Applied Biological Research 26(4): 441-450; (2024)
DOI: 10.48165/abr.2024.26.01.51

REVIEW ARTICLE

NEUROPHYSIOLOGICAL BASIS IN CARDIAC NOCICEPTION-INDUCED REFLEXES FROM THE HEART: A COMPREHENSIVE REVIEW

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(Received 20 June, 2024; accepted 9 November, 2024)

ABSTRACT

The heart is considered an important reflexogenic organ and the stimulation of cardiac nociceptors is responsible for the elicitation of different cardiogenic reflexes. Most likely this is the basic reason behind different clinical presentations associated with heart failure, or myocardial infarction (MI). Clinically, heart failure due to myocardial ischemia is associated with bradycardia, hypotension, urge to pass urine, and stool. It is well established that different chemical substances like lactic acid, prostaglandins, bradykinin, and K+, are released during myocardial ischemia which, in turn, is responsible for the elicitation of cardiac pain that may result in different visceral and somatic reflexes. So, understanding the basic physiological mechanism behind such clinical association between cardiac ischemia-induced heart failure may help clinicians manage this fatal condition. This paper presents a comprehensive review on neurophysiological basis of different clinical presentations associated with MI-induced heart failure. The review also analyses the neural pathway for different cardiogenic reflexes which are associated with different clinical signs or symptoms associated with cardiac failure and thereby may be responsible for the diagnosis of early heart failure.

Keywords: Cardiogenic reflexes, cardiac nociceptors, cardiac ischemia, myocardial infarction-induced heart failure, neurophysiology of cardiac nociception

1. INTRODUCTION

The heart, as a vital organ, is not only responsible for pumping blood but also serves as a critical sensory structure for generating and transmitting signals of pain or discomfort, known as cardiac nociception (Coote and Chauhan 2016, Wink *et al.,* 2020). This intricate system of nociceptive signalling plays pivotal role in various reflexes that arise in response to harmful or potentially damaging stimuli within the heart. These cardiogenic reflexes (Koley *et al.*, 1997, 1999; Stern, 2005) can provide great insight into the early diagnosis of clinical presentation of myocardial ischemia and related heart failures. As the yearly prevalence of death due to heart failure is markedly increased (Fig 1), understanding the neurophysiological mechanisms behind these cardiac nociception-induced reflexes is essential for comprehending the broader autonomic responses and pain perception related to the cardiac events such as ischemia, angina, and myocardial infarction. These reflexes can give insight into managing cardiac failure in clinical practice. These understandings are also essential to understand the reperfusion injury after cardiac ischemia-induced heart failure (Giannino *et al.*, 2024). This review paper delves into the complex neural pathways and the interactions between heart and central nervous system that gives rise to these reflexes. By exploring the interplay of sensory neurons and nociceptive receptors, and their role in eliciting different cardiogenic reflexes, this article also sheds light on how the body processes respond to the pain originating from the heart. These insights

can apprise better clinical approaches to manage cardiac pain and improve the outcomes for patients experiencing heart-related distress. Understanding the neurophysiological basis of these reflexes opens new avenues for research and therapeutic interventions in cardiac health including the diagnosis of early heart failure especially in case of silent myocardial ischemia.

