Case Series

A Case Series of Cardio-Biliary Reflex Presenting as High-Grade Atrioventricular Block in Acute Cholecystitis

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Cardio-biliary reflex (CBR), also known as Cope's sign, is a rare vagally mediated reflex phenomenon in which gallbladder pathology presents as acute cardiac rhythm disturbances. Although sinus bradycardia is the most commonly described manifestation, higher-grade atrioventricular conduction abnormalities are reported and may mimic primary cardiac pathology, resulting in a diagnostic dilemma and delays in management.

We describe a series of three patients who presented to the emergency department with acute abdominal pain associated with syncope, hypotension, and significant electrocardiographical abnormalities in the setting of acute cholecystitis. Electrocardiographic findings included complete heart block in two patients (case 1 and 3) and second-degree atrioventricular block (Mobitz type II) in one patient (case 2). Despite hemodynamic instability, the cardiac biomarkers, echocardiography, and electrolyte profiles were unremarkable in all three cases. Point-of-care ultrasonography and computed tomography subsequently identified underlying biliary pathology, including acute calculous and acalculous cholecystitis. Clinical improvement in heart rate and hemodynamic status occurred following analgesia and management of the underlying gallbladder disease, supporting the diagnosis of cardio-biliary reflex.

This case series highlights the importance of recognising cardio-biliary reflex as a reversible extracardiac cause of severe bradyarrhythmias and conduction disturbances.

Prompt identification of this phenomenon by treating physicians may help avoid unnecessary invasive cardiac interventions and facilitate timely identification of underlying biliary disease in patients.

Access this article online

Website: www.cijmr.com

DOI: 10.58999/cijmr.v5i02.462

Keywords: Cardio-biliary reflex; Cope's sign; Acute cholecystitis; Atrioventricular block.

Introduction

Cardio-biliary reflex (CBR), also referred to as Cope's sign, is an uncommon but clinically significant vagally mediated reflex in which gallbladder pathology induces cardiovascular manifestations, most notably cardiac conduction abnormalities and hypotension. First described by Sir Zachary Cope and later formally reported by O'Reilly and Krauthamer in 1971, the phenomenon is believed to result from autonomic cross-talk between the gallbladder and the cardiovascular system through vagal and sympathetic neural pathways.[1]

The reflex is typically triggered by mechanical or inflammatory stimulation of the gallbladder, leading to enhanced parasympathetic activity and suppression of cardiac conduction. While sinus bradycardia is the most frequently reported manifestation, more severe conduction abnormalities such as high-grade atrioventricular block, complete heart block, sinus arrest, and even asystole have been described in isolated reports. In addition, electrocardiographic changes associated with CBR may mimic acute coronary syndrome, creating a diagnostic challenge in emergency settings.[2]

Acute calculous cholecystitis remains the most commonly associated pathology; however, similar cardiac manifestations have also been reported in acalculous cholecystitis, biliary colic, gallbladder torsion, and during laparoscopic manipulation of the gallbladder.[3]

Recognition of this entity is important, as appropriate treatment of the underlying biliary pathology often results in reversal of the cardiac manifestations, thereby avoiding unnecessary invasive cardiac procedures.

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Submitted: 20/06/2026 Revision: 25/06/2026
Accepted: 22/07/2026 Published: 15/08/2026

How to cite this article: Shalini K, Karmegam G, Parthiban, Manisha Shree B, Ramaswamy V, Adalarasan S. A Case Series of Cardio-Biliary Reflex Presenting as High-Grade Atrioventricular Block in Acute Cholecystitis. Central India Journal of Medical Research. 2026;5(2):245-250.

We report a retrospective case series of three consecutive patients who presented to the emergency department with cardio-biliary reflex secondary to acute cholecystitis. Notably, two patients developed complete heart block and one developed second-degree atrioventricular block (Mobitz type II), all of which resolved following treatment of the underlying biliary pathology. This series highlights the varied spectrum of high-grade conduction abnormalities associated with cardio-biliary reflex and emphasizes the importance of early recognition to avoid unnecessary cardiac interventions

Case Series

We here describe 3 case presentations of cardio biliary reflex or Cope's sign seen in patients presented to the emergency department of Rajiv Gandhi Government General Hospital.

