

CARDIAC NOCICEPTION INDUCED RECTAL RESPONSE: RELATION WITH HAEMODYNAMIC CHANGES

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Abstract: Epicardial application of nicotine (200 µg/ml) over the left ventricle or occlusion of the left anterior descending coronary artery (LAD) in lightly anaesthetised cats resulted a biphasic change in rectal motility-initial relaxation followed by contraction along with biphasic changes of blood pressure (B.P.) with epicardial nicotine and only hypotension with LAD occlusion. Desensitisation of ventricular receptors by epicardial application of 2% lignocaine abolished the rectal response and the biphasic blood pressure response but not the LAD occlusion induced hypotension. Sectioning of left inferior cardiac nerve (LICN) abolished such cardio-rectal reflex but not the B.P. changes. Stimulation of central cut end of LICN elicited similar cardio-rectal reflex keeping the B.P. unaltered. Atropinisation (1 mg/kg) abolished only the contractile phase of the cardio-rectal reflex and also the hypotension induced by epicardial nicotine. Intra-arterial N^G-nitro-L-Arginine (LNNA) at a dose of 2 mg/kg abolished the relaxation phase of such cardio-rectal reflex keeping the B.P. changes unaltered. LAD occlusion induced hypotension was neither counteracted by atropine nor by LNNA pretreatment. These indicate that though the cardio-rectal reflexes are associated with B.P. changes, they do not have any direct correlation.

Key words : epicardial nicotine
cardio-rectal reflex

LAD occlusion
LNNA

INTRODUCTION

It is now well documented that different chemical mediators eg. bradykinin, prostaglandins, lactic acid etc. are released during myocardial ischemia which take part in the genesis of cardiac pain by exciting the cardiac nociceptors. It is also reported

by White (1) and Koley and his associates (2-4) that occlusion of coronary artery in lightly anaesthetised cats causes a pain like or pseudo affective response as described by Sherrington (5) with increased sympathetic activity. Sympathetic afferent fibres transmit this sensation of pain (6-7) which initiates different reflexes. Brown (8)

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and Malliani and his associates (9) reported that experimental coronary artery occlusion initiates cardiac reflexes in lightly anaesthetised cats. Abrahamsson and Thoren (10) and Thoren (11) also reported the bradycardia and hypotension by epicardial application of chemical substances. They also reported a marked reflex relaxation of the stomach as reported by Koley and his groups (3). Recently Koley et al (12) observed that stimulation of the cardiac nociceptors of the left ventricle either by LAD occlusion or local application of different algescic agents over the surface of the left ventricle elicit cardio-rectal reflexes. But whether this cardio-rectal reflex is directly due to the stimulation of the ventricular receptors or it is the secondary effect due to the B.P. changes is not yet known. So in the present set of experiments attempts have been made to investigate the relationship between the B.P. changes and cardio-rectal reflex induced by coronary artery occlusion or epicardial application of algescic agent like nicotine.

METHODS

Experiments were carried out on 22 cats of either sex having body weight 2-3 kg after overnight fast with water *ad libitum*. The animals were anaesthetised with α -chloralose (60 mg/kg, i.v.) after initial induction with anaesthetic ether. The trachea was cannulated for artificial respiration. The femoral artery and vein were routinely cannulated. Glucose solution (5%) in physiological saline (0.9%) was administered by drip feed into the femoral vein (0.5 ml/min) throughout the experiment to maintain body fluid and pH. Blood

pressure (B.P.) was recorded from femoral artery on a Beckman RM Dynograph using a Bell and Howel pressure transducer.

Opening of the chest : The left thorax was opened after removing thoracic ribs 2-6, keeping the animal under artificial respiration. The pericardium was cut longitudinally and a pool was made using the cut ends. The left stellate ganglion and the left inferior cardiac nerve (LICN) were exposed carefully from the surrounding connective tissues under a dissecting microscope (Vickers Instrument, England). The central cut end of LICN was stimulated by Grass SD 9 stimulator with square wave pulses (40-60 Hz, 4-6 v; 0.2 ms for 60 secs) if and when required.

For desensitisation of ventricular receptors 2% lignocaine, soaked with a fine cotton film was applied over the epicardial surface of the left ventricle for 5-6 min if and when required.

Left anterior descending coronary artery (LAD) occlusion and application of Nicotine : The LAD was dissected along its length for 2-3 mm from the surrounding tissue under a dissecting microscope and a nylon thread was placed loosely around the LAD to prepare a snare. Occlusion was induced by pulling the nylon thread forward and pushing the polyethylene tube to the coronary artery for 2 min. Nicotine (200 μ g/ml) was applied over the surface of the left ventricle with the help of a cotton applicator for 1 min. After 1 min cotton applicator was removed and ventricular surface was washed with physiological warm saline at least for 3 times to remove all traces of nicotine.