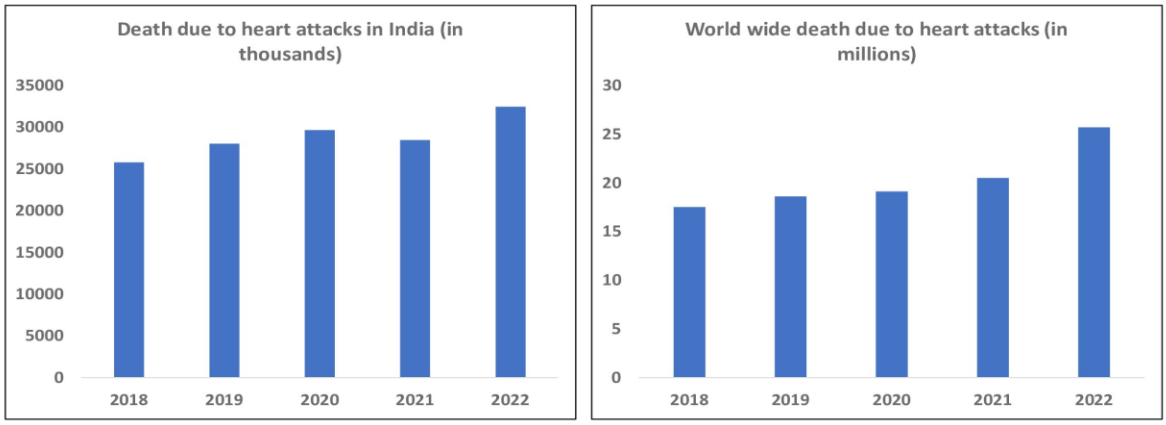

Fig. 1: Prevalence of death due to heart failure from 2018 to 2022 (Data source: *https://www.indiatoday.in/health/story/sudden-heart-attack-deaths-increased-by-12-in-2022-government-data-2471760-2023-12-04; https://www.ajpmonline.org/article/S0749-3797(23)00465-8/fulltext*)

2. MECHANISM OF CARDIAC NOCICEPTION

Sutton and Leuth (1930) were first to report that the reduction of coronary blood flow leads to myocardial ischemia, and often elicits pain which was later authenticated by Guzman *et al.* (1962). Brown (1967) reported that the occlusion of left main coronary artery of lightly anesthetized cats was accompanied by a pain-like sensation called 'pseudo-affective response', the term first coined by Sherrington (1906). This anginal pain during ischemia may be due to the failure of coronary arteries to properly supply oxygen to the cardiac muscle (Yam *et al.*, 2018). Different algesic chemicals may stimulate cardiac nociceptors during myocardial ischemia (Guo *et al.*, 2007; Eckle *et al.*, 2008; Hans *et al.*, 2010; Koeppen *et al.*, 2011). The excitation of polymodal nociceptors by chemicals and the sensation of pain or pseudo-affective responses produced by their administration indicates that these substances under certain conditions may act as intermediaries. In fact, these

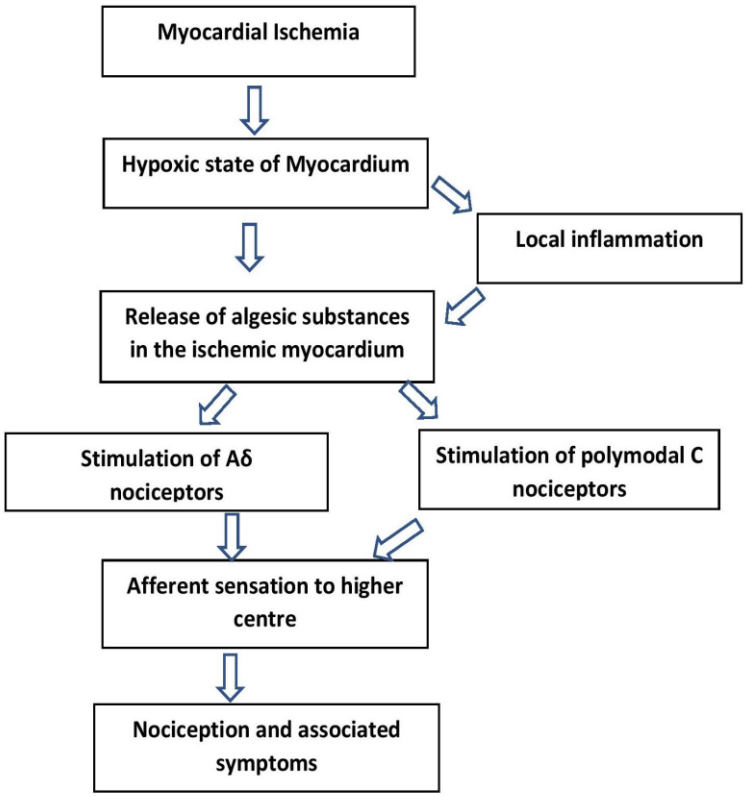

Fig. 2: Overview of mechanism of cardiac nociception

intermediates are released by severe nociceptive stimuli during painful inflammatory states; and activate or sensitize nociceptors. The induction of myocardial ischemia by coronary artery occlusion or epicardial application of different chemicals stimulate the ventricular chemoreceptors which, in turn, is responsible for chest pain sensation by modulating the autonomic nervous system (Sadowska, 2024) through activation of NTS of medulla (Li *et al.,* 2015). The basic mechanism of this cardiac nociception is illustrated in Fig. 2.

