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VENTRICULAR NOCICEPTION INDUCED VESICULAR MOTILITY AND URINE FLOW : THEIR RELATIONSHIP

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Abstract : Heart acts as an important reflexogenic organ. Reflex urination and defaecation are two of the most important visceral symptoms observed in patients with myocardial ischaemia, infarction etc. In experimental animals also ventricular nociceptor stimulation by left anterior descending coronary artery (LAD) occlusion and nicotine application causes biphasic changes in urinary bladder movement and urine flow. Aim of the present study is to elucidate if there is any correlation between urine formation by the kidneys and movement of the urinary ladder under such experimental conditions. The experiments performed on intact cats show apparent coincidence of the two events. But, subsequent experiments following denervation of vagi and inferior cardiac nerve (ICN), spinal transaction and decerebration experiments indicate that these two are separate events. Further, experiments with different neurotransmitter blockers indicate that ventricular nocieptor induced urine formation and urinary bladder movements are two separate reflex responses and not dependent on each other.

Key words : cardiac nociceptor vesicualr motility urine flow

INTRODUCTION

In patients with coronary heart diseases (CHD) the most important visceral symptoms are urination and defaecation. In experimental animals also, coronary artery occlusion or application of algesic agents like nicotine or lactic acid over the epicardial surface of the left ventricle induce visceral responses like changes in rectal and vesicular movements (1–5). Abrahamsson and Thoren (6), Johannsen et al (7), Koley et al (8, 9) have observed that cardiac receptors can reflexly induce gastric

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relaxation. It has also been observed that experimental coronary artery occlusion or epicardial nicotine application alters urine flow rate (10). In normal human and animal, primary stimulus for the micturition reflex is the urine volume and consequent distension of the urinary bladder (11). This storage of urine in the bladder and consequent distension of the same is naturally dependent on the diuretic function of the kidney. During storage, evacuation is normally inhibited (continence); when evacuation starts urine storage is interrupted and is thought to be kept inhibited during micturition (12). But, there is no evidence that whether the process of urine formation in the kidney also remains inhibited during the micturition reflex or increased intravesicular pressure. Moreover, in case of CHD when the ventricular nociceptors are stimulated the relationship between the renal diuretic function and vesicular motility is not very clear. Therefore, the present study is aimed to elucidate whether there is any correlation between ventricular nociceptor induced vesicular motility and urine flow.

METHODS

Experiments were carried out on 51 adult cat of either sex weighing 2–3 kg anaesthetised with chloralose (60 mg/kg, b.w). The femoral vein was cannulated for intravenous administration of anaesthetics, different drugs and also 5% glucose saline (with 1M $NaHCO_3$ solution when required). The trachea was cannulated for giving artificial ventilation as and when required. The urinary bladder was cannulated via the urethra with the help of a polyethylene catheter. The cannula was connected to an INCO polygraph (Model No 201) through an INCO pressure transducer (Model No T301) via three way stopcock to record the bladder movement in terms of intravesicular pressure (IVP). In the record, the bladder contraction is reflected as increase of intravesicular pressure and relaxation or inhibition as decrease of intravesicular pressure (IVP). The left ureter was cannulated with a fine polyethylene catheter and the catheter was connected to a drop counter and urine drops were recorded as spike per drop on the INCO polygraph. Spikes per minute were counted to calculate the urine flow as drops/min. The left chest was opened by removing 2^{nd} to 6^{th} left thoracic ribs keeping the animal under artificial ventilation. The heart was exposed by a midline incision in the pericardium and a pericardial cradle was made with the cut ends of the pericardium. A small length of the left anterior descending coronary artery (LAD) was cleared from the surrounding tissue and a snare was made with a fine silk thread around it. The artery was occluded reversibly for 3–4 mins by pulling the snare giving an interval of 20-30 mins between two successive occlusions. Nicotine (100-200 µg/ml) was applied for 30-60 secs directly over the epicardial surface with the help of a fine cotton film of 7–9 mm diameter soaked with nicotine. The epicardial surface along the with the pericardial cradle was washed with normal saline at least 3–4 times to remove all traces of nicotine from the surface and the next dose of nicotine was applied after at least 20–30 mins. Agonists and antagonists of different neurotransmitters were dissolved in physiological saline at a concentration so that the required dose was present in 0.5 ml and administered intravenously.

Immediately after such administration, 0.5 ml saline was injected intravenously so that no drug remained within the cannula.

