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NEUROPHYSIOLOGICAL BASIS OF MYOCARDIAL ISCHEMIC PAIN-INDUCED RECTAL REFLEX IN THE ANESTHETIZED CAT: AN EXPERIMENTAL STUDY

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Abstract:
Background: Clinically it has been observed that heart failure due to cardiac ischemia is often associated with different reflexes like bradycardia, hypotension, urge of urination, and stool. It is also well documented that different chemical mediators e.g.; bradykinin, prostaglandins, lactic acid, etc. are released during myocardial ischemia which takes part in the genesis of cardiac pain to initiate different visceral and somatic reflexes. The present set of investigations is designed to study the afferent and efferent pathways responsible for this cardiogenic defecatory reflex by studying rectal movement.

Methods; Experiments were carried out on 54 lightly anesthetized, artificially ventilated cats of either sex after an overnight fast with water ad libitum. Cardiac nociceptors are stimulated by epicardial application of nicotine or lactic acid or capsaicin and its effect on rectal motility was studied along with its neurophysiological mechanism.

Results; Epicardial application of nicotine, lactic acid, or prostaglandin induced the biphasic rectal response which was abolished after sectioning of the Left inferior cardiac sympathetic nerve (LICN) but not by cardiac vagotomy. The same response was also abolished by pelvic nerve sectioning but not by sectioning of the gastric vagus or splanchnic nerve.

Conclusions; Thus the present study reveals that epicardial application of algesic agents like nicotine, lactic acid, and prostaglandin excites the cardiac nociceptors to initiate a biphasic rectal response that might be the causative factor of defecation during cardiac ischemia-induced heart failure. It also indicates that the afferent and efferent limb for such reflex is the cardiac sympathetic and the pelvic nerve respectively.

Keywords: Cardiogenic reflex, Algesic agent-induced rectal response, Cardiac ischemic pain, and Gastro Intestinal movement

Introduction:

Heart failure is one of the predominant pandemics affecting at least 26 million people worldwide and even its prevalence is increasing day by day. Though there are advancements in preventive and

therapeutic measures for this disease the mortality, and morbidity of this disease are significantly high. This deadly disease is basically the syndrome that, evokes a group of signs and symptoms like shortness of breath, excessive fatigue, and chest pain including angina caused by an impairment of the heart's blood pumping function. Clinically it has also been observed that heart failure due to cardiac ischemia or Myocardial infarction (MI) is often associated with different reflex responses like bradycardia, hypotension, the urge to urinate, and stool [1-5]. It is also well documented that different chemical mediators e.g.; bradykinin, prostaglandins, lactic acid, etc.[6-12] are released during myocardial ischemia which takes part in the genesis of cardiac pain by exciting the cardiac nociceptors which in turn initiate different visceral and somatic reflexes. Application of these substances over the epicardial surface of the left ventricle results in different reflex responses like hypotension, bradycardia, gastric relaxation, urination, defecation etc[1-5] by exciting either sympathetic or vagal afferents. Hence it seems reasonable to propose that if cardiac pain results activation of cardiac afferent endings by chemicals and if a number of these substances are released during myocardial ischemia then it is likely that they may produce cardiac pain which in turn causes various gastrointestinal symptoms and other reflexes by stimulating either vagus or sympathetic nerves.

Materials and Methods:

Protocols for animal preparation: Experiments were carried out on 54 cats of either sex having a body weight of 2-3 kg after an overnight fast with water ad libitum. The animals were purchased from commercial and authorized animal saler (M/S Reeta Ghosh & Co., Kolkata) as and when required and were kept in the in-house animal house for at least 7 days in comfortable ambient and closely monitored. A simple randomization method was followed for each day's experiment with a single animal and the results were compared between the effect of algesic agents before and after the treatment or nerve sectioning. On a single day, only one animal was anesthetized and experimentation was done on that particular anesthetized animal. The same experimental protocol was followed for at least 6 animals in which at least 3 reproducible results per animal were found. The animals that did not produce any rectal biphasic response induced by epicardial application of algesic agents were not considered for the study report.

The pregnant, lactating, and below 2 kg animals were excluded from this study. After the day's experiment, the anesthetized animal was killed by injecting KCl solution by heart puncture for instant and painless killing.

