal with the possible mechanisms contributing to the observed cardiovascular and respiratory changes during the urinary bladder distension in cats. A working hypothesis is mainly focused to the role of the kidney in releasing pressor substances during distension of the urinary bladder by saline infusion and also during direct electrical stimulation of the afferents from the bladder. Preliminary experiments were also carried out regarding the contibution of the suprarenals during the electrical stimulation of the afferents from the bladder.

3.4.1. Role of the kidney

3.4.1.1. Effects of the electrical stimulation of the pelvic and the hypogastric nerves after bilateral renal denervation.

In order to test the possible role of the renal nerves during electrical stimulation of the afferents from the bladder, the

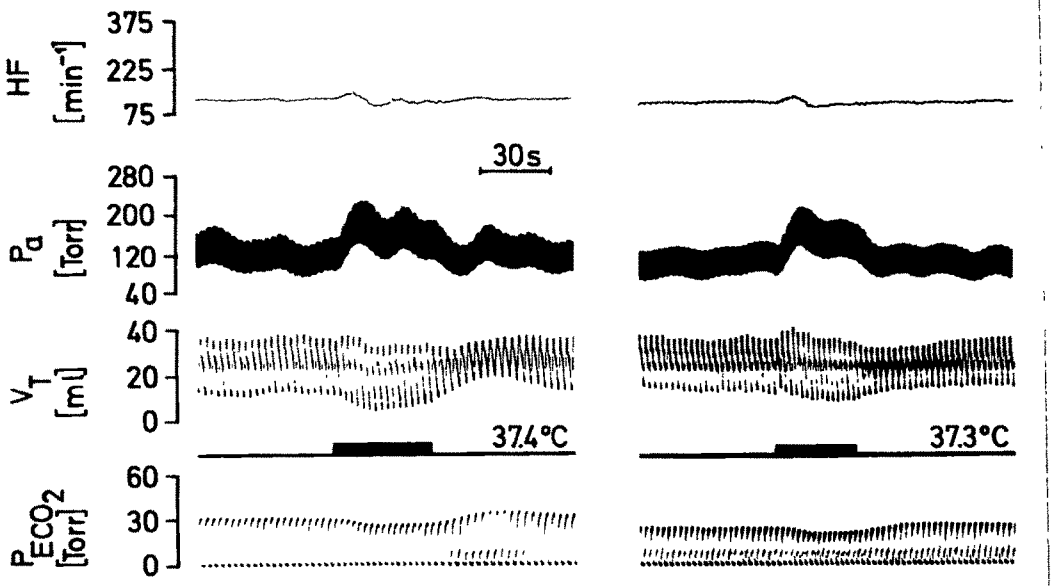
experiments were carried out in the following way: In six cats after sino-aortic denervation the cardiovascular and respiratory changes were studied during the electrical stimulation of the cut central ends of the pelvic and the hypogastric nerves. The results obtained from these experiments were treated as controls. In five of these cats after bilateral renal denervation the stimulation of the afferents from the baldder was repeated and the results were compared to the controls. An example representing this group of experiments was shown in the figure 21 a and b.

3.4.1.1.1. Arterial pressure

In the example shown in figure 21(a)electrical stimulation of the cut central end of the pelvic nerve in the sino-aortic denervated cat resulted in an increase of the systolic pressure from 177.6 to 254 Torr (+ 43.2 %) and the diastolic pressure 115.2 to 172.8 Torr (+ 50 %). After the bilateral renal denervation repeating the electrical stimulation led to an elevation of the arterial pressure to about + 41.7 % (244.8 Torr systolic and 163.2 Torr diastolic). This increase of the arterial pressure was almost the same as before the renal denervation.

In the same experiment (Fig. 21 b) electrical stimulation of the hypogastric nerve with intact renal nerves led to an elevation of the systolic pressure from 127.8 to 264 Torr (+ 52.8 %) and the diastolic pressure from 105.6 to 168 Torr (+59 %). Repeating the electrical stimulation after bilateral renal denervation resulted in an increase of the systolic pressure to 225.6 Torr and the diastolic pressure to 158.4 Torr. These increases of the systolic and diastolic pressures after renal denervation were - 38.4 and -9.6 Torr less as compared to the corresponding values before renal denervation.

Quantitative analysis of this group of experiments have shown that after bilateral renal denervation the prestimulus systolic and the diastolic pressures were about 28 to 24 Torr respectively less than



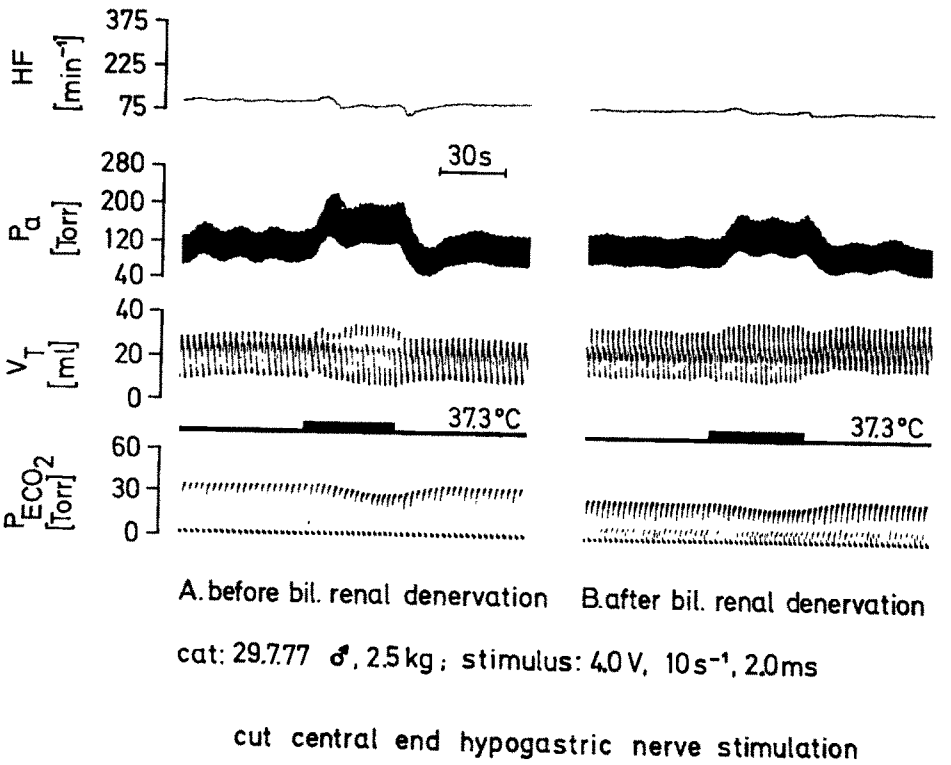


Figure 21 (a and b): Effect of electrical stimulation of the pelvic (a) and the hypogastric (b) before (a) and after (B) bilateral renal denervation. In hypogastric nerve stimulation after bilateral renal denervation there was a reduction of the systolic pressure response, whereas in pelvic nerve stimulation such a reduction was not seen. Respiratory changes were not affected by renal denervation. Black horizontal bars represent the period of electrical stimulation.

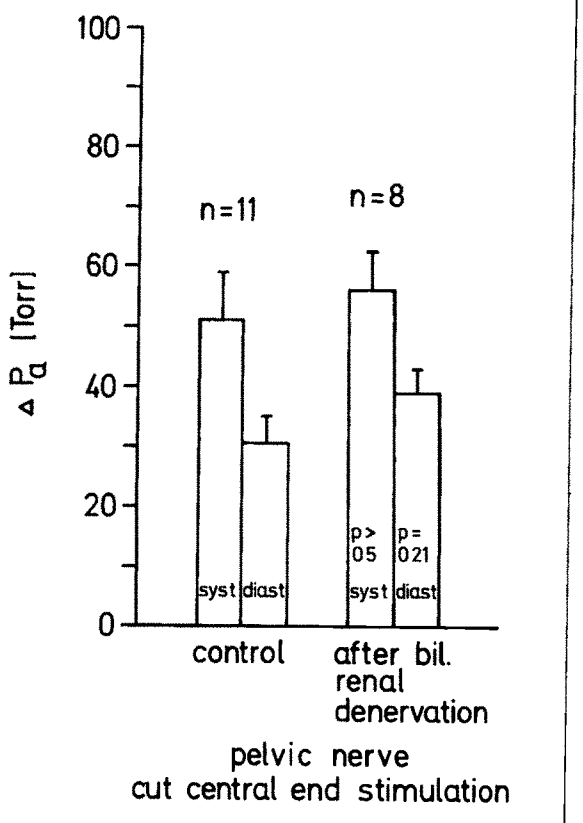
the controls (systolic pressure P = 0.002; diastolic pressure P = 0.01, n = 8). Because of the significant reduction of the control arterial pressure in the renal denervated group, for the purpose of comparison the relative increase of the arterial pressure (stimulus-prestimulus) during the stimulation was analysed.

With intact renal nerves electrical stimulation of the hypogastric nerve resulted in a maximum increase of the systolic pressure to +88 ± 4.4 Torr and the diastolic pressure to +48 ± 3.2 Torr. After renal denervation stimulation of the same nerve with identical stimulus parameters has resulted in an increase of the systolic pressure to +65 ± 5.6 Torr and the diastolic pressure to +45 ± 4.9 Torr. Thus after renal denervation the elevation of the systolic pressure was 23 Torr less as compared with controls. The diminution of this systolic pressure increase after the renal denervation was significant (P = 0.006, n = 7). As it can be seen in figure 22.(a) the increase of the diastolic pressure was not affected by the renal denervation.

On the other hand, bilateral renal denervation did not affect the increase of the arterial pressure obtained with pelvic nerve stimulation (Fig. 22 b).