Vagi of both sides were separated from sympathoaortic nerves and sectioned either at cervical or thoracic level. Inferior cardiac nerves (ICN) were isolated under dissecting microscope (Vicker's Instrument) as they descend from the left stellate ganglion and sectioned. Stellatectomy was also performed on either side. Laminectomy was performed at the level of C_7–C_8. 0.1 ml of 2% lignocaine was injected into the duramater of the spinal cord to prevent the spinal shock. After 5 minutes, two knots were placed at I cm apart on the spinal cord and transected. After at least 2 hour of spinal transection experiments were performed on these spinal cats. Decerebration was performed at the midcollicular level under ether anaesthesia following the method of Sherrington (13). After 2 hours of decerebration experiments were performed in such cats.

Drugs used

Anaesthetic ether (Kabra Drugs Ltd., India), α–chloralose (Koch-Light Lab, U.K.), Nicotine [(–) Nicotine, Merck-Schuchardts], Lignocaine ("Xylocaine", Astra-IDL Ltd., India), Atropin sulphate (Bengal Immunity, India), Phentolamine mesylate ("Regitine", Ciba-Geigy, U.K.), Atenolol ("Aten 25", Kopran Ltd., India), Salbutamol sulphate (Opec Innovations, India).

RESULTS

Cardiac nociception, vesicular motility and urine flow

LAD occlusion for 3–4 mins, evoked a biphasic response of both vesicular motility and urine flow. There was an initial large contraction of the urinary bladder and at the same time a decrease in urine flow rate (antidiuresis). After this, the vesicular movement was inhibited and urine flow rate was increased. Epicardial application of nicotine (100–200 µg/ml) for 30 secs also evoked similar type of responses of the vesicular motility and the urine flow (Fig. 1, Table I).

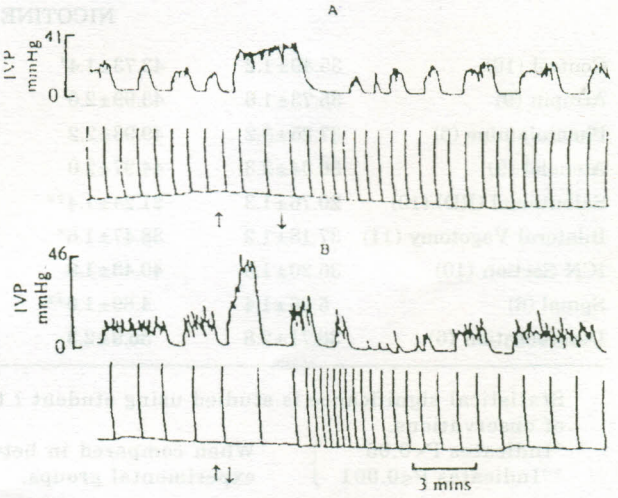

Fig. 1: Typical response pattern of the urinary bladder motility (upper tracings) and urine flow (lower tracings) in response to LAD occlusion (A) or epicardial nicotine application (B) in anaesthetised cats. Arrows indicate the duration of LAD occlusion or nicotine application.

Role of cardiac afferents

Bilateral vagotomy partially but significantly counteracted ($P<0.001$) the

TABLE I: Changes of intravesicular pressure (IVP) and urine flow rate (UFR) (±SEM) in animals under different experimental conditions following LAD occlusion or nicotine application.

