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Scoping review of the association between postsurgical pain and heart rate variability parameters

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Abstract

Surgical interventions can elicit neuroendocrine and sympathovagal responses, leading to cardiac autonomic imbalance. Cardiac complications account for approximately 30% of postoperative complications. Altered heart rate variability (HRV) was initially described in the 1970s as a predictor of acute coronary syndromes and has more recently been shown to be an independent predictor of postoperative morbidity and mortality after noncardiac surgery. In general, HRV reflects autonomic balance, and altered HRV measures have been associated with anesthetic use, chronic pain conditions, and experimental pain. Despite the well-documented relationship between altered HRV and postsurgical outcomes and various pain conditions, there has not been a review of available evidence describing the association between postsurgical pain and HRV. We examined the relationship between postsurgical pain and HRV. MEDLINE and EMBASE databases were searched until December 2020 and included all studies with primary data. Two reviewers independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Review of Interventions. A total of 8 studies and 1002 participants were included. Studies examined the association of postsurgical pain and HRV or analgesia nociception index derived from HRV. There was a statistically significant association between HRV measures and postsurgical pain in 6 of 8 studies. Heterogeneity of studies precluded meta-analyses. No studies reported cardiovascular outcomes. There is a potential association between postsurgical pain and HRV or analgesia nociception index, although results are likely impacted by confounding variables. Future studies are required to better delineate the relationship between postsurgical pain and HRV and impacts on cardiovascular outcomes.

Keywords: Heart rate variability, Postsurgical pain, Analgesia nociception index

1. Background

Surgery produces tissue injury that can elicit sympathovagal imbalance, ultimately affecting cardiac autonomic function.[15,34] Unfortunately, after noncardiac surgery, 7% to 11% of patients experience postoperative complications, most of which are cardiac related.[11,36,54] There are various predictors of adverse postsurgical cardiovascular events such as troponin,[17,21,34,43,74] brain natriuretic peptide,[74] and C-reactive protein.[74] Heart rate variability (HRV), defined as variation in the R-R time interval between heartbeats,[18] was initially described in the 1970s as a predictor of acute coronary syndromes in the setting of altered HRV.[68] This led to many studies which demonstrated that altered HRV is an independent predictor of postoperative morbidity and mortality.[19,22,36,37,52] Furthermore, altered HRV was shown to increase the risk of postoperative complications such as cardiac

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ischemia,[37] delirium,[20] infections,[19] prolonged hospital stay,[52] and hypotension.[52]

Heart rate variability can be derived from continuous ECG recordings to detect R waves,[2] and processed by spectral analysis to derive time-domain indices and frequency-domain indices, representing the amount of HRV observed during monitoring periods and the relative amount of signal energy, respectively.[2,18] The frequency components are commonly subdivided into high frequency (0.20–0.40 Hz) and low frequency (0.04–0.15 Hz) components.[2,18] The analgesia nociception index (ANI) is derived from the high frequency component of HRV, incorporating the respiratory rate (RR) as a confounder.[7,16,26,30,49,58] Generally, HRV is suggested to be an indicator of autonomic balance,[2] where high-frequency components reflects parasympathetic nervous system changes and the low-frequency component may indicate changes in both the parasympathetic and sympathetic nervous system, although low-frequency measurements are heavily debated.[2] Similarly, higher ANI scores suggest parasympathetic predominance.[26,30]

Altered HRV has also been associated with use of general anesthetics,[25,47] spinal anesthetics,[23] anticholinergics,[51] antihypertensives,[50] antihistamines,[48] opioids,[23] and beta-blockers.[14] Furthermore, HRV abnormalities are implicated in pain conditions, including breakthrough pain in cancer,[44] complex regional pain syndrome,[60] fibromyalgia,[46] neck pain,[31] and experimentally induced pain.[10,24,33,62] 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 pain. In this article, we review available evidence describing the association between postsurgical pain and HRV alterations in the early postoperative period, which may ultimately affect the risk of cardiovascular events after noncardiac surgery.

2. Methods

The review protocol has been previously published[57] and was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.[45]

2.1. Types of studies

All study types meeting the eligibility criteria with primary data available were included in this scoping review. Any studies with less than 10 participants were excluded to minimize small study bias.[59]

2.2. Patient population

Studies of adults (>18 years of age) undergoing noncardiac surgery were included, irrespective of the presence or absence of cardiovascular risk factors.

2.3. Inclusion criteria

(1) Studies of any design that include measures of pain intensity or pain relief within the first 30 days after noncardiac surgery;
(2) Pain intensity or pain relief quantified using a validated measurement instrument (eg, 0–10 Numerical Rating Scale or 0–100 mm Visual Analog Scale (VAS) for pain intensity; category scale for pain relief); and
(3) 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 (0.04–0.015 Hz), high-frequency power (0.15–0.45 Hz), very low-frequency power (0.0033–0.04 Hz), or ratios of low to high frequencies or high or low frequencies. Time-domain indices of HRV include standard deviation of time interval between R peaks (or NN interval) of the NN complex (SDNN), standard deviation of the averages of NN intervals, 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). Nonlinear measures include ultrashort entropy (UsEn). Heart rate variability measurements also include ANI derived from the high-frequency component and the RR

2.4. Exclusion criteria

(1) Animal studies (no human data)
(2) Review articles (no primary data)
(3) Cardiac surgery
(4) Studies not written in the English language

