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# Association Between Post-Surgical Pain and Heart Rate Variability: Protocol for a Scoping Review



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**Title: Association Between Postsurgical Pain and Heart Rate Variability: Protocol for a Scoping Review**

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## Abstract

**Introduction:** Cardiac complications account for 30% of post-operative complications and is the leading cause of morbidity and mortality following non-cardiac surgery. One cardiovascular parameter—heart rate variability (HRV) has been found to be predictive of post-operative morbidity and mortality. HRV is defined as variation in time intervals between heartbeats and is affected by autonomic dysfunction. Furthermore, abnormal HRV has been shown to predict cardiovascular events in nonsurgical settings. In multiple studies, experimentally induced pain in healthy humans leads to impaired HRV suggesting a causal relationship. In a different set of studies, chronic pain has also been associated with impaired HRV, however, in the setting of clinical pain conditions it remains unclear how much HRV impairment is due to pain itself versus possible contributions from analgesic therapies.

**Objectives**: We aim to review the available evidence describing the association between postsurgical pain, as well as analgesic treatment, and impaired HRV in the early postoperative period.

**Methodology:** We will conduct a scoping review of relevant studies using detailed searches of MEDLINE and EMBASE, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Included studies will involve participants undergoing non-cardiac surgery and investigate outcomes of: 1) measures of pain intensity, or relief, or analgesic use; 2) measures of HRV; and 3) statistical assessment of association between #1 and #2. As secondary review outcomes included studies will also be examined for other cardiovascular events.

**Discussion:** We will conduct a scoping review on the relationship between post-surgical pain and HRV, and possibly, adverse cardiovascular outcomes. This work aims to synthesize available evidence to inform future research questions related to post-surgical pain and cardiac complications.

**Ethics and Dissemination**: Ethics review and approval is not required for this review. Following completion, we plan to publish this review in a biomedical journal with online access.


**Strengths and Limitations of this Study:**

- There are currently no reviews synthesizing evidence of the relationship between post-operative pain, or its treatment, and heart rate variability (HRV), which is likely relevant to the risk of post-operative cardiovascular complications.
- Our study includes a comprehensive and systematic literature search and detailed assessment of bias in accordance with the PRISMA-P statements and the pre-defined methodology based on the Cochrane Handbook for Systematic Reviews of Interventions
- Diverse studies included in this review may be heterogeneous with respect to various factors

# 1. Background

## 1.1 Post-Operative Cardiac Complications in Non-Cardiac Surgery

Annually, over 4% of the world's population (~200 million adults) undergoes non-cardiac surgery[1]. Unfortunately, following non-cardiac surgery 7-11% of patients experience post-operative complications, most of which (~30-40%) are cardiac-related [2–4]. Additionally, post-operative complications result in a mortality rate of 0.8-1.5% [5,6], and is the 3rd leading cause of death in the United States [7].

Although post-operative cardiac risk varies substantially based on surgical factors such as invasiveness, type of surgery, duration of procedure, and blood loss, it is important to consider the stress response that occurs following surgery [6,8]. For example, surgical interventions produce tissue injury that elicits neuro-endocrine responses and sympathovagal imbalance [6,8]. Other surgical stresses come from anesthesia-related physiologic perturbations, acute anemia, hypercoagulability, blood pressure changes, fluid shifts, and hypothermia [7]. These stressors can increase myocardial oxygen demand and lead to hemodynamic derangements, ultimately resulting in various cardiac complications especially in patients with pre-existing cardiovascular risk factors [6,9]. Some post-operative cardiac complications include perioperative myocardial infarction (PMI) , cardiac arrest, or congestive heart failure [7] and myocardial injury after noncardiac surgery (MINS), with MINS being the most common post-operative cardiovascular complication [4, 7,10,11].

## 1.2 Predictors of Adverse Post-Surgical Cardiovascular Events

Practice guidelines currently suggest – for patients with cardiovascular risk factors – routine post-operative assessment of cardiac troponin levels, mainly to detect PMI and MINS. The rationale for these guidelines is that elevated levels of troponin are a sensitive and specific biomarker for myocardial injury, and have also been shown to predict 30 day and one-year mortality in patients undergoing non-cardiac surgery [6,12–14]. Specifically, the diagnosis of MI requires elevated troponin levels (above 99th percentile) accompanied by characteristic chest pain, new ST segment changes or left bundle branch block, ventricular wall motion abnormalities, or intracoronary thrombus on angiography [15]. In contrast to non-operative patients, post-operative patients receiving analgesia do not commonly experience typical MI chest pain, do not always show pathognomonic ECG changes [2]. In fact, in one study by Puelacher et al, PMI was only accompanied by typical chest pain in 6% of patients, and ischemic symptoms in 18% of patients [16].

Since many patients sustaining myocardial injury in the post-operative period do not meet the diagnostic criteria for MI, a new diagnosis has been established for patients with elevated troponin levels judged due to an ischemic etiology (i.e., no evidence of a non-ischemic etiology like rapid atrial fibrillation, sepsis, pulmonary embolism) irrespective of the presence of ischemic symptoms or electrocardiographic findings, termed myocardial injury after noncardiac surgery (MINS) [4]. In this large cohort study, elevated troponin levels judged due to an ischemic etiology (meeting MINS criteria) was an independent predictor of 30-day mortality [4]. Importantly, an international, randomised controlled trial conducted in 2018 demonstrated that treatment with anticoagulant therapy (dabigatran

110 mg twice daily) can lower the risk of major cardiovascular complications for patients with MINS, suggesting that the suboptimal prognosis of MINS is modifiable [17].

More recently, a meta-analysis conducted in 2019 by Zhang, et al, suggested that various cardiac biomarkers are predictive of postoperative major adverse cardiovascular events (MACE) in patients undergoing non-cardiac surgery [18]. The definition of MACE included a variety of cardiovascular conditions of various ischemic and non-ischemic etiologies [18]. In this study, various biomarkers such as elevated levels of brain natriuretic peptide (BNP), high sensitivity C-reactive protein (hs-CRP), and high-sensitivity cardiac troponin T were shown to lead to up to 4.5-fold increase, 4-fold increase, and 6-fold increase in the risk of MACE respectively [18]. These findings suggest that various biomarkers can predict cardiovascular outcomes that are not necessarily due to ischemic etiologies (as presumed in MINS), such as all-cause mortality, heart failure, and arrhythmias. Taken together, various biomarkers (troponin, hs-CRP, BNP) exist which are valuable biomarkers of post-surgical cardiovascular events, but other predictive factors should be explored that might guide cardiac prevention efforts and provide additional prognostic value in the post-surgical setting for adverse cardiovascular events.

### 1.3 Heart Rate Variability as a Predictors of Adverse Cardiovascular Events

Healthy individuals exhibit a rhythmic variation in time intervals from one R wave to the next on electrocardiogram (ECG). Abnormal HRV is defined as an abnormal pattern of variation in the R-R time interval between heartbeats, which can be further subdivided into high frequency (HF; 0.20-0.40 Hz) and low frequency (LF; 0.04-0.15Hz) components following spectral analysis [19]. Interestingly, variability in HF components reflects changes in the parasympathetic nervous system, whereas LF variability indicates changes in both the parasympathetic and sympathetic nervous system [19]. Taken together, HRV is an important measure of the balance between the sympathetic nervous system and parasympathetic nervous system, and may indicate autonomic dysfunction [19].