Recording of the rectal motility

The motility of rectum as intrarectal pressure (IRP) was recorded on the INCO Polygraph by placing a balloon (1.0-1.5 cm of a condom distended with 8-12 ml of water at 37°C) within it and connecting the balloon to a pressure transducer (Model 301, INCO, India) via a polyethylene tube. Studies were performed on the pancuronium (1 mg/kg, iv), skeletal muscle-relaxant supplemented animals to eliminate the participation of external anal sphincter and other adjoining skeletal muscles in the resting IRP (13).

Statistical analysis

Results are expressed as mean \pm SEM. Significance test was performed using Student's 't' test.

Drug used

Nicotine hydrogen tartrate (BDH, U.K); Lignocaine ('Xylocaine' Astra-IDL, India); Atropine sulphate (Bengal Immunity, India); Pancuronium ('Pavulon', Infar (India) Ltd., India); N^G-nitro-L-arginine (Sigma, USA).

RESULTS

1. Effects of LAD occlusion on rectal movement and blood pressure: Occlusion of the LAD for 2 min resulted in a biphasic rectal response-initial inhibition or decrease of the spontaneous motility with or without relaxation followed by a large sustained contraction (Fig. 1A₁). The relaxation phase starts 30-45 seconds after the occlusion and continues for 3.5 to 5.0 minutes followed by the contractile phase which lasts for another 3.0 to 5.0 minutes. The normal mean IRP

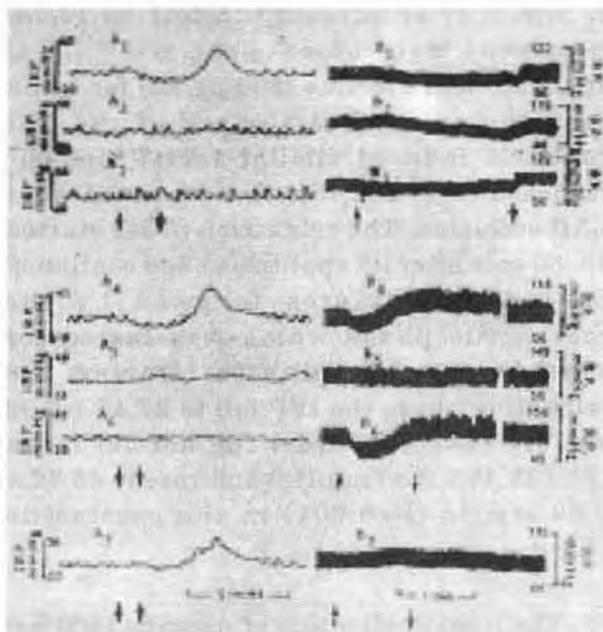


Fig. 1: Typical response pattern of the rectal movement in the form of intrarectal pressure (I.R.P.; Series-A) and Blood pressure (B.P.; Series-B) in response to LAD occlusion (1-3) and epicardial nicotine (4-6) in control (A₁ & B₁/A₄ & B₄), Lignocaine pretreated (A₂ & B₂/A₅ & B₅), LICN sectioned (A₃ & B₃/A₆ & B₆) animals. Tracing A₇ & B₇ show the IRP and BP response pattern to LICN afferent stimulation. Arrows (↑ ↓) indicate the duration of LAD occlusion/nicotine application.

(33.36 \pm 0.90 mmHg) fell to 27.47 \pm 0.93 mmHg, (P<0.001) and thereafter rose to 47.73 \pm 0.99 mmHg (P<0.001). These changes are statistically significant.

LAD occlusion for 2 min caused significant hypotension (Fig. 1B₁). The B.P. started to fall within 5 seconds of the occlusion and this fall lasted as long as the occlusion was continued. After withdrawal of the occlusion B.P. returned to normal range within 10-15 seconds. The mean B.P. (96.32 \pm 1.79 mmHg) fell to 79.32 \pm 1.52 mmHg (P<0.001) during LAD occlusion.

2. *Effect of epicardial nicotine on rectal movement and blood pressure:* Local application of nicotine (200 µg/ml) for 1 min over the epicardial surface of the left ventricle induced similar rectal biphasic response (Fig. 1A₄) as that observed after LAD occlusion. The relaxation phase started 15–30 secs after its application and continued for 3.5–5.0 minutes followed by the contractile phase which was lasted for another 3.0–5.0 minutes. During the relaxation phase the IRP fell to 27.47 ± 0.93 mm Hg ($P < 0.001$) from the normal mean IRP (33.36 ± 0.90 mmHg) and rose to 45.72 ± 1.64 mmHg ($P < 0.001$) in the contractile phase.