2.5. Primary outcomes

(1) Measures of pain intensity or changes in pain intensity (pain relief)
(2) Heart rate variability within the first 30 days after noncardiac surgery in humans
(3) Change from preoperative baseline HRV within the first 30 days after noncardiac surgery in humans
(4) Statistical assessment of the association between (1) and (2) or between (1) and (3)

2.6. Secondary outcomes

(1) Cardiovascular events (eg, myocardial infarction, stroke, and pulmonary embolism)
(2) Other autonomic parameters (eg, skin conductance level and fluctuations, photoplethysmographic pulse wave amplitude, and catecholamine levels)
(3) Use of analgesics and differences in analgesia between study groups

2.7. Search methods

We conducted a detailed search on MEDLINE and EMBASE. Detailed searches were conducted from the inception of databases until December 2020. The search included terms related to HRV, postsurgical pain, noncardiac surgery, and relevant cardiovascular outcomes (eg, myocardial infarction and pulmonary embolism). The bibliography of identified articles was cross-referenced to check for additional studies to include in the review. The search strategy was developed in consultation with a librarian specialising in literature searches. The detailed search strategy is available in Appendix 1 (available as supplemental digital content at http://links.lww.com/PR9/A140).

2.8. Data collection and extraction

Two reviewers (V.S. and M.B.) independently evaluated studies for eligibility. Screening for eligibility of studies was 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 underwent full-text evaluation to determine eligibility by 2 independent reviewers. Two reviewers (V.S. and M.B.) independently extracted data using a standardized form and

checked for consensus. Any disagreements between the 2 reviewers for screening or data extraction were resolved through discussion and consensus, and a third reviewer the senior author (I.G.) was consulted if required. The standardised forms were used to capture information about types of postsurgical pain, details of postsurgical pain management, pain intensity, cardiovascular risk factors, measures of HRV, and participant characteristics. As an optional secondary outcome for the review, postoperative cardiovascular outcomes were recorded if included in eligible studies.

2.9. Risk of bias

Two reviewers (V.S. and M.B.) independently assessed the risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Review of Interventions.[28] Disagreements between reviewers were resolved with discussion and consensus and, if necessary, resolution by the senior author (I.G.). Each category of bias was assigned an unclear, low or high risk of bias and summarised in a risk-of-bias chart.

In each study, we assessed the following risks of bias: (1) selection bias due to incomplete data collection, (2) incomplete outcome data due to loss to follow-up for risk for attrition bias, (3) selective reporting for detection bias (4) number of participants for possible biases (eg, publication bias) that are confounded by the small sample size, (5) information bias (including recall and observer biases) to address how data are obtained from study groups, which will be especially important for studies with nonrandomised interventions, and (6) confounding bias because of differences in comorbidities, demographic and surgical characteristics, baseline HRV differences, differences in analgesic use, and other patient factors between study groups.

2.10. Statistical analysis plan

A descriptive approach was planned to report primary and secondary outcomes, for which significant variation existed across identified studies precluding formal meta-analysis. For studies that were similar with respect to study design, participant population, measures used, and analysis methods for the association between pain and HRV, meta-analysis was planned to be performed in consultation with a biostatistician.

3. Results

3.1. Search results

A flow diagram of the search results is shown in **Figure 1**. A detailed search of MEDLINE and EMBASE was conducted according to our published protocol[57] and yielded 230 records. No additional studies were identified in clinical trial registries or reference lists of included studies. No duplicates were identified. After initial screening of titles and abstracts, 22 relevant articles were retrieved. On full-text review, 14 studies were excluded and 8 studies fulfilled the inclusion criteria.[9,10,13,38,40,55,66]

3.2. Included studies

All the included studies used a prospective observational study design.[9,10,13,38,40,55,66] A summary of the study features is shown in **Table 1**. The studies analyzed data from a total of 1002 participants undergoing noncardiac surgery. Of the 8 studies, 4 studies included plastic surgeries,[10,38–40] 4 studies included orthopedic surgeries,[9,38–40] 3 studies included general surgeries,[13,39,40] 2 studies included spinal surgeries,[55,66] 2 studies included otolaryngological (ear, nose, and throat) surgeries,[9,10] and 1 study included endoscopies.[10] No studies included in this review evaluated postsurgical cardiovascular events.[9,10,13,38,40,55,66]

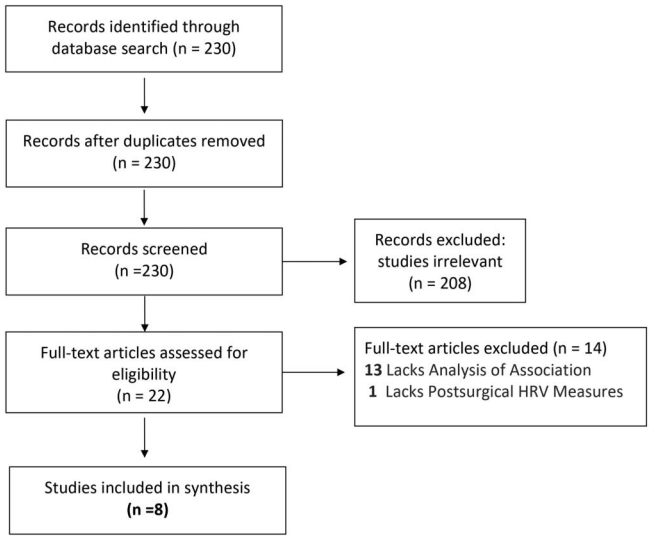

Figure 1. Study flow diagram.