Of relevance to this review, various comorbid conditions – as well as medications used during the perioperative period – have been associated with altered HRV, including general anesthetics[20,21], anticholinergic agents[22], antihypertensive agents [23], antihistamines [24], and beta-blockers [25]. Recently, HRV has been proposed as a tool to measure the physiological stress response during general anesthesia, as well as in the post-operative period [19]. Similar to troponin measurements, low heart rate variability (HRV) has been shown to independently predict post-operative morbidity and long term mortality [3, 12,26,27]. Additionally, depressed HRV before induction of anesthesia was shown to be predictive of 30-day mortality in the post-surgical setting [12,26]. These data suggest HRV is a useful tool to detect autonomic instability in the pre-operative and early post-operative setting and is useful for identifying patients who are at high risk for poor post-operative outcomes due to low autonomic physiology reserves.

### 1.4 Pain and Anesthetic Agents Alter Heart Rate Variability

Given that the autonomic nervous system is significantly affected by the experience of pain [28,29], it is likely that autonomic parameters such as HRV are abnormal in the setting of pain. In support of this notion, abnormal HRV has been reported in a variety of patients

with chronic pain conditions [30], such as breakthrough pain in cancer [31], complex regional pain syndrome [32], fibromyalgia [33], and chronic neck pain [34].

In contrast, there are fewer studies looking at the relationship between HRV and acute pain or nociception in healthy adults [35]. Nevertheless, studies have suggested that high-frequency HRV is strongly correlated to pain intensity in both adults and children [36,37]. In addition, healthy patients with self-reported symptoms of pain may have lower parasympathetic activity and altered HRV [38]. In another study by Treister et al., the authors demonstrated that decreased HRV could differentiate between painful stimuli and non-painful stimuli, although HRV alone could not discriminate between different pain intensity (low, medium, or high pain categories) [39]. However, in this same study, the linear combination of the multiple autonomic parameters including HRV, heart rate, skin conductance levels and fluctuations, and photoplethysmographic pulse wave amplitude, differentiated not only the presence of pain but could discriminate between the different pain categories [39]. Moreover, studies have suggested that greater low-frequency HRV is associated with higher thresholds for pain [40].

In addition to acute and chronic pain conditions, changes in HRV has also been observed following the administration of pharmacologic agents for acute pain management and anesthesia. For example, the administration of spinal anesthesia (isobaric bupivacaine) has been shown to significantly decrease the LF/HF ratio of HRV [41]. This may be due to a shift in the balance towards the parasympathetic system, related to the sympathetic block caused by spinal anesthesia. Interestingly, in the same study, the change in LF/HF was attenuated by co-administering intrathecal fentanyl, providing further evidence that opioid medications (e.g. fentanyl) commonly used for pain management can have direct effects on HRV [41]. Other studies further support the notion that induction of anesthesia can alter HRV, specifically that decreases in HRV occur following fentanyl-based induction of anesthesia [42]. Likewise, there is evidence that various anesthetic agents such as general anesthesia [43], propofol [21,44], isoflurane [45], and sevoflurane [20] can also alter HRV following administration. Taken together, these studies suggest that pain is associated with changes in the autonomic nervous system, and autonomic measures such as HRV can be altered in the acute and chronic pain setting, as well as during the use of opioids.

### 1.5 Rationale for Studying the Association Between Heart Rate Variability and Post-Surgical Pain Management

Given emerging evidence that pain, as well as pain medications such as opioids, have pronounced respiratory, cardiovascular, and autonomic effects [46,47], and pain has been shown to lead to autonomic dysfunction, it is critical to review the current evidence so as to guide future research efforts to better understand the relationship between altered HRV and post-surgical pain. Furthermore, treatment interventions for post-surgical pain also may affect HRV. Therefore, the evidence surrounding a possible association between post-surgical pain and HRV, which could ultimately influence the risk for post-operative cardiovascular complications, is highly relevant.

### 1.6 Objectives and Research Question

The aim of this scoping review is to synthesize and review studies describing the association between postsurgical pain and pain medication and heart rate variability in patients undergoing non-cardiac surgery.

## 2. Methods

This protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA-P) [48], and will be registered in the PROSPERO register (protocol number pending).

### 2.1 Study Selection

Types of Studies

We will include all study types with primary data available (no review articles) published in a peer-reviewed journal. To minimize the risk of publication bias (small study bias) [49], any studies with less than 10 participants will be excluded.

Patient Population

We will include studies involving adults aged 18 years and over who are undergoing non-cardiac surgery, regardless of the presence or absence of cardiovascular risk factors. Patients must have heart rate variability measured and have undergone assessment for post-surgical pain (i.e. using a validated measure of pain intensity or relief) and/or description/quantification of any postsurgical pain treatment interventions administered within the post-operative period (up to 30 days after surgery).

Inclusion Criteria

a) Studies of any design that include measures of pain intensity, pain relief, or use of analgesics within the first 30 days after non-cardiac surgery;
b) Pain intensity, or pain relief quantified using a validated measurement instrument (e.g. 0-10 numerical rating scale or 0-100mm visual analog scale for pain intensity; category scale for pain relief); and
c) Heart rate variability measurements presented as frequency bands of low-frequency power (LF; 0.04-0.015 Hz), high frequency power (HF; 0.15-0.45Hz), or ratios of LF/HF or HF/LF.

Exclusion Criteria

a) Animal studies (no human data)
b) Review papers (no primary data)
c) Cardiac surgery
d) Studies not written in the English language

### 2.2 Identification of Studies and Search Strategy

We will conduct a detailed search on MEDLINE and EMBASE. Detailed searches will be conducted from the inception of the database until the date the searches are run (see Appendix 1). The search will include terms related to heart rate variability, post-surgical pain, non-cardiac surgery, and relevant cardiovascular outcomes (e.g. myocardial infarction, pulmonary embolism). The bibliography of identified articles will be cross-referenced to check for additional studies to include in the review. The search strategy will be developed in consultation with a librarian specializing in literature searches.

### 2.3 Types of Outcome Measures

Primary Outcomes

a) Measures of pain intensity and pain relief, and use of analgesics;
b) Heart rate variability within the first 30 days after noncardiac surgery in humans; or
c) Change from preoperative baseline heart rate variability within the first 30 days after noncardiac surgery in humans;
d) Statistical assessment of the association between a) and b), or between a) and c)

Secondary Outcomes

a) Cardiovascular events (e.g. myocardial infarction, stroke, pulmonary embolism)
b) Other autonomic parameters (e.g. skin conductance level and fluctuations, photoplethysmographic pulse wave amplitude, catecholamine levels)

## 2.4 Data Collection and Extraction

Two authors will independently evaluate studies for eligibility. Screening for eligibility of studies will be performed on titles and abstracts, followed by full-text screening for citations considered potentially eligible by either screener. All citations identified in the screening process as potentially eligible will undergo full text evaluation to determine eligibility by two independent reviewers. Any disagreements between the two reviewers will be resolved through discussion and consensus, and a third reviewer will be consulted if required. Following full-text review, data from eligible studies will be recorded using standardized extraction forms using the Covidence web source (www.COVIDENCE.org). The standardized forms will capture information about types of post-surgical pain, details of post-surgical pain management, pain intensity, cardiovascular risk factors, measures of heart rate variability, and participant characteristics. As an optional secondary outcome for the review, post-operative cardiovascular outcomes will be recorded if it is included in eligible studies.

## 2.5 Risk of Bias

Risk of bias for each eligible study will be independent assessed by 2 reviewers using the criteria outlined in the Cochrane Handbook for Systematic Review of Interventions [50]. For any study that includes multiple pain-related measures or interventions (e.g. pain intensity, pain relief, use of analgesics), each measure will be assessed independently for risk of bias. Disagreements between the two reviewers will be resolved through discussion and consensus, and a third reviewer will be consulted if needed. Each category of bias will be assigned an unclear, low, or high risk of bias and summarized in a risk of bias chart.