Case 1

A 48-year-old female presented to the emergency department with complaints of sudden onset severe abdominal pain for two hours, followed by fainting and profuse sweating. She also had two episodes of vomiting. The patient reported two previous similar episodes that had resolved with analgesics administered at a local healthcare facility.

On arrival, the patient was hemodynamically unstable, with a pulse rate of 30–40/min and blood pressure of 60/40 mmHg. Peripheral oxygen saturation could not be recorded properly. Her Glasgow Coma Scale (GCS) score was E2V2M5, and capillary blood glucose was 205 mg/dL. Electrocardiography demonstrated complete heart block (as shown in Figure 1). Bedside echocardiography showed preserved biventricular systolic function without regional wall motion abnormalities or pericardial effusion. The inferior vena cava was collapsible and measured 1.32 cm in diameter. Troponin-I, NT-proBNP, serum electrolytes, and arterial blood gas analysis were within normal limits.

The patient received oxygen via non-rebreathing mask, intravenous atropine 1 mg every 3–5 minutes for a total of three doses, and adrenaline infusion for persistent bradycardia and hypotension as per ACLS protocol. There was only transient improvement in hemodynamic parameters, with pulse rate increasing to 47/min and blood pressure improving to 90/60 mmHg. However, abdominal pain and altered sensorium persisted.

Given the absence of biochemical and echocardiographic cardiac abnormalities and presence of persistent abdominal pain, abdominal point-of-care ultrasonography (POCUS) was performed to identify an alternative etiology. POCUS demonstrated a distended gallbladder containing multiple calculi with associated gallbladder wall thickening, suggestive of acute calculous cholecystitis (as shown in Figure 2)

In view of the suspected cardio-biliary reflex, intravenous diclofenac and ketorolac were administered for pain control. Following this, there was gradual improvement in heart rate and blood pressure, with pulse rate increasing to 66/min and blood pressure stabilizing at 100/60 mmHg while on tapering inotropic support. The complete heart block was presumed to be transient and vagally mediated in view of its reversibility following symptomatic management and treatment of the underlying pathology.

Computed tomography (CT) abdomen subsequently confirmed acute calculous cholecystitis. Multidisciplinary consultations with cardiology, general medicine, and general surgery teams were obtained. The patient was transferred to the surgical unit for planned elective cholecystectomy following stabilization.

Case 2

A 57-year-old male Watchman presented to the emergency department in the early morning with sudden-onset abdominal pain followed by fainting and profuse sweating while on duty. He was a known hypertensive on regular treatment and had a past history of cholecystitis without further follow-up. The patient had no other co-morbidities.

On arrival, the patient had poor vitals; heart rate was 45/min, blood pressure 90/60 mmHg, oxygen saturation 92% on room air, and GCS score E2V3M4. Capillary blood glucose was 157 mg/dL.

Electrocardiography showed second-degree atrioventricular block, Mobitz type II (as shown in Figure 3). Echocardiography revealed an ejection fraction of 48% without regional wall motion abnormalities or chamber dilatation, although left ventricular hypertrophy was noted. Cardiac biomarkers and electrolyte levels were normal. A point-of-care ultrasonography was done to evaluate the abdominal pain, which revealed a distended gallbladder with sludge.

The patient received atropine, intravenous diclofenac, paracetamol infusion, and pantoprazole. Subsequently, heart rate improved to 58/min and gradually improved to a stable rhythm. Serum electrolytes were within normal range. CT abdomen revealed acute acalculous cholecystitis (as shown in Figure 4). Surgical consultation was offered however; the patient declined operative procedure and was managed conservatively.

Case 3

A 42-year-old female was referred from a peripheral hospital as a case of complete heart block (ECG shown in Figure 5) with hypotension requiring inotropic support. She had received three doses of intravenous atropine (1 mg each) as part of ACLS protocol prior to transfer.

On arrival, pulse rate was 30/min and blood pressure was 90/50 mmHg while on adrenaline infusion. The patient complained of severe persistent abdominal pain and appeared irritable and agitated.