3.3. Excluded studies

After full-text review, 14 studies were excluded (**Fig. 1**). Of the studies excluded, 13 studies were excluded because of the lack of statistical analysis of the association between postsurgical pain and HRV measures. In addition, 1 study was excluded because of the lack of postsurgical HRV measures; only the association between presurgical HRV measures and postsurgical pain was analyzed.

3.4. Risk of bias

Risk of bias for each individual study is shown in **Figure 2**. A summary of the risk of bias across included studies is shown in **Figure 3**. No included studies were high risk for incomplete data collection (selection bias) or recall and observer biases (information biases) because of the prospective nature of the included studies and short study duration across studies from arrival to discharge from the postanesthesia care unit (PACU).[9,10,13,38,40,55,66] Notably, there was a lack of baseline (presurgical) HRV or ANI measures in 7 of 8 studies included, which contributed to the high risk of confounding bias in most studies.

3.5. Pain measures and pain subgroups

Of the included studies, 6 of 8 studies rated pain using the Numerical Pain Rating Scale (NRS)[9,10,38,40,55] and 2 of 8 studies used the VAS.[13,66] Only 1 study used multiple pain scales such as VAS, short-form McGill pain questionnaire (SF-MPQ), and the present pain intensity score.[13] Across studies, pain was measured in the early postoperative setting on arrival at the PACU.[9,10,13,38,40,55,66]

Of the included studies, 6 studies subcategorized participants into pain severity groups. More specifically, 3 studies divided

Table 1

Summary of study features.

References (y)	Sample size	Age of participants (y)	Surgical procedure	Exclusion criteria	Pain severity subgroups*
Ledowski et al. (2011)	220	Range: 18–84	Minor elective surgery: Plastic surgery: 20 Orthopedic: 129 General surgery: 71	Age < 18 y, autonomic neuropathy, pacemaker, chronic pain medication, anticholinergic, sympathomimetic or sympatholytic drugs, history of arterial hypertension, purely regional anaesthesia, and postoperative analgesia with continuous opioid infusion	NRS 0–4 and NRS 5–10
Ledowski et al. (2012)	85 included and 84 analyzed	Mean ± SD: 31 ± 11	Minor elective orthopedic surgery: Plastic surgery: 42 Orthopedic: 42	Age < 18 y, pacemaker, anticholinergic, sympathomimetic, antihypertensive, sympatholytic drugs, hypersensitivity to drugs in study, medications with corticosteroids that affect stress hormone plasma levels, or hemodynamic parameters	NRS 0, NRS 1–3, NRS 4–5, and NRS 6–10
Chang et al. (2012)	34	Mean ± SD: 45.2 ± 18.5 Range: 18–79	Cholecystectomy: Traditional: 4 Laparoscopic: 30	History of stroke, peripheral vascular neuropathy, spinal cord nerve damage, carotid atherosclerosis, and antiarrhythmic medications	No pain severity subgroups
Sesay et al. (2015)	120	Mean ± SD: 51 ± 14	Minor spinal surgery: Lumbar laminectomy: 23 Cervical discectomy: 45 Lumbar discectomy: 52	Age < 18 y, pregnancy, diabetes, heart and neurological diseases, pacemaker or defibrillator, opioid use, ketamine, clonidine intake, and hemodynamic drug requirements in the postoperative period	NRS 0, NRS 1–3, NRS 4–5, and NRS 6–10
Ledowski et al. (2013)	120 included and 114 analyzed	Mean ± SD: 35 ± 14	Nonemergency surgery: Plastic surgery: 48 Orthopedic: 38 General surgery: 21 Other surgeries: 7	Beta blockers, ketamine, clonidine, any vasoactive substance (eg, metaraminol or ephedrine), neostigmine, atropine, and glycopyrrolate	NRS 0, NRS 1–3, NRS 4–5, and NRS 6–10
Boselli et al. (2013)	200	NRS ≤ 3: Mean ± SD: 41 ± 18 NRS > 3: Mean ± SD: 44 ± 15	ENT: 138 Endoscopy: 29 Plastic surgery: 43	Age < 18 y or >75 y, arrhythmia, preoperative use of beta blockers, administration of anticholinergic or neuromuscular block reversal in 20 min previous to measurements, preoperative pain treated with opioids, psychiatric diseases, autonomic nerve system disorders, epilepsy, and inability to understand verbal rating pain scale	NRS ≤ 3 and NRS > 3 Subgroup analysis: NRS > 3 and NRS ≥ 7
Boselli et al. (2014)	237 included and 200 analyzed	NRS ≤ 3: mean ± SD: 44 ± 18 NRS > 3: mean ± SD: 51 ± 17	ENT or lower-limb orthopedic surgery	Age < 18 y or >75 y, arrhythmia, medications that alter HRV such as beta blocker, atropine, vasopressor, antiepileptics, neuromuscular block reversal (neostigmine and anticholinergics) within 20 min of measurements, preoperative pain treated with opioids, psychiatric diseases, autonomic nervous system disorders, epilepsy, and inability to understand the verbal rating pain scale	NRS ≤ 3 and NRS > 3
Turan et al. (2017)	30	Group S mean ± SD: 56.3 ± 8.3 Group T mean ± SD: 54.3 ± 9.8	Spinal surgery	Arrhythmia, beta blockers, neuromuscular or neurological disease, diabetes mellitus, pregnancy, interrupted ANI monitoring, perioperative beta blocker infusion, and patients requiring transfer to ICU without postoperative arousal	No pain severity subgroups

* Study participants categorized into pain severity subgroups for heart rate variability analyses.

