Scoping Review of the Association Between Postsurgical Pain and Heart Rate Variability Parameters

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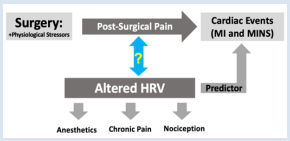
Introduction and Rationale



Surgery elicits neuroendocrine and sympathovagal responses, leading to cardiac autonomic imbalance [1,2]. Cardiac complications account for ~30% of post-operative complications [3]. Altered heart rate variability (HRV) was initially described in the 1970s as a predictor of postoperative morbidity and mortality after noncardiac surgery [4]. In general, HRV reflects autonomic balance [5], and altered HRV measures have been associated with anesthetic use [6,7], chronic pain conditions [8,9], and experimental pain [10]. 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.

Heart Rate Variability (HRV)

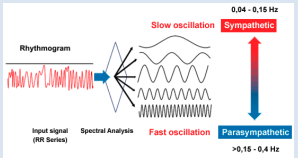


Fig 1. Components of HRV

HRV is the variation between successive heartbeats (between R-R intervals)[1]. HRV is divided into time and frequency components. Frequency domain indices can be subdivided with spectral analysis (Fig 1) into high frequency (HF) and low HRV is the variation between successive heartbeats (between R-R intervals)[1]. HRV is divided into time and frequency components. Frequency domain indices can be subdivided with spectral analysis (Fig 1) into high frequency (HF) and low frequency (LF) components [1,5]. In general, HF reflects parasympathetic activity and LF reflects the balance of parasympathetic and sympathetic activity [1,5]. In addition, the analgesia nociception index (ANI) is derived from the HF component of HRV, incorporating respiratory rate as a confounder [1,5].

Altered HRV Predicts Cardiac Events, Mortality, Chronic Pain, and Anesthetic Use

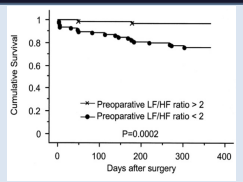


Fig 2. Alerted HRV predicts post-operative mortality [12]

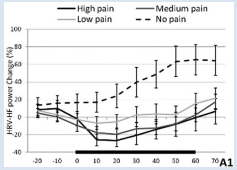


Fig 3. Relationship Between HRV And experimentally induced pain [10]

Altered HRV independently predicts post-operative morbidity and mortality (Fig 2) [11,12]. Moreover, depressed HRV before induction of anesthesia was predictive of 30-day mortality in the post-surgical setting [11,12]. Therefore, HRV may be a useful to identify patients at risk for post-operative outcomes due to poor autonomic physiology reserves. Additionally, given that the autonomic nervous system is affected by the experience of pain, it is likely that autonomic parameters like HRV are altered in the setting of pain. In fact, HRV changes has been reported in a variety of chronic pain conditions [8,9]. Also, HRV changes are correlated with self-reported symptoms of pain (Fig 3) [10]. Lastly, changes in HRV have been observed with use of anesthetics and opioids [13,14].

Objectives

Objectives: synthesize and review studies describing the association between post-surgical pain and heart rate variability in patients undergoing non-cardiac surgery.

Secondary Aims:

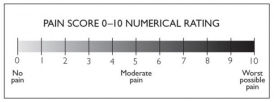
1. Investigate cardiovascular outcomes in relation to HRV measurements and post-surgical pain
2. Investigate a study's attempts to control for analgesic treatment, and pre-surgical differences in HRV in the data analysis

Methods and Identification of Studies

Search Strategy: MEDLINE and EMBASE search include terms related to HRV, post-surgical pain, non-cardiac surgery, and relevant cardiovascular outcomes. Includes any study with primary data available

Inclusion Criteria:

1. Age > 18 years old
2. Non-cardiac surgery
3. HRV measurements
4. Measurements of post-surgical pain
5. Measurements made in post-operative period (30 days after surgery)



Outcome Measures

Primary Outcomes:

1. Measures of pain intensity or changes in pain intensity
2. HRV measurements within the first 30 days after noncardiac surgery
3. Statistical association between a) and b), or between a) and c)

Secondary Outcomes

1. Cardiovascular events (e.g. MI, stroke, pulmonary embolism)
2. Use of analgesics and differences in analgesia between study groups

Study Features

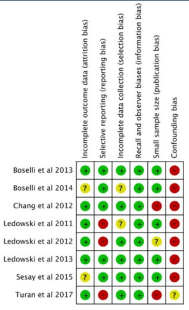


Fig 4. Risk of Bias Summary

Reference (yr)	Sample Size	Pain Measure	Type of Anesthesia	Types of HRV Measures
Ledowski et al (2011) [15]	220	NRS	Not reported	HRV: LF, HF, LF/HF, TP, UsEn
Ledowski et al (2012) [16]	85 included 84 analyzed	NRS	Not reported	HRV: LF, HF, LF/HF, UsEn
Chang et al (2012) [17]	34	VAS, SF-MPQ, PPIS	Not reported	HRV: SDNN, HF, LF, VLF, and LF/HF
Sesay et al (2015) [18]	120	NRS	GA	HRV: LF, HF, and LF/HF
Ledowski et al (2013) [19]	120 included 114 analyzed	NRS	GA	ANI
Boselli et al (2013) [20]	200	NRS	GA or Regional	ANI
Boselli et al (2014) [21]	237 included 200 analyzed	NRS	GA or Regional	ANI
Turan et al (2017) [22]	30	VAS	TIVA	ANI