In each study, we will assess for the following risk of biases:

a) Selection bias due to incomplete data collection
b) Incomplete outcome data due to lost to follow-up for risk for attrition bias
c) Selective reporting for detection bias
d) Number of participants for possible biases (e.g. publication bias) that are confounded by small sample size

e) Information bias (including recall and observer biases) to address how data is obtained from study groups including, which will be especially important for studies with non-randomized interventions
f) Confounding bias due to differences in comorbidities, demographic and surgical characteristics, baseline HRV differences, and other patient factors between study groups.

## 2.6 Analysis Plan

A descriptive approach will be used to report primary and secondary outcomes due to the variation which will likely exist across identified studies. For studies that are similar with respect to study design, participant population, measures used and analysis methods for the association between pain and HRV, meta-analysis will be performed in consultation with a biostatistician.

## 3. Discussion

Cardiovascular complications are a common cause of morbidity and mortality in the post-operative setting [2–4]. Among several cardiovascular factors, HRV has been shown to be an independent predictor of post-operative morbidity and long-term mortality following non-cardiac surgery [3, 12,26,27]. In general, abnormal HRV reflects autonomic imbalance and has been associated with anesthetic use [20,21,45], chronic pain conditions [31–33], and acute experimental pain in healthy patients [35,38–40]. Despite the well-documented relationship between post-surgical outcomes and HRV, and the presence of HRV in various pain conditions, there has not been a review of available evidence describing the association between post-surgical pain and heart rate variability. This scoping review aims to synthesize information surrounding the relationship between post-surgical pain and heart rate variability, which may have important implications for adverse cardiovascular outcomes following non-cardiac surgery.

In summary, this scoping review will explore the association between HRV and post-surgical pain and pain management. Depending on the identified studies and the data available, associations between HRV and post-surgical cardiovascular outcomes may also be assessed, with the overall aim to inform future research questions to better understand cardiovascular outcomes following non-cardiac surgery.

## Limitations and Challenges

The strengths of this review include the comprehensive and systematic search in accordance with the PRISMA-P statements and the pre-defined methodology based on the Cochrane Handbook for Systematic Reviews of Interventions. Potential limitations of our review include the quality of the studies due to broad inclusion criteria and possible low number of eligible studies.

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**Contributors**

VS wrote the manuscript. IG is the primary investigator, conceived the study concept, and was involved in the drafting of the protocol manuscript. JP is a co-investigator and content expert on heart rate variability. GK, JL, PJD, RA and JP are co-investigators and content experts in post-operative outcomes. All authors were involved in the editing of the manuscript and have approved the publication of the protocol.

**Competing Interests**

None declared.

## Appendix 1: Search Strategy

Database: Ovid MEDLINE(R), Ovid MEDLINE(R) Daily and Epub Ahead of Print, In-Process & Other Non-Indexed Citations <1946 to Present> Search Strategy:

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1 impaired heart rate*.mp. (143)
2 heart rate variability.mp. (18824)
3 beat to beat.mp. (5415)
4 interbeat interval*.mp. (541)
5 inter beat interval*.mp. (211)
6 r r interval*.mp. (3672)
7 hrv.mp. (11603)
8 interbeat variability.mp. (7)
9 inter beat variability.mp. (4)
10 or/1-9 (27831)
11 Pain, Postoperative/ (39337)
12 (postoperative adj3 pain*).mp. (53652)
13 (post operative adj3 pain*).mp. (3878)
14 11 or 12 or 13 (55548)
15 10 and 14 (37)
16 after surgery.mp. (155261)
17 post operative.mp. (61086)
18 postoperative.mp. (797129)
19 perioperative period/ (3223)
20 anesthesia recovery period/ (5184)
21 exp General Surgery/ (38830)
22 surg*.mp. (3150935)
23 operation*.mp. (506410)
24 or/16-23 (3523635)
25 pain*.mp. (789689)
26 exp Anti-Inflammatory Agents/ (507771)
27 exp Anesthetics/ (243875)
28 exp Anesthetics, Local/ (104541)
29 exp Lidocaine/ (24430)
30 exp Ketamine/ (12470)
31 exp Pain/ (395623)
32 Pain Management/ (34025)
33 Pain Measurement/ (85945)
34 or/25-33 (1545630)
35 10 and 24 and 34 (242)
36 15 or 35 (242)
37 exp Cardiac Surgical Procedures/ (217850)
38 36 not 37 (230)

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# Association Between Post-Surgical Pain and Heart Rate Variability: Protocol for a Scoping Review

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**Title: Association Between Post-surgical Pain and Heart Rate Variability: Protocol for a Scoping Review**

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## Abstract

**Introduction:**
Surgical interventions can elicit neuroendocrine responses and sympathovagal imbalance, ultimately affecting cardiac autonomic function. Cardiac complications account for 30% of post-operative complications and are the leading cause of morbidity and mortality following non-cardiac surgery. One cardiovascular parameter, heart rate variability (HRV), has been found to be predictive of post-operative morbidity and mortality. HRV is defined as variation in time intervals between heartbeats and is affected by cardiac autonomic balance. Furthermore, altered HRV has been shown to predict cardiovascular events in nonsurgical settings. In multiple studies, experimentally induced pain in healthy humans leads to reduced HRV suggesting a causal relationship. In a different studies, chronic pain has been associated with altered HRV, however, in the setting of clinical pain conditions it remains unclear how much HRV impairment is due to pain itself versus autonomic changes related to analgesia.

**Objectives**: We aim to review the available evidence describing the association between post-surgical pain and HRV alterations in the early post-operative period.

**Methodology:** We will conduct a scoping review of relevant studies using detailed searches of MEDLINE and EMBASE, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Included studies will involve participants undergoing non-cardiac surgery and investigate outcomes of: 1) measures of pain intensity; 2) measures of HRV; and 3) statistical assessment of association between #1 and #2. As secondary review outcomes included studies will also be examined for other cardiovascular events and for their attempts to control for analgesic treatment and pre-surgical HRV differences amongst treatment groups in the analysis.

**Discussion:** We will conduct a scoping review on the relationship between post-surgical pain and HRV, and possibly, adverse cardiovascular outcomes. This work aims to synthesize available evidence to inform future research questions related to post-surgical pain and cardiac complications.

**Ethics and Dissemination**: Ethics review and approval is not required for this review.


**Strengths and Limitations of this Study:**

- There are currently no reviews synthesizing evidence of the relationship between post-operative pain and heart rate variability (HRV), which is likely relevant to the risk of post-operative cardiovascular complications.
- Our study includes a comprehensive and systematic literature search and detailed assessment of bias in accordance with the PRISMA-P statements and the pre-defined methodology based on the Cochrane Handbook for Systematic Reviews of Interventions
- Diverse studies included in this review may be heterogeneous with respect to various factors

# 1. Background

## 1.1 Post-Operative Cardiac Complications in Non-Cardiac Surgery

Annually, over 4% of the world's population (~200 million adults) undergo non-cardiac surgery(1). Unfortunately, following non-cardiac surgery 7-11% of patients experience post-operative complications, most of which (~30-40%) are cardiac-related (2–4). Additionally, post-operative complications result in a mortality rate of 0.8-1.5% (5,6), and are the 3rd leading cause of death in the United States (7).