ENT, ear, nose, and throat (otorhinolaryngology); Group S, sevoflurane–remifentanil anaesthesia; Group T, total intravenous anaesthesia with propofol–remifentanil; HRV, heart rate variability; NRS, Numerical Rating Scale.

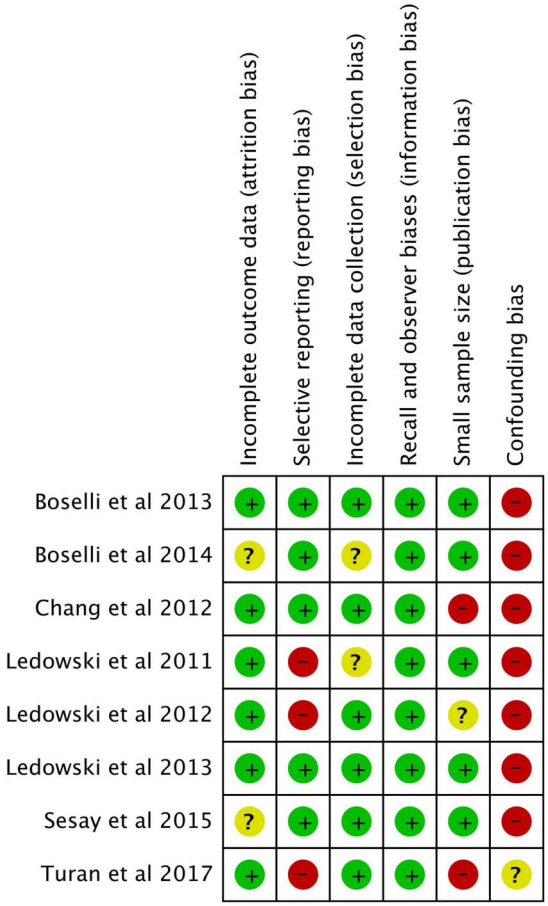

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

participants into groups based on NRS including NRS 0 (no pain), NRS 1 to 3 (mild pain), NRS 4 to 5 (moderate pain), and NRS 6 to 10 (severe pain).[38,40,55] The other studies categorized the participants into 2 pain severity groups, either NRS $\leq$ 3 and NRS $>$ 3 (2 studies)[9,10] or NRS 0 to 4 and NRS 5 to 10 (1 study).[39]

3.6. Postsurgical pain management and type of anesthetic

Each individual study's use of regional and neuraxial anesthesia, pain measurements time schedule, and pain treatment are shown in **Table 2**. For the type of anesthesia used, 3 of 8 studies used general anesthesia or total IV anaesthesia, without the use of regional or neuraxial anesthesia.[40,55,66] In addition, 2 of 8 studies allowed regional or neuraxial anesthesia techniques,[9,10] and 3 of 8 studies did not report the type of anesthesia used or was provided at the discretion of the attending anesthetist.[13,38,39] Pain treatment involved fentanyl (3/8 studies)[38–40] or morphine (3/8 studies)[9,10,55] in a majority of studies included. Only 2 of 8 studies reported the amount of analgesia used during PACU stay, noting higher use of analgesics in higher pain severity groups compared with low pain severity groups.[9,10]

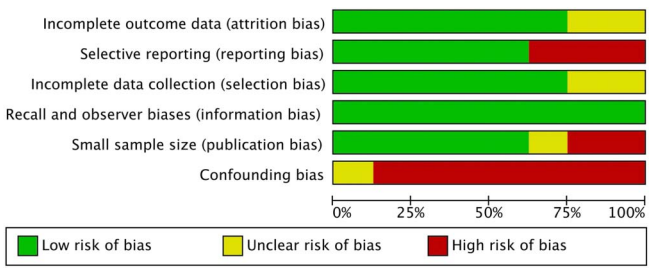

Figure 3. Risk of bias graph: review authors' judgment about each risk of bias item presented as percentages across all included studies.

3.7. Heart rate variability and analgesia nociception index measures

Each individual study's HRV measurements are shown in **Table 3**. Of the studies included, 4 of 8 measured HRV parameters[13,38,39,55] and 4 of 8 measured ANI.[9,10,40,66] All studies measuring HRV included measures of low frequency, high frequency, and the ratio of low to high frequencies.[13,38,39,55] In addition, a few HRV studies included measures of UsEn (2 studies),[38,39] total power (1 study),[39] very low frequencies,[13] and SDNN (1 study).[13] Most studies, specifically 7 of 8 studies, measured HRV or ANI measures at the time of pain measurements.[10,13,38,40,55,66] One study measured ANI values at the time of extubation and pain on arrival at PACU.[9]

3.8. Statistical analysis of postsurgical heart rate variability or analgesia nociception index measures and postsurgical pain

Each individual study's statistical analysis of postsurgical pain and HRV or ANI measures is shown in **Table 4**. Of the included studies, 5 or 8 studies used a *t* test or Mann–Whitney *U* test to analyze differences in HRV or ANI measures between pain severity groups[9,10,38,39] or between different treatment groups (sevoflurane–remifentanil anesthesia compared with total intravenous anesthesia with propofol–remifentanil).[66] One study used a linear mixed model approach to compare HRV measures among multiple pain severity groups (NRS 0, NRS 1–3, NRS 4–6, and NRS 7–10).[55] Of the aforementioned studies, 4 studies identified statistically significant differences among treatment groups for ANI or HRV measures.[9,10,39,55]

