Does Heart Rate Variability (HRV) Predict Hypotension on Induction in Patients Undergoing Surgery for Cervical Myelopathy?

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Does Heart Rate Variability (HRV) Predict Hypotension on Induction in Patients Undergoing Surgery for Cervical Myelopathy?

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Project Summary

Cervical myelopathy is commonly associated with degenerative spinal disease. Dysfunction of the autonomic nervous system is also evident in many cases of cervical myelopathy. Autonomic dysfunction may result in haemodynamic instability and hypotension under anaesthesia. It is important to maintain adequate mean arterial pressure in order to perfuse the spinal cord and prevent cord ischemia. Heart rate variability, the physiological variations of the differences between heart beats, has been used to diagnose autonomic dysfunction. In patients with cervical myelopathy it may enable the anaesthetist to predict hypotension thereby allowing for early treatment and prevention of spinal cord ischemia.

Background

Cervical myelopathy is commonly associated with degenerative spinal disease. It is a common cause of spinal cord dysfunction in the aging population. The predominant pathology seen in these patients is spondylosis which includes degeneration of joints, discs and ligaments. (1). Spinal cord ischemia may also contribute to these pathological processes but the exact mechanism remains unclear. Magnetic resonance imaging may reveal disc herniation, osteophytic narrowing of the spinal canal and hypertrophic changes to the ligamentum flavum (2). Patients may present with a wide range of symptoms ranging from neck pain and decreases in dexterity in mild cases to sphincter dysfunction and complete loss of motor function in severe cases (3). Dysfunction of the autonomic nervous system is also evident in many cases of cervical myelopathy (4). In many of these patients, the spinal cord is at risk of ischemia due to decreased blood flow as a result of compressive lesions. Any further reduction in spinal cord blood flow may not be well tolerated. Mean arterial pressure (MAP) is one of the important factors that determine the adequacy of perfusion to the spinal cord and hypotension has been shown to be associated with poor outcome in patients with spinal cord injury.

Autonomic nervous system dysfunction is often seen in patients with acute spinal cord injury. (5). A recent study has shown autonomic nervous system involvement in up to 50% of patients with compressive cervical myelopathy (4). The autonomic nervous system (ANS) is responsible for the normal regulation of visceral organ function including the cardiovascular system. They are the primary regulator of heart rate and blood pressure.

Surgical treatment of cervical myelopathy may involve anterior and/or posterior decompression of spinal cord with or without instrumented fusion. The main purpose of the surgery is to prevent further deterioration of spinal cord function. Patients with cervical myelopathy often pose a significant challenge to the anesthesiologists. In addition to challenges with airway management and patient positioning, the most important anesthetic consideration in these patients is to maintain the mean arterial blood pressure (MAP) >70 mmHg during the surgery.

Anesthetic induction may cause hypotension and this may be profound in some patients. Common causes of post-induction hypotension include vasodilatation, myocardial depression (6), hypovolemia and altered autonomic nervous system activity. Studies have shown that

patients with autonomic system dysfunction are more prone to anaesthesia induced hypotension. It has been shown that patients with autonomic dysfunction require increased vasopressor support to maintain blood pressure (7). Hence patients with cervical myelopathy, because of their associated autonomic system dysfuction, are possibly more prone to hypotension on induction of anesthesia. This hypotension may put these patients at risk for spinal cord ischmia. Identifying patients at risk for hypotension can be useful to prevent hypotension and to prepare to treat hypotension sooner so that the risk of spinal cord ischemia can be minimized.

Assessment of Autonomic Nervous System Function

Multiple methods have been used for the assessment of the ANS including, Valsalva test, isometric handgrip test, cold pressor test and active standing test. (8) Most of these tests are time consuming, labour intensive and are not easy to perform in the perioperative setting. Another method of assesment of ANS tone which affects cardiovascular function may be assessed by an analytical method called heart rate variability analysis. Guo et al. have shown that heart rate variability measurement is a simple useful alternative to conventional tests. (9).

Heart Rate Variability (HRV)

Under normal physiological conditions the interval between successive cardiac cycles is not static but varies in response to several factors that place changing demands on the cardiovascular system. A decrease in the variability of the interval between cycles i.e. a decrease in heart rate variability has been shown to be associated with several pathological conditions that affect the autonomic nervous system (10).

Heart rate variability may be analysed accord to either the frequency domain or the time domain. With regard to time domain analysis, the SDNN or Standard Deviation of normal R-R intervals is calculated during the period of ECG monitoring, the N-N interval being the interval between two successive normal beats. Using Fourier transformation, fluctuations in the frequency domain may also be analysed. The low frequency (LF) band (0.04-0.15 Hz) relates to sympathetic and parasympathetic modulation. The high frequency (HF) band (0.15-0.4Hz) largely reflects parasympathetic contribution. The ratio between low frequency and high frequency (LF: HF) is used to determine sympathetic-parasympathetic balance (11).

Heart rate variability may be analysed using standard hospital electrocardiographic equipment and the relevant software to perform the analysis. Power spectral analysis of the

electrocardiogram can be used to measure autonomic dysfunction. A short (5 minute) ECG recording can be analysed to provide several useful measurements of autonomic function. Therefore, heart rate variability analysis provides a non-invasive, bedside method of assessing the status of the autonomic nervous system that can be used in the perioperative setting without significant change to standard operating procedures.