Before the experimentation, the animals were anesthetized with α-chloralose at a dose of 60 mg/kg body weight after initial induction with anaesthetic ether. Anaesthesia was maintained throughout the experiment with a maintenance dose of α-chloralose (10 mg/kg, i.v.) as and when required. The femoral artery, the femoral vein, and the trachea were routinely cannulated. The glucose solution (5%) in physiological saline (0.9%) was administered by drip feed into the femoral vein (l ml/min) throughout the experiment to maintain body fluid and pH. Blood pressure was recorded from the femoral artery on a Beckman RM Dynograph using a Bell & Howel pressure transducer (Type-4327-0129). For monitoring the body temperature a thermometer was placed into the anus and body temperature was maintained at 37^{o}C with a heating pad. The entire study was approved by the Ethical Committee under the Dept. of Physiology, University of Calcutta, Kolkata considering all the requisite maintenance of proper animal care and handling before, during and after the experimentation process.

Opening of the chest and surgical procedure; The Chest was opened by removing thoracic ribs 2-6 keeping the animals under artificial respiration with a Starling Ideal Respiratory Pump. The left stellate ganglion and the left inferior cardiac nerve (LICN), branches of the vagus to the heart were exposed carefully and cleared from the surrounding connective tissues under a dissecting microscope. Stellalectomy or LICN sectioning was performed in animals according to the experimental protocol and left the animals at rest for a minimum of one hour.

The vagus nerve was isolated below the diaphragm level and the splanchnic nerves and inferior mesenteric ganglia were also isolated and sectioned as and when required. Laminectomy was performed at the Sacral (L1-S4) level and the spinal cord was opened following Koley and Mukherjee[13]. The ventral roots of the S2- S4 level were isolated and transected as per requirement. After the transection of each nerve or ganglia or ventral root, the animals were rested for at least one hour and after that period further experimentation was performed.

Stimulation of sensory fibers: To stimulate the cardiac sensory receptors, different algesic substances like Nicotine (200-400 µg/ml), Lactic Acid (600-800 µg/ml), and Prostaglandin (100-200 µg/ml) were applied over the epicardial surface of the left ventricle with the help of a very light cotton applicator for 60 sec taking care to prevent any mechanical disturbance of this region. The epicardial surface was washed at least three times with normal saline after removal of the cotton applicator from the ventricular surface to wash out all traces of nicotine/ lactic acid/ prostaglandin and allowed to rest for 30 min before repeating the procedure.

Recording of rectal motility: Rectal motility in the form of intrarectal pressure was recorded on the INCO polygraph by a distended balloon inserted into the rectum. A flaccid balloon (1.0-1.5 cm of a condom) distended with 8-12 ml of warm saline via a polyethylene tube was inserted into the rectum aborally by a small incision in the descending colon and fixed at the incision point. In all the animals the experiments were repeated after recording at least 3 reproducible cardiorectal reflexes in response to the application of any particular algesic agents. In a particular animal setup up effect of only one algesic agent on rectal motility was studied so that there is no interference of other algesic agents over that response produced. The same experimental protocol was repeated several times during the period of study and similar results were reproduced.

Drugs used: α-chloralose (Koch-Light Lab, UK); Nicotine hydrogen tartrate (BDH, U.K); Lactic acid & Prostaglandin (Sigma, USA); Lignocaine ('Xylocaine', Astra-IDL, India). The nicotine, lactic acid and prostaglandin was diluted in physiological saline and applied at a required dose. All the drugs used were dissolved in physiological saline at a concentration so that not more than 0.5 ml needed to be introduced for the drug application.

Statistical analysis:

Results were expressed as mean ± S.E.M. Statistical significance was done using the student's 't' test between pre and post-experimental conditions. In the case of the control cardio-rectal reflex, the significance tests were performed using the average initial intrarectal pressure (in mmHg) and the peak intrarectal pressure during the reflex relaxation and contraction phase. The intrarectal pressure (percentage changes) during rectal reflex relaxation and contraction was compared between the control group and each experimental group.

Result:

Reflex rectal responses of cardiac origin by epicardial application of Nicotine: Application of nicotine for 60 sec locally over the epicardial surface of the left ventricle caused a biphasic response of the rectum- initial relaxation followed by contraction (Fig.1A). During the relaxation phase the mean intrarectal pressure (IRP) was reduced by 25.16+1.14% and during the contractile phase the mean IRP was increased by 42.68±1.68% (Fig 2) from that of normal mean IRP.