Statistical associations between postsurgical pain and HRV or ANI measures were performed in all studies and included statistical tests such as area under the receiver operating characteristic curve (AUROC, 5 of 8 studies),[9,10,38,40,55] Spearman rho coefficient (ρ, 4/8 studies),[13,39,40,55] coefficient of determination (r^2, 2/8 studies),[9,10] and χ^2 test (1 of 8 studies).[66] Of the various statistical tests used, 6 of 8 studies observed a statistically significant association between at least one HRV or ANI measure and postsurgical pain score.[9,10,13,40,55,66]

3.9. Association between other autonomic parameters and postsurgical pain

Each individual study's statistical analysis of the association between postsurgical pain and autonomic measures is shown in **Table 5**. Of the included studies, 2 of 8 studies measured other autonomic parameters in addition to HRV or ANI measures, including heart rate (HR), RR, blood pressure, mean arterial pressure, or adrenaline or epinephrine and noradrenaline or norepinephrine concentrations.[38,39] Of the 2 studies, both found a statistically significant correlation between autonomic parameters and postsurgical pain.[38,39] Specifically, the studies found a significant correlation between NRS and blood pressure on PACU arrival[39] and a significant correlation between NRS and RR at PACU discharge.[38]

Table 2

Type of anaesthetics and postsurgical pain management.

References (y)	Use regional and neuraxial anaesthesia	Pain measures	Pain measurements time schedule	Pain treatment
Ledowski et al. (2011)	Type of anaesthetic used not reported, provided at the discretion of the attending anaesthetist. Purely regional anaesthesia cases were excluded	NRS	Pain measured on arrival at PACU	20 μg of IV fentanyl if NRS ≥ 3, every 3 min as appropriate until NRS < 3
Ledowski et al. (2012)	Type of anaesthetic used not reported	NRS	Pain measured on arrival at PACU. Analgesia provided depending on NRS	20 μg of IV fentanyl if NRS ≥ 3, repeated at 3-min intervals as appropriate
Chang et al. (2012)	Type of anaesthetic used not reported	VAS SF-MPQ and PPIS	Pain measured on arrival at PACU. Analgesia provided depending on VAS or SF-MPQ	50 mg pethidine intramuscular injections every 4 h as needed
Sesay et al. (2015)	No use of regional or neuraxial anaesthesia reported. Surgery performed under general anaesthesia	NRS	Pain measured on arrival at PACU. Analgesia provided depending on NRS	2 mg morphine if NRS ≥ 3, every 3 min as appropriate until NRS < 3
Ledowski et al. (2013)	No use of regional or neuraxial anaesthesia reported. Surgery performed under sevoflurane anaesthesia	NRS	Pain measured on arrival at PACU. Analgesia provided depending on NRS	20 mg IV fentanyl if NRS 4–10 on PACU admission
Boselli et al. (2013)	Surgery performed under general anaesthesia. Regional anaesthesia techniques (peripheral nerve block or wound infiltration) used in some cases. Proportion of regional anaesthetic used not described for each study group	NRS	Pain measured within 10 min of arrival at PACU. Analgesia provided depending on NRS	1–3 mg morphine IV boluses if NRS > 3, every 5 min as appropriate until NRS ≤ 3
Boselli et al. (2014)	Surgery performed under general anaesthesia. Regional anaesthesia techniques (peripheral nerve block) used in some cases in PACU. Peripheral nerve block used for 10% of cases for NRS ≤ 3 and 36% of cases for NRS > 3 ($P < 0.01$)	NRS	Pain measured within 10 minutes of arrival at PACU. Analgesia provided depending on NRS	Morphine IV titration if NRS > 3 or peripheral nerve block until NRS ≤ 3
Turan et al. (2017)	No use of regional or neuraxial anaesthesia reported. Surgery performed under total IV anaesthesia (propofol and remifentanil) or sevoflurane–remifentanil anaesthesia	VAS	Pain measured 5, 15, and 30 min postoperatively. Analgesia provided 30 min before the end of surgery	All patients received paracetamol 1 g.100 mL^{-1} (IV infusion), diclofenac sodium 20 mg (IV), and tramadol 100 mg (IV infusion) 30 min before the end of surgery

IV, intravenous; NRS, Numerical Rating Scale; PACU, postanaesthesia care unit; PPIS, present pain intensity score; SF-MPQ, Short-form McGill Pain Questionnaire; VAS, Visual Analog Scale.

Table 3

Presurgical and postsurgical HRV measurements.