The local application of nicotine (200 µg/ml) over the epicardial surface also induced the biphasic changes in blood pressure (Fig. 1B₄). Hypotension ensued immediately after epicardial nicotine application and lasted for

about 30–60 seconds, after that the B.P. was started to rise above the normal level and this hypertension persisted for further 1.5–2 min. During hypotension the normal mean B.P (96.32 ± 1.79 mmHg) was reduced to 71.49 ± 1.85 mmHg ($P < 0.001$) and during hypertension it was increased to 118.60 ± 1.87 mmHg ($P < 0.001$).

3. *Effect of LAD occlusion and epicardial nicotine in different experimental conditions :*

(a) *Ventricular receptor desensitisation :* 10–15 minutes after lignocaine application both LAD occlusion (Fig. 1A₂) and epicardial nicotine (Fig. 1A₅) failed to elicit the biphasic changes of rectal movement and also B.P. in response to epicardial nicotine (Fig. 1B₅). However, the LAD occlusion induced hypotension was not abolished (Fig. 1B₂ and Table I).

TABLE I : Intrarectal pressure (IRP) and blood pressure (B.P.) changes in response to LAD occlusion in control and different experimental conditions.

Experimental conditions	LAD occlusion				
	Intrarectal pressure (mm Hg)			Blood pressure (mm Hg)	
	Initial IRP ± SEM (n)	During relaxation Mean IRP ± SEM (n)	During contraction Mean IRP ± SEM (n)	Initial Mean IRP ± SEM (n)	During hypotension Mean BP ± SEM (n)
Control	33.36±0.90(36)	27.47±0.93(36) ^c	47.73±0.99(36) ^c	96.32±1.79(36)	79.32±1.52(36) ^c
Lignocaine	34.92±2.19(8)	33.17±1.94(8)	36.76±2.31(8)	93.7±4.10(22)	80.32±4.06(6) ^a
LICN Sectioning	32.32±1.27(8)	31.46±1.21(8)	35.00±1.57(8)	90.89±3.54(6)	77.78±2.59(6) ^b
Atropine	29.16±0.48(10)	23.31±1.57(8) ^b	29.75±1.89(8)	99.56±4.14(6)	73.89±1.21(6) ^b
LNNA	30.00±2.21(8)	29.00±2.19(6)	48.66±5.48(6) ^c	99.06±3.86(6)	73.89±1.21(6) ^b
LNNA+atropine	35.53±2.93(6)	34.65±2.93(6)	37.12±2.93(6)	100.02±3.96(6)	82.30±3.89(6) ^b

a = $P < 0.05$; b = $P < 0.01$; c = $P < 0.001$.

Number in parentheses indicates the number of observations. In all the cases the values of mean IRP and BP are in mmHg.

(b) *LICN sectioning and stimulation* : In LICN sectioned animals both LAD occlusion (Fig. 1A₃) and epicardial nicotine (Fig. 1A₆) failed to induce any change in rectal motility. However, the B.P. response to LAD occlusion (Fig. 1B₃) and epicardial nicotine (Fig. 1B₆) remained unaltered. The B.P. change after LICN sectioning is insignificant in comparison to that of intact animals. Electrical stimulation of the central cut end of LICN induced similar rectal relaxation followed by contraction (Fig. 1A₇) as that of LAD occlusion or epicardial nicotine in intact animals. The mean IRP (32.32 ± 1.27 mmHg) was reduced to 125.49 ± 1.29 mmHg during the relaxation phase and increased to 146.89 ± 11.50 mmHg during the contractile phase due to LICN stimulation. But similar LICN stimulation did not evoke any significant change in B.P. (Fig. 1B₇) which was increased to 93.17 ± 1.82 mmHg from that of normal mean B.P. (90.89 ± 3.54 mmHg).