Experimental conditions	*Initial Peak IVP (mmHg)*	*IVP Changes (mmHg)*		*Initial UFR Drops/min*	*UFR Changes Drops/min*	
		Increase	*Decrease*		*Antidiuresis*	*Diuresis*
			LAD OCCLUSION			
Control (10)	35.49±1.2	42.68±1.5$^{\#}$	27.05±1.0$^{\#\#}$	3.62±0.26	1.0±0.26$^{\#\#}$	4.8 ±0.2$^{\#}$
Atropin (9)	35.73±1.4	43.05±2.1	26.72±1.4	3.5±0.3	2.0±0.1*	4.6 ±0.2
Phentolamine (6)	37.25±1.2	44.86±2.3	27.41±2.8	3.2±0.3	1.1±0.2	4.0 ±0.3*
Atenolol (9)	36.34±2.3	43.73±2.1	33.03±2.2*	3.6±0.3	3.0±0.1*	4.4 ±0.1
Salbutamol (RD) (10)	20.76±1.3	21.15±1.2**	15.92±1.1	3.2±0.6	1.0±0.04	4.6 ±0.1
Bilateral Vagotomy (11)	37.18±1.2	39.72±1.6*	27.85±1.1	2.8±0.1	0.7±0.2	3.3 ±0.3*
ICN Section (10)	35.20±1.5	42.50±2.3	33.13±1.3*	3.2±0.3	2.8±0.6*	6.0 ±0.3
Spinal (6)	5.06±1.4	5.25±1.3**	4.91±0.9**	3.7±0.2	1.2±0.3	4.6 ±0.04
Decerebration (6)	36.71±2.8	36.98±2.6	20.24±2.8	4.2±0.3	1.0±0.2	5.8 ±0.2
			NICOTINE APPLICATION			
Control (10)	35.49±1.2	43.73±1.4$^{\#}$	13.28±1.3$^{\#\#}$	3.62±0.26	1.1±0.1$^{\#\#}$	5.7 ±0.4$^{\#\#}$
Atropin (9)	35.73±1.6	43.99±2.0	14.18±1.5	3.62±0.3	3.0±0.9*	5.9 ±0.8
Phentolamine (6)	37.25±3.2	49.93±2.2	14.65±2.3	3.2±0.3	0.9±0.05	3.4 ±0.5*
Atenolol (9)	36.34±2.3	44.97±2.0	34.77±2.0**	3.2±0.4	2.6±0.1*	4.3 ±0.1
Salbutamol (RD) (10)	20.76±1.3	21.24±1.4**	8.03±0.6	3.8±0.6	1.1±0.07	5.5 ±0.1
Bilateral Vagotomy (11)	37.18±1.2	38.47±1.6*	14.91±1.1	2.8±0.1	2.0±0.2	3.8 ±0.6*
ICN Section (10)	35.20±1.5	40.43±1.9	32.82±1.4**	3.2±0.3	3.6±0.4**	5.9 ±0.4
Spinal (6)	5.06±1.4	4.89±1.0**	4.84±1.1**	3.8±0.1	1.2±0.1	5.2 ±0.2
Decerebration (6)	36.71±2.8	36.9±2.3	10.42±1.69	4.2±0.3	1.0±0.5	6.9 ±0.1

Statistical significance is studied using student *t* test. Number within the parentheses indicates the number of observations.

*Indicates P<0.05, **Indicates P<0.001 — When compared in between control and experimental groups.

$^{\#}$Indicates P<0.05, $^{\#\#}$Indicates P<0.001 — When compared in between initial and changed values in control animals.

initial large contraction of the urinary bladder but the initial antidiuresis remained unaffected. But the late diuretic phase induced by coronary occlusion or epicardial nicotine application was completely abolished by vagotomy keeping the inhibitory phase of the vesicular response unaltered (Fig. 2, Table I).

Sectioning of inferior cardiac nerve (ICN) partially but significantly (P<0.05) counteracted the LAD occlusion or nicotine induced initial large contraction and completely abolished the inhibitory phase of the bladder response. On the other hand, ICN sectioning abolished the initial antidiuretic phase only. The late

diuretic phase remained unaltered (Fig. 2, Table I).

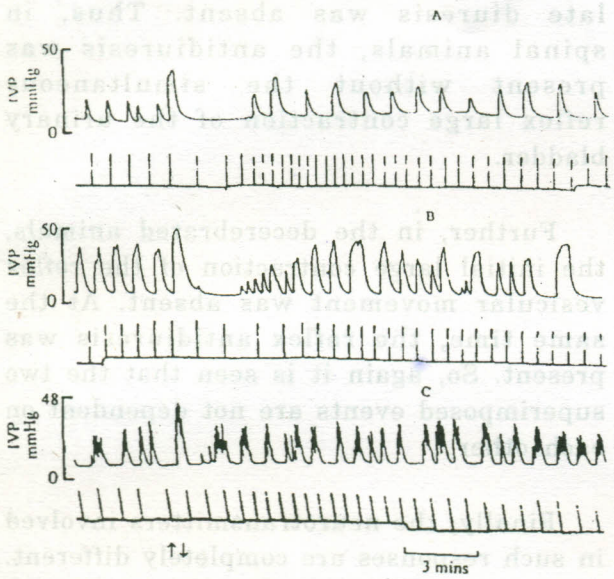

Fig. 2 : Typical response pattern of the urinary bladder motility (upper tracings) and urine-flow (lower tracings) to epicardial nicotine application in control (A), bilateral vagotomised (B) and in inferior cardiac nerve (INC) sectioned (C) animals. The arrows indicate the duration of nicotine application.

Role of spinal cord

Spinal transection at the C7–C8 level completely abolished the spontaneous motility of the urinary bladder and also the reflex response of the bladder movement. Spinal transection decreased spontaneous urine flow rate. In such animals, LAD occlusion or epicardial nicotine induced antidiuresis was unaltered but the diuretic phase was counteracted completely (Fig. 3, Table I).