Reflex rectal responses of cardiac origin by epicardial application of Lactic acid: Application of lactic acid for 60 sec locally over the epicardial surface of the left ventricle also caused a similar biphasic response as seen after the application of nicotine as shown by the fig. 1 B. During the relaxation phase the mean intrarectal pressure (IRP) was reduced by 25.68+1.22% and during the contractile phase the mean IRP was increased by 45.14±1.32% (Fig 2) from that of normal mean IRP.

Reflex rectal responses of cardiac origin by epicardial application of Prostaglandin: Epicardial ***a***pplication of prostaglandin for 60 sec locally over the left ventricular surface also caused a similar biphasic response (Fig 1 C) as seen after nicotine or lactic acid application. It was observed that during the relaxation phase, the mean intrarectal pressure (IRP) was reduced by 28.16+1.56 %, and during the contractile phase the mean IRP was increased by 45.42±2.54 % (Fig 2) from that of normal mean IRP.

Fig. 1: Intrarectal pressure changes (IRP in mmHg) in response to epicardial application of Nicotine (A), Lactic acid (B), and Prostaglandin (C). The arrows indicate the duration of application of these algesic agents.

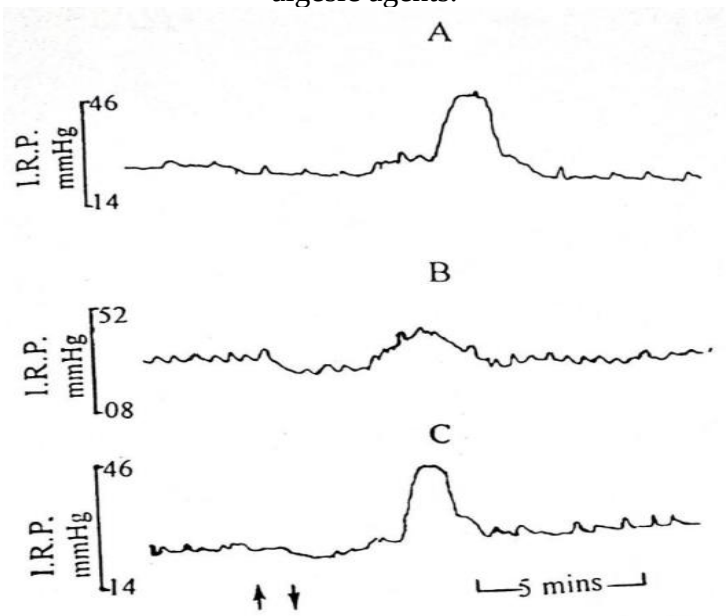
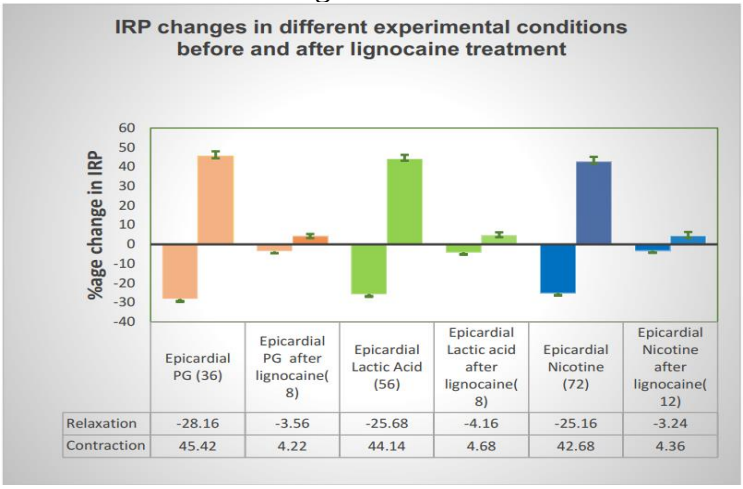


Fig. 1

Epicardial application of algesic chemicals after desensitization of ventricular receptor: Desensitisation of the ventricular sensory receptors, by epicardial application of local anaesthetics (by 2% lignocaine for 5- 10 minutes with the help of fine cotton film) was performed and after 5 minutes of withdrawal of the lignocaine-soaked cotton film, epicardial application of nicotine or lactic acid or prostaglandin failed to evoke any biphasic rectal response (Fig 2).