Although post-operative cardiac risk varies substantially based on surgical factors such as invasiveness, type of surgery, duration of procedure, and blood loss, it is important to consider the stress response that occurs following surgery (6,8). For example, surgical interventions produce tissue injury that elicits neuro-endocrine responses and sympathovagal imbalance (6,8). Other surgical stresses come from anesthesia-related physiologic perturbations, acute anemia, hypercoagulability, blood pressure changes, fluid shifts, and hypothermia (7). These stressors can increase myocardial oxygen demand and lead to hemodynamic derangements, ultimately resulting in various cardiac complications especially in patients with pre-existing cardiovascular risk factors (6,9). Some post-operative cardiac complications include perioperative myocardial infarction (PMI), cardiac arrest, congestive heart failure (7), and myocardial injury after noncardiac surgery (MINS), with MINS being the most common post-operative cardiovascular complication (4,7,10,11).

## 1.2 Predictors of Adverse Post-Surgical Cardiovascular Events

Practice guidelines currently suggest routine post-operative assessment of cardiac troponin levels for patients with cardiovascular risk factors, mainly to detect PMI and MINS. The rationale for these guidelines is that elevated troponin concentration is a sensitive and specific biomarker for myocardial injury, and have also been shown to predict 30 day and one-year mortality in patients undergoing non-cardiac surgery (6,12–14). Specifically, the diagnosis of MI requires elevated troponin levels (above 99th percentile) accompanied by characteristic chest pain, new ST segment changes or left bundle branch block, ventricular wall motion abnormalities, or intracoronary thrombus on angiography (15). In contrast to non-operative patients, post-operative patients receiving analgesia do not commonly experience chest pain typical of MI and do not always show pathognomonic electrocardiogram (ECG) changes (2). In fact, in one study by Puelacher et al, PMI was only accompanied by typical chest pain in 6% of patients, and ischemic symptoms in 18% of patients (16).

Since many patients sustaining myocardial injury in the post-operative period do not meet the diagnostic criteria for MI, a new diagnosis has been established for patients with elevated troponin, irrespective of the presence of ischemic symptoms or electrocardiographic findings, known as MINS (4). MINS is believed to be due to an ischemic etiology, and requires exclusion of non-ischemic etiology such as rapid atrial fibrillation, sepsis, and pulmonary embolism as the underlying cause of abnormalities. In one large cohort study, elevated troponin levels judged due to an ischemic etiology (meeting MINS criteria) was an independent predictor of 30-day mortality (4). Importantly,

an international, randomised controlled trial conducted in 2018 demonstrated that treatment with anticoagulant therapy (dabigatran 110 mg twice daily) can lower the risk of major cardiovascular complications for patients with MINS, suggesting that the suboptimal prognosis of MINS is modifiable (17).

More recently, a meta-analysis conducted in 2019 by Zhang, et al, suggested that various cardiac biomarkers are predictive of post-operative major adverse cardiovascular events (MACE) in patients undergoing non-cardiac surgery (18). The definition of MACE included a variety of cardiovascular conditions of various ischemic and non-ischemic etiologies (18). In this study, various biomarkers such as elevated levels of brain natriuretic peptide (BNP), high sensitivity C-reactive protein (hs-CRP), and high-sensitivity cardiac troponin T were shown to lead to up to 4.5-fold increase, 4-fold increase, and 6-fold increase in the risk of MACE respectively (18). These findings suggest that these various biomarkers can predict cardiovascular outcomes that are not necessarily due to ischemic etiologies (as presumed in MINS), such as all-cause mortality, heart failure, and arrhythmias. Taken together, there are various biomarkers of post-surgical cardiovascular events, but other predictive factors should be explored to further guide cardiac prevention efforts and provide additional prognostic value in the post-surgical setting for adverse cardiovascular events.

### 1.3 Heart Rate Variability as a Predictor of Adverse Cardiovascular Events

Healthy individuals exhibit a rhythmic variation in time intervals from one R wave to the next on ECG. HRV is defined as the pattern of variation in the R-R time interval between heartbeats. HRV can be subdivided into time-domain indices and frequency-domain values, both of which are linear phenomena (19). The time domain indices quantify the amount of HRV observed during monitoring periods (19). In contrast, frequency-domain values represent the absolute or relative amount of signal energy within component bands, and can be further subdivided into high frequency (HF; 0.20-0.40 Hz) and low frequency (LF; 0.04-0.15 Hz) components following spectral analysis (20). Interestingly, variability in HF components reflects changes in the parasympathetic nervous system (PNS). On the other hand, LF variability may indicate changes in both the PNS and sympathetic nervous system (SNS) (20), although the utility of this measurement is heavily debated and highly dependent on data collection procedures (21). Taken together, HRV is an important measure of PNS (and possibly the balance between PNS and SNS), and may serve as an indicator of autonomic balance (20).

Of relevance to this review, various comorbid conditions – as well as medications used during the perioperative period – have been associated with altered HRV, including general anesthetics(22,23), anticholinergic agents(24), antihypertensive agents (25), antihistamines (26), and beta-blockers (27). Recently, HRV has been proposed as a tool to measure the physiological stress response during general anesthesia, as well as in the post-operative period (20). Similar to troponin measurements, low HRV has been shown to independently predict post-operative morbidity and long term mortality (3,12,28,29). Additionally, depressed HRV before induction of anesthesia was shown to be predictive of 30-day mortality in the post-surgical setting (12,28). These data suggest HRV may be a useful tool to detect autonomic instability in the pre-operative and early post-operative

setting and may be useful for identifying patients who are at high risk for poor post-operative outcomes due to low autonomic physiology reserves.

## 1.4 Pain and Anesthetic Agents Alter Heart Rate Variability

Given that the autonomic nervous system is significantly affected by the experience of pain (30,31), it is likely that autonomic parameters such as HRV are altered in the setting of pain. In support of this notion, HRV changes have been reported in a variety of patients with chronic pain conditions (32), such as breakthrough pain in cancer (33), complex regional pain syndrome (34), fibromyalgia (35), and chronic neck pain (36).

In contrast, there are fewer studies looking at the relationship between HRV and acute pain or nociception in healthy adults (37). Nevertheless, studies have suggested that high-frequency HRV is strongly correlated with pain intensity in both adults and children (38,39). In addition, healthy patients with self-reported symptoms of pain may have lower parasympathetic activity and altered HRV (40). In another study by Treister et al., the authors demonstrated that decreased HRV (HF component) could differentiate between painful stimuli and non-painful stimuli, although HRV alone could not discriminate between differences in pain intensity (low, medium, or high pain categories) (41). However, in this same study, the linear combination of the multiple autonomic parameters including HRV, heart rate, skin conductance levels and fluctuations, and photoplethysmographic pulse wave amplitude, differentiated not only the presence of pain but could discriminate between the different pain categories (41). Moreover, studies have suggested that greater HRV (LF measurements) are associated with higher thresholds for pain (42), although the utility of LF HRV measurements are highly disputed and should be interpreted with caution (21).

In addition to acute and chronic pain conditions, changes in HRV have also been observed following the administration of pharmacologic agents for acute pain management and anesthesia. For example, the administration of spinal anesthesia (isobaric bupivacaine) has been shown to significantly decrease the LF/HF ratio of HRV (43). This may be due to a shift in the balance towards the parasympathetic system, related to the sympathetic block caused by spinal anesthesia. Interestingly, in the same study, the change in LF/HF was attenuated by co-administering intrathecal fentanyl, providing further evidence that opioid medications (e.g. fentanyl) commonly used for pain management can have direct effects on HRV (43). Other studies support the notion that induction of anesthesia can alter HRV, with decreases in non-linear HRV indices (approximate entropy, peak approximate entropy, and point correlation dimension) following fentanyl-based induction of anesthesia (44). Likewise, there is evidence that various anesthetic agents such as general anesthesia (45), propofol (23,46), isoflurane (47), and sevoflurane (22) can also alter HRV following administration. Taken together, these studies suggest that pain is associated with changes in the autonomic nervous system, and autonomic measures such as HRV can be altered in the acute and chronic pain setting, as well as during the use of opioids.