3.4.1.1.2. Heart frequency

In the experiment shown in figure 21(b)before the renal denervation electrical stimulation of the hypogastric nerve resulted in an increase of the heart frequency from 157 to 172 min^{-1} (+9.6 %). This tachycardia persisted for about 4 to 5 s. Later it was followed by a bradycardia of about -14 % (135 min^{-1}). Stimulation of the same nerve after bilateral renal denervation led to an initial tachycardia of about +7 % (165 min^{-1}) from the control value of 154 min^{-1}. This tachycardia was followed by a less marked bradycardia (-2.6 %). As soon as the stimulus was stopped with intact renal nerves there was a marked bradycardia



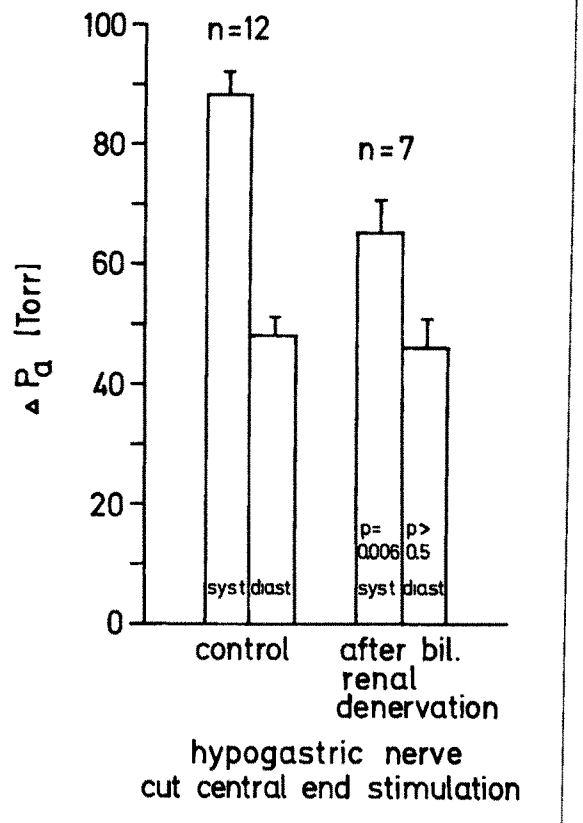


Figure 22 (a and b): Quantitative analysis of the systolic and the diastolic pressure changes before and after bilateral renal denervation during the electrical stimulation of the hypogastric and the pelvic nerve. The stimulus parameters were 4 - 5 V, 10 - 20 imp·sec^{-1} and 2 ms. The systolic pressure increase during hypogastric nerve stimulation was significantly reduced after bilateral renal denervation. The data presented are the average values of stimulus-prestimulus ($\bar{X}$ = Δ Pa Torr) with the standard error of the mean.

of -23.6 % (120 min^{-1}). Whereas after bilateral renal denervation the post stimulus bradycardia was only -7.8 % (142 min^{-1}). In the same cat heart frequency responses resulting from the stimulation of the pelvic nerve were not appreciably altered after renal denervation (Fig. 21 a).

Quantitative analysis of the heart frequency responses in this group of experiments are as follows (Fig. 23 a and b):The initial tachycardia during the stimulation of the hypogastric nerve was almost the same in the renal denervated group in comparison to the controls. Following the tachycardic response there appeared a bradycardia in both groups. The maximum bradycardia in the control group was 150 $\pm$ 19.8 min^{-1}. Whereas after the renal denervation it was 163 $\pm$ 13.9 min^{-1}, which is 13 min^{-1} less as compared to the control group. In the post-stimulation period the bradycardia in the control group was -23.9 min^{-1} (165.3 $\pm$ 13.3 min^{-1}). Whereas in the renal denervated group it was only -9 min^{-1} (163 $\pm$ 9.1 min^{-1}). It seems, however, impossible to recognize systematic differences.

Bilateral renal denervation did not alter appreciably the heart frequency responses with electrical stimulation of the pelvic nerve.

3.4.1.1.3. Respiratory parameters

Average values of the respiratory changes obtained with stimulation of the afferents from the bladder before and after bilateral renal denervation have shown no difference in the prestimulus respiratory parameters between the bilateral renal denervated group and that of the controls. As a result of stimulation of the pelvic and the hypogastric nerves the increase of the respiratory parameters (i.e., tidal volume, respiratory frequency and minute ventilation) observed in the denervated group were not appreciably different from the controls. Similarly, after stopping the stimulus with pelvic and hypogastric nerves the respiratory parameters returned

nearly to the prestimulus values in controls as well as in renal denervated animals.

Thus this group of experiments has shown that, in sino-aortic denervated cats the increase of the systolic pressure observed with the hypogastric nerve stimulation was markedly reduced after the bilateral renal denervation, while the increase of the diastolic pressure was not altered. Bilateral renal denervation did not affect the increase of the systolic and diastolic pressures seen during the stimulation of the pelvic nerve. Respiratory changes resulting from the electrical stimulation of the afferents from the bladder were not appreciably altered in the renal denervated animals in comparison to controls.

3.4.1.2. Changes in the efferent renal nerve activity during the electrical stimulation of the afferents from the bladder

The foregoing experiments are suggestive of the participation of the renal nerves in the elevation of the arterial pressure (particularly the systolic) during the electrical stimulation of the hypogastric nerve. In order to test this possibility in three sino-aortic denervated, and artificially ventilated cats efferent renal nerve activity (left renal nerve) was monitored along with the arterial pressure during the electrical stimulation of the cut central end of the left hypogastric and also the left pelvic nerve.

It can be seen from figure 24(a)that as soon as the electrical stimulation of the hypogastric nerve began, there was an increase in the efferent renal nerve activity even before any change in the arterial pressure was seen. This increase in the renal nerve activity was maintained during the stimulation period. As the electrical stimulation was stopped, the activity of the renal nerve promptly returned to the prestimulus level.

With identical stimulus parameters stimulation of the pelvic nerve also resulted in an increase of the arterial pressure, but

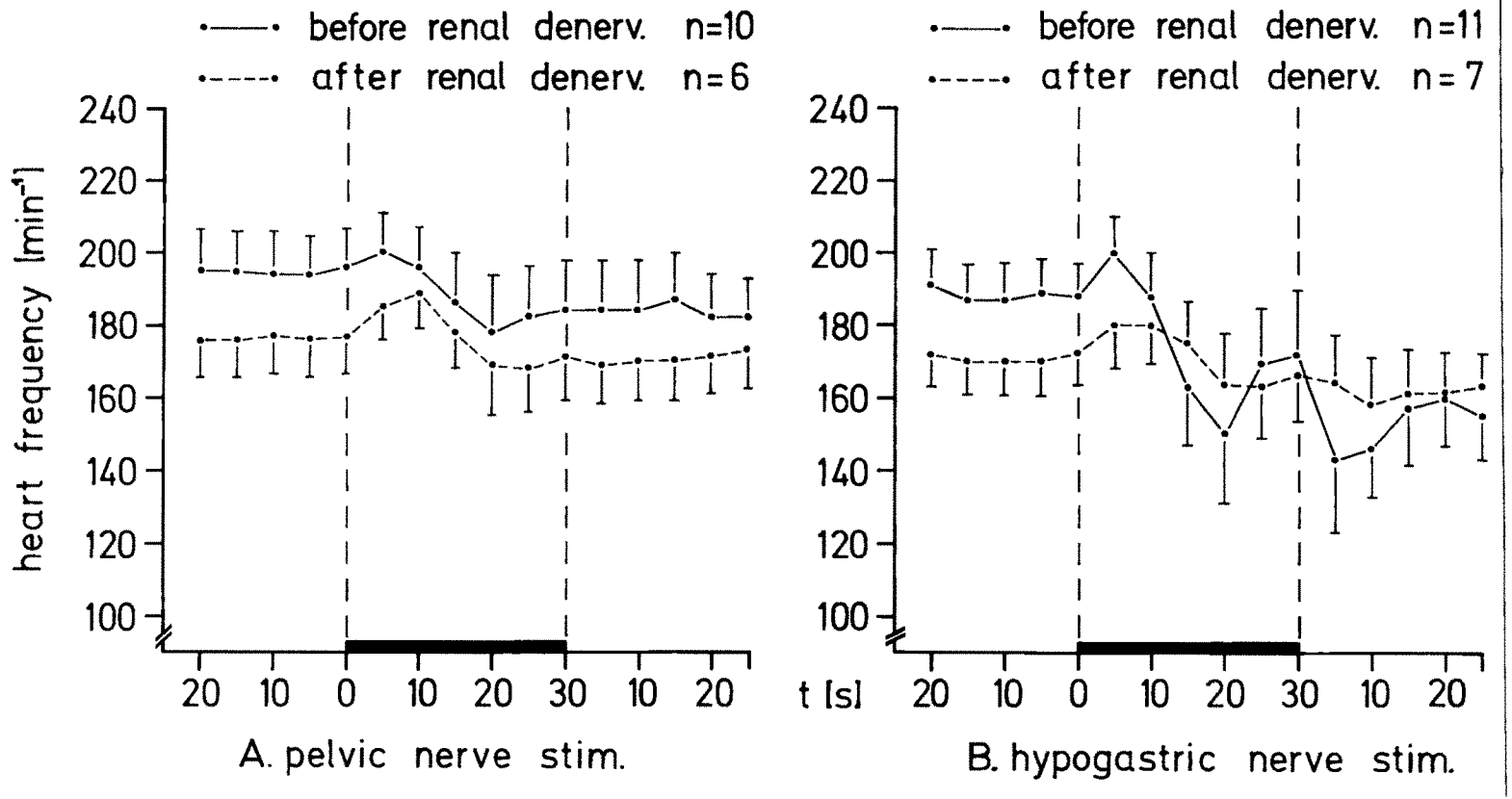


Figure 23 (a and b): Average heart frequency responses during electrical stimulation of pelvic (a) and hypogastric nerves (b) before and after renal denervation. The stimulus parameters were 4 - 5 V; 10 - 20 imp·sec^{-1} and 2 ms. The data presented are the average values ($\bar{X}$) with the standard error of the mean. The vertical dotted lines are the beginning and the end of the stimulation.

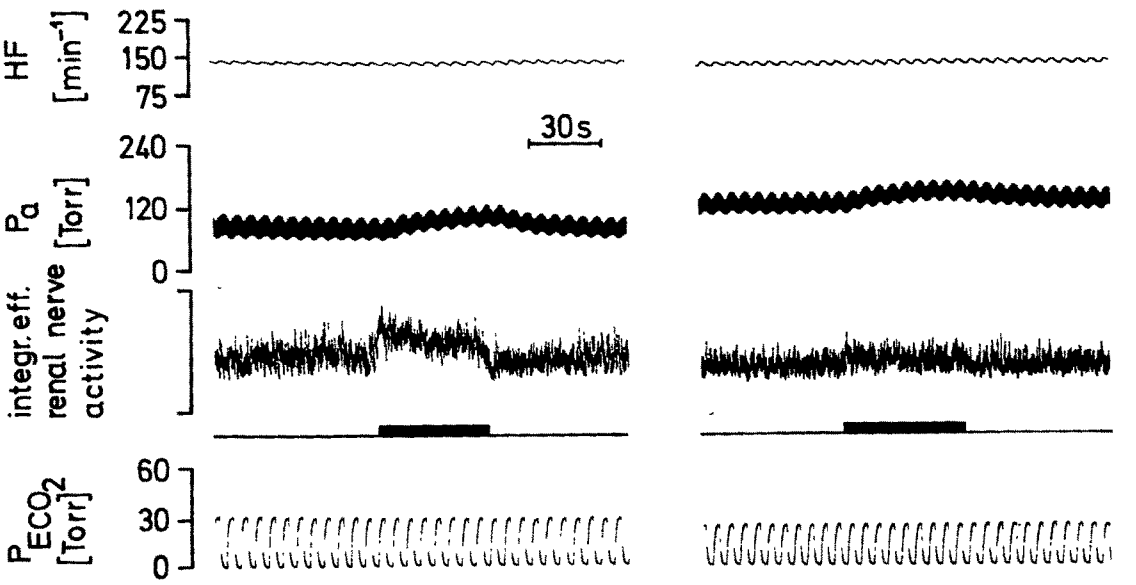


Figure 24 (a and b): Continuous record of the registration of heart frequency (HF min^{-1}), arterial pressure Pa (Torr) and the integrated efferent renal nerve activity and end tidal P_{ECO_2} (Torr) in an anaesthetized cat. The cat was paralysed with Flaxedil (6 $mg \cdot kg^{-1}$ i.v.) and artificially ventilated. Note that with hypogastric nerve stimulation there was an increase in the efferent renal nerve activity before any change in the arterial pressure.

this increase in the arterial pressure was preceded by only a very slight increase in the efferent renal nerve activity (Fig. 24 b).