Mechanism of cardiac nociception-induced reflexes of heart including the neural pathways

The signal from ischemic myocardium to brain appear to be responsible for the elicitation of different reflexes (Fig. 2), which might be the basis of different signs and symptoms associated with anginal pain or ischemia-induced heart failure. Various reflexes originated from this ischemic myocardium as reported to date are as follows:

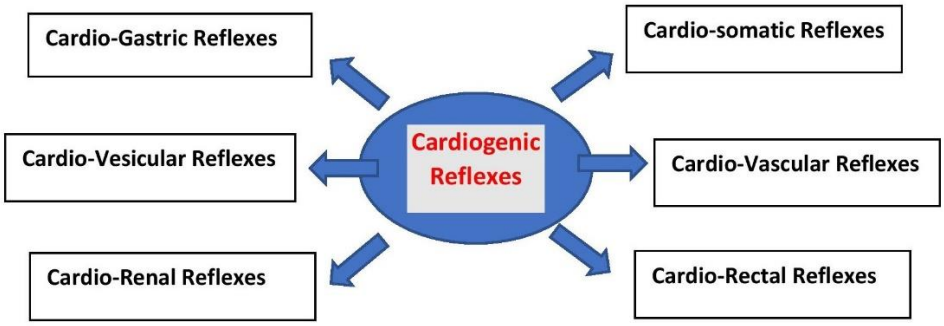

Fig. 2: Different cardiogenic reflexes

i. Cardio-vascular reflex. It is well established that the stimulation of reflexogenic areas of the heart can result in dramatic alterations in normal cardiovascular functions like the changes in heart rate and blood pressure. Bezold (1867) opined on the role of depressor nerves that originate from pressure-sensitive endings in the heart in reflex regulation of vascular resistance. They also reported that the injection of veratridine in the coronary artery results in decrease in arterial blood pressure and heart rate which abolishes after bilateral vagotomy. These findings were supported by Jarisch and Richter (1939). This type of bradycardia and hypotension, observed immediately after intravenous administration of various chemicals with their afferent pathways lying in the vagus nerves, is known as the "Bezold-Jarisch reflex". Further, they reported that this reflex originated from the ventricular myocardium. Similar types of reflexes (e.g. Bainbridge reflex) were also observed by Crystal and Salem (2012) wherein they found that infusing fluid into the circulatory system of dogs lead to an increase in heart rate regardless of the change in arterial blood pressure, however when central venous pressure increased enough it caused distension of right atrium. Bilateral vagotomy abolishes such type of response (Hall and Guyton, 2024). Paintal (1963) reported that distention of left atrium results in a reflex fall in systemic blood pressure indicating the role of left atrial receptors in eliciting cardiogenic reflexes. Numerous reports have demonstrated that various chemicals can trigger such Bezold-Jarisch effect and the most commonly used stimulants are veratrum alkaloids, although other agents such as nicotine (Koley *et al.*, 1995), bradykinin (Gaspardone *et al.,* 1999, Qin *et al.,* 2009), prostaglandins (Berger *et al*., 1977) and lactic acid (Koley *et al*., 1999) have been identified as reflex initiators.

Dzavik *et al*. (2007) reported that hypotension associated with myocardial ischemia is due to the increased expression of inducible NO synthase, and the excessive release of NO leads to vasodilation, myocardial depression, and interference with catecholamine action. However, Reynolds and Hochman (2008) reported that the isoform-nonselective NO synthase inhibitors appeared to improve hemo-dynamics. In contrast, monomethyl-L-arginine at the same dose (0.5 to 20 mg kg^{-1} h^{-1} and duration (7 or 14 days) did not observe any reduction in mortality in a large multicentre trial ((Lopex *et al.*, 2004). Moreover, numerous studies have reported significant changes in heart rate in response to mechanical stimulation of ventricular receptors (Aviado and Schmidt, 1959; Jou *et al.*, 2001; Rosen, 2012).