## 1.5 Rationale for Studying the Association Between Heart Rate Variability and Post-Surgical Pain Management

Given emerging evidence that pain, as well as pain medications such as opioids, have pronounced respiratory, cardiovascular, and autonomic effects (48,49), and pain has been shown to influence cardiac autonomic nervous system indices, it is critical to review the current evidence so as to guide future research efforts to better understand the relationship between altered HRV and post-surgical pain. Therefore, the evidence surrounding a possible association between post-surgical pain and HRV, which could ultimately influence the risk for post-operative cardiovascular complications, is highly relevant.

### 1.6 Objectives and Research Question

The aim of this scoping review is to synthesize and review studies describing the association between post-surgical pain and heart rate variability in patients undergoing non-cardiac surgery. A secondary aim is to investigate cardiovascular outcomes in relation to HRV measurements and post-surgical pain, as well as to investigate a study's attempts to control for analgesic treatment and pre-surgical differences in HRV in the data analysis.

## 2. Methods

This protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA-P) (50).

### 2.1 Study Selection

Types of Studies

We will include all study types with primary data available (no review articles) published in a peer-reviewed journal. To minimize the risk of publication bias (small study bias) (51), any studies with less than 10 participants will be excluded.

Patient Population

We will include studies involving adults aged 18 years and over who are undergoing non-cardiac surgery, regardless of the presence or absence of cardiovascular risk factors. Studies must include patients who have had heart rate variability measured and who have undergone assessment for post-surgical pain (i.e. using a validated measure of pain intensity or change in pain intensity (pain relief)) within the post-operative period (up to 30 days after surgery).

Inclusion Criteria

a) Studies of any design that include measures of pain intensity or pain relief within the first 30 days after non-cardiac surgery;
b) Pain intensity or pain relief quantified using a validated measurement instrument (e.g. 0-10 numerical rating scale or 0-100mm visual analog scale for pain intensity; category scale for pain relief); and
c) Heart rate variability measurements such as frequency bands, ratios of frequency bands, time indices of HRV, and total power. Frequency bands include low-frequency power (LF; 0.04-0.015 Hz), high frequency power (HF; 0.15-0.45Hz), or ratios of LF/HF or HF/LF. Time domain indices of HRV include standard deviation

of NN intervals (SDNN), standard deviation of the averages of NN intervals (SDANN), square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), and standard deviation of differences between adjacent NN intervals (SDSD).

Exclusion Criteria

a) Animal studies (no human data)
b) Review papers (no primary data)
c) Cardiac surgery
d) Studies not written in the English language

## 2.2 Identification of Studies and Search Strategy

We will conduct a detailed search on MEDLINE and EMBASE. Detailed searches will be conducted from the inception of the database until the date the searches are run (see Appendix 1). The search will include terms related to heart rate variability, post-surgical pain, non-cardiac surgery, and relevant cardiovascular outcomes (e.g. myocardial infarction, pulmonary embolism). The bibliography of identified articles will be cross-referenced to check for additional studies to include in the review. The search strategy will be developed in consultation with a librarian specializing in literature searches.

## 2.3 Types of Outcome Measures

Primary Outcomes

a) Measures of pain intensity and/or changes in pain intensity (pain relief),
b) Heart rate variability within the first 30 days after noncardiac surgery in humans; or
c) Change from preoperative baseline heart rate variability within the first 30 days after noncardiac surgery in humans;
d) Statistical assessment of the association between a) and b), or between a) and c)

Secondary Outcomes

a) Cardiovascular events (e.g. myocardial infarction, stroke, pulmonary embolism)
b) Other autonomic parameters (e.g. skin conductance level and fluctuations, photoplethysmographic pulse wave amplitude, catecholamine levels)
c) Use of analgesics and differences in analgesia between study groups

## 2.4 Data Collection and Extraction

Two authors will independently evaluate studies for eligibility. Screening for eligibility of studies will be performed on titles and abstracts, followed by full-text screening for citations considered potentially eligible by either screener. All citations identified in the screening process as potentially eligible will undergo full text evaluation to determine eligibility by two independent reviewers. Any disagreements between the two reviewers will be resolved through discussion and consensus, and a third reviewer will be consulted if required. Following full-text review, data from eligible studies will be recorded using standardized extraction forms using the Covidence web source (www.COVIDENCE.org). The standardized forms will capture information about types of post-surgical pain, details

of post-surgical pain management, pain intensity, cardiovascular risk factors, measures of heart rate variability, and participant characteristics. As an optional secondary outcome for the review, post-operative cardiovascular outcomes will be recorded if it is included in eligible studies.

## 2.5 Risk of Bias

Risk of bias for each eligible study will be independent assessed by 2 reviewers using the criteria outlined in the Cochrane Handbook for Systematic Review of Interventions (52). For any study that includes multiple pain-related measures or interventions (e.g. pain intensity or change in pain intensity), each measure will be assessed independently for risk of bias. Disagreements between the two reviewers will be resolved through discussion and consensus, and a third reviewer will be consulted if needed. Each category of bias will be assigned an unclear, low, or high risk of bias and summarized in a risk of bias chart.

In each study, we will assess for the following risk of biases:

a) Selection bias due to incomplete data collection
b) Incomplete outcome data due to lost to follow-up for risk for attrition bias
c) Selective reporting for detection bias
d) Number of participants for possible biases (e.g. publication bias) that are confounded by small sample size
e) Information bias (including recall and observer biases) to address how data is obtained from study groups including, which will be especially important for studies with non-randomized interventions
f) Confounding bias due to differences in comorbidities, demographic and surgical characteristics, baseline HRV differences, differences in analgesic use, and other patient factors between study groups.

## 2.6 Analysis Plan

A descriptive approach will be used to report primary and secondary outcomes due to the variation which will likely exist across identified studies. For studies that are similar with respect to study design, participant population, measures used and analysis methods for the association between pain and HRV, meta-analysis will be performed in consultation with a biostatistician.

## 2.7 Patient and Public Involvement:

No patients involved.

## 3. Discussion

Cardiovascular complications are a common cause of morbidity and mortality in the post-operative setting (2–4). Among several cardiovascular factors, HRV has been shown to be an independent predictor of post-operative morbidity and long-term mortality following non-cardiac surgery (3,12,28,29). In general, abnormal HRV reflects autonomic imbalance and has been associated with anesthetic use (22,23,47), chronic pain conditions (33–35), and acute experimental pain in healthy patients (37,40–42). Despite the well-documented relationship between post-surgical outcomes and HRV, and the presence of HRV in various pain conditions, there has not been a review of available evidence describing the association between post-surgical pain and heart rate variability. This scoping review aims to synthesize information surrounding the relationship between post-surgical pain and heart rate variability, which may have important implications for adverse cardiovascular outcomes following non-cardiac surgery.

In summary, this scoping review will explore the association between HRV and post-surgical pain and pain management. Depending on the identified studies and the data available, associations between HRV and post-surgical cardiovascular outcomes may also be assessed, with the overall aim to inform future research questions to better understand cardiovascular outcomes following non-cardiac surgery.

## Limitations and Challenges

The strengths of this review include the comprehensive and systematic search in accordance with the PRISMA-P statements and the pre-defined methodology based on the Cochrane Handbook for Systematic Reviews of Interventions. Potential limitations of our review include the quality of the studies due to broad inclusion criteria and possible low number of eligible studies.