3.4.1.3. Cardiovascular and respiratory changes during the bladder distension after renal denervation and clamping of the renal vessels

This setup of experiments is continuation of the foregoing. The aim of it is to compare the cardiovascular and the respiratory responses under electrcial stimulation of the afferents from the bladder with the responses to distension of the urinary bladder by infusing saline solution. Again the cats were divided into two groups. Sino-aortic denervated and ureter cannulated cats served as controls, whereas the results obtained in the same cats after bilateral renal denervation and also after clamping of the renal vessels served as the test group. Figure 25 depicts an example of this group of experiments.

3.4.1.3.1. Arterial pressure

In the experiment shown in the figure 25 as a result of increasing the intravesical pressure the arterial pressure increased. The elevation of the arterial pressure reached its maximum at 0 - 60 s of the distension. The maximum increase of the systolic and the diastolic pressures were 153.6 to 192 (+25 %) and from 115 to 139 (+20.8 %) Torr respectively. After this maximum increase there was some adaptation and the systolic and the diastolic pressures were stabilized at an elevated level of 187 (+21.7 %) and 134.4 (+16.7 %) Torr respectively. The same animal was then subjected to bilateral renal denervation and the distension of the bladder was repeated. The maximum response of the systolic and the diastolic pressures at 0 - 60 s of distension were from 139.2 to 177.6 (+27.6 %) and from 110.4 to 148.8 (+34.8 %) Torr. Then the arterial pressure especially the systolic pressure

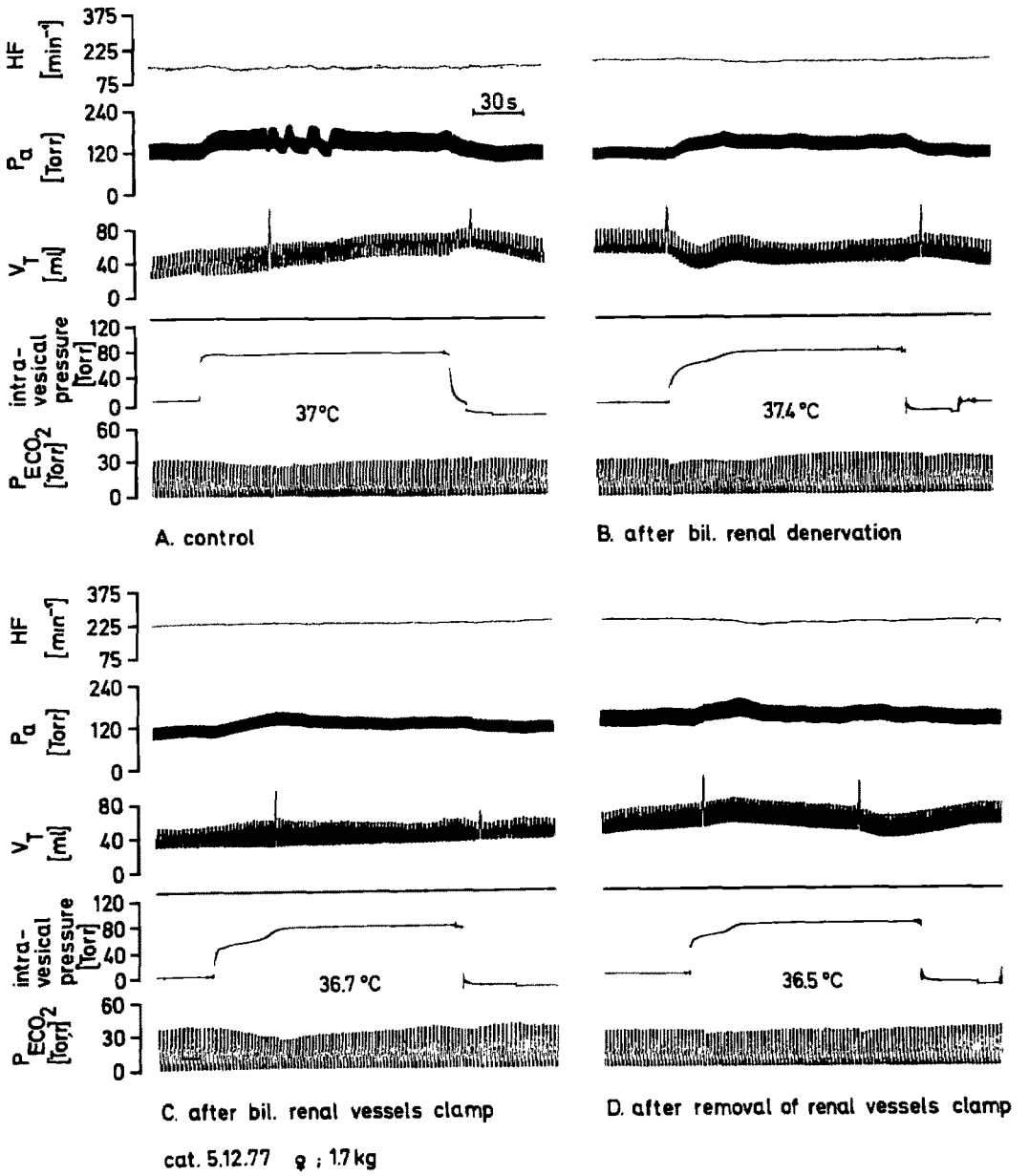


Figure 25: Continuous record of the heart frequency (HF min^{-1}), arterial pressure (Pa Torr), tidal volume (V_T ml), intravesical pressure (Torr) and end tidal CO_2 (P_E CO_2 Torr), before and after bilateral renal denervation, after bilateral clamping of the renal vessels and recovery of the responses after removal of the clamp with urinary bladder distension.

quickly adapted and stabilized at 158 Torr (+13.5 %) and the diastolic at 134.4 Torr (+21.7 %). As the next step the renal vessels were clamped. After this procedure the prestimulus arterial pressure was decreased by about 10 Torr. The maximum increase of the systolic pressure during bladder distension was from 139.2 to 168 (+15 %) and the diastolic pressure was from 110.4 to 139.2 (+31.8 %). After 0 - 90 s of distension both the systolic and diastolic pressures quickly adapted to levels of 148.8 (+10.7 %) systolic pressure and 120 (+13.6 %) Torr diastolic pressure. 30 min. after releasing the renal vessel clamp the arterial pressure response to bladder distension recovered.

The results obtained in five cats studied in this group of experiments are as follows: In the control group the average predistension systolic pressure was 171.3 ± 5.8 and the diastolic pressure was 132.4 ± 4.4 Torr. As a result of bilateral renal denervation the systolic pressure was reduced by about -5 % (162.8 ± 6.0 Torr), and the diastolic pressure by about -3 % (128.7 ± 5.3 % Torr). Clamping the renal vessels (both the artery and the vein) bilaterally resulted in a further reduction of the arterial pressure. With clamped renal vessels the predistension systolic and the diastolic pressures were 138.2 ± 3.7 Torr and 110.4 ± 3.6 Torr respectively. These values were less by about -19 % (systolic) and -17 % (diastolic) than in the controls. Because of the reduction in the predistension arterial pressure the differences between the test and control (i.e., distension - predistension) values were analysed. Figure 26 represents the analysis of the results.

The increase of the systolic and the diastolic pressures were almost the same up to 0 - 90 s of bladder distension in the renal denervated group as compared to the controls. But after 0 - 90 s of distension in the renal denervated group the elevation of the arterial pressure was less marked in comparison to the controls. Thus at 0 - 150 s of distension in the renal denervated group the systolic pressure was less by about +7.9 ± 3.6 Torr and the diastolic pressure was +8.2 ± 2.5 Torr above the predistension values as compared to controls. The reduced pressor responses were found to be significant compared to control group (P = 0.035 systolic

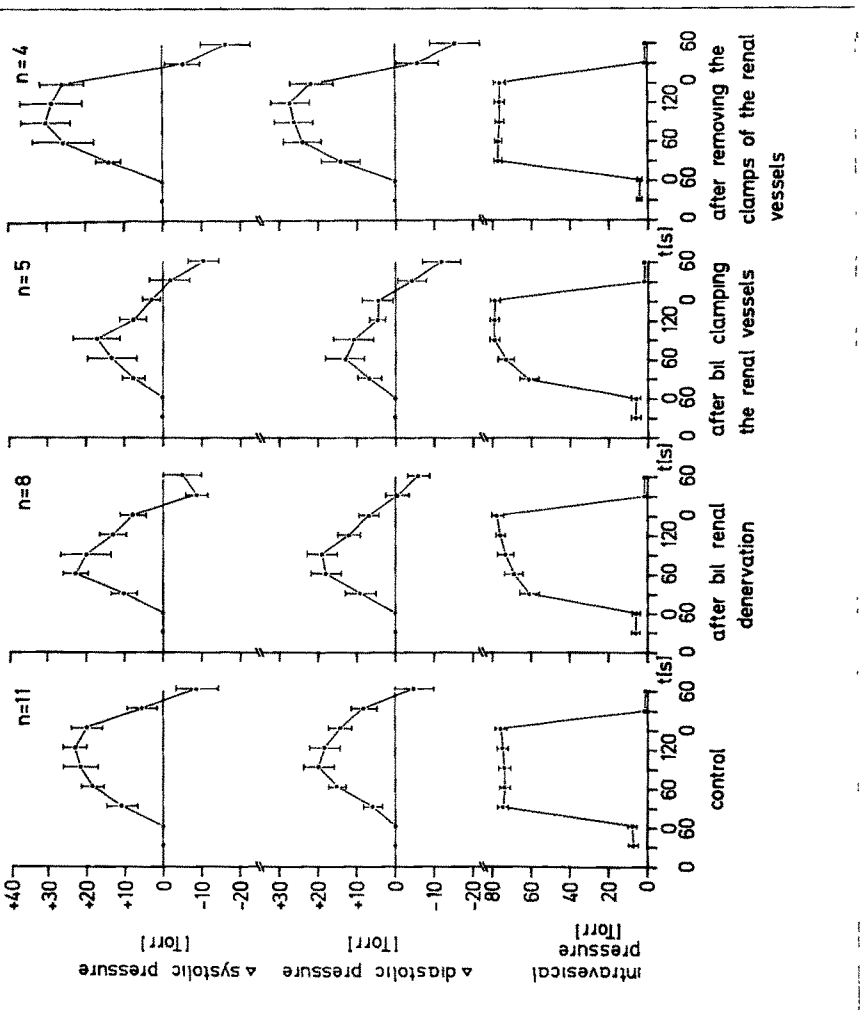


Figure 26: Comparison of the arterial pressure responses during the bladder distension, after bilateral renal denervation and after bilateral clamping of the renal vessels. The data presented are the average values of the difference of the distension-predistension values (ΔX) with their standard error of the mean. The numbers indicate the number of observations. After bilateral renal denervation and clamping of the renal vessels the pressor response during the later phase of the bladder distension (0-90s) was not maintained. After removal of the clamps of the renal vessels there was a recovery of the pressor response during bladder distension.

and diastolic n = 8).