ii. Cardio-somatic reflex: The stimulation of ventricular nociceptors by coronary artery occlusion results in increased forelimb contraction which is termed as a pseudo-affective response (Sherrington, 1906). Coronary artery occlusion or application of different algesic agents like nicotine, prostaglandins, bradykinin, and lactic acid over epicardial surface caused a tremor-like flexor movement of forelimbs and also the contraction of nictitating membrane in lightly anesthetized cats (Koley *et al.*, 1999). Using the single fiber technique, they reported that the afferent limb of such cardio-somatic reflexes lies in left cardiac sympathetic nerve (LICN). Jou *et al.* (2001) demonstrated that muscle contractions generated by chemical activation of cardiac receptors result in muscle spasms. These reflex responses were absent in sympathectomy (Jou *et al.*, 2000) and vagal nerve stimulation (Johannsen *et al*., 1981; Fruergaard *et al.*, 1996). Jou *et al.* (2004) showed that sympathetic cardiac afferents (SCA) play a critical role in the generation of muscle hyperalgesia, while vagal cardiac afferents (VCA) have physiological importance in the modulation of cardiac pain. The stimulation of SCA by applying various algesic agents in epicardial surface resulted in the spasmodic muscle contractions, whereas the inhibition of VCA augmented muscle contraction. The resulting muscle contractions was indicated as angina-like referred pain.

Cardiac ischemic pain referred to the chest and upper arm is transmitted via sympathetic afferent fibers to thoracic cells; whereas the same pain referred to the jaw and neck is transmitted via vagal afferent fibers into cervical cells (Foreman, 2007). They further reported that both somatic and cardiac inputs converge at T1-T5 segments which then passes to the brain for perception of ischemic pain.

iii. Cardio-visceral reflexes: The stimulation of cardiac receptors also initiates different types of cardio-visceral reflexes i.e. cardio-renal, cardio-vesicular, cardio-gastric, and cardio-rectal reflexes.

a. Cardio-gastric reflex: The application of various algesic agents, including nicotine, lactic acid, bradykinin, prostaglandin, etc., on epicardial surface stimulate ventricular nociceptors (Johannsen *et al.*, 1981; Mark, 1983; Koley *et al.*, 1995). This, in turn, triggers various gastrointestinal symptoms such as vomiting, defecation, etc. Fruergaard *et al.* (1996) suggested that disorders like pulmonary embolism, gastro-oesophageal diseases, and chest wall syndromes can identify non-acute myocardial infarction. Sole *et al.* (1996) reported T wave inversions on electrocardiograms (ECGs) due to myocardial ischemia in some patients experiencing epigastric pain. Similarly, Voskuil *et al.* (1996) found that the patients with chest pain exhibited symptomatic gastroesophageal reflux. Coronary artery occlusion reduces median lower oesophageal sphincter function, blood pressure, and heart rate, with these effects being abolished by cervical vagotomy (Caldwell *et al.*, 1995). Therefore, it can be argued that a direct vagal reflex may explain the high incidence of gastro-oesophageal reflux in patients with coronary artery disease. On the other hand, reports reveal that the activation of non-myelinated vagal afferents from left ventricle of heart not only induces reflex bradycardia and hypotension but also leads to a significant reflex relaxation of stomach (Abrahamsson and Thoren, 1972).

a. Cardio-rectal reflex: Clinically, reflex urination and defecation are the two most important visceral symptoms observed in patients suffering myocardial ischemia, infarction, etc. The stimulation of cardiac nociceptors of the left ventricle by occlusion of the left anterior descending coronary artery (LAD) or local application of different algesic agents on the surface of left ventricle produces biphasic rectal response-initial relaxation followed by contraction (Koley *et al.*, 1995, 1999; Basak *et al*., 2003). They proposed that this rectal response may be the real reason behind the clinical signs of heart failure-induced defecatory urge. The rectal biphasic change is reported to be purely reflexogenic as the reflex is generally absent after LAD occlusion and epicardial application of different algesic agents. The sensory pathway of this type of reflex is a cardiac sympathetic nerve which transmits the pain signal to the higher centre to modulate the rectal contraction. Myocardial ischemia induced by LAD occlusion is the origin of rectal biphasic response, which may account for defecatory urge during myocardial infarction-induced heart failure (Basak, 2023; Basak and Koley, 2024). The efferent and afferent limbs for these reflexo-

genic rectal responses are mediated via sacral pelvic nerve and cardiac sympathetic nerve, respectively. In addition, the relaxation and contractile phases of this response are mediated through NO pathway and the cholinergic pathway, respectively. Koley *et al.* (1997; 1999) also demonstrated that similar clinical presentation can be observed once different algesic agents like nicotine, prostaglandin, and bradykinins are applied over the pericardial surface of left heart.