References (y)	Types of HRV measures	Baseline HRV (presurgery)	Mean HRV measurements (postsurgical)	Timing of HRV measurements	HRV and pain measured at the same time?
Ledowski et al. (2011)	LF, HF, LF/HF ratio, TP, and UsEn	Not measured	Mean TP (SEM) = 1139 (99) for NRS 0–4 and 1030 (108) for NRS 5–10 Mean LF (SEM) = 815 (68) for NRS 0–4, 751 (76) for NRS 5–10 Mean HF (SEM) = 324 (38) for NRS 0–4, 281 (41) for NRS 5–10 Mean LF/HF (SEM) = 6.7 (0.47) for NRS 0–4, and 7.7 (0.56) for NRS 5–10 Mean UsEn (SEM) = 47 (0.8) or NRS 0–4 and 46 (0.9) for NRS 5–10	At the time of pain measures on arrival at PACU	Yes
Ledowski et al. (2012)	LF, HF, LF/HF, and UsEn	Not measured	Mean LF (SEM) = 799 (343) for NRS 0, 1393 (199) for NRS 1–3, 1256 (238) for NRS 4–5, and 909 (314) for NRS 6–10 Mean HF (SEM) = 390 (14) for NRS 0, 507 (91) for NRS 1–3, 499 (103) for NRS 4–5, and 450 (125) for NRS 6–10 Mean LF/HF (SEM) = 5.8 (1.1) for NRS 0, 5.6 (0.7) for NRS 1–3, 5.6 (0.8) for NRS 4–5, and 6.3 (1.0) for NRS 6–10 Mean UsEn (SEM) = 48 (2) for NRS 0, 51 (1.3) for NRS 1–3, 51 (1.5) for NRS 4–5, and 49 (1.7) for NRS 6–10	At the time of pain measures, on arrival at PACU	Yes
Chang et al. (2012)	SDNN, HF, LF, VLF, and LF/HF	Not measured	Values described for groups based on surgical position (supine vs semifowler), diabetes status, and hypertension status. No values described for different study groups based on pain scores	At the time of pain measures	Yes
Sesay et al. (2015)	LF, HF, and LF/HF	Not measured	Data not reported	At the time of pain measures. Taken on arrival at PACU, every 30 min until PACU discharge	Yes
Ledowski et al. (2013)	ANI	Not measured	Data not reported	At the time of pain measures, on arrival at PACU	Yes
Boselli et al. (2013)	ANI	Not measured	Mean ANI values (SD) on PACU arrival: NRS ≤ 3 = 73(17) and NRS > 3 = 49(14) ANI values not described at discharge from PACU	At the time of pain measures, within 10 min of arrival at PACU	Yes
Boselli et al. (2014)	ANI	Not measured	Mean ANI values (SD) on PACU arrival: NRS ≤ 3 = 68 (18) and NRS > 3 = 42(12)	At the time of extubation, pain measured at arrival in PACU	No
Turan et al. (2017)	ANI	Baseline ANI: No differences between group S and T	Data not reported	At the time of pain measures: at baseline, induction, intubation, after incision, throughout surgery, at the end of anaesthesia, extubation, 5, 15, and 30 min postoperatively	Yes

ANI, analgesia nociception index (N.B. also incorporates measures of respiratory rate); Group S, sevoflurane–remifentanil anaesthesia; Group T, total intravenous anaesthesia with propofol–remifentanil; HF, high-frequency component ($ms^2 \cdot Hz^{-1}$) of HRV; HRV, heart rate variability; LF, low-frequency component ($ms^2 \cdot Hz^{-1}$) of HRV; NRS, Numerical Rating Scale; PACU, postanaesthesia care unit; SEM, standard error of the mean; SD, standard deviation; SDNN, standard deviations of all the NN intervals in HRV measurements; TP, total power component ($ms^2 \cdot Hz^{-1}$) of HRV; UsEn, ultrashort entropy; VLF, very low-frequency component of HRV.

Table 4

Statistical association between postsurgical pain and postsurgical HRV measures.

References (y)	Statistical analyses	Statistical analysis of relationship between pain and HRV	Significant association between HRV and pain*
Ledowski et al. (2011)	T test, ROC, and Spearman rho coefficient (ρ)	T tests: LF/HF significantly lower ($P < 0.05$) and UsEn levels significantly higher ($P < 0.05$) in NRS 0–4, compared with NRS 5–10 groups. No statistical significance between NRS groups for LF, HF, or TP ROC: <0.5 specificity and sensitivity for all HRV measurements Correlation (ρ) = not significant (values not specified)	No
Ledowski et al. (2012)	T test or Wilcoxon test, AUROC	T test or Wilcoxon test: No differences between NRS groups and severe pain (NRS 6–10) for LF, HF, LF/HF, and UsEn AUROC (95% CI): LF AUROC = 0.506 (0.410–0.602), HF AUROC = 0.520 (0.426–0.614), LF/HF AUROC = 0.463 (0.369–0.557), and UsEn AUROC = 0.498 (0.404–0.592)	No
Chang et al. (2012)	Spearman rho coefficient (ρ)	Correlation (ρ): LF measurements significantly correlate ($P < 0.05$, $\rho = -0.360$) with VAS. LF/HF ratios significantly correlate with SF-MPQ scores ($P < 0.05$, $\rho = 0.362$) and SF-MPQ(s) scores ($P < 0.05$, $\rho = 0.412$). No other significant correlations between PPIS and HRV measures or pain scores [VAS, PPIS, SF-MPQ, SF-MPQ(s), and SF-MPQ(e)] and HF, SDNN, or VLF	Yes
Sesay et al. (2015)	Linear mixed model, AUROC, and Spearman rho coefficient (ρ)	Linear mixed model: LF levels and LF/HF significantly higher ($P < 0.001$) in the NRS 4–6 group and NRS 7–10 groups compared with NRS 0 and NRS 1–3. No statistical differences in HF values among NRS groups Correlation (ρ): LF measurements significantly correlate ($P < 0.05$, $\rho = 0.29$) with NRS scores. LF/HF measurements significantly correlate ($P < 0.05$, $\rho = 0.31$) with NRS scores. No significant correlation between HF values and NRS values AUROC (95% CI): LF and LF/HF AUROCs significantly correlate with NRS ($P < 0.001$ for both measures). LF AUROC = 0.73 (0.68–0.78) and LF/HF AUROC = 0.79 (0.75–0.83). HF AUROCs did not statistically correlate with NRS. HF AUROC = 0.51 (0.46–0.55)	Yes
Ledowski et al. (2013)	Spearman rho coefficient (ρ) and AUROC	Correlation (ρ): 0.075 for ANI and NRS, $P < 0.05$ AUROC: 0.43 for ANI and NRS	Yes for correlation No for AUROC
Boselli et al. (2013)	T test, Mann-Whitney *U* test, coefficient of determination (r^2), AUROC	T test or Mann-Whitney *U* test: On arrival at PACU, NRS ≤ 3 had significantly higher ($P < 0.01$) ANI than NRS > 3. This difference was not seen at PACU discharge, after morphine titration and IV analgesia. Coefficient of determination (r^2): 0.41, $P < 0.05$ for ANI and NRS AUROC (95% CI): 0.86 (0.80–0.91) for ANI predicting NRS > 3, 0.91 (0.86–0.95) for ANI predicting NRS ≥ 7	Yes
Boselli et al. (2014)	T test, Mann–Whitney *U* test, coefficient of determination (r^2), and AUROC	T test or Mann–Whitney *U* test: On arrival at PACU, NRS ≤ 3 had significantly higher ($P < 0.01$) ANI than NRS > 3 Coefficient of determination (r^2): 0.33, $P < 0.01$ for ANI and NRS AUROC (95% CI) 0.89 (0.84–0.93) for ANI predicting NRS > 3	Yes
Turan et al. (2017)	T test, Mann–Whitney *U* test, and chi-squared test	T tests: No statistical differences between group S and group T for VAS scores or mean ANI scores at all timepoints measured Chi-squared test: Significant correlation between ANI values and VAS values at the end of anaesthesia ($P = 0.066$). Strength of association between ANI values and VAS values decreased at 5 minutes ($P = 0.109$), 15 min ($P = 0.259$), and 30 minutes ($P = 0.052$) after extubation. For this analysis, group S and T were analyzed together	Yes, at the end of anaesthesia only