In the same animals after bilateral clamping of the renal vessels the urinary bladder again was distended. The elevation of the arterial pressure was not maintained after 0 - 90 s of the distension. At 0 - 150 s of distension the remaining increase of the systolic pressure was only +3.7 ± 2.4 Torr and the diastolic pressure +4.7 ± 2.2 Torr as compared to the predistension values. Compared to the corresponding values in the control group the reduced responses in the systolic and the diastolic pressures were found to be significant (systolic P = 0.0027; diastolic P = 0.024 for n = 5).

In four cats after removing the renal vessels clamp the reversibility of the pressor responses was studied. As it can be seen from the figure 26 the arterial pressure responses with bladder distension had almost recovered in these animals. After emptying the bladder in general the arterial pressure showed an undershoot in all groups.

Changes in the heart frequency during the bladder distension were not consistent in this group of experiments.

3.4.1.3.2. Respiratory parameters

In the example shown in figure 25 the tidal volume and the respiratory frequency were increased from 24 to 27.8 ml and 27.7 to 32 min^{-1} respectively during the initial phases of bladder distension. The minute ventilation responded with an increase from 670 $ml \cdot min^{-1}$ to 892 $ml \cdot min^{-1}$ (+222 $ml \cdot min^{-1}$). In the same animals after bilateral renal denervation in response to the bladder distension increase of the ventilatory parameters was almost the same. But after clamping the renal vessels, distension of the bladder resulted in a more pronounced increase of the ventilatory parameters. The increase of the tidal volume was 28.6 ml (+6ml) from the control value of 22.4 ml, and the respiratory frequency was 32 min^{-1} from the predistension value of 27 min^{-1}. Similarly the minute ventilation responded with an increase from the predis-

tension value of 636 ml·min^{-1} to 952 ml·min^{-1} (+316 ml·min^{-1}). After removing the clamps of the renal vessels the marked increases in the ventilatory parameters in response to the bladder distension disappeared.

Quantitative analysis of the ventilatory parameters in this group of experiments are as follows: In the control group the average predistension tidal volume and the respiratory frequency were 20.6 ± 0.8 ml and 25.6 ± 0.9 min^{-1} repectively. The minute ventilation was 529 ± 34.1 ml·min^{-1}. After the renal denervation these values were almost the same (tidal volume 20.4 ± 1.5 ml; frequency 25.6 ± 1.0 min^{-1}; minute ventilation 528 ± 52.8 ml.min^{-1}). But after clamping the renal vessels there was a reduction in the tidal volume by about -10 % (18.4 ± 1.2 ml) and the respiratory frequency by about -3% (24.8 ± 1.1 min^{-1}), in comparison to the corresponding values in the control group. The minute ventilation was 454 ± 44.0 ml.min^{-1} which is 75 ml·min^{-1} less as compared to controls. Regarding these variations in the predistension values, ratios of the distension/predistension of the respiratory parameters were analysed. The respiratory changes resulting from the bladder distension were not significantly different in the test groups (i.e., after renal denervation and clamping of the renal vessels compared to controls (P values above 0.05 for n = 8 renal denervated group, n=5 after clamping the renal vessels).

This group of experiments have shown that the pressor response was reduced in its magnitude from 0 - 90 s of bladder distension after bilateral renal denervation and also after clamping of the renal vessels. The pressor responses are reversible after removing the clamps of the renal vessels.

3.4.1.4. Cardiovascular and respiratory changes during the bladder distension after administration of angiotensin II antagonist

The experimental findings so far are suggesting indirectly a

possible involvement of a pressor substance of renal origin. Therefore, the following experiments were conducted to evaluate the influence of angiotensin on the pressor responses observed during the bladder distension. Cardiovascular and respiratory parameters were analysed during the bladder distension in sino-aortic denervated and ureter cannulated cats (n = 5). These results served as controls. Then an angiotensin II antagonist (1-sarcosine-8-leucine AT II) was infused intravenously for 25 minutes at a rate of 2 - 5 $\mu g \cdot min^{-1} \cdot kg^{-1}$. The volume of the infused solution was 2 - 5ml. The specificity of the antagonist was tested by recording the pressor responses of intravenous infusions of 0.5 $\mu g \cdot ml^{-1}$ angiotensin II and 2 $\mu g \cdot ml^{-1}$ of norepinephrine. As it can be seen from figure 27 a and b, the pressor response of angiotensin II was almost blocked after the infusion of the antagonist, whereas the pressor response of norepinephrine was unaltered. After confirming the efficacy of the antagonist the distension of the bladder was repeated, cardiovascular and respiratory parameters were analysed and compared with observations in the control group.

3.4.1.4.1. Cardiovascular changes

An example of this group of experiments is shown in the figure 28. In this experiment before the infusion of the antagonist the predistension systolic pressure was 129.6 and the diastolic pressure was 91.2 Torr. As a result of the bladder distension the maximum increase of the systolic pressure was to 168 Torr (+38.4), and the diastolic pressure to 132 Torr (+40.8). After this maximal increase the arterial pressure was adapted and stabilized at an elevated level of 158.4 (+28.8) and 124.8 (+33.6) Torr of systolic and diastolic pressures respectively. After the infusion of the antagonist (3.5 $\mu g \cdot kg^{-1} min^{-1}$) the predistension systolic and diastolic pressures were markedly decreased. The systolic pressure was decreased to 100.8 Torr (-22 %) and the diastolic to 62.4 Torr (-31.5 %) compared to the values before infusion of the antagonist. During the initial 0 - 30 s of the bladder distension the systolic pressure increased by +38.4 Torr (from 100.8 to 139.2 Torr) and

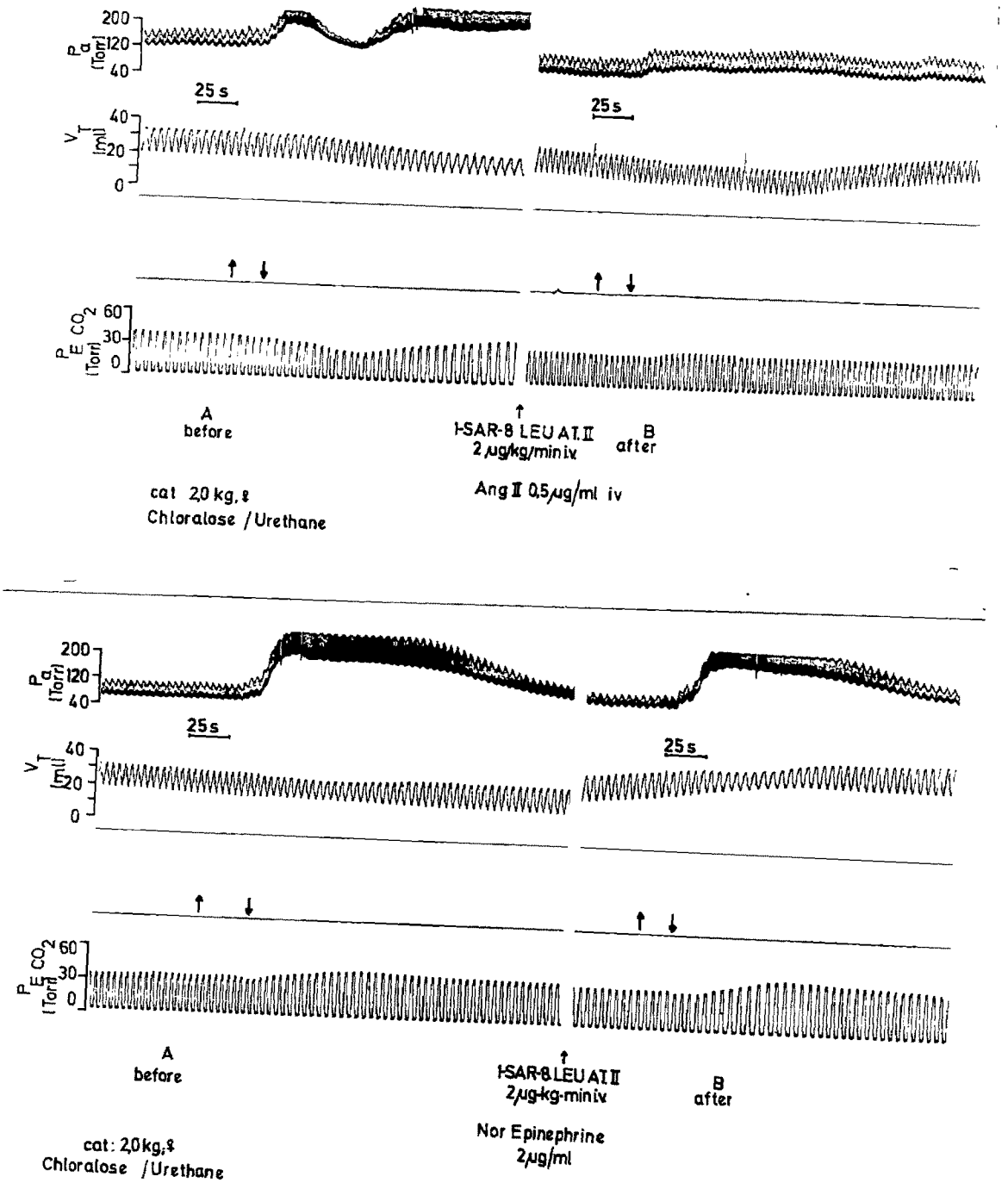


Figure 27 (a and b): Example of an experiment demonstrating the blocking effect of the pressor response of angiotensin II 0.5 $\mu g/ml^{-1}$ i.v. by the angiotensin II antagonist 1 sar-8-LEU.AT II $2\mu g \cdot kg^{-1}$ min^{-1} i.v. In the same experiment the pressor response of 2 $\mu g \cdot ml^{-1}$ of norepinephrine was not affected by the angiotensin II antagonist. The arrows (↑) indicate the beginning of the infusion and (↓) indicate the end of the infusion of the drugs.