Effect of decerebration

Decerebration at the mid collicular level abolished the initial large contraction of the cardiovesicular reflex and potentiated the inhibitory phase. Decerebration reduced the spontaneous urine flow rate, but, the reflex biphasic changes of the urine flow were not altered (Fig. 3, Table I).

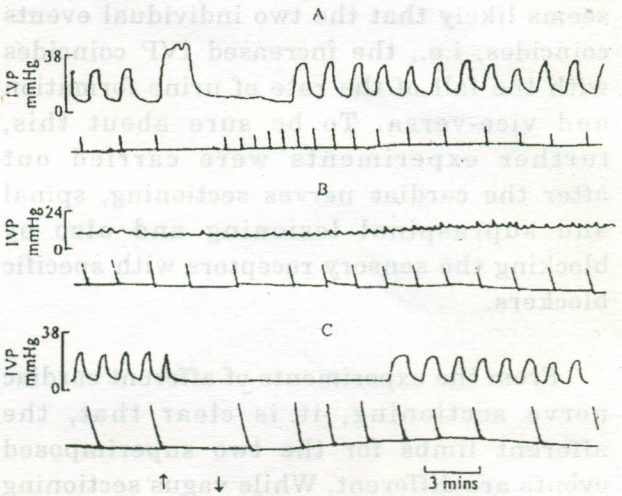

Fig. 3 : Typical response pattern of the urinary bladder motility (upper tracings) and urine flow (lower tracings) to LAD occlusion in control (A), spinal (B) and decerebrate (C) animals. Arrows indicate the duration of LAD occlusion.

Effect of neurotransmitter blockers

The initial large contraction and the inhibition of vesicular contraction were abolished by β2 and β1 adrenoreceptor antagonist respectively. On the other hand, the initial antidiuresis was counteracted by atropine which had no effect on vesicular movement (Table I). The diuretic phase was significantly counteracted by phentolamine which had no effect on cardiovesicular reflex (Table I).

DISCUSSION

It has been observed that LAD occlusion

or nicotine application caused biphasic responses in both vesicular movement and rate of urine formation (urine flow). Where the vesicular movement first rises and then declines, the rate of urine formation first declines and then increase. At this stage it seems likely that the two individual events coincides, i.e., the increased IVP coincides with the fall of the rate of urine formation and vice-versa. To be sure about this, further experiments were carried out after the cardiac nerves sectioning, spinal and supraspinal lesioning and also by blocking the sensory receptors with specific blockers.

From the experiments of afferent cardiac nerve sectioning, it is clear that, the afferent limbs for the two superimposed events are different. While vagus sectioning partially counteracted the initial large contraction, ICN sectioning completely abolished the initial antidiuretic phase. Similarly, while ICN sectioning partially counteracted the initial large contraction of the vesicular response and completely abolished the late inhibition phase, the late diuretic phase was completely abolished by vagotomy. Thus, in partial absence of the initial large contraction in vagotomised animals, the initial antidiuresis was still present, rather, the late diuretic phase was abolished. So, the initial antidiuretic phase was not dependent upon the intravesicular pressure rise. Similarly, the diuretic phase was also not dependent on the inhibition of vesicular contraction.

In spinal animals at the level of C7–C8 the vesicular motility – both spontaneous and reflex, were completely absent. But, at the same time, the initial reflex antidiuresis was present although the late diuresis was absent. Thus, in spinal animals, the antidiuresis was present without the simultaneous reflex large contraction of the urinary bladder.

Further, in the decerebrated animals, the initial large contraction of the reflex vesicular movement was absent. At the same time, the reflex antidiuresis was present. So, again it is seen that the two superimposed events are not dependent on each other.

Finally, the neurotransmitters involved in such responses are completely different. Atropine, which was totally ineffective in the manifestation of the reflex vesicular motility, counteracted the initial antidiuresis. Thus, in presence of initial large contraction of the vesicular movement, the antidiuresis was prevented.

From all these observations, it is now clear that, although in the intact control cats, the biphasic changes of the vesicular motility and rate of urine formation (urine flow rate) were superimposed, these are not interdependent. The subsequent experimental results clearly showed that the initial antidiuresis can take place even in absence of initial large contraction of the vesicular motility, i.e., when the intravesicular pressure rises. Thus the increased IVP plays no significant role in inhibiting the urine formation rate by the stimulation of cardiac nociceptors.

Similarly, it has also been observed that, the inhibition of bladder contraction had no effect on increased rate of urine formation (diuresis).

So, it can be opined that the reflex changes of vesicular motility and reflex changes of urine formation are not dependent on each other, rather these are two separate reflex effects in response to ventricular nociceptor stimulation.

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