4. *Atropinisation and LNNA pretreatment*: Intravenous administration of atropine at a dose of 1 mg/kg completely abolished the nicotine (Fig. 2A₆) or LAD occlusion (Fig. 2A₂ & Table I) induced rectal contractile phase keeping the relaxation phase unaltered and the nitric oxide inhibitor N^G-nitro-L-arginine (LNNA) blocked the relaxation phase only without altering the contraction (Fig. 2A₃, 2A₇ & Table I) of the rectum. Atropine pretreatment abolished the nicotine induced hypotension without altering the hypertension (Fig. 2B₆) but failed to alter the hypotension induced by LAD occlusion (Fig. 2B₂ & Table I). In LNNA pretreated animals, LAD occlusion (Fig. 2B₃) and epicardial nicotine (Fig. 2B₇) induced B.P. response were remain unaltered. In

LNNA + atropine pretreated animals the cardio-rectal reflex was totally absent (Fig. 2A₄ and 2A₈) but the B.P. response to LAD occlusion remained unaltered (Fig. 2B₁ and Table I) though nicotine induced hypotension was abolished keeping the hypertension unaltered (Fig. 2B₈).

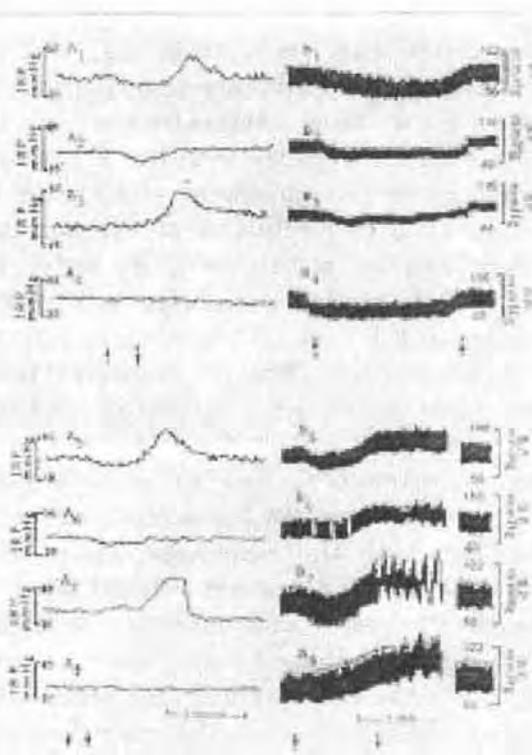


Fig.2 : Typical response pattern of the rectal movement in the form of intrarectal pressure (I.R.P.; Series - A) and Blood pressure (B.P.; Series-B) in response to LAD occlusion (1-4) and epicardial nicotine (5-8) in control (A₁ & B₁/A₅ & B₅), atropinised (A₂ & B₂/A₆ & B₆), LNNA pretreated (A₃ & B₃/A₇ & B₇) and LNNA + atropine pretreated (A₄ & B₄/A₈ & B₈) animals. Arrows (↑ ↓) indicate the duration of LAD occlusion/nicotine application.

DISCUSSION

Epicardial application of nicotine over the left ventricle or occlusion of the left

coronary artery excites the cardiac receptors presumably nociceptors (14, 15) which in turn elicits different visceral reflexes eg. cardio-rectal reflexes (12), cardio-visceral and cardio-renal reflexes (16) it has also been reported earlier that stimulation of ventricular receptors either by different algescic agents or by LAD occlusion results hypotension and bradycardia (11, 17). The present set of experiments also suggests the same view that stimulation of the ventricular receptors results a biphasic change in rectal movement along with the change of B.P. Occlusion of the coronary artery causes a fall of B.P. only, but epicardial nicotine results a biphasic changes in B.P.- initial hypotension followed by hypertension. The cardio-rectal reflex and also epicardial nicotine induced B.P. changes are reflex in nature as desensitisation of ventricular receptors with local anaesthetics, 2% lignocaine completely abolished both the responses. These blood pressure changes are not related with the changes in rectal movement as sectioning of the LICN abolished rectal movement but the B.P. change remained unaltered. It is further confirmed when the central cut end of LICN was stimulated showing thereby similar changes in rectal movement but without any change in B.P. LAD occlusion induced hypotension is probably not a reflex and may be due to loss of contractile power of the ischemic myocardium as lignocaine does not abolish such response.

Further the cardio-rectal reflex is totally abolished by cholinergic muscarinic receptor antagonist atropine in combination with nonadrenergic noncholinergic nitric oxide blocker, LNNA. The contractile phase is abolished by atropine alone whereas the relaxation phase is abolished by LNNA. But neither the atropine nor the LNNA and even their combination could alter the LAD occlusion induced hypotension and epicardial nicotine induced hypertension though the epicardial nicotine induced hypotension is abolished by atropine keeping the relaxation phase of the cardio-rectal reflex unaltered. The epicardial nicotine induced hypotension and the contraction phase of the biphasic cardio-rectal reflex is mediated through the neurotransmitter acetylcholine as both the responses are abolished after atropinisation.

Thus it may be presumed that the rectal response is solely of cardiac origin and has no direct correlation with the altered blood pressure.

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