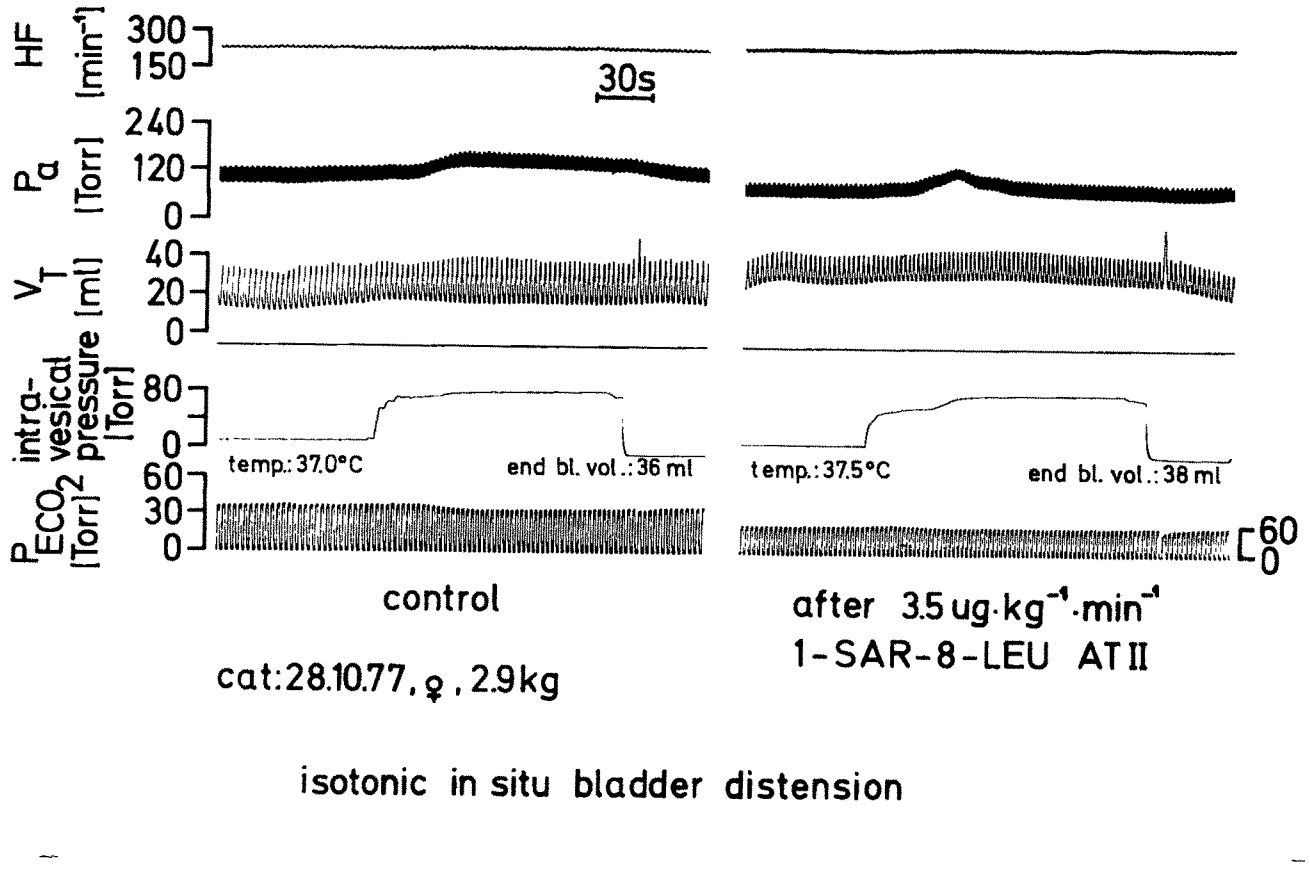


Figure 28: Example of an experiment demonstrating the inhibition of the pressor response resulting from the bladder distension after angiotensin II antagonist infusion. Note the pressor response after the angiotensin II antagonist quickly gets adapted though the intravesical pressure is at an elevated level. Also after the antagonist there is a decrease of tidal volume and increase of the respiratory frequency during the predistension phase.

the diastolic pressure by +52.8 Torr (from 62.4 to 115.2 Torr). After the initial increase the arterial pressure quickly returned to predistension levels, inspite of the elevated intravesical pressure of 75.4 Torr.

Similar results were obtained almost in all experiments in this group. Before the infusion of the antagonist the average predistension systolic and diastolic pressures were 150 ± 6.5 and 100.8 ± 1.6 Torr respectively. After the infusion of the antagonist the control systolic and diastolic pressures were decreased by 25.5 % (111.8 ± 4.2 Torr and 35.7 % (64.8 ± 4.0 Torr) respectively in comparison to the corresponding values before the administration of the antagonist. The decrease in the arterial pressure after the infusion of the antagonist was significant (P less than 0.0002 for n = 7).

Regarding the decrease in the predistension arterial pressure after the infusion of the angiotensin II antagonist, ratios (distension/predistension) of the systolic and diastolic pressures were analysed during bladder distension in control group and in the test group. It can be seen from the figure 29 before the infusion of the antagonist, there was a marked elevation of the systolic and diastolic pressures in response to increased intravesical pressure. After the infusion of the angiotensin II antagonist (2 - 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) up to 0 - 60 s of the bladder distension there was no significant difference in the elevation of the systolic and diastolic presssures as compared to the controls i.e., before the infusion of the AT II antagonist (P = 0.3 for n = 7). In the test group (i.e., after the AT II antagonist) form 0 - 60 s of distension onwards there was a progressive diminution of the pressor response inspite of the elevated intravesical pressure of 72 ± 1.9 Torr. At the end of the 0 - 150 s of distension period the arterial pressure (both the systolic and the diastolic pressures) fell below the predistension value (Fig.29). The diminution of the pressor response from 0 - 60 s of the bladder distension in the test group was found to be statistically significant as compared to controls (Table 10). Upon releasing the intravesical pressure the arterial pressure showed an undershoot

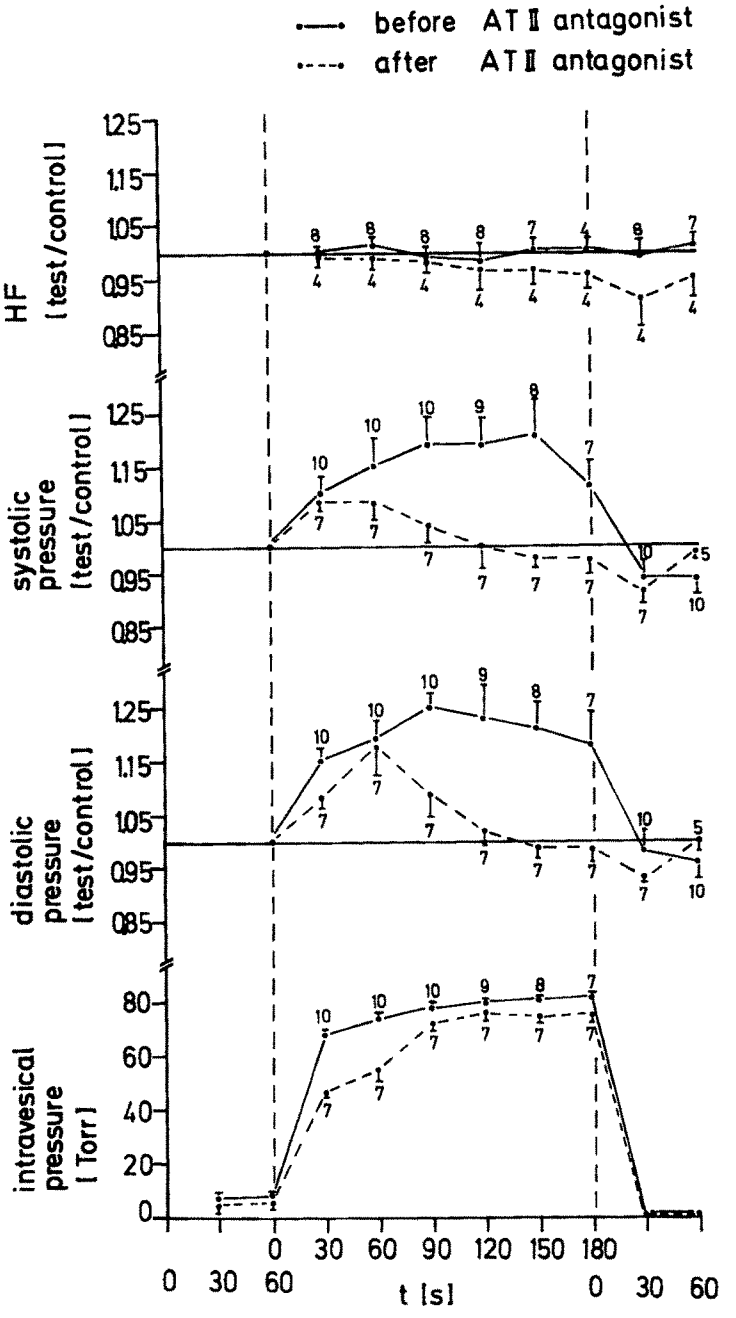


Figure 29: Comparison of the cardiovascular changes with the bladder distension before and after the angiotensin II antagonist infusion. The data presented are the average values of the ratios of the distension/predistension with their standard error of the mean (Sm). Numbers above the points indicate the number of observations obtained from five cats. Vertical dotted lines indicate the duration of the bladder distension. After the infusion of the angiotensin II antagonist the pressor response during the later phases of bladder distension i.e., 0-60 s was adapted as compared to the pressor response before the infusion of the antagonist.

		time (s)	DISTENSION 0-30	30-60	60-90	90-120	120-150	150-180	POSTDISTENSION 0-30	30-60
SYST. PRESSURE Test/Control	A) Before AT II antagonist	$\bar{X}$	1.09	1.15	1.18	1.18	1.21	1.12	0.94	0.94
		Sm	0.03	0.05	0.05	0.05	0.06	0.06	0.04	0.05
		n	10	10	10	9	8	7	10	10
	B) After AT II antagonist	$\bar{X}$	1.08	1.08	1.04	1.0	0.97	0.98	0.92	0.99
		Sm	0.03	0.04	0.05	0.04	0.03	0.05	0.02	0.01
		n	7	7	7	7	7	7	7	5
	A vs B	t	0.24	1.09	2.0	3.0	3.58	1.79	0.45	1.0
		P	>0.5	0.3	0.6	0.008	0.0027	0.07	>0.5	0.34
DIAST. PRESSURE Test/Control	A) Before AT II antagonist	$\bar{X}$	1.12	1.24	1.24	1.22	1.17	1.16	0.96	0.96
		Sm	0.02	0.04	0.04	0.04	0.04	0.05	0.05	0.04
		n	10	10	10	9	8	7	10	10
	B) After AT II antagonist	$\bar{X}$	1.08	1.18	1.09	1.02	0.99	0.92	0.93	1.0
		Sm	0.04	0.11	0.05	0.03	0.02	0.03	0.01	0.02
		n	7	7	7	7	7	7	7	5
	A vs B	t	0.90	0.5	2.34	4.0	4.0	4.13	0.6	0.9
		P	>0.5	>0.5	0.035	0.0010	0.0015	0.0015	>0.5	>0.5

