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Short paper

# Epidemiology, risk factors and outcomes associated with in-hospital reflex-mediated cardiac arrest

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## Abstract

**Aim of the study**: Overactivation of the parasympathetic nervous system can lead to reflex syncope (RS) and, in extreme cases, trigger an unusual and underrecognized form of cardiac arrest. We characterized the epidemiology and prognosis of reflex-mediated cardiac arrest (RMCA) and hypothesized it is associated with intervenable patient factors.

**Methods**: This retrospective case-control study examined RMCAs at two academic hospitals from 1/2016 to 6/2022 using a resuscitation quality improvement database. RMCA cases were identified as cardiac arrests preceded by vagal trigger(s). Cases of RS, defined as syncope with bradycardia and hypotension preceded by vagal trigger(s), between 1/2021 and 12/2021 were used as controls. For the secondary analysis, RMCA outcomes were compared to in-hospital cardiac arrest (IHCA) of other causes.

**Results**: We identified 46 RMCA and 67 RS cases. Compared to RS patients, RMCA patients were more likely to have spinal cord injury (13.0% vs 1.5%, $p = 0.02$). Airway clearance i.e., coughing and suctioning triggered a higher proportion of RMCA events than RS events (23.9% vs 3.0%, $p < 0.01$). Compared to 1,021 IHCAs of other causes, RMCAs had 100% return of spontaneous circulation, were more likely to survive to discharge (84.8% vs 36.2%, $p < 0.001$) and have favorable neurological outcomes (cerebral performance category 1 or 2, 58.7% vs 26.9%, $p < 0.001$).

**Conclusions**: RMCA has a favorable prognosis compared to other IHCAs and is potentially preventable. Spinal cord injury and airway clearance were patient factors significantly associated with RMCA.

**Keywords**: Resuscitation, Reflex-mediated, Vagal-mediated, Cardiac arrest

## Introduction

The mechanisms underlying in-hospital cardiac arrest (IHCA) range from respiratory failure to progressive sepsis and sudden ventricular fibrillation.[1,2] IHCA outcomes vary but emergency team recognition of the arrest cause is associated with improved survival.[3,4] An unusual and possibly underrecognized etiology of IHCA is vagal- or reflex-mediated cardiac arrest (RMCA).[5–10] Although the parasympathetic nervous system is an important component of hemodynamic stability, excessive vagal tone can lead to reflex syncope (RS) and, in extreme cases, trigger cardiac arrest (CA).[5–10] Although RS is well characterized, the more extreme form of RMCA is not.[11]

In this study, we sought to characterize the epidemiology and prognosis of RMCA. We hypothesized that identifiable and intervenable patient factors are associated with RMCA.

## Methods

This was a retrospective case-control study examining in-hospital RMCA at two large academic hospitals with a combined capacity of 799 beds in San Diego, CA, USA from January 2016 to June 2022 using an established resuscitation quality improvement (QI) database (UCSD-IRB #801738).

Out-of-hospital CAs and patients <18-years-old were excluded. Cardiac arrest was defined as absence of palpable pulse, perfor-

*Abbreviations*: IHCA, in-hospital cardiac arrest, RMCA, reflex-mediated cardiac arrest, RS, reflex syncope, CA, cardiac arrest

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mance of chest compressions, and/or defibrillation attempt. CAs were categorized by etiology using *a priori* criteria.[1] The four primary categories include circulation, ventilation, dysrhythmia and neurological. Vagal- or reflex-mediated is one of the subcategories within dysrhythmia. RMCA cases were identified as CAs presenting as bradycardic pulseless electrical activity or asystole preceded by vagal trigger(s) e.g., pain, medical procedure, airway clearance, nausea or vomiting, defecation, micturition and/or positioning.[12,13] Airway clearance includes coughing and suctioning. Positioning includes prolonged standing or sitting and repositioning.[14] RMCA cases were compared to RS controls to identify factors that may predispose a patient who experienced a reflex response to arrest as opposed to syncopize. Cases of RS, defined as syncope with concurrent bradycardia and hypotension preceded by vagal trigger(s), were identified by reviewing a rapid response QI database between January and December 2021.[15] RMCA cases and RS controls were confirmed based on thorough chart review by two reviewers who were not blinded to the study outcomes. The agreement between reviewers i.e., Kappa was 0.96. Demographic, comorbidities, arrest setting, and outcome data along with suspected triggers were abstracted from the database and the electronic health record (EHR). Charlson Comorbidity Index (CCI) scores were calculated for each case.[16]

For the secondary analysis, RMCA patients were compared to patients who suffered IHCA for causes other than RMCA between January 2016 and June 2022. Outcomes included return of spontaneous circulation (ROSC), survival to discharge and favorable neurological outcome defined by cerebral performance category (CPC) score 1 or 2.[17]

Statistical analyses were performed using R-4.1.2. Patient characteristics between RMCA and RS cases were compared using *t*-test, Mann-Whitney *U*, $\chi^2$ and Fisher's exact tests where applicable. RMCA patient outcomes were compared with RS cases and IHCAs of other causes using $\chi^2$ test.