Fig 2: Percentage changes of intrarectal pressure (IRP) in different experimental conditions before and after lignocaine treatment.



	Epicardial PG (36)	Epicardial PG after lignocaine(8)	Epicardial Lactic Acid (56)	Epicardial Lactic acid after lignocaine(8)	Epicardial Nicotine (72)	Epicardial Nicotine after lignocaine(12)
Relaxation	-28.16	-3.56	-25.68	-4.16	-25.16	-3.24
Contraction	45.42	4.22	44.14	4.68	42.68	4.36

Fig. 2

5. Study of Afferent Pathways:

a. Role of Vagal Afferents in rectal response of cardiac origin:

Bilateral vagotomy: After 60 mins of sectioning of a branch of the vagus nerve supplying the heart the cardiac nociceptors were stimulated by local application of nicotine or lactic acids or capsaicin over the left ventricular surface and rectal movement was recorded in each case. In such vagotomised animals, the reflex biphasic rectal movement induced by nicotine or lactic acid or prostaglandin (Fig.3 and Fig. 5) remained unaltered.

The change in reflex IRP induced by epicardial nicotine or lactic acid or capsaicin in control and bilateral vagotomised animals is statistically insignificant and the values are presented in Table-1.

b) Role of Sympathetic afferents:

Transection of LICN: In another set of experiments, the left inferior cardiac sympathetic nerve (LICN) arising from the stellate ganglia, was sectioned. In such cases, epicardial nicotine or lactic acid or prostaglandin (Fig 4 & 5) application failed to initiate the reflex rectal biphasic response as observed by no significant changes of IRP (Table 1) from the normal level.

Fig. 3: Intrarectal pressure changes (IRP in mmHg) in response to epicardial application of Nicotine (A) and Lactic acid (B) . The recordings of upper panels in both A and B indicate the control i.e. intact animals and lower panels indicate the response in vagotomised animals. The arrows indicate the duration of application of these algesic agents.

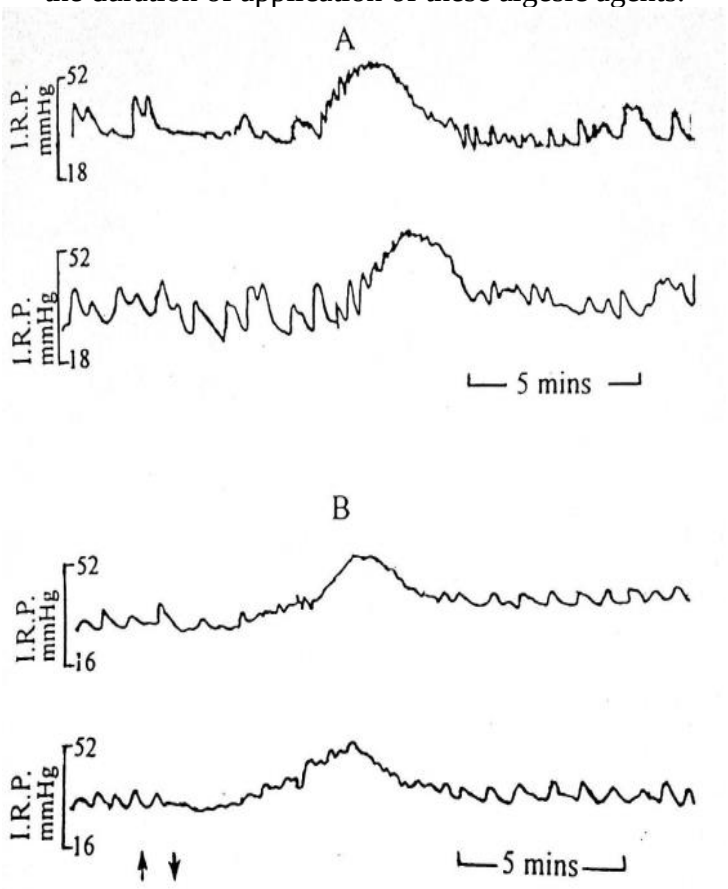


Fig. 3

Fig.4: Intrarectal pressure changes (IRP in mmHg) in response to epicardial application of Nicotine (A) and Lactic acid (B). The recordings of upper panels in both A and B indicate the control i.e. intact animals and lower panels indicate the response in LICN-sectioned animals. The arrows indicate the duration of application of these algesic agents.