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## Contributors

VS wrote the manuscript. IG is the primary investigator, conceived the study concept, and was involved in the drafting of the protocol manuscript. JP is a co-investigator and content expert on heart rate variability. GK, JL, PJD, MM, RA and JP are co-investigators and content experts in post-operative outcomes. All authors were involved in the editing of the manuscript and have approved the publication of the protocol.

## Competing Interests

None declared.

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## Competing Interests

None declared.

## Data Sharing

Data sharing not applicable

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## Appendix 1: Search Strategy

Database: Ovid MEDLINE(R), Ovid MEDLINE(R) Daily and Epub Ahead of Print, In-Process & Other Non-Indexed Citations <1946 to Present> Search Strategy:

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1 impaired heart rate*.mp. (143)
2 heart rate variability.mp. (18824)
3 beat to beat.mp. (5415)
4 interbeat interval*.mp. (541)
5 inter beat interval*.mp. (211)
6 r r interval*.mp. (3672)
7 hrv.mp. (11603)
8 interbeat variability.mp. (7)
9 inter beat variability.mp. (4)
10 or/1-9 (27831)
11 Pain, Postoperative/ (39337)
12 (postoperative adj3 pain*).mp. (53652)
13 (post operative adj3 pain*).mp. (3878)
14 11 or 12 or 13 (55548)
15 10 and 14 (37)
16 after surgery.mp. (155261)
17 post operative.mp. (61086)
18 postoperative.mp. (797129)
19 perioperative period/ (3223)
20 anesthesia recovery period/ (5184)
21 exp General Surgery/ (38830)
22 surg*.mp. (3150935)
23 operation*.mp. (506410)
24 or/16-23 (3523635)
25 pain*.mp. (789689)
26 exp Anti-Inflammatory Agents/ (507771)
27 exp Anesthetics/ (243875)
28 exp Anesthetics, Local/ (104541)
29 exp Lidocaine/ (24430)
30 exp Ketamine/ (12470)
31 exp Pain/ (395623)
32 Pain Management/ (34025)
33 Pain Measurement/ (85945)
34 or/25-33 (1545630)
35 10 and 24 and 34 (242)
36 15 or 35 (242)
37 exp Cardiac Surgical Procedures/ (217850)
38 36 not 37 (230)

BMJ Open

# Association Between Post-Surgical Pain and Heart Rate Variability: Protocol for a Scoping Review

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**Title: Association Between Post-surgical Pain and Heart Rate Variability: Protocol for a Scoping Review**

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## Abstract

**Introduction:**
Surgical interventions can elicit neuroendocrine responses and sympathovagal imbalance, ultimately affecting cardiac autonomic function. Cardiac complications account for 30% of post-operative complications and are the leading cause of morbidity and mortality following non-cardiac surgery. One cardiovascular parameter, heart rate variability (HRV), has been found to be predictive of post-operative morbidity and mortality. HRV is defined as variation in time intervals between heartbeats and is affected by cardiac autonomic balance. Furthermore, altered HRV has been shown to predict cardiovascular events in nonsurgical settings. In multiple studies, experimentally induced pain in healthy humans leads to reduced HRV suggesting a causal relationship. In a different studies, chronic pain has been associated with altered HRV, however, in the setting of clinical pain conditions it remains unclear how much HRV impairment is due to pain itself versus autonomic changes related to analgesia. We aim to review the available evidence describing the association between post-surgical pain and HRV alterations in the early post-operative period.

**Methods and Analysis:** We will conduct a scoping review of relevant studies using detailed searches of MEDLINE and EMBASE, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Included studies will involve participants undergoing non-cardiac surgery and investigate outcomes of: 1) measures of pain intensity; 2) measures of HRV; and 3) statistical assessment of association between #1 and #2. As secondary review outcomes included studies will also be examined for other cardiovascular events and for their attempts to control for analgesic treatment and pre-surgical HRV differences amongst treatment groups in the analysis. This work aims to synthesize available evidence to inform future research questions related to post-surgical pain and cardiac complications.

**Ethics and Dissemination**: Ethics review and approval is not required for this review. The results will be submitted for publication in peer-reviewed journals.


**Strengths and Limitations of this Study:**

- There are currently no reviews synthesizing evidence of the relationship between post-operative pain and heart rate variability (HRV), which is likely relevant to the risk of post-operative cardiovascular complications.
- Our study includes a comprehensive and systematic literature search and detailed assessment of bias in accordance with the PRISMA-P statements and the pre-defined methodology based on the Cochrane Handbook for Systematic Reviews of Interventions
- Diverse studies included in this review may be heterogeneous with respect to various factors

## 1. Background

### 1.1 Post-Operative Cardiac Complications in Non-Cardiac Surgery

Annually, over 4% of the world's population (~200 million adults) undergo non-cardiac surgery(1). Unfortunately, following non-cardiac surgery 7-11% of patients experience post-operative complications, most of which (~30-40%) are cardiac-related (2–4). Additionally, post-operative complications result in a mortality rate of 0.8-1.5% (5,6), and are the 3rd leading cause of death in the United States (7).

Although post-operative cardiac risk varies substantially based on surgical factors such as invasiveness, type of surgery, duration of procedure, and blood loss, it is important to consider the stress response that occurs following surgery (6,8). For example, surgical interventions produce tissue injury that elicits neuro-endocrine responses and sympathovagal imbalance (6,8). Other surgical stresses come from anesthesia-related physiologic perturbations, acute anemia, hypercoagulability, blood pressure changes, fluid shifts, and hypothermia (7). These stressors can increase myocardial oxygen demand and lead to hemodynamic derangements, ultimately resulting in various cardiac complications especially in patients with pre-existing cardiovascular risk factors (6,9). Some post-operative cardiac complications include perioperative myocardial infarction (PMI), cardiac arrest, congestive heart failure (7), and myocardial injury after noncardiac surgery (MINS), with MINS being the most common post-operative cardiovascular complication (4,7,10,11).

## 1.2 Predictors of Adverse Post-Surgical Cardiovascular Events

Practice guidelines currently suggest routine post-operative assessment of cardiac troponin levels for patients with cardiovascular risk factors, mainly to detect PMI and MINS. The rationale for these guidelines is that elevated troponin concentration is a sensitive and specific biomarker for myocardial injury, and have also been shown to predict 30 day and one-year mortality in patients undergoing non-cardiac surgery (6,12–14). Specifically, the diagnosis of MI requires elevated troponin levels (above 99th percentile) accompanied by characteristic chest pain, new ST segment changes or left bundle branch block, ventricular wall motion abnormalities, or intracoronary thrombus on angiography (15). In contrast to non-operative patients, post-operative patients receiving analgesia do not commonly experience chest pain typical of MI and do not always show pathognomonic electrocardiogram (ECG) changes (2). In fact, in one study by Puelacher et al, PMI was only accompanied by typical chest pain in 6% of patients, and ischemic symptoms in 18% of patients (16).

Since many patients sustaining myocardial injury in the post-operative period do not meet the diagnostic criteria for MI, a new diagnosis has been established for patients with elevated troponin, irrespective of the presence of ischemic symptoms or electrocardiographic findings, known as MINS (4). MINS is believed to be due to an ischemic etiology, and requires exclusion of non-ischemic etiology such as rapid atrial fibrillation, sepsis, and pulmonary embolism as the underlying cause of abnormalities. In one large cohort study, elevated troponin levels judged due to an ischemic etiology (meeting MINS criteria) was an independent predictor of 30-day mortality (4). Importantly, an international, randomised controlled trial conducted in 2018 demonstrated that treatment with anticoagulant therapy (dabigatran 110 mg twice daily) can lower the risk

of major cardiovascular complications for patients with MINS, suggesting that the suboptimal prognosis of MINS is modifiable (17).