## Results

We identified 46 RMCA out of 1,067 IHCAs and 67 RS cases out of 3,501 rapid responses. No patient had both RMCA and RS events. Patient characteristics are shown in Table 1. The two groups were similar in age (58 ± 16 vs 63 ± 19 years, $p = 0.16$), sex (44.8% vs 52.2% male, $p = 0.45$), BMI (25.8 ± 6.6 vs 27.1 ± 7.0 kg/m$^2$, $p = 0.34$) and CCI (4.1 ± 2.6 vs 4.3 ± 2.9, $p = 0.81$). Compared to RS patients, RMCA patients were more likely to have pre-existing spinal cord injury (13.0% vs 1.5%, $p = 0.02$). While defecation and positioning i.e., prolonged standing or sitting and repositioning were similarly frequent triggers in both RMCA and RS events, airway clearance i.e., coughing and suctioning triggered a higher proportion of RMCA events than RS events (23.9% vs 3.0%, $p < 0.01$). The proportion of vagal triggers observed among RMCA and RS events are shown in Fig. 1.

In the secondary analysis, we reviewed 1,021 IHCAs of other causes other than RMCA. There were 6.0 other IHCAs per 1,000 patient-discharges compared to 0.2 RMCAs per 1,000 patient-discharges. Compared to other IHCAs, RMCA more often occurred outside the ICU (57.1% vs 39.1%, $p = 0.02$) (Table 1). RMCA patients had 100% ROSC and, compared to patients of other IHCAs, were more likely to survive to discharge (84.8% vs 36.2%, $p < 0.001$) and have favorable neurological outcomes (CPC 1 or 2, 58.7% vs 26.9%, $p < 0.001$) (Fig. 2).

## Discussion

While rare, RMCA events requiring emergency response do occur and data are sparse. In our large inpatient cohort, the incidence of RMCA was low, accounting for 0.2 per 1,000 patient-discharges, and not predicted by a prior RS event.

We found patients with spinal cord injury represented a larger proportion of RMCA cases than RS cases (13.0% vs 1.5%, $p = 0.02$). A relatively common complication of patients with spinal cord injury above the level of T6 is autonomic dysreflexia. Dysregulation of the autonomic system leads to an uncoordinated response to a noxious stimulus below the level of a spinal injury. The uninhibited sympathetic response leads to diffuse vasoconstriction and hypertension, and the compensatory parasympathetic response leads to vasodilation and bradycardia.[18] The profound changes on blood pressure and heart rate can be complicated by cardiac arrest.[19] RMCA may be a manifestation of autonomic dysreflexia secondary to spinal cord injury and providers should recognize this possible life-threatening complication.

We also found airway clearance more commonly associated with RMCA than RS events (23.9% vs 3.0%, $p < 0.01$), identifying a potentially intervenable factor. Both coughing and suctioning invoke rapid changes in intrathoracic pressure leading to neurally-mediated systemic effects including catecholamine release, hypoxia and vagal stimulation.[20–23] Similar to the pathophysiology of autonomic dysreflexia, the resulting blood pressure and heart rate changes likely contribute to the underlying mechanism of RMCA. Identifying risk factors and understanding vagal pathophysiology may promote future interventions to prevent RMCA. Future studies should investigate if atropine or airway clearance techniques could be used in high-risk patients i.e., those with spinal cord injury to mitigate excessive vagal tone and impact RMCA.

We also found patients with RMCA had a better prognosis than patients of other IHCAs. They achieved 100% ROSC, higher survival to discharge (84.8% vs 36.2%, $p < 0.001$) and better neurologic outcomes (CPC 1 or 2, 58.7% vs 26.9%, $p < 0.001$) (Fig. 2). While these patients already have excellent rate of ROSC, identifying risk factors and interventions may help target improvement in neurologic outcomes in this patient cohort. These findings may also inform providers when discussing prognoses with patients and their families regarding end-of-life care e.g., do-not-resuscitate order.