b. ***Cardio-renal and vesicular reflex***: The stimulation of ventricular receptors, induced by either coronary artery occlusion or epicardial application of nicotine, resulted in biphasic urinary bladder motility (Koley *et al*., 1995; Das *et al*., 2000). Additionally, there were biphasic changes in urine flow, with vesicular movement initially rising and then showing decline. Conversely, the rate of urine formation first declined and then increased. The afferent limbs for the two superimposed events are distinct (Koley *et al*., 2001). Vagus sectioning partially counteracted the initial large contraction, and sectioning of inferior cardiac sympathetic nerve (ICN) completely abolished the initial antidiuretic phase. Similarly, ICN sectioning partially counteracted the initial large contraction of the vesicular response and completely abolished the late inhibition phase. The late diuretic phase was entirely abolished by vagotomy.

The atrial receptors can initiate different reflexes, with a relatively larger effect on renal circulation as compared to the vascular beds. Linden *et al.* (1980), while examining the nature of atrial receptors responsible for decrease in renal nerve activity, found that this decrease not only affects the renal blood flow but also contributes to the changes in renal function along with humoral agents and hemodynamic factors. Diuretic and natriuretic responses to atrial receptor stimulation were established by Karim *et al.* (1989). The localized stimulation of left atrial receptors not only cause significant increase in heart rate and systemic blood pressure but also increase renal blood flow, glomerular filtration rate, urine volume, sodium excretion, and osmolar excretion (Karim and Allobaidi, 1992). The overall neural basis of different cardiogenic reflexes is given in Table 1.

Table 1: Overview of neural basis of different cardiogenic reflexes

Type of reflex	Response	Afferent pathway
Cardio vascular	• Inhibitory responses like bradycardia and hypotension • Stimulatory like tachycardia	• Vagus • Sympathetic
Cardio somatic	• Flexor movement of forelimb • Contraction of nictitating membrane	• Sympathetic • Sympathetic
Cardio gastric	• Gastric relaxation • Vomiting	• Vagus • Not known
Cardio rectal	• Biphasic (Initial relaxation followed by contraction)	• Cardiac sympathetic
Cardio renal	• Biphasic (Initial antidiuresis followed by diuresis)	• Both vagus and cardiac sympathetic
Cardio vesicular	• Biphasic (Initial contraction followed by relaxation)	• Both vagus and cardiac sympathetic.

3. RESEARCH GAPS

The studies on cardiac nociception, or how the heart perceives and transmits pain signals, play a crucial role in understanding cardiovascular health and developing treatments for the conditions like angina and myocardial infarction. Though significant progress has been made in understanding the neural pathways and the reflexive responses involved in cardiac pain, yet there are several research gaps which hinder the thorough understanding of these processes. Filling these gaps is essential to improve the clinical approaches and therapeutic interventions related to heart-related pain and its reflexive effects on the body.

- How the central nervous system (CNS) process nociceptive signals originating from the heart is not yet clear. Further, the mechanisms by which the brain integrates cardiac nociception with emotional, behavioural, and autonomic responses are underexplored. Studies are required to

identify the brain regions (insular cortex, anterior cingulate cortex, and hypothalamus), actively involved in the processing of heart pain.