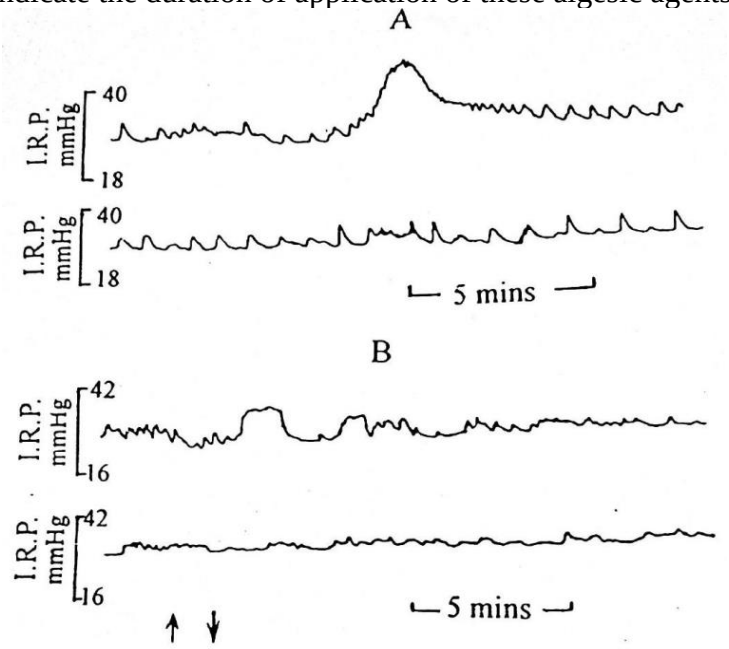


Fig. 4

Fig: 5: Percentage change of intra-rectal pressure (IRP) in response to epicardial application of prostaglandin (PG) before and after vagotomy and cardiac sympathectomy.

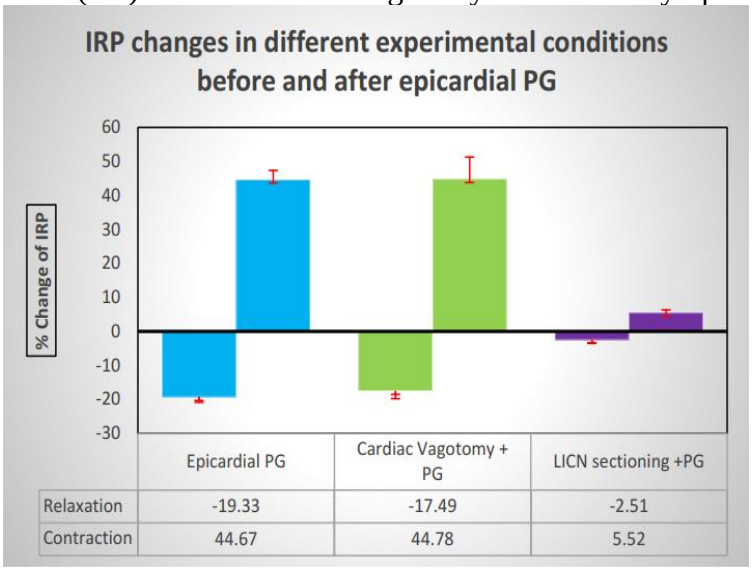


Fig. 5

6. Study of Efferent pathways:

a) Role of Vagus:

i.) Vagotomy below the diaphragm level: Bilateral vagotomy below the diaphragm level did not alter the normal movement of the rectum. In such animals, epicardial nicotine (Fig. 6), lactic acid, and prostaglandin (Fig 7) application-induced biphasic rectal response remained unaltered. There were no significant changes in mean IRP during both the relaxation and contraction phase in response to epicardial nicotine / lactic acid/ prostaglandin from that observed in nerve-intact animals (Table 2).

b) Role of splanchnic nerve:

i) Splanchnic nerve section: Sectioning of the Splanchnic nerve at the abdominal level did neither alter the normal spontaneous movement nor abolish the epicardial nicotine (Fig. 6) or lactic acid or prostaglandin (Fig 7) induced biphasic rectal response. The mean IRP was reduced by 21.52+ 1.82% during the relaxation phase and increased by 21.52+1.82 % during the contractile phase in response to epicardial nicotine (Table 2). The average percentage changes are not significant from that of the control observation. Similar responses are also observed with the epicardial application of lactic acid and prostaglandin (Fig 7).