We acknowledge some limitations. First, our study was conducted at two hospitals within a single health system, thus generalizability could be questioned. Second, our retrospective study was reliant on QI databases and the EHR. Events that did not have hemodynamic monitoring may misdiagnosis cardiac arrests and/or their etiologies. Reflex-mediated events that did not result in an emergency response were not captured, making our study susceptible to potential ascertainment bias and perhaps leading to exclusion of less severe cases on non-ICU units or RS cases occurring in the ICU, where an RS event would be unlikely to prompt an emergency response. Given the low observed incidence of RMCA, a prospective study would not be easily feasible without considerable resources and multiple centers. Third, given the observational nature of our study, we are not able to make any causal inferences regarding

**Table 1 – Characteristics of patients who had a reflex-mediated cardiac arrest, reflex syncope, or all other in-hospital cardiac arrest.**

| | RMCA (*n* = 46) | RS (*n* = 67) | *p* | All Other IHCA (*n* = 1,021) |
|---|---|---|---|---|
| Demographics | | | | |
| Mean age ± SD, years | 59 ± 16 | 63 ± 19 | 0.16 | 61 + 16 |
| Sex, % male (*n*) | 52.2 (24) | 44.8 (30) | 0.45 | 65.7 (671) |
| Mean BMI ± SD, kg/m$^2$ | 25.8 ± 6.6 | 27.1 ± 7.0 | 0.34 | |
| Comorbidities, % (*n*) | | | | |
| Neurological | 23.9 (11) | 13.4 (9) | 0.21 | |
| Cerebrovascular disease | 10.9 (5) | 6.0 (4) | 0.48 | |
| Major neurocognitive disorder | 0 (0) | 6.0 (4) | 0.14 | |
| Spinal cord injury | 13.0 (6) | 1.5 (1) | 0.02 | |
| Cardiovascular | 52.2 (24) | 62.7 (42) | 0.33 | |
| Arrhythmia | 8.7 (4) | 11.9 (8) | 0.76 | |
| Coronary artery disease | 15.2 (7) | 17.9 (12) | 0.80 | |
| Heart failure, preserved ejection fraction | 8.7 (4) | 7.5 (5) | 1.00 | |
| Heart failure, reduced ejection fraction | 8.7 (4) | 4.5 (3) | 0.44 | |
| Hypertension | 52.2 (24) | 55.2 (37) | 0.85 | |
| Peripheral artery disease | 6.5 (3) | 1.5 (1) | 0.30 | |
| Pulmonary | 15.2 (7) | 19.4 (13) | 0.62 | |
| Acute pulmonary embolism | 8.7 (4) | 3.0 (2) | 0.22 | |
| Chronic obstructive pulmonary disease | 6.5 (3) | 6.0 (4) | 1.00 | |
| Obstructive sleep apnea | 2.2 (1) | 11.9 (8) | 0.08 | |
| Renal | 23.9 (11) | 10.4 (7) | 0.07 | |
| Chronic kidney disease | 8.7 (4) | 6.0 (4) | 0.71 | |
| Renal replacement therapy | 15.2 (7) | 4.5 (3) | 0.09 | |
| Cirrhosis | 6.5 (3) | 1.5 (1) | 0.30 | |
| Type 2 diabetes | 26.1 (12) | 25.4 (17) | 1.00 | |
| Active cancer | 28.3 (13) | 37.3 (25) | 0.42 | |
| Depression and/or anxiety | 10.9 (5) | 20.9 (14) | 0.20 | |
| Mean CCI ± SD | 4.1 ± 2.6 | 4.3 ± 2.9 | 0.81 | |
| Arrest Setting, % (*n*) | | | | |
| Intensive care unit | 39.1 (18) | 1.5 (1) | <0.001 | 57.1 (583) |
| Surgical service | 45.7 (21) | 46.3 (31) | 1.00 | |
| Initial rhythm | | | | |
| Ventricular fibrillation | 0 (0) | | | 10.2 (104) |
| Pulseless ventricular tachycardia | 0 (0) | | | 12.1 (124) |
| Pulseless electrical activity | 80.4 (37) | | | 73.3 (748) |
| Asystole | 19.6 (9) | | | 3.7 (38) |
| Bradycardia | 0 (0) | | | 0.4 (4) |
| Shockable | 0 (0) | | | 22.3 (228) |
| Unknown | 0 (0) | | | 0.3 (3) |

RMCA = reflex-mediated cardiac arrest. RS = reflex syncope. IHCA = in-hospital cardiac arrest. SD = standard deviation. BMI = body mass index. CCI = Charlson Comorbidity Index.

the impact of interventions. Despite these limitations, our findings provide an important substrate for future research.

## Conclusions

Although rare, RMCA has a favorable prognosis compared to other IHCAs and is a potentially preventable form of CA. We found spinal cord injury and airway clearance were significant patient factors associated with in-hospital RMCA.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Thaidan T. Pham, Atul Malhotra and Rebecca E. Sell contributed to the conception and design of the study. Thaidan T. Pham acquired data. Theoren Loo analyzed and interpreted data. Thaidan T. Pham and Atul Malhotra drafted the manuscript. Alex K. Pearce and Rebecca E. Sell critically revised the manuscript. All authors approved the final version of the manuscript submitted for publication.