More recently, a meta-analysis conducted in 2019 by Zhang, et al, suggested that various cardiac biomarkers are predictive of post-operative major adverse cardiovascular events (MACE) in patients undergoing non-cardiac surgery (18). The definition of MACE included a variety of cardiovascular conditions of various ischemic and non-ischemic etiologies (18). In this study, various biomarkers such as elevated levels of brain natriuretic peptide (BNP), high sensitivity C-reactive protein (hs-CRP), and high-sensitivity cardiac troponin T were shown to lead to up to 4.5-fold increase, 4-fold increase, and 6-fold increase in the risk of MACE respectively (18). These findings suggest that these various biomarkers can predict cardiovascular outcomes that are not necessarily due to ischemic etiologies (as presumed in MINS), such as all-cause mortality, heart failure, and arrhythmias. Taken together, there are various biomarkers of post-surgical cardiovascular events, but other predictive factors should be explored to further guide cardiac prevention efforts and provide additional prognostic value in the post-surgical setting for adverse cardiovascular events.

### 1.3 Heart Rate Variability as a Predictor of Adverse Cardiovascular Events

Healthy individuals exhibit a rhythmic variation in time intervals from one R wave to the next on ECG. HRV is defined as the pattern of variation in the R-R time interval between heartbeats. HRV can be subdivided into time-domain indices and frequency-domain values, both of which are linear phenomena (19). The time domain indices quantify the amount of HRV observed during monitoring periods (19). In contrast, frequency-domain values represent the absolute or relative amount of signal energy within component bands, and can be further subdivided into high frequency (HF; 0.20-0.40 Hz) and low frequency (LF; 0.04-0.15 Hz) components following spectral analysis (20). Interestingly, variability in HF components reflects changes in the parasympathetic nervous system (PNS). On the other hand, LF variability may indicate changes in both the PNS and sympathetic nervous system (SNS) (20), although the utility of this measurement is heavily debated and highly dependent on data collection procedures (21). Taken together, HRV is an important measure of PNS (and possibly the balance between PNS and SNS), and may serve as an indicator of autonomic balance (20).

Of relevance to this review, various comorbid conditions – as well as medications used during the perioperative period – have been associated with altered HRV, including general anesthetics(22,23), anticholinergic agents(24), antihypertensive agents (25), antihistamines (26), and beta-blockers (27). Recently, HRV has been proposed as a tool to measure the physiological stress response during general anesthesia, as well as in the post-operative period (20). Similar to troponin measurements, low HRV has been shown to independently predict post-operative morbidity and long term mortality (3,12,28,29). Additionally, depressed HRV before induction of anesthesia was shown to be predictive of 30-day mortality in the post-surgical setting (12,28). These data suggest HRV may be a useful tool to detect autonomic instability in the pre-operative and early post-operative setting and may be useful for identifying patients who are at high risk for poor post-operative outcomes due to low autonomic physiology reserves.

## 1.4 Pain and Anesthetic Agents Alter Heart Rate Variability

Given that the autonomic nervous system is significantly affected by the experience of pain (30,31), it is likely that autonomic parameters such as HRV are altered in the setting of pain. In support of this notion, HRV changes have been reported in a variety of patients with chronic pain conditions (32), such as breakthrough pain in cancer (33), complex regional pain syndrome (34), fibromyalgia (35), and chronic neck pain (36).

In contrast, there are fewer studies looking at the relationship between HRV and acute pain or nociception in healthy adults (37). Nevertheless, studies have suggested that high-frequency HRV is strongly correlated with pain intensity in both adults and children (38,39). In addition, healthy patients with self-reported symptoms of pain may have lower parasympathetic activity and altered HRV (40). In another study by Treister et al., the authors demonstrated that decreased HRV (HF component) could differentiate between painful stimuli and non-painful stimuli, although HRV alone could not discriminate between differences in pain intensity (low, medium, or high pain categories) (41). However, in this same study, the linear combination of the multiple autonomic parameters including HRV, heart rate, skin conductance levels and fluctuations, and photoplethysmographic pulse wave amplitude, differentiated not only the presence of pain but could discriminate between the different pain categories (41). Moreover, studies have suggested that greater HRV (LF measurements) are associated with higher thresholds for pain (42), although the utility of LF HRV measurements are highly disputed and should be interpreted with caution (21).

In addition to acute and chronic pain conditions, changes in HRV have also been observed following the administration of pharmacologic agents for acute pain management and anesthesia. For example, the administration of spinal anesthesia (isobaric bupivacaine) has been shown to significantly decrease the LF/HF ratio of HRV (43). This may be due to a shift in the balance towards the parasympathetic system, related to the sympathetic block caused by spinal anesthesia. Interestingly, in the same study, the change in LF/HF was attenuated by co-administering intrathecal fentanyl, providing further evidence that opioid medications (e.g. fentanyl) commonly used for pain management can have direct effects on HRV (43). Other studies support the notion that induction of anesthesia can alter HRV, with decreases in non-linear HRV indices (approximate entropy, peak approximate entropy, and point correlation dimension) following fentanyl-based induction of anesthesia (44). Likewise, there is evidence that various anesthetic agents such as general anesthesia (45), propofol (23,46), isoflurane (47), and sevoflurane (22) can also alter HRV following administration. Taken together, these studies suggest that pain is associated with changes in the autonomic nervous system, and autonomic measures such as HRV can be altered in the acute and chronic pain setting, as well as during the use of opioids.

## 1.5 Rationale for Studying the Association Between Heart Rate Variability and Post-Surgical Pain Management

Given emerging evidence that pain, as well as pain medications such as opioids, have pronounced respiratory, cardiovascular, and autonomic effects (48,49), and pain has

been shown to influence cardiac autonomic nervous system indices, it is critical to review the current evidence so as to guide future research efforts to better understand the relationship between altered HRV and post-surgical pain. Therefore, the evidence surrounding a possible association between post-surgical pain and HRV, which could ultimately influence the risk for post-operative cardiovascular complications, is highly relevant.

### 1.6 Objectives and Research Question

The aim of this scoping review is to synthesize and review studies describing the association between post-surgical pain and heart rate variability in patients undergoing non-cardiac surgery. A secondary aim is to investigate cardiovascular outcomes in relation to HRV measurements and post-surgical pain, as well as to investigate a study's attempts to control for analgesic treatment, and pre-surgical differences in HRV in the data analysis.

## 2. Methods

This protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA-P) (50).

### 2.1 Study Selection

Types of Studies

We will include all study types with primary data available (no review articles) published in a peer-reviewed journal. To minimize the risk of publication bias (small study bias) (51), any studies with less than 10 participants will be excluded.

Patient Population

We will include studies involving adults aged 18 years and over who are undergoing non-cardiac surgery, regardless of the presence or absence of cardiovascular risk factors. Studies must include patients who have had heart rate variability measured and who have undergone assessment for post-surgical pain (i.e. using a validated measure of pain intensity or change in pain intensity (pain relief)) within the post-operative period (up to 30 days after surgery).

Inclusion Criteria

a) Studies of any design that include measures of pain intensity or pain relief within the first 30 days after non-cardiac surgery;
b) Pain intensity or pain relief quantified using a validated measurement instrument (e.g. 0-10 numerical rating scale or 0-100mm visual analog scale for pain intensity; category scale for pain relief); and
c) Heart rate variability measurements such as frequency bands, ratios of frequency bands, time indices of HRV, and total power. Frequency bands include low-frequency power (LF; 0.04-0.015 Hz), high frequency power (HF; 0.15-0.45Hz), or ratios of LF/HF or HF/LF. Time domain indices of HRV include standard deviation of NN intervals (SDNN), standard deviation of the averages of NN intervals (SDANN), square root of the mean of the sum of the squares of differences

between adjacent NN intervals (RMSSD), and standard deviation of differences between adjacent NN intervals (SDSD).