c) Role of Inferior Mesenteric Ganglia:

i) Sectioning of inferior mesenteric ganglia: Sectioning of the inferior mesenteric ganglia also failed to alter the epicardial nicotine-induced rectal biphasic response as demonstrated in Fig 5. There was an insignificant percentage change in mean IRP during both the relaxation and contraction from the control biphasic response (Table 2). In the case of epicardial lactic acid or prostaglandin, the same result was observed (Table 2 and Fig 7).

d) Role of Pe1vic Nerve:

i) Ventral rhizotomy at S2-S4 level: Ventral root sectioning at the sacral (S2-S4) region or spinal transection at the S2-S4 level reduced the spontaneous movement of the rectum significantly (P<O.O1, n=10). The rectal biphasic response induced by epicardial nicotine or lactic acid or prostaglandin was also absent in such ventral rhizotomised or spinal transected (S2-S4) animals (Fig.6, and Fig 7). There was a significant percentage change in mean IRP during both the relaxation and contraction phases from that of the control observation (Table 2).

Fig. 6: Intrarectal pressure changes (IRP) in response to epicardial application of Nicotine in intact animal (A), in gastric vagotomised animal (B), in Splanchnic nerve sectioned animal (C), in Inferior mesenteric ganglia ectomised animal (D), and in ventral rhizotomised animals (E). The arrows indicate the duration of application of these algesic agents.

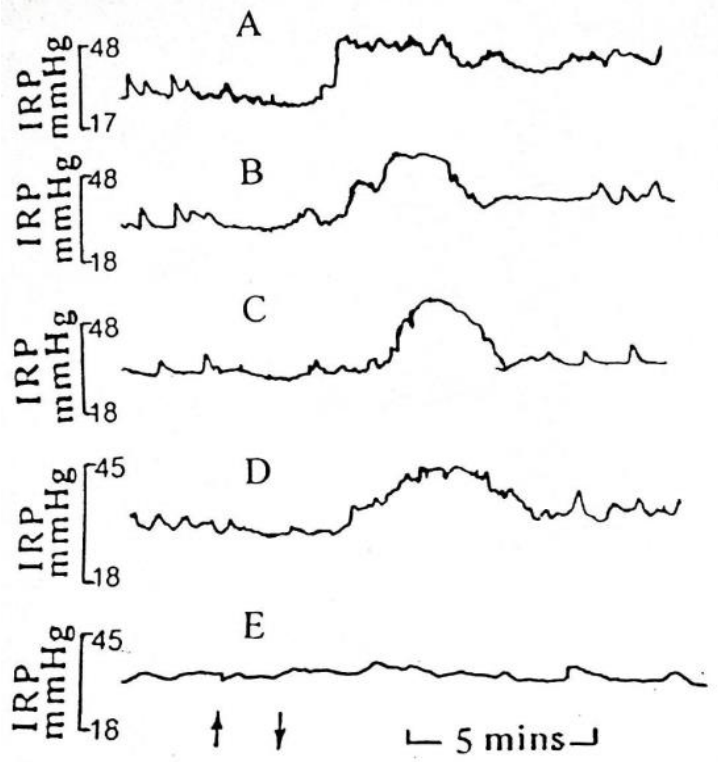


Fig. 6

Fig: 7: Percentage change of intra-rectal pressure (IRP) in response to epicardial application of Prostaglandin before and after gastric vagotomy, Splanchnic nerve sectioning, inferior mesenteric ganglionectomy, and Sacral (S2-S4) ventral rhizotomy.