Cardiac biomarkers, echocardiography, serum electrolytes, and other cardiac evaluations were unremarkable. Due to persistent bradycardia and hemodynamic instability, temporary pacemaker insertion was planned. During preparation for the procedure, intravenous ketamine (1 mg/kg slow bolus) was administered for analgesia and procedural sedation. On administration, gradual improvement in heart rate was noted during the procedure. In view of this, screening ultrasonography and bedside echocardiography demonstrated a distended gallbladder with calculus in neck of gall bladder, (as shown figure 6) without other significant abnormalities. CT abdomen confirmed acute calculous cholecystitis.

Following discussion between cardiology and surgical teams, the patient was admitted under surgery and planned for emergency laparoscopic cholecystectomy.

No temporary or permanent pacemaker implantation was required in any of the three patients. The patients were not followed up at 1 month, as all demonstrated complete clinical stabilization during hospitalisation and no indication for short-term follow-up was identified. The clinical characteristics and management of the three patients are summarized in Table 1, while the temporal

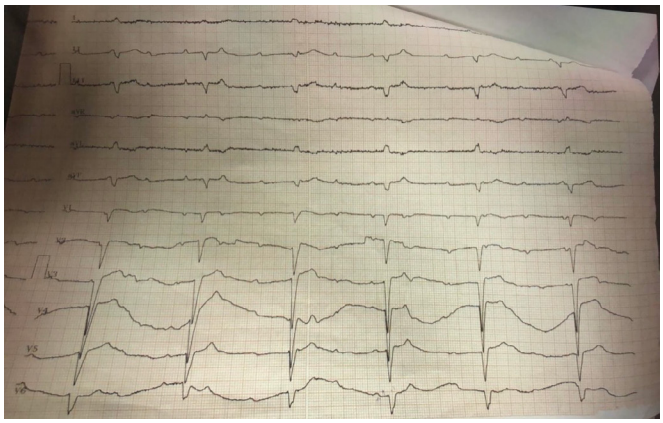

Figure 1: 12 lead ECG of patient showing complete heart block

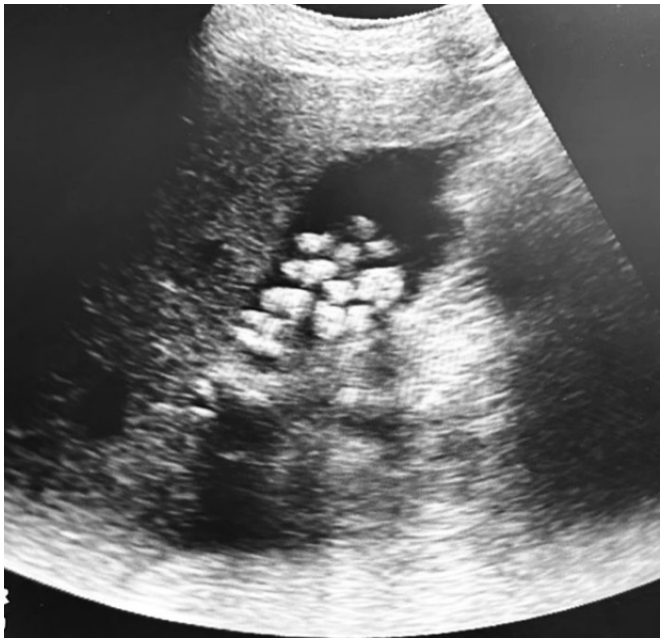

Figure 2 : POCUS Ultrasound of gall bladder showing multiple calculi and gall bladder thickening.