Table 10: Comparison of the ratios (test/control) of the systolic and diastolic pressures during the urinary bladder distension before and after administration of angiotensin II antagonist. The data presented are the average values of the ratios ($\bar{X}$ test/control) with the standard error of the mean (Sm). n is the number of observations. t is the t value according to Fisher's t-test and P is the probability of the null hypothesis. The underlined P values indicate that they are statistically significant.

		time (s)	DISTENSION 0-30	30-60	60-90	90-120	120-150	150-180	POSTDISTENSION 0-30	30-60
V_T ml $\frac{\text{dist.}}{\text{predist.}}$	A)Before AT II antagonist	$\bar{X}$	0.95	1.0	1.03	1.07	1.03	1.02	1.02	1.06
		Sm	0.03	0.03	0.02	0.02	0.02	0.02	0.02	0.02
		n	10	10	10	9	8	7	10	10
	B)After AT II antagonist	$\bar{X}$	0.97	0.99	1.07	0.98	0.99	0.98	1.03	0.90
		Sm	0.03	0.04	0.07	0.05	0.04	0.04	0.04	0.04
		n	7	7	7	7	7	7	7	5
	A vs B	t	0.5	0.2	0.06	1.8	1.0	1.0	0.25	4.0
		P	>0.5	>0.5	>0.5	0.09	0.36	0.36	>0.5	0.002
$f \cdot min^{-1}$ $\frac{\text{dist.}}{\text{predist.}}$	A)Before AT II antagonist	$\bar{X}$	1.06	1.07	1.06	1.05	1.05	1.05	1.01	1.05
		Sm	0.02	0.02	0.02	0.02	0.01	0.02	0.01	0.02
		n	10	10	10	9	8	7	10	10
	B)After AT II antagonist	$\bar{X}$	0.97	0.97	1.01	0.94	1.0	0.99	0.92	0.96
		Sm	0.03	0.03	0.03	0.06	0 02	0.02	0.04	0.02
		n	7	7	7	7	7	7	7	5
	A vs B	t	3.0	3.3	1.7	2.2	2.5	2.0	2.3	3.0
		P	0.01	0.005	0.1 2	0.04	0.03	0.06	0.035	0.01
$\dot{V}_E$ ml $\cdot$ min^{-1} $\frac{\text{dist.}}{\text{predist.}}$	A)Before AT II antagonist	$\bar{X}$	1.0	1.06	1.10	1.11	1.09	1.08	1.03	1.11
		Sm	0.04	0.04	0.03	0.02	0.02	0.03	0.03	0.03
		n	10	10	10	9	8	7	10	10
	B)After AT II antagonist	$\bar{X}$	0.98	1.0	1.14	0.95	1.02	0.99	0.99	0.86
		Sm	0.04	0.06	0.07	0.07	0.06	0.05	0.05	0.06
		n	7	7	7	7	7	7	7	5
	A vs B	t	0.3	1.5	0.5	2.3	1.2	1.5	0.7	3.6
		P	>0.5	0.15	>0.5	0.03	0.26	0.16	>0.5	0.0035

Table 11: Comparison of the ratios (distension/predistension) of the tidal volume ($V_T$ml), respiratory frequency ($f \cdot min^{-1}$) and minute ventilation ($\dot{V}_E$ ml$\cdot$min^{-1}) during the distension of the urinary bladder before and after administration of angiotensin II antagonist. The data presented are the average values of the ratios ($\bar{X}$ distension/predistension) with the standard error of the mean (Sm). n is the number of observations, t is the t value according to Fisher's t-test and P is the probability of the null hypothesis. The underlined P values indicate that they are statistically significant.

in both groups.

In the individual experiments of this group there was a large variation in the heart frequency response. Before the administration of the angiotensin II antagonist, the average predistension heart rate was about 272 ± 12.2 min^{-1}. As a result of the administration of the AT II antagonist the heart frequency was decreased by about -26 min^{-1} (246 ± 10.3 min^{-1}) compared to controls. Because of the decrease in the predistension heart rate, ratios (distension/predistension) of the heart rate changes during the bladder distension were analysed and represented in the figure 29. Elevating the intravesical pressure resulted in a progressive bradycardia in both groups. After releasing the bladder pressure there was an undershoot in the control as well as in test group.

3.4.1.4.2. Respiratory changes

In the control group (i.e., before the administration of the AT II antagonist) the predistension tidal volume was 19.9 ± 0.7 ml and the respiratory frequency was 24.5 ± 0.8 min^{-1}. After the infusion of the antagonist the tidal volume was decreased by about -4.6 ml (15.3 ± 0.5 ml) with a simultaneous increase of the respiratory frequency by about +8 min^{-1} (32.3 ± 1.9 min^{-1}) compared to the corresponding values of the control group. The decrease of the predistension tidal volume in the test group was significant at a P value less than 0.0002 (for n = 7) and the increase of the respiratory frequency was significant at a P value of 0.0027 (n = 7). Due to significant alterationsin the predistension tidal volume and respiratory frequency after the infusion of angiotensin II antagonist ratios of the ventilatory changes (distension/predistension) were analysed in the control and the test group, and presented in the table 11. During bladder distension the changes in the tidal volume and minute ventilation were not appreciably altered in the test group (i.e., after angiotensin II antagonist) compared to the control group. The increase of the respiratory frequency, during the bladder distension, however, was diminished

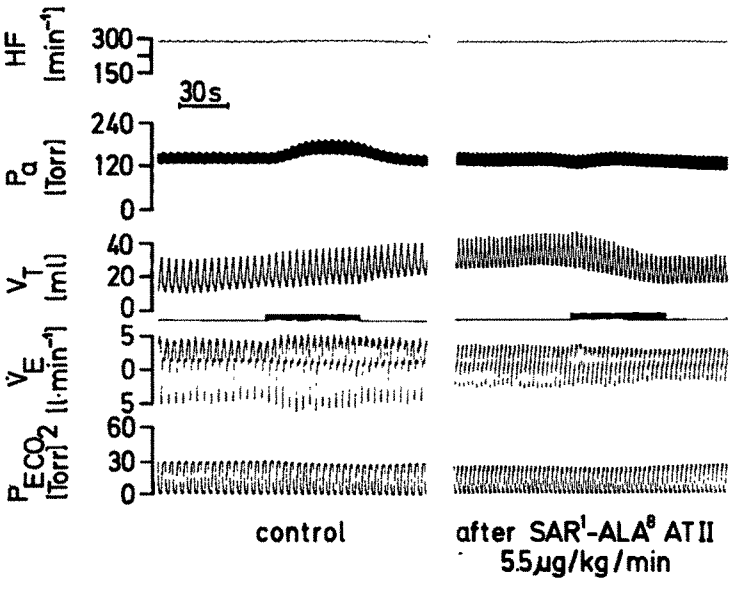
in the test group compared to the controls (table 11).

3.4.1.5. Effects of electrical stimulation of the afferents from the bladder after administration of angiotensin II antagonist

In continuation of the foregoing experiments, electrical stimulation of the afferents from the bladder namely the pelvic and the hypogastric nerves was carried out in sino-aortic denervated cats. These results were treated as a control group. Then in the same animals the angiotensin II antagonist 1-sarcosine 8-alanine-angiotensin II was infused intravenously for a period of 25 min. The dosage of the antagonist used was 5 - 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The volume of the infused solution was 2.5 ml. Before and immediately after the infusion of the antagonist the pressor responses of intravenous injection of 0.5 $\mu g \cdot ml^{-1}$ of angiotensin II and 2 $\mu g \cdot ml^{-1}$ norepinephrine were recorded. If the pressor response of angiotensin II (0.5 $\mu g \cdot ml^{-1}$) was blocked leaving unaltered the response of norepinephine (2 $\mu g \cdot ml^{-1}$) it was considered that blockade of the angiotensin II antagonist was achieved. In this group of experiments five cats were studied, but in one experiment the blockade of the antagonist was not achieved. So results obtained from four cats are presented.

3.4.1.5.1. Cardiovascular changes

An example of this group of experiments is illustrated in figure 30 a and b. Before the infusion of the angiotensin II antagonist, electrical stimulation of the pelvic nerve (4 V, 10 $imp \cdot s^{-1}$ 2ms) resulted in an increase of the systolic pressure from 144 to 172.8 Torr (+28.8 Torr) and the diastolic pressure from 120 to 139.2 Torr (+19.2 Torr). After the infusion of the antagonist, repeating the electrical stimulation led to an increase of the systolic pressure from 134.4 to 139.2 Torr and the diastolic



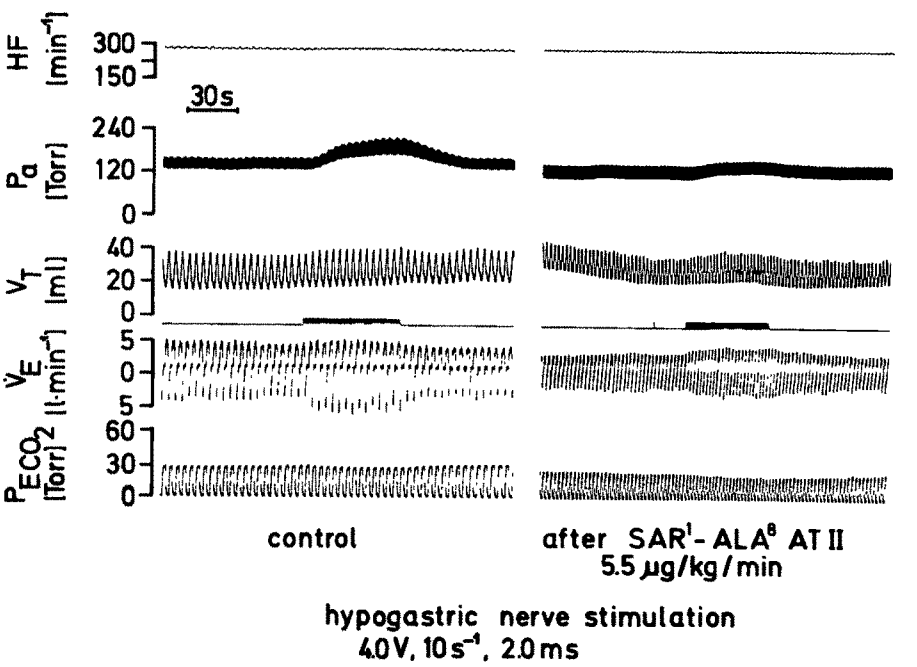


Figure 30 (a and b): Example of an experiment demonstrating the reduction of the pressor response induced by electrical stimulation of the pelvic and the hypogastric nerves after the infusion of the angiotensin II antagonist. After the infusion of the antagonist during the prestimulus period there was an increase of the respiratory frequency with a simultaneous decrease of tidal volume.

pressure from 105.6 to 110.4 Torr. These increases in the arterial pressure were only +4.8 Torr more than the prestimulus values (Fig. 30a). Stopping of the electrical stimulus brought the arterial pressure back to the prestimulus value in the control and after the antagonist.