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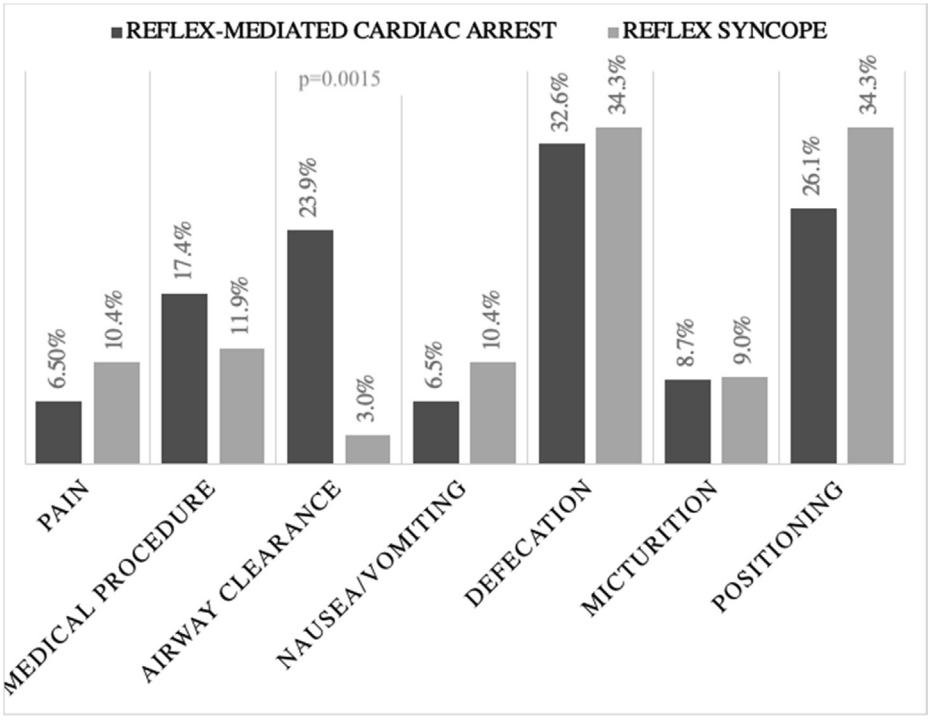


**Fig. 1 – Proportion of vagal triggers among reflex-mediated cardiac arrest (*n* = 46) and reflex syncope events (*n* = 67). Airway clearance includes coughing and suctioning. Positioning includes prolonged standing or sitting and repositioning.**

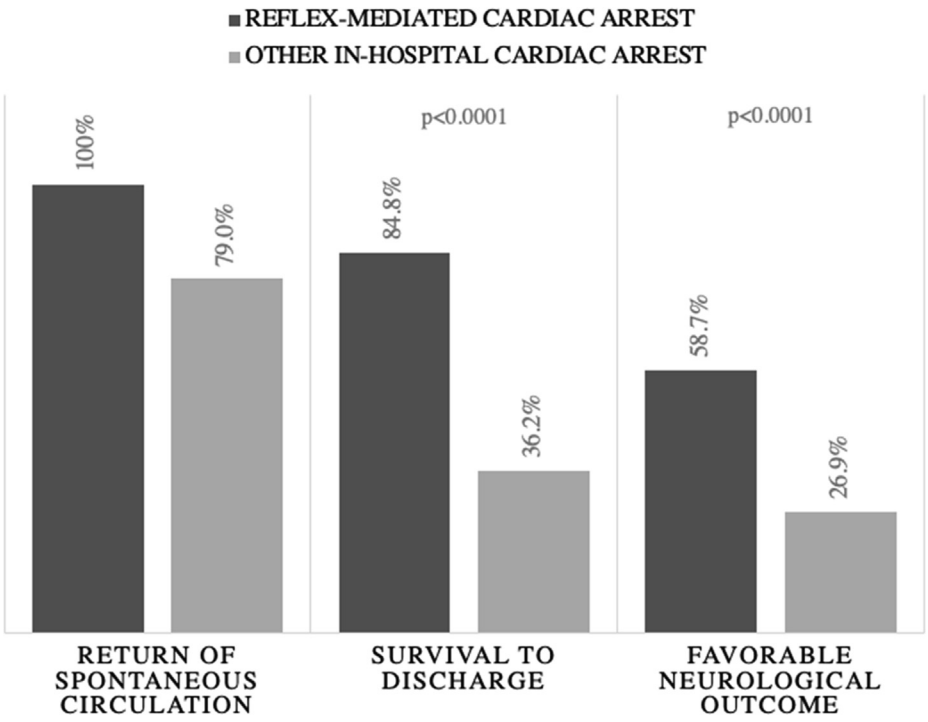


**Fig. 2 – Outcomes of patients who had a reflex-mediated cardiac arrest (*n* = 46) compared to all other in-hospital cardiac arrest (*n* = 1,021). Favorable neurological outcome as defined by cerebral performance score of 1 or 2.**

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