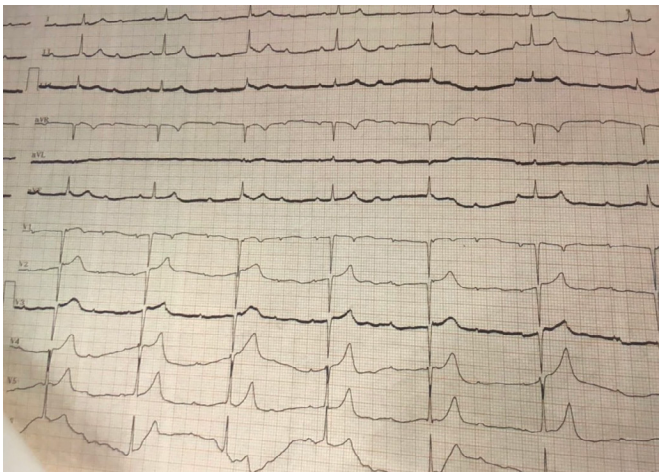

Figure 3 : 12 lead ECG of patient revealing second-degree atrioventricular block Mobitz type II

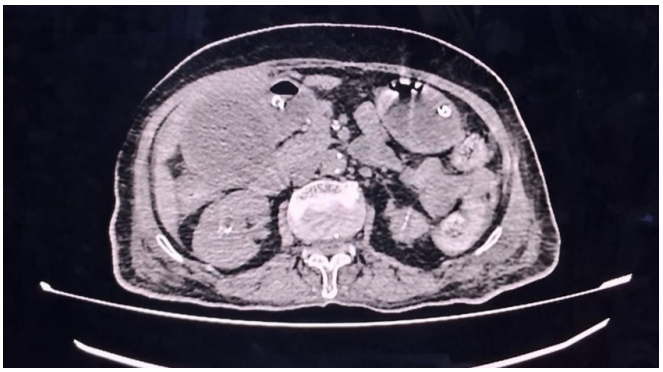

Figure 4 : Computed Tomography transverse section showing acute cholecystitis.

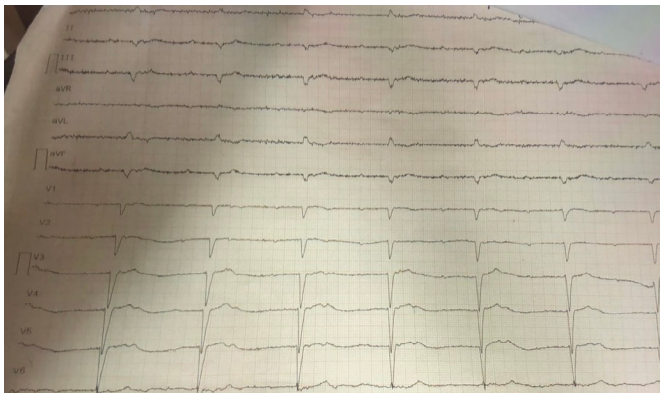

Figure 5: 12-lead ECG showing complete heart block

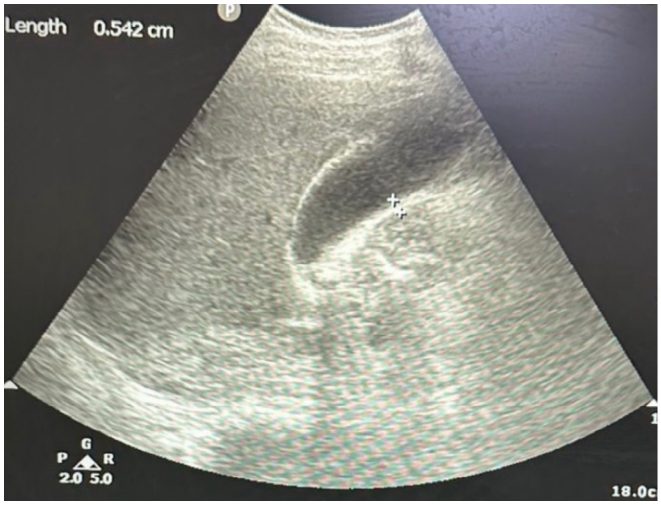

Figure 6: Ultrasound showing calculus in neck of gall bladder

sequence of presentation, investigation, treatment, and follow-up is presented in Table 2

Discussion

Cardio-biliary reflex (CBR), also referred to as Cope's sign, was first described by Sir Zachary Cope and later formally reported by O'Reilly and Krauthamer in 1971.[1] It classically describes reflex bradycardia occurring in the setting of acute cholecystitis. Clinically, the reflex may manifest with bradycardia, vasodilation, hypotension, or even syncope.