In the same experiment (Fig. 30 b) before the administration of the angiotensin II antagonist electrical stimulation of the hypogastric nerve led to an elevation of the systolic pressure from 144 to 187 Torr (+43 Torr) and the diastolic pressure from 120 to 144 Torr (+24 Torr). After the infusion of the antagonist the prestimulus systolic and diastolic pressures were decreased. The systolic pressure was 120 Torr which is 24 Torr less and the diastolic pressure was 91.2 Torr which is 28.8 Torr less than the prestimulus values prior to the infusion of the antagonist. Repeating the electrical stimulation now resulted in an increase of the systolic and the diastolic pressures only to +9.6 Torr above prestimulus value (120 to 129.6 Torr systolic; 91.2 to 100.8 Torr diastolic). After stopping the electrical stimulation, the arterial pressure promptly returned to the prestimulus value, before and after the administration of the antagonist.

The reduced pressor responses after the administration of the angiotensin II antagonist with the electrical stimulation of the afferents from the bladder were reproducible in all the five experiments performed on four cats.

After the infusion of the 1-sarcosine-8-alanine-angiotensin II the control arterial pressure was decreased to about -17 to 20 Torr. Because of the reduction in the prestimulus arterial pressure in the antagonist treated group, for the purpose of statistical comparison the differences between the stimulus to the prestimulus arterial pressures were analysed. The results obtained after the administration of the antagonist were compared with those before the antagonist. Figure 31 a and b represents the analysis of the results of this group.

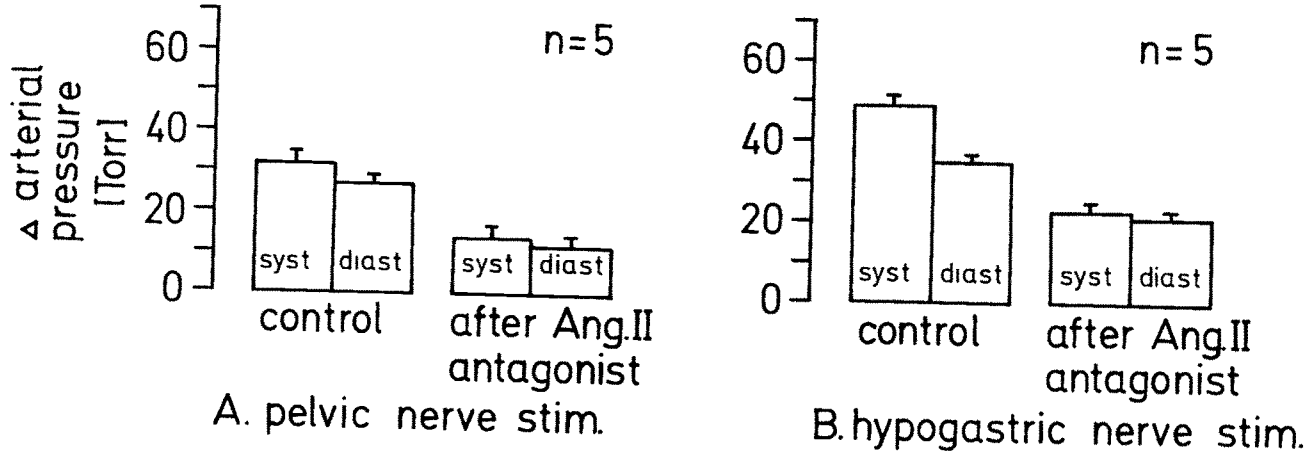


Figure 31 (a and b): Quantitative analysis of the arterial pressure response induced by the cut central ends of the pelvic and the hypogastric nerve stimulations before and after angiotensin II antagonist. The data presented are the average values of the differences of stimulus-prestimulus ($\Delta \bar{X}$) with the standard error of the mean (Sm). n is the number of observations obtained from 4 cats. The stimulus parameters were 4 - 5 V, 10 - 20 imp·sec^{-1}, 2 ms.

Electrical stimulation of the cut central ends of the pelvic nerve (4 - 5 V, 10 - 20 imp.s^{-1}, 2 ms) before the administration of the antagonist resulted in average increase of the systolic pressure of +31.8 ± 3.2 Torr from the control value of 134.4 Torr, and the diastolic pressure of +27.2 ± 0.9 Torr from the prestimulus value of 115.6 ± 2.4 Torr. After the administration of the angiotensin II antagonist repeating the electrical stimulation led to an average increase of the systolic pressure of +14.4 ± 3.0 Torr from the prestimulus value of 127 Torr and of the diastolic pressure of +12.5 ± 2.2 Torr from the control value of 97.9 Torr. The pressor responses after the administration of the angiotensin II antagonist were significantly less compared to the pressor responses in the control group (P = 0.005 systolic and P = 0.0005 diastolic, n = 5, Fig. 31 a). Stimulation with identical stimulus parameters of the hypogastric nerve in the control group resulted in an average increase of the systolic pressure of +48.9 ± 2.5 Torr from the control value of 158.4 ± 6.7 Torr, and the diastolic pressure of +34.6 ± 1.6 Torr from the prestimulus value of 120.4 ± 5.2 Torr. After the administration of the angiotensin II antagonist, repeating the stimulus resulted in an increase of the systolic pressure of +21.1 ± 1.1 Torr from 109.4 ± 5.2 Torr. The pressor response in the test group was significantly less compared to the responses in control group (P less than 0.0002, n = 5, Fig. 31b).

In this group of experiments the heart frequency responses were not consistent both in the control and in the test group.

3.4.1.5.2. Respiratory changes

After the infusion of angiotensin II antagonist the prestimulus respiratory frequency was increased by about 8 min^{-1} (26.6 ± 1.4 min^{-1}) compared to the respiratory frequency of the control group (18.5 ± 1.6 min^{-1}). As a result the minute ventilation was also increased by +150.5 $ml \cdot min^{-1}$ (to 504.7 $ml \cdot min^{-1}$) in comparison with the minute ventilation before the antagonist which is

354.2 ± 23.9 ml·min^{-1}). These increases were found to be statistically significant (P = 0.005, n = 5).

During the stimulation of the pelvic nerve before the antagonist the increase in the minute ventilation was to 406.6 ± 22.1 ml·min^{-1} (+52.4 ml·min^{-1}) from the prestimulus value of 354.2 ± 23.9 ml.min^{-1}. Repeating the stimulus after the angiotensin II antagonist the minute ventilation increased to 538.4 ± 26.1 ml·min^{-1} (+33.7 ml ·min^{-1}) from the prestimulus value of 504.7 ± 34.7 ml.min^{-1}. With the hypogastric nerve stimulation in the control group (i.e., before the antagonist) the increase in the minute ventilation was from 392.9 ± 25.8 ml·min^{-1} to 541.9 ± 32.3 (+149.0 ml·min^{-1}). After the antagonist the increase in the ventilation was from 513.9 ± 27.3 to 615.6 ± 25.6 (+101.7 ml.min^{-1}). Thus, there was no appreciable alteration in the ventilatory responses resulting from the stimulation of afferents from the bladder after the infusion of the angiotensin II antagonist.

This group of experiments have shown that the pressor responses during the bladder distension and with electrical stimulation of the afferents from the bladder were reduced after the angiotensin II antagonist. The heart frequency and the respiratory responses were not affected after the antagonist infusion.

3.4.2. Effect of electrical stimulation of the bladder afferents after adrenalectomy

This group of experiments were performed to test the role of the adrenals (suprarenal glands) in the observed pressor responses during the electrical stimulation of the afferents from the bladder. In five sino-aortic, and renal denervated cats the effect of the electrical stimulation of the afferents from the bladder were studied. These results served as controls. In the same cats bilateral adrenalectomy was performed and the electrical stimulations were repeated. The results obtained were compared with the controls. As a result of bilateral adrenalectomy the prestimulus systolic and

the diastolic pressures were reduced by about 10 to 15 Torr. Due to the reductions in the prestimulus values after the adrenalectomy the differences between the stimulus to the prestimulus values were analysed in both groups.

The results obtained in this group of experiments are as follows: Before adrenalectomy with the pelvic nerve stimulation the maximum average increase in the systolic pressure was +56.6 ± 6.6 Torr and the diastolic pressure +39.0 ± 4.4 Torr. After bilateral adrenalectomy the average maximum increase was +39.2 ± 8.4 Torr systolic pressure and +35.4 ± 7.8 Torr diastolic pressure. The arterial pressure changes after adrenalectomy were not significantly different compared to controls ($P = 0.1$, $n = 8$).

Similarly in the hypogastric nerve stimulation in the control group the maximum average increases in the systolic and diastolic pressures were +65.1 ± 5.7 and 45.9 ± 4.9 Torr respectively. Repeating the stimulation after adrenalectomy resulted in a maximum increase of the systolic and diastolic pressures of about +49.8 ± 7.3 and +56.4 ± 8.3 Torr. In the test group the increase of the systolic pressure was 15.3 Torr less. Whereas the diastolic pressure was 10.5 Torr more than in the controls. These changes in the arterial pressure were not significantly different compared to controls ($P = 0.1$, $n = 7$).

The responses of theheart frequency and ventilation during the stimulation of the afferents from the bladder were not altered after the adrenalectomy.

Thus this group of experiments has shown that adrenalectomy has not affected the pressor responses and the ventilatory changes observed with stimulation of the afferents from the bladder.

3.5. Effect of prolonged distension of the urinary bladder on cardiovascular and respiratory parameters

So far, in the experiments described the distension period was

maintained between 2 - 3 minutes. Keeping in view the bladder disturbances reported in human subjects, the distension period of the bladder has been extended to 30 - 120 minutes. The effect of prolonged distension of the bladder on cardiovascular parameters was observed both in cats and dogs. The respiratory changes were analysed only in cats.

3.5.1. Cardiovascular changes

In four cats with intact buffer nerves the urinary bladder was distended in situ. In these experiments the flow rates of the saline used for distending the bladder were 17 to 20 $ml.min^{-1}$ with a pressure head of 80 Torr. These slow flow rates were chosen because they were found to be not damaging the bladder mucosa, though the distension was carried out for a 30 minutes period. As a result of slow infusion of saline into the bladder in situ, within one minute the intravesical pressure was increased to about 61.5 ± 4.7 Torr. The systolic and the diastolic pressures responded with an increase to 174.6 ± 7.36 (+6.6 %) and 128.4 ± 8.55 (+5.9 %) Torr from the control values of 163.8 ± 6.14 and 121.2 ± 4.91 Torr respectively. Within 3 minutes the increase in the arterial pressure reached its maximum. The maximum increase of the systolic pressure was to 190.2 ± 14.1 Torr which is + 16 % and the diastolic pressure was to 147.6 ± 11.8 Torr which is 21.7 % above the prestimulus value. After this maximal increase, the arterial pressure started to fall, though the intravesical pressure was still increasing. Thus, at the end of 30 minutes, the systolic pressure was 168.0 ± 8.8 Torr and the diastolic 128.4 ± 10.4 Torr above their respective control values (i.e., +2.6 and +5.9%). The fall in the arterial pressure occurred inspite of the elevated intravesical pressure of 71.4 ± 3.8 Torr. After releasing the bladder pressure the arterial pressure showed an undershoot phenomenon. Even 5 minutes after the release of the bladder pressure the systolic pressure was 5.5 % (154.8 ± 6.2 Torr) and the diastolic pressure was about 5 % (115.2 ± 7.2 Torr) below the predistension values.