- The autonomic nervous system (ANS), specifically its sympathetic and parasympathetic branches, plays central role in modulating the heart's response to nociceptive stimuli. Though much is known about the sympathetic nervous system's activation during stress and pain, the contribution of parasympathetic nervous system, particularly the vagus nerve, in reflexive responses to cardiac nociception is less understood. Specifically, understanding how the balance between sympathetic and parasympathetic responses affects the overall pain response by the body could lead to new therapeutic strategies for managing cardiac pain, including better management of autonomic disturbances that often accompany heart disease.
- Central sensitization is a well-known phenomenon in other types of chronic pain, like musculo-skeletal pain and neuropathic pain, where the CNS becomes hypersensitized to pain stimuli, leading to exaggerated pain responses (McBeth and Jones, 2007; Woolf, 2011). The scanty information is available on the role of central sensitization in chronic cardiac pain, such as recurring angina or post-myocardial infarction pain. Given that many patients experience persistent cardiac pain even after treatment of the underlying condition, understanding the potential role of central sensitization in these cases could open new avenues for pain management, including the therapies aimed at desensitizing the CNS.
- The recent advances in neuro-imaging and electrophysiological techniques have improved our ability to explore the brain and nervous system, yet there are some technological limitations in mapping the precise pathways involved in cardiac nociception. Current imaging techniques like functional magnetic resonance imaging (fMRI) have limitations in capturing the rapid transmission of nociceptive signals from the heart (Chen and Glover, 2015). Additionally, while electrophysiological methods like electroencephalography (EEG) offer insights into brain activity, they often lack the spatial resolution needed to pinpoint specific neural circuits involved in cardiac pain. Further improvement in these technologies may help in uncovering the details of neural mechanisms underlying the cardiac nociception.

Addressing these research gaps is critical for understanding of the neurophysiological basis of cardiac nociception-induced reflexes. More studies on central pain processing, the role of autonomic nervous system, central sensitization, and the translation of animal model findings into human research are needed to comprehensively understand how heart communicates pain and how the body responds. By addressing these gaps, researchers and clinicians can develop more effective treatments and interventions to manage cardiac pain and improve patient.

4. FUTURE STRATEGIES

The neurophysiological basis of cardiac nociception-induced reflexes is a burgeoning area of research that holds great promise in advancing our understanding the mechanism of distress communications in heart and pain signals to the brain. The intricate web of nociceptive pathways that link the heart to nervous system, particularly in the context of cardiac diseases such as myocardial infarction and ischemia, is crucial for both clinical and research purposes. Based on this comprehensive review, future strategies can be formulated and executed towards meaningful contributions in this field. The key strategies that need to be considered while embarking on this critical area of cardiovascular research are as under:

i) Interdisciplinary collaboration: Given the multidisciplinary nature of cardiac nociception-induced reflexes, which encompass cardiology, neurophysiology, pain research, and autonomic nervous system studies, future strategies are:

a. Involvement of experts across the fields as collaborative approaches offer fresh perspectives and ensure that the review is not overly focused on any single aspect of cardiac nociception but rather captures the complexity of its neurophysiological underpinnings.

b. Integration of animal and human studies that can provide a more robust understanding of neuro-physiological mechanisms at play.

c. Explore the new technologies like functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) scans, electrophysiological mapping, and neuro-stimulation techniques to uncover the cardiac nociception phenomenon and mechanisms.

ii) Central sensitization: It refers to the process by which the CNS becomes sensitized to pain, amplifying nociceptive signals and leading to heightened pain perception. This concept has extensively been studied in the context of chronic pain conditions, but its application to cardiac nociception is still in its early stages. If central sensitization plays a significant role in cardiac nociception, this could open new avenues for therapeutic interventions.

iii) Clinical practice: An essential element of this review is to not only map the neurophysiological mechanisms but also to address how these insights can be applied to clinical practice like:

a. **Development of targeted therapies**: Understanding the neural circuits and pathways involved in cardiac nociception could lead to more targeted therapies for cardiac pain, reducing the need for general pain medications like opioids, which have high risk of side-effects and dependency.

b. **Improved diagnostic tools**: Insights from neurophysiological research could improve the diagnostic tools for cardiac pain. For instance, identifying the specific biomarkers of cardiac nociception could help in differentiating the various types of chest pain, leading to quick and accurate diagnoses in clinical settings.

Conclusion: The future of research on the neurophysiological basis of cardiac nociception-induced reflexes is bright, with numerous strategies available to advance our understanding. By embracing interdisciplinary collaboration, incorporating new technologies, and focusing on key areas like the role of autonomic nervous system and central sensitization, future reviews can not only map out the existing knowledge but also provide a clear roadmap for new research and clinical applications. The ultimate goal is to enhance the understanding and treatment of cardiac pain, improving patient outcomes.

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