The afferent limb of the reflex originates from the gallbladder and is triggered by mechanical or inflammatory stimulation, resulting in vagally mediated bradyarrhythmias, including varying degrees of atrioventricular (AV) block, which may occasionally progress to high-grade or complete heart block.[2] These afferent impulses travel via the vagus nerve to the nucleus tractus solitarius in the medulla oblongata, with efferent transmission occurring through the cardiac branches of the vagus nerve, ultimately increasing parasympathetic output to the heart. In addition, the gallbladder and heart share autonomic innervation from spinal segments T4–T6, with intermediate neuronal connections facilitating this cardio-biliary crosstalk.

CBR has been most commonly described in acute calculous cholecystitis and has largely been documented through isolated case reports. However, the phenomenon is not restricted to calculous disease alone. Similar reflex cardiac manifestations have also been reported in acute acalculous cholecystitis, biliary colic without overt inflammation, and rare entities such as gallbladder torsion.

Furthermore, intraoperative gallbladder manipulation during laparoscopic cholecystectomy has also been shown to precipitate the reflex, suggesting that neural irritation itself, rather than inflammation alone, may act as the primary trigger for activation of the reflex arc.

The cardiac manifestations associated with CBR are diverse. Sinus bradycardia remains the most frequently reported presentation; however, more severe rhythm disturbances have also been documented, including first-degree AV block, second-degree AV block, complete heart block, sinus pauses, and sinus arrest. In certain patients, associated electrocardiographic changes may mimic acute coronary syndrome (ACS), including ST-segment deviations and T-wave inversions, particularly involving the inferior leads.[3]

In patients presenting with symptomatic or dynamically evolving arrhythmia, careful evaluation of cardiac biomarkers remains essential. In cases where gallbladder pathology presents with Cope's sign, cardiac enzymes are typically within normal limits despite significant ECG abnormalities.[4] This distinction is clinically important, as it may help differentiate extracardiac causes of ECG changes from primary ischemic cardiac events. Similarly, a normal echocardiographic study demonstrates preserved cardiac structure and function without regional wall motion abnormalities, in conjunction with ultrasonographic evidence of biliary pathology, is important in establishing the diagnosis of cardio-biliary reflex.

Iatrogenically, the reflex has also been observed during laparoscopic cholecystectomy, where surgical manipulation of the gallbladder itself can stimulate the vagus nerve and precipitate Cope's sign intraoperatively.[5] Experimental evidence further suggests that presynaptic N-methyl-D-aspartate (NMDA) receptors expressed on vagal afferent terminals surrounding the gallbladder may play a role in regulating the CBR activity.[6] In this

Table 1: Comparison of the 3 presentation of cardio biliary reflex

Parameters	*Case 1*	*Case 2*	*Case 3*
Age/Sex	48/F	57/M	42/F
Presentation	Abdominal pain, syncope	Abdominal pain, syncope	Abdominal pain, syncope
Initial HR (bpm)	30-40	45	30
BP (mmHg)	60/40	90/60	90/50
ECG	Complete heart block	Mobitz II AV block	Complete heart block
Cardiac work-up	Troponin, electrolytes, echocardiography normal	Troponin, electrolytes, echocardiography normal	Troponin, electrolytes, echocardiography normal
POCUS/CT findings	Acute calculous cholecystitis	Acute acalculous cholecystitis	Acute calculous cholecystitis
Initial management	Atropine, adrenaline, analgesia (Ketorolac)	Atropine, analgesia (Diclofenac)	Atropine, planned temporary pacing, analgesia (Ketamine)
Clinical response	Resolution of AV block and hemodynamic improvement	Resolution of AV block	Resolution of AV block and hemodynamic improvement
Definitive management	Elective cholecystectomy	Conservative management	Emergency laparoscopic cholecystectomy