* Significant association: defined as $P < 0.05$ for correlation analysis (eg, Spearman rho), coefficient of determination (r^2), χ^2 test, or AUROC value (or value >0.8 for AUROC).

ANI, analgesia nociception index (N.B. also incorporates measures of respiratory rate); AUROC, area under the receiver operating characteristic curve; Group S, sevoflurane–remifentanil anaesthesia; Group T, total intravenous anaesthesia with propofol–remifentanil; HF, high-frequency component of HRV; HRV, heart rate variability; LF, low-frequency component of HRV; NRS, Numerical Rating Scale; n.s., no statistical significance; PACU, postanaesthesia care unit; ρ, Spearman rho coefficient; r^2, coefficient of determination; ROC, receiver operating characteristic curve; SF-MPQ, Short-form McGill Pain Questionnaire; TP, total power component of HRV; UsEn, ultrashort entropy; VAS, Visual Analog Scale.

Table 5

Other autonomic parameters and statistical associations with pain scores.

References (y)	Other autonomic measures	Statistical analysis of relationship between autonomic and pain measures	Significant correlation between autonomic parameters and pain
Ledowski et al. (2011)	BP, HR, and RR	T tests: No statistical differences between NRS groups and severe pain (NRS 6–10) for BP, HR, and RR. ROC: <0.50 for sensitivity and sensitivity for BP predicting NRS levels Correlation (ρ): Statistically significant positive correlations found between NRS score and BP ($\rho = 0.21$, $P < 0.01$). No significant correlations between NRS score and HR or RR	Yes: correlation between NRS and BP
Ledowski et al. (2012)	HR, RR, MAP, adrenaline (EPI), and noradrenaline (NE)	T test (MAP): MAP levels significantly lower ($P < 0.05$) in NRS 0 and NRS 1–3 groups compared with NRS 6–10 group (severe pain). No statistically significant difference in HR or RR between NRS groups and severe pain group (NRS 6–10). From PACU admission to discharge, HR ($P < 0.05$) significant decreased. T test (EPI/NE): Noradrenaline levels statistically lower ($P < 0.05$) in NRS 0 and NRS 1–3 groups compared with the NRS 6–10 group (severe pain). No statistically significant difference in adrenaline levels between NRS groups and NRS 6–10 (severe pain). From PACU admission to discharge, EPI levels ($P < 0.05$) significant decreased. Correlation (ρ): Statistically significant correlations at the time of PACU admission found between MAP and HR ($\rho = 0.314$, $P < 0.01$), MAP and NE ($\rho = 0.391$; $P < 0.01$), and MAP and EPI ($\rho = 0.237$, $P < 0.05$). At the time of PACU discharge, only the correlation between NRS and RR was found to be significant ($\rho = 0.296$, $P < 0.05$)	Yes: correlation between NRS and RR at PACU discharge

BP, blood pressure (mm Hg); EPI, adrenaline (epinephrine) concentration; HR, heart rate (bpm); MAP, mean arterial pressure (mm Hg); NE, noradrenaline (norepinephrine) concentration; NRS, Numerical Rating Scale; PACU, postanaesthesia care unit; ROC, receiver operating characteristic curve; ρ, Spearman rho coefficient; RR, respiratory rate (min^{-1}).