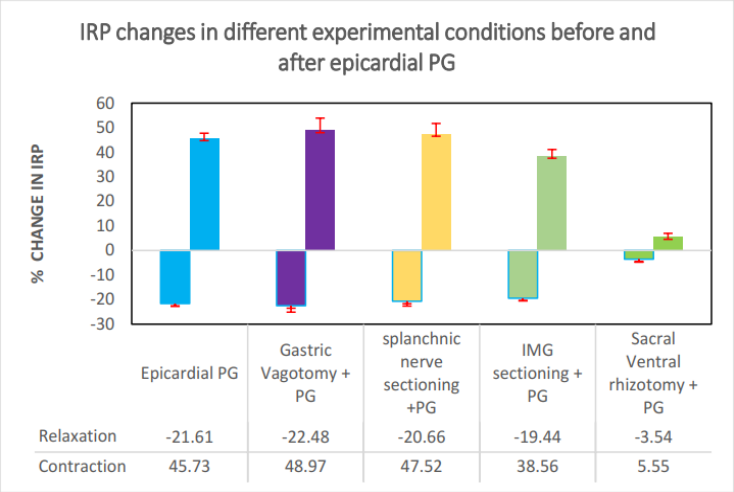


Fig. 7

Table 1: Data showing epicardial nicotine and lactic acid-induced rectal biphasic changes in different experimental conditions in relation to the study of the afferent pathway

Exptl. Condition	Initial Mean IRP + SEM	Epicardial Nicotine		Epicardial Lactic acid	
	(No of observation)	Relax (% fall + SEM	Contra (% rise + SEM	Relax (% fall + SEM	Contra (% rise + SEM
In intact animal (Control)	32.67 ± 1.10 (24)	20.87 ±1.84 [a]	42.76± 2.39[b]	21.0± 1.11 [a]	46.95 ±2.42 [b]
Cardiac vagotomised	33.89 ±1.81 (8)	16.58 ±2.88 [a]	39.34 ±4.16 [b]	22.89 ± 2.78 [a]	49.71± 3.13 [b]
LICN sectioned	32.44 ±1.11 (8)	3.23 ± 1.23	4.40± 1.01	3.01± 1.14	3.12 ± 1.31

[a] indicates $P < 0.01$, [b] indicates $P < 0.001$

Table 2: Data showing epicardial nicotine and lactic acid-induced rectal biphasic changes in different experimental conditions in relation to the study of efferent pathway

Exptl. Condition	Initial Mean IRP + SEM	Epicardial Nicotine		Epicardial Lactic acid	
	(No of Observation)	Relax (% fall + SEM	Contra (% rise + SEM	Relax (% fall + SEM	Contra (% rise + SEM
In intact animal (Control)	29.67 ± 1.32 (32)	18.86 ±0.75 [a]	42.83± 1.93[b]	19.0± 1.21 [a]	45.95 ±2.42 [b]
Gastric vagotomised	32.89 ±1.81 (8)	20.78 ±3.35 [a]	44.87 ±5.21 [b]	20.83 ± 1.78 [a]	48.12± 4.13 [b]
Splanchnic nerve sectioned	32.32± 1.71 (6)	21.52± 1.82 [a]	46.43± 3.35 [b]	19.16± 1.32 [a]	43.83 ±1.24 [b]
IMG sectioned	25.04 ±1.61 (10)	19.91 ± 1.52 [a]	42.73± 1.83 [b]	19.44± 1.14 [a]	48.12 ± 1.01 [b]
Sacral ventral Rhizotomised	30.48 ±1.11 (10)	4.24 ±0.97	3.76+ 1.58	3.54± 1.42	5.42 ±1.34

[a] indicates $P < 0.01$, [b] indicates $P < 0.001$

Discussion; It is well documented that different chemical mediators e.g.; bradykinin, prostaglandins, lactic acid, etc. are released during myocardial ischemia which takes part in the genesis of cardiac pain by exciting the cardiac nociceptors [6-12]. This cardiac pain initiates different visceral and somatic reflexes [1-5]. Though in experimental terms pain is a conscious experience as per Woodworth and Sherrington[14] and Sherrington[15] animals recovering from anesthesia i.e. light anesthesia or in decerebrate acute preparations it is quite easy to obtain the pseudo affective reflexes by applying noxious stimuli to the heart. Later on, Brown in 1967[16,] and also Malliani and his associates in 1969[17]