Table 2: Showing the timeline of presentation of the 3 cases

Event	*Case 1*	*Case 2*	*Case 3*
ED presentation	Yes	Yes	Yes
Initial ECG	Complete heart block	Mobitz II AV block	Complete heart block
Cardiac work-up	Normal	Normal	Normal
POCUS	Calculous cholecystitis	Acalculous cholecystitis	Calculous cholecystitis
Analgesia	Ketorolac	Diclofenac	Ketamine
ECG improvement	Yes	Yes	Yes
CT confirmation	Yes	Yes	Yes
Definitive management	Elective cholecystectomy	Conservative	Emergency laparoscopic cholecystectomy
Follow up ECG	AV Block completely resolved	AV Block completely resolved	AV Block completely resolved
Any Recurrence of Conduction defects	*No Recurrence*	*No recurrence*	*No recurrence*

context, a randomized controlled trial conducted by Zhang et al. in 2025 demonstrated that administration of a single dose of esketamine significantly reduced the incidence of cardio-biliary reflex during laparoscopic cholecystectomy.[5] The authors proposed that esketamine may attenuate vagally mediated responses by deepening anesthesia and improving hemodynamic stability during gallbladder manipulation, although the exact mechanism remains to be elucidated through further experimental and clinical studies.

Cardio-biliary reflex is primarily a diagnosis of exclusion, alternative causes of atrioventricular block were carefully considered in our patients. Acute coronary syndrome was considered unlikely because serial cardiac biomarkers were within normal limits and transthoracic echocardiography demonstrated preserved ventricular function without regional wall motion abnormalities. Electrolyte disturbances were excluded by normal serum electrolyte profiles. None of the patients had a history of receiving atrioventricular nodal blocking agents, making drug-induced conduction abnormalities unlikely. Degenerative conduction disease was considered less probable given the relatively young age of the patients, the acute onset of symptoms, and the complete resolution of conduction abnormalities following treatment of the underlying biliary pathology. There were no clinical features suggestive of myocarditis or hypothyroidism, and Lyme disease was considered

unlikely given its low prevalence in our geographical region and the absence of compatible clinical features. The treatment of acute cholecystitis leading to resolution of the bradyarrhythmias strongly supports cardio-biliary reflex as the most likely diagnosis.

Iftikhar et al. in 2022 described a similar case of cardio-biliary reflex in a patient with acute calculous cholecystitis.[7] The presenting symptoms in their report were comparable to those observed in our Cases 1 and 3. However, their patient demonstrated sinus bradycardia, whereas both of our patients exhibited complete heart block on ECG, representing a considerably rarer manifestation of the reflex. Similarly, Lau YM et al. reported a case of acute acalculous cholecystitis associated with cardio-biliary reflex, which bears resemblance to our Case 2.[8] Nevertheless, while their patient developed sinus arrest with bradycardia, our patient demonstrated second-degree AV block (Mobitz type II), again highlighting the relatively uncommon and varied spectrum of conduction abnormalities associated with this reflex phenomenon.

Conclusion

Cardio-biliary reflex is an uncommon but important reversible cause of bradyarrhythmias associated with gallbladder pathology. Although sinus bradycardia is the most frequently reported manifestation, our series demonstrates that severe conduction disturbances such as complete heart block and second-degree atrioventricular block may also occur. In patients presenting with unexplained bradyarrhythmias accompanied by abdominal pain, syncope, or hypotension, clinicians should maintain a high index of suspicion for underlying biliary disease, particularly when cardiac biomarkers and echocardiography are unremarkable.

Early bedside ultrasonography and recognition of the extracardiac origin of the arrhythmia may help avoid unnecessary invasive cardiac interventions and facilitate timely surgical or conservative management of the biliary pathology. Our case series further expands the limited literature on severe conduction abnormalities associated with cardio-biliary reflex and underscores the need for greater awareness of this rare clinical entity among emergency physicians, cardiologists, anesthesiologists, and surgeons.

Limitations

This study has several limitations. First, it is a retrospective case series involving only three patients from a single tertiary care centre, limiting the generalizability of the findings. Second, although the temporal resolution of the conduction abnormalities following treatment of the underlying biliary pathology strongly supports the diagnosis of cardio-biliary reflex, a definite causal relationship cannot be established. Finally, long-term follow-up was limited, precluding assessment of recurrence or delayed cardiac events. Despite these limitations, the rarity of high-grade atrioventricular block associated with cardio-biliary reflex makes this series a valuable contribution to the existing literature.

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