Table 1. Features of Eligible Studies and HRV Measures

ANI, analgesia nociception index; HF, high frequency component, LF, low frequency component; NRS, Numerical Rating Scale; PACU, postanaesthesia care unit; PPIS, present pain intensity score; SF-MPQ, Short-form McGill Pain Questionnaire; TP, total power; UsEn, ultrashort entropy VAS, Visual Analog Scale; VLF, very low frequency

- All included studies used a prospective observational design [15-22]
- There was lack of baseline (presurgical) HRV or ANI measures in 7/8 studies [15-21], leading to high risk of confounding bias in studies
- Many studies used NRS pain scores (6/8) [15,16,18-21] and did not consistently record the type of anesthetic used (5/8 studies) [15-17, 20,21]

Association Between Postsurgical Pain and HRV

Reference (yr)	Statistical analyses	Pain Measure	Types of HRV Measures	Significant Association Between HRV and Pain	Measures Significantly Associated with Pain	Pain measured on arrival at PACU	Other Autonomic Measures Recorded
Ledowski et al (2011) [15]	T test, ROC, and Spearman rho coefficient (r)	NRS	HRV: LF, HF, LF/HF, TP, UsEn	No	----	Yes	BP, HR, RR
Ledowski et al (2012) [16]	T test or Wilcoxon test, AUROC	NRS	HRV: LF, HF, LF/HF, UsEn	No	----	Yes	HR, RR, MAP, adrenaline, noradrenaline
Chang et al (2012) [17]	Spearman rho coefficient (r)	VAS, SF-MPQ, PPIS	HRV: SDNN, HF, LF, VLF, and LF/HF	Yes	LF with VAS (r, Correlation) LF/HF with SF-MPQ (r, Correlation)	Yes	----
Sesay et al (2015) [18]	Linear mixed model, AUROC, and Spearman rho coefficient (r)	NRS	HRV: LF, HF, and LF/HF	Yes	LF and NRS (r, Correlation) LF/HF and NRS (r, Correlation) LF (AUROC) and NRS LF/HF (AUROC) and NRS	Yes	----
Ledowski et al (2013) [19]	Spearman rho coefficient (r) and AUROC	NRS	ANI	Yes for correlation No for AUROC	ANI and NRS (r, Correlation)	Yes	----
Boselli et al (2013) [20]	T test, Mann–Whitney U test, AUROC; coefficient of determination (r2)	NRS	ANI	Yes	ANI and NRS (Coefficient of Determination) ANI and NRS (AUROC)	Yes	----
Boselli et al (2014) [21]	T test, Mann–Whitney U test, AUROC; coefficient of determination (r2),	NRS	ANI	Yes	ANI and NRS (Coefficient of Determination) ANI and NRS (AUROC)	Yes	----
Turan et al (2017) [22]	T test, Mann–Whitney U test, and chi-squared test	VAS	ANI	Yes	ANI and VAS (Chi-Squared Test)	Yes	----

Table 2. Statistical Association Between Pain and HRV/ANI Measures

Significant Association: defined as P < 0.05 for correlation analysis (eg, Spearman rho), coefficient of determination (r2), chi-squared test, or AUROC value >0.8

Abbreviations: ANI, analgesia nociception; AUROC, area under the receiver operating characteristic curve; HF, high-frequency component of HRV; HRV, heart rate variability; LF, low-frequency component of HRV; NRS, Numerical Rating Scale; PACU, postanaesthesia care unit; PPIS, present pain intensity score; r2, coefficient of determination; ROC, receiver operating characteristic curve; SF-MPQ, Short-form McGill Pain Questionnaire; Spearman rho coefficient; TP, total power component of HRV; UsEn, ultrashort entropy; VAS, Visual Analog Scale

- 6 of 8 studies (2/4 HRV [17,18] and 4/4 ANI [19-22] studies) observed a significant association between HRV measures and postsurgical pain
- Of the included studies, 2 of 8 studies [15,16] measured other autonomic parameters and both found a significant correlation between autonomic parameters and postsurgical pain
- Limitations of these studies include:
  1. Excluding patients with cardiac risk factors, limiting generalizability
  2. Confounding variables include: lack of baseline HRV measures, inconsistent use of anesthetics, lack of BMI or weight measures which influence HRV measures
  3. Poor generalizability due to use of single pain severity score
  4. No study reported cardiovascular outcomes in post-operative period

Conclusion and Future Directions

- At least 6 of 8 positive studies [17-22] suggest at least the potential for an association between pain and HRV/ANI
- Study heterogeneity did not allow for meta-analysis
- Impact of HRV/postsurgical pain on cardiovascular outcomes is unclear
- Future studies required with consideration for confounding variables and baseline HRV/ANI measurements to better delineate relationship

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