reported that experimental coronary artery occlusion in lightly anesthetized cats often provokes cardiac reflexes. Excitation of cardiac sensory receptors by epicardial application of chemical substances e.g.; bradykinin, nicotine, prostaglandins, lactic acid, and veratridine may elicit bradycardia, hypotension along with the relaxation of the stomach[1-5]. Koley and hér groups also reported that [3-5] stimulation of the cardiac nociceptors of the left ventricle by LAD occlusion or local application of different algesic agents on the surface of the left ventricle initiates increased forelimb movement, contraction of the nictitating membrane, increase urine flow and contraction of the urinary bladder and also rectum. The present study confirms that epicardial application of different algesic agents like nicotine or lactic acid or prostaglandin excites the cardiac sensory receptors presumably nociceptors to initiate a biphasic rectal response. It is also confirmed that during cardiac ischemia different algesic substances are released in the cardiac muscle which in turn initiates cardiac pain that evokes different reflexes like defecation by contracting the rectum. Moreover, these changes in rectal motility following epicardial application of nicotine or lactic acid, or prostaglandin is reflexogenic as it is totally abolished after desensitization of cardiac sensory receptors by epicardial application of lignocaine which may be due to the inhibition of catecholamine release from sympathetic nerve endings in the ischemic myocardium by its endo-anesthetic and membrane stabilizing properties[18].

The present study also confirms our previous study that the afferent limb for such reflex is lying in the cardiac sympathetic as because sectioning of the cardiac vagal fibers did not alter such reflex but in such sympathectomised animals application of nicotine or lactic acid or prostaglandin over the surface of the left ventricle failed to show such rectal biphasic response. It is accepted that sympathetic nerves are essential to the perception of cardiac pain [19,20]. Malliani and Brown[21], Brown and Malliani[22] recorded impulse activity of afferent cardiac sympathetic nerve fibers that were excited by interruption of left coronary artery flow leading to myocardial ischemia. Brown and Malliani[22] and Uchida and Murao23 observed a few silent fibers in the sympathetic that became active during the interruption of coronary artery blood flow. Guzman el al. [6]., and Pal et al. [24] have also reported that the application of bradykinin, lactic acid, or nicotine and also occlusion of the left anterior descendant coronary artery resulted in an increase of afferent sympathetic activity. They have shown clearly that cardiac nociception is related to the excitation of the cardiac sympathetic A-delta and C fiber endings. Thus, it indicates that cardiac receptors presumably nociceptors [24,25] are excited due to the application of nicotine or lactic acid or prostaglandin directly over the epicardial surface resulting in cardio-rectal reflexes having their afferent pathways lying in the cardiac sympathetic fibers.

Gastrointestinal motility is influenced by two divisions of efferent nervous activity - sympathetic and parasympathetic. The sympathetic fibers emerge from the thoracolumbar spinal cord and parasympathetic axons leave the cerebrospinal axis as vagal innervation and pelvic innervation[26]. The present study revealed that the biphasic rectal response of cardiac origin is mediated through the efferent activity of the spinal sacral ventral roots which originate from the pelvic nerve plexus. Both the rectal relaxation and contraction are mediated through the sacral ventral roots as sacral ventral rhizotomy or spinal transection at the S2-S4 region totally abolishes such reflex action. This is further evident from the stimulation of the ventral roots which resulted in both relaxation and contraction. On the other hand, this is further found that epicardial nicotine or lactic acid or prostaglandin-induced rectal relaxation and contraction were present even after sectioning of the inferior mesenteric ganglia from which the hypogastric nerve plexus arises. In other words, sectioning of the inferior mesenteric ganglia failed to abolish such cardio-rectal reflex indicating no role of such ganglia in mediating such type of rectal biphasic response. The vagus or splanchnic nerve has also got no role in eliciting such reflex as gastric vagotomy or splanchnic nerve sectioning failed to alter such cardio-rectal reflex. Stimulation of either of these nerves also failed to induce such biphasic change of the rectum. Thus, it may be concluded that the pelvic nerve is the efferent limb for such a reflex rectal biphasic response.

Conclusions: The present study thus concludes that the cardiac ischemic pain induced by epicardial application of different algesic agents like nicotine, lactic acid, and prostaglandin results in the origin of rectal biphasic response which may be due to the reason for defecatory urge during MI-induced heart failure. It is also concluded that the efferent and afferent pathway for such reflexogenic rectal response is the sacral pelvic nerve and cardiac sympathetic nerve respectively.

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Authors contribution; Sole author contribution

Ethical approval; Adhered to ARRIVE guidelines and ***The entire study was approved by the Ethical Committee under the Dept. of Physiology, University of Calcutta, Kolkata.***

Competing Interests: None

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List of Abbreviation:
LICN- Left inferior cardiac sympathetic nerve
IRP- Intra rectal pressure
LAD- Left Anterior Descending coronary artery

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