4. Discussion

There is some evidence to support the association between pain and HRV in 6 of 8 studies,[9,10,38,40,55,66] despite considerable variation in the altered HRV parameters. Of the 4 studies measuring HRV, 2 studies demonstrated a significant correlation between HRV and postsurgical pain,[13,55] although these results should be interpreted cautiously as low-frequency measurements are heavily debated.[2] No studies noted a significant correlation between high-frequency parameters and postsurgical pain scores.[13,38,39,55] All studies assessing the relationship between ANI and postsurgical pain found a significant correlation,[9,10,40,66] where higher pain scores are associated with lower ANI scores.[9,10,40,66] These results may indicate that ANI measurements are more predictive of postsurgical pain than HRV measurements, likely because of considerations for RR in ANI scores.[7,16,26,30,49,58] These findings suggest that pain may impair the parasympathetic nervous system (reflected by lower ANI scores[9,10,40,66]) and lead to increased sympathetic tone (reflected by increased low frequency[55] and low/high frequency ratios[13,55]).[2,26,30] This would be unsurprising since pain activates the sympathetic stress response and may lead to an imbalance of the parasympathetic and sympathetic nervous system, which could create unfavorable cardiac conditions such as tachycardia[5] and hypertension,[39,53] ultimately increasing myocardial oxygen demand and thus increasing the risk of cardiac complications in the postoperative period.

Altered HRV is likely multifactorial, as HRV is influenced by various cardiovascular medications,[4,64] cardiac conditions,[8,27,32] neurological conditions,[1,12,35] anesthetics,[25,47] analgesia,[23] and pain.[10,24,31,33,44,46,60,62] This review provides some evidence that postsurgical pain itself may alter HRV. Therefore, improved methods to reduce pain even without directly altering cardiac autonomic balance may improve cardiovascular outcomes after surgery. In support of this notion, various modalities unlikely to directly affect cardiac autonomic balance have been shown to reduce pain and influence HRV.[3,29,41,61,67,69,71,72] These modalities include acupuncture,[3] acupoint electrical stimulation,[72] virtual reality to reduce anxiety,[71] music,[29,41,67] foot massage,[69] and reducing mental stress.[61] We hypothesize that the most effective modalities to reduce cardiovascular events in the postsurgical setting will be modalities that not only reduce postsurgical pain but also address underlying HRV derangements. This is important, as most of the aforementioned nonpharmacological modalities lower the ratio of low to high HRV frequencies,[3,29,67,69,71] and may be ineffective at addressing other derangements.

Taken together, it is likely that pain itself influences HRV parameters, although the impact on cardiovascular outcomes is not described in our review. However, various studies have suggested higher pain scores are associated with adverse cardiac outcomes, such as myocardial injury[65] and ischemia[6] in the early postoperative period. Although these studies demonstrate that postsurgical pain may influence cardiovascular outcomes, the results are likely confounded by differences in the use of analgesics, which can alter HRV. It is therefore uncertain if the altered cardiovascular risk is attributed to altered HRV because of pain itself or analgesic use.

Although these studies suggest a possible association between postsurgical pain and HRV measures, there may be poor generalizability. Notably, 7 of 8 studies used a single pain severity score,[9,10,38,40,55,66] limiting the generalizability of results to other pain scores. In support of this notion, in the study by Chang et al.[13] that used multiple pain severity scores, the association of postsurgical pain and HRV measures was highly variable depending on the type of pain severity score and HRV measures assessed. More specifically, low-frequency HRV measurements were significantly correlated with VAS and low to high frequency ratios of HRV significantly correlated with SF-MPQ and SF-MPQ(s) scores,[13] further highlighting the possibility of poor generalizability of results when one pain score is used.[9,10,38,40,55,66] Similarly, included studies excluded patients with increased cardiovascular risk such as

patients with a history of stroke,[13] diabetes mellitus,[55,66] neurological diseases,[9,10,13,39,55,66] pacemakers,[38,39,55] or taking cardiac medications,[9,10,38,40,66] further limiting the generalizability of results.

This review was performed in accordance with parameters described in the AMSTAR 2 instrument.[56] Nevertheless, our study has several limitations. First, our review retrieved a small number of studies eligible for inclusion. In addition, various confounding variables likely introduced biases in the included studies. One confounding variable present in most studies was the lack of baseline HRV measurements.[9,10,13,38,40,55] In addition, 5 of 8 studies were inconsistent in the type of anesthetic used,[9,10,13,38,39] which can further affect the validity of results, as HRV measures have been shown to be influenced by anesthetics and analgesia.[23,25,42,47] In addition, only 2 of 4 studies measuring HRV parameters recorded RR,[38,39] which influences HRV measures.[7,16,26,30,49,58] This review was also limited by the lack of reported cardiovascular outcomes in studies because of short study duration across studies.[9,10,13,38,40,55,66]

Future studies should address these shortcomings by including baseline HRV measurements, control for anesthetic uses, and account for RR, to provide stronger evidence for a possible association between postsurgical pain and HRV measures. Consideration should also be given to recording additional demographic information such as body mass index or weight, which has been suggested to influence HRV measures.[63,70,73] In addition, future studies should be sized appropriately to also look at cardiovascular outcomes, which was not evaluated in this review.[9,10,13,38,40,55,66]

In summary, this is a review of the evidence for the association between HRV and postsurgical pain. Although study heterogeneity did not allow for the combining of studies for meta-analysis, the existence of at least 6 positive studies suggest at least the potential for an association between pain and HRV/ANI. The impact of this relationship on postoperative cardiovascular outcomes is unclear. Future studies are required to better delineate the relationship between HRV and postsurgical pain, with consideration paid to confounding variables and baseline HRV measurement. Future studies should also be adequately powered to include cardiovascular outcomes.

Disclosures

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A140.

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