Exclusion Criteria

a) Animal studies (no human data)
b) Review papers (no primary data)
c) Cardiac surgery
d) Studies not written in the English language

## 2.2 Identification of Studies and Search Strategy

We will conduct a detailed search on MEDLINE and EMBASE. Detailed searches will be conducted from the inception of the database until the date the searches are run (see Appendix 1). The search will include terms related to heart rate variability, post-surgical pain, non-cardiac surgery, and relevant cardiovascular outcomes (e.g. myocardial infarction, pulmonary embolism). The bibliography of identified articles will be cross-referenced to check for additional studies to include in the review. The search strategy will be developed in consultation with a librarian specializing in literature searches.

## 2.3 Types of Outcome Measures

Primary Outcomes

a) Measures of pain intensity and/or changes in pain intensity (pain relief),
b) Heart rate variability within the first 30 days after noncardiac surgery in humans; or
c) Change from preoperative baseline heart rate variability within the first 30 days after noncardiac surgery in humans;
d) Statistical assessment of the association between a) and b), or between a) and c)

Secondary Outcomes

a) Cardiovascular events (e.g. myocardial infarction, stroke, pulmonary embolism)
b) Other autonomic parameters (e.g. skin conductance level and fluctuations, photoplethysmographic pulse wave amplitude, catecholamine levels)
c) Use of analgesics and differences in analgesia between study groups

## 2.4 Data Collection and Extraction

Two authors will independently evaluate studies for eligibility. Screening for eligibility of studies will be performed on titles and abstracts, followed by full-text screening for citations considered potentially eligible by either screener. All citations identified in the screening process as potentially eligible will undergo full text evaluation to determine eligibility by two independent reviewers. Any disagreements between the two reviewers will be resolved through discussion and consensus, and a third reviewer will be consulted if required. Following full-text review, data from eligible studies will be recorded using standardized extraction forms using the Covidence web source (www.COVIDENCE.org). The standardized forms will capture information about types of post-surgical pain, details of post-surgical pain management, pain intensity, cardiovascular risk factors, measures of heart rate variability, and participant characteristics. As an optional secondary outcome

for the review, post-operative cardiovascular outcomes will be recorded if it is included in eligible studies.

## 2.5 Risk of Bias

Risk of bias for each eligible study will be independent assessed by 2 reviewers using the criteria outlined in the Cochrane Handbook for Systematic Review of Interventions (52). For any study that includes multiple pain-related measures or interventions (e.g. pain intensity or change in pain intensity), each measure will be assessed independently for risk of bias. Disagreements between the two reviewers will be resolved through discussion and consensus, and a third reviewer will be consulted if needed. Each category of bias will be assigned an unclear, low, or high risk of bias and summarized in a risk of bias chart.

In each study, we will assess for the following risk of biases:

a) Selection bias due to incomplete data collection
b) Incomplete outcome data due to lost to follow-up for risk for attrition bias
c) Selective reporting for detection bias
d) Number of participants for possible biases (e.g. publication bias) that are confounded by small sample size
e) Information bias (including recall and observer biases) to address how data is obtained from study groups including, which will be especially important for studies with non-randomized interventions
f) Confounding bias due to differences in comorbidities, demographic and surgical characteristics, baseline HRV differences, differences in analgesic use, and other patient factors between study groups.

## 2.6 Analysis Plan

A descriptive approach will be used to report primary and secondary outcomes due to the variation which will likely exist across identified studies. For studies that are similar with respect to study design, participant population, measures used and analysis methods for the association between pain and HRV, meta-analysis will be performed in consultation with a biostatistician.

## 2.7 Patient and Public Involvement:

No patients involved.

## 3. Discussion

Cardiovascular complications are a common cause of morbidity and mortality in the post-operative setting (2–4). Among several cardiovascular factors, HRV has been shown to be an independent predictor of post-operative morbidity and long-term mortality following non-cardiac surgery (3,12,28,29). In general, abnormal HRV reflects autonomic imbalance and has been associated with anesthetic use (22,23,47), chronic pain conditions (33–35), and acute experimental pain in healthy patients (37,40–42). Despite the well-documented relationship between post-surgical outcomes and HRV, and the presence of HRV in various pain conditions, there has not been a review of available evidence describing the association between post-surgical pain and heart rate variability. This scoping review aims to synthesize information surrounding the relationship between post-surgical pain and heart rate variability, which may have important implications for adverse cardiovascular outcomes following non-cardiac surgery.

In summary, this scoping review will explore the association between HRV and post-surgical pain and pain management. Depending on the identified studies and the data available, associations between HRV and post-surgical cardiovascular outcomes may also be assessed, with the overall aim to inform future research questions to better understand cardiovascular outcomes following non-cardiac surgery.

## Limitations and Challenges

The strengths of this review include the comprehensive and systematic search in accordance with the PRISMA-P statements and the pre-defined methodology based on the Cochrane Handbook for Systematic Reviews of Interventions. Potential limitations of our review include the quality of the studies due to broad inclusion criteria and possible low number of eligible studies.

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## Contributors

VS wrote the manuscript. IG is the primary investigator, conceived the study concept, and was involved in the drafting of the protocol manuscript. JP is a co-investigator and content expert on heart rate variability. GK, JL, PJD, MM, RA and JP are co-investigators and content experts in post-operative outcomes. All authors were involved in the editing of the manuscript and have approved the publication of the protocol.

## Competing Interests

None declared.

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## Data Sharing

Data sharing not applicable

## Citations

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## Appendix 1: Search Strategy

Database: Ovid MEDLINE(R), Ovid MEDLINE(R) Daily and Epub Ahead of Print, In-Process & Other Non-Indexed Citations <1946 to Present> Search Strategy:

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1 impaired heart rate*.mp. (143)
2 heart rate variability.mp. (18824)
3 beat to beat.mp. (5415)
4 interbeat interval*.mp. (541)
5 inter beat interval*.mp. (211)
6 r r interval*.mp. (3672)
7 hrv.mp. (11603)
8 interbeat variability.mp. (7)
9 inter beat variability.mp. (4)
10 or/1-9 (27831)
11 Pain, Postoperative/ (39337)
12 (postoperative adj3 pain*).mp. (53652)
13 (post operative adj3 pain*).mp. (3878)
14 11 or 12 or 13 (55548)
15 10 and 14 (37)
16 after surgery.mp. (155261)
17 post operative.mp. (61086)
18 postoperative.mp. (797129)
19 perioperative period/ (3223)
20 anesthesia recovery period/ (5184)
21 exp General Surgery/ (38830)
22 surg*.mp. (3150935)
23 operation*.mp. (506410)
24 or/16-23 (3523635)
25 pain*.mp. (789689)
26 exp Anti-Inflammatory Agents/ (507771)
27 exp Anesthetics/ (243875)
28 exp Anesthetics, Local/ (104541)
29 exp Lidocaine/ (24430)
30 exp Ketamine/ (12470)
31 exp Pain/ (395623)
32 Pain Management/ (34025)
33 Pain Measurement/ (85945)
34 or/25-33 (1545630)
35 10 and 24 and 34 (242)
36 15 or 35 (242)
37 exp Cardiac Surgical Procedures/ (217850)
38 36 not 37 (230)