In order to avoid the mechanical disturbances arising from the bladder distension in situ in the same cats the bladder was exteriorized from the abdominal cavity (keeping the vascular and nervous supply intact) and the distension procedure was repeated. Also with the exteriorized distension the increase in the arterial pressure reached its maximum value after 3 min. period of the distension. The maximal elevation of the systolic was from 162 ± 3.6 to 193.2 ± 1.9 Torr (+19.3 %) and the diastolic pressure from 121.2 ± 3.6 to 148.8 ± 3.8 Torr (+22.8 %). From 3 min. of distension onwards there was a falling tendency in the arterial pressure. This decrease of the arterial pressure, however, was not as severe as it was with the distension in situ. At the end of 30 min, the systolic pressure was about +11.8 % (181 ± 3.2 Torr) and the diastolic pressure was about +12.0 % (136 ± 6.3 Torr) above the control values. After releasing the bladder pressure, within 5 minutes the arterial pressure returned almost to its control value (Fig. 32).

During bladder distension in situ for a 30 min period the heart frequency responded with a progressive bradycardia. At the end of the 30 min of distension the heart frequency was 225 ± 15.8 min^{-1}, which is about 17 min^{-1} less than the predistension value of 242 ± 20.1 min^{-1}. During exteriorized distension, there was an initial bradycardia which reached its maximum at 10 min of distension. The decrease in the heart frequency was about -11 min^{-1} (214 ± 20.7min^{-1}) from the predistension value of 225 ± 17.8 min^{-1}. From 10 min of the distension period the heart frequency showed a tendency towards tachycardia. Thus at the end of 30 min of distension it was 229 ± 21 min^{-1}, which is about 4 beats min^{-1} above the control value.

Even 5 min after releasing the pressure of the bladder in situ, the heart frequency remained about 11 beats min^{-1} (229 ± 14.6 min^{-1}) below the predistension value of 240 ± 18.9 min^{-1}. In contrast, during the exteriorized situation, releasing the bladder pressure resulted in a tachycardia. At 5 min of the postdistension period the heart frequency was about 23.5 beats·min^{-1} (249 ± 21.3 min^{-1}) above the predistension value (225 ± 17.79 min^{-1}).

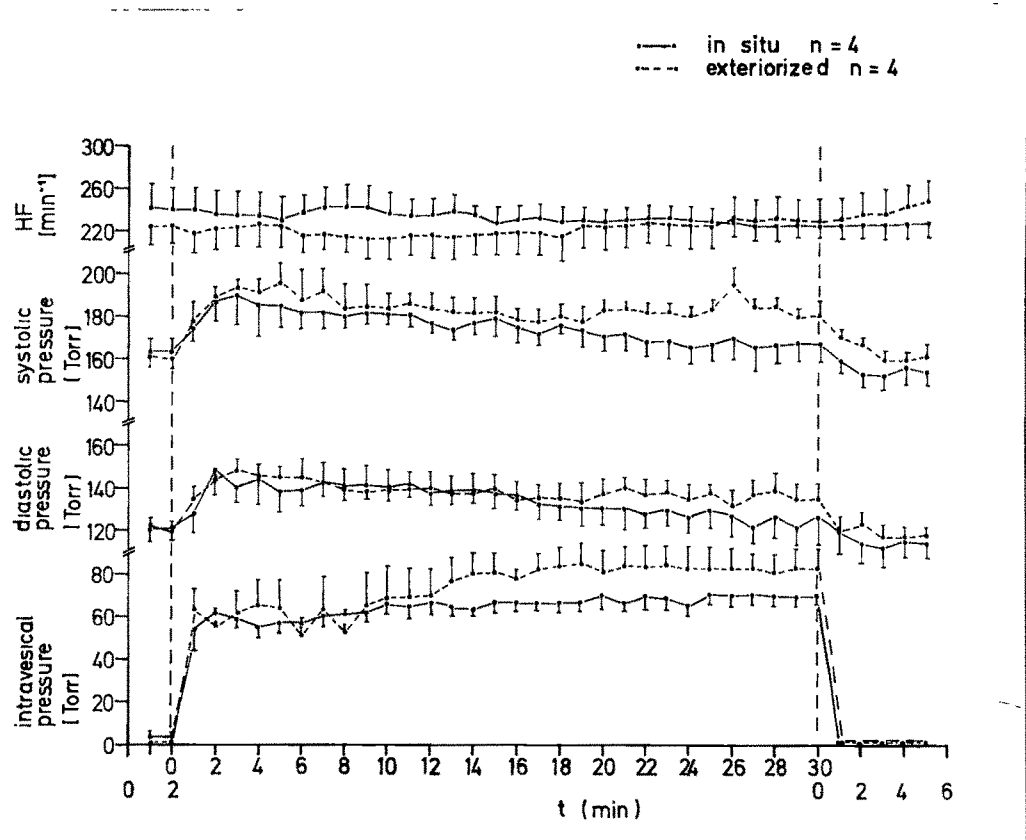


Figure 32: Average changes in the heart frequency (HF min^{-1}), the systolic and the diastolic pressures (Torr) during prolonged bladder distension in situ and exteriorized bladder distension. The data presented are the average values ($\bar{X}$) with standard error of the mean (Sm). n is the number of observations obtained from four cats. During bladder distension in situ the pressor response progressively adapted inspite of the elevated intravesical pressure. Such an adaptation was not marked with exteriorized bladder distension.

In five dogs the urinary bladder was distended for a period of 120 min. With bladder distension in situ, the mean arterial pressure decreased during the prolonged distension of the bladder for 120 min. At the end of 120 min of distension the mean arterial pressure was 97.2 ± 13.9 Torr which is 29.6 Torr less than the predistension value of 126.8 ± 8.6 Torr. The fall in the arterial pressure occurred though the intravesical pressure was 49.6 ± 7.1 Torr. Whereas in the same animals, distension of the bladder in the exteriorized situation for the same period of time (i.e., 120 min) resulted in a progressive increase of the arterial pressure. The average increase of the mean arterial pressure was from 123 ± 6.2 to 139 ± 7.3 Torr (+16.0 Torr) (Fig. 33).

In 3 of these experiments the peripheral venous pressure distal of the bladder and the inferior venocaval pressure proximal of the bladder were measured. During the bladder distension in situ, the peripheral venous pressure increased by about +17 ± 1.1 cm H_2O and the inferior venocaval pressure decreased by about -0.6 ± 0.1 cm H_2O.

After releasing the pressure of the bladder in situ the arterial pressure did not return to the predistension value even after 15 min. Whereas with exteriorized distension the arterial pressure almost returned to the control value (Fig. 33).

3.5.2. Ventilatory changes during the prolonged distension of the bladder

These experiments were performed only on cats. As a result of progressive distension of the urinary bladder in situ the tidal volume and the minute ventilation increased. The respiratory frequency did not appreciably change. The maximum increase of the tidal volume was to 25.0 ± 2.1 ml (+13.6 %) from the control value of 22 ± 2.5 ml. The increase of the minute ventilation was to 547 ± 55.3 $ml \cdot min^{-1}$ (+12.6 %) from the predistension value of 486

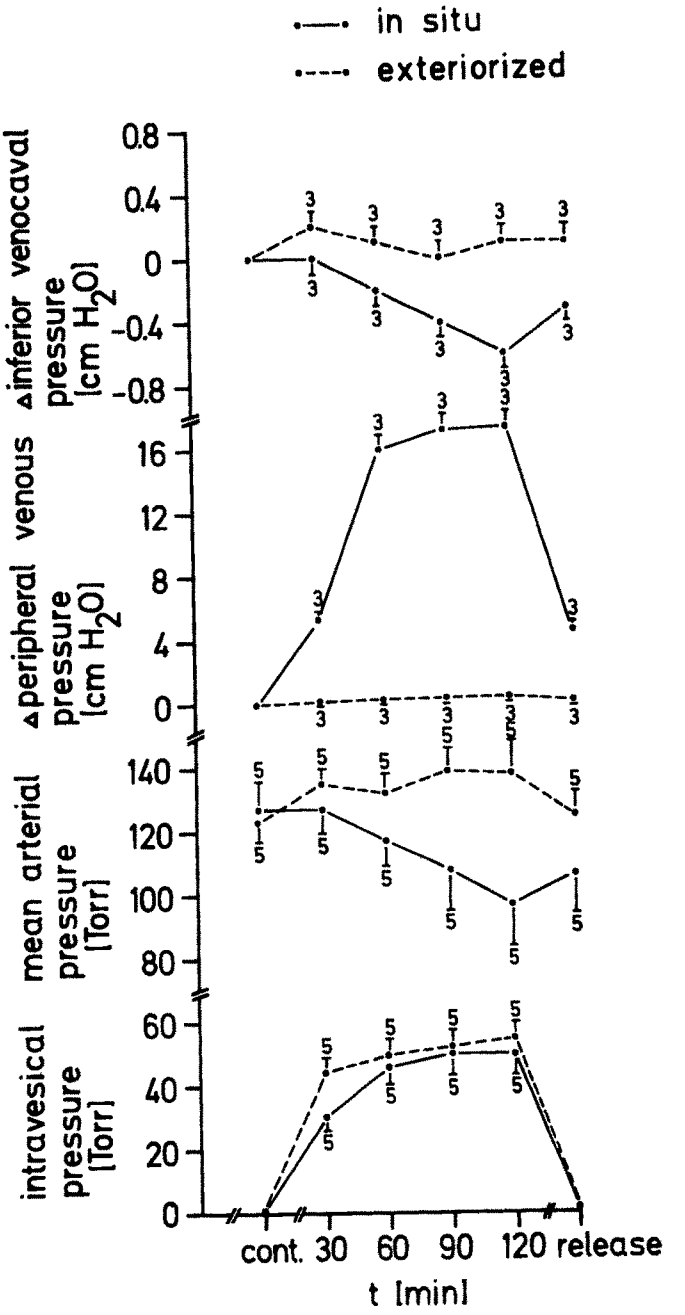


Figure 33: Average changes in the mean arterial pressure ($\bar{P}a$ Torr), Δ Peripheral venous pressure ($\bar{C}m$ H_2O) distal of the bladder and Δ Inferior venocaval pressure (Cm H_2O) proximal of the bladder with bladder distension in situ and exteriorized bladder distension in anaesthetized dogs. The data presented are the average values ($\bar{X}$) with standard error of the mean (Sm). The numbers above the data represent the number of observations obtained from five dogs.