HRV as a predictor of Hypotension under Anesthesia

Haemodynamic stability under anaesthesia depends in a large part on the integrity of the autonomic pathways that feedback into cardiovascular regulatory centres and control variables like heart rate, contractility and vascular tone. As an indicator of autonomic function, heart rate variability may therefore have a role to play in predicting haemodynamic instability. Studies show that heart rate variability may be used as a predictor of haemodynamic fluctuations under anaesthesia. Hanss et al (12) have shown that the LF: HF ratio can be used to predict severe hypotension during spinal anaesthesia. In a study of patients under general anaesthesia Huang et al (13) showed that spectral analysis of heart rate variability could be used as a sensitive predictor of hypotension and that heart rate variability may be superior to traditional tests of autonomic function.

Heart rate variability is being increasingly used in the setting of general and regional anaesthesia as both a diagnostic and prognostic tool (8).

At present the incidence of decreased HRV in patients with cervical myelopathy is unknown as well as whether this is predictive of hypotension on induction of general anaesthesia. Therefore, the aim of our study is to determine the incidence of abnormalities in HRV in patients undergoing surgery for cervical myelopathy and to determine whether decreased heart rate variability is predictive of hypotension on induction in these patients.

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Hypothesis

We hypothesise that decreased HRV is common in patients undergoing surgery for cervical myelopathy and that decreased HRV is a predictor of hypotension on induction of general anaesthesia. We also hypothesise that there is a relationship between severity of myelopathy and degree of abnormalities in HRV.

Significance of the study

Identifying patients at risk for hypotension can be useful to prevent hypotension and to prepare to treat hypotension sooner so that the risk of spinal cord ischemia can be minimized.

Proposed methodology

Study design

This is a single centre, prospective observational study.

Trial Population

The study participants will be recruited from patients with cervical myelopathy presenting for cervical spine surgery at Toronto Western Hospital.

Inclusion Criteria

Adults patients, aged 18 – 70 years with the history of cervical myelopathy, presenting for anterior or posterior cervical decompression and fusion.

Exclusion Criteria

1. Patients with arrhythmias or absence of sinus rhythm
2. Diabetic patients
3. Degenerative neurological disease e.g. Parkinson's disease
4. Complete SCI
5. Inherited autonomic dysfunction

Protocol

1. Standard perioperative management

Routine standard preparation of the patients will be carried out as per our institutional standard for all patients undergoing cervical spine surgery. All routine physiological monitoring (ECG, invasive arterial blood pressure, SPO2, end tidal CO2, temperature and depth of anaesthesia monitoring) will be performed. The induction of anesthesia will be performed with propofol (2-5 mg/kg), fentanyl (3mcg/Kg) and rocuronium (0.6 mg/kg) for intubation of the patient's trachea once peripheral nerve stimulation shows no muscle twitches. After tracheal intubation, the lungs will be ventilated using volume-controlled mode to maintain PaCo2 between 33-35 mmHg. Anesthesia will be maintained with total intravenous anaesthesia or balanced inhalational anaesthesia as per standard management. Hemodynamic management will target a MAP > 70 mmHg using standard inotropes and

vasopressors (phenylephrine and ephedrine). Prophylactic antibiotics (Cefazolin or Clindamycin), antiemetic (Ondansetron) and steroids (Dexamethasone) will be administered as per our routine practice. Intraoperative, 25 mcg bolus dose of fentanyl will be given for additional analgesia as indicated by clinical judgment. After the skin closure, anesthetic agents will be turned off and the neuromuscular blockade will be reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. Patient's trachea will be extubated after meeting the extubation criteria. Patients will be transferred to recovery room and standard postoperative care will be carried out. General care of the patients in the post-anesthetic recovery room will be as per our standard practice in terms of oxygen therapy, monitoring and assessment of neurological status, pain, nausea and vomiting and degree of sedation. Fentanyl 25 mcg i.v will be administered every 5 min to the maximum of 200 mcg to maintain a Numeric Pain Score (NRS) < 4 of 10. Morphine or hydromorphone will be used as additional analgesia after fentanyl. Nausea and vomiting will be treated with dimenhydrinate 25-50 mg i.v. Postoperative pain management will be provided with oral or parenteral opioid analgesia as per our standard of care

2. Study protocol

Before general anesthesia, following a 10 minute stabilization period with the patient lying supine and breathing at a rate of 12 – 15 breaths per minute, a 5 minute ECG recording will be obtained. ECG data will be downloaded onto a study laptop for later analysis using LabChart Software (ADInstruments,Colarado Springs,CO,USA) to determine HRV values (Total power, high frequency, low frequency and low frequency : high frequency ratios). Hemodynamic data (heart rate, systolic diastolic and mean blood pressure) and depth of anaesthesia (Entropy) will be collected from the preinduction period until skin incision at 1 minute intervals. The study will be complete after skin incision.

Data Collection and Management

Data Collection

The following data will be collected: patient demographics, surgical data including position technique, number of levels, duration, anaesthetic data including agents used, hemodynamic measurements from preinduction to surgical incision, Japanese Orthopaedic Association Score. The incidence of hypotension and the number of interventions required to keep mean arterial blood pressure above 70 mmHg will be recorded.

Data Management

An electronic data management system will be used. All data will be entered directly on the electronic system. Pre specified automated data entry checks will be performed on all entered data to prevent the entry of impossible values or the omission of key data fields. All study databases will be in the password protected UHN server. Any data containing participant identifying details will be stored separately and securely from study documents.

Analysis

The incidence of low HRV as indicated by a total power below the normal range of 3466 ms^2 ± 1018 ms^2 will be determined as well as the incidence of hypotension. We will determine the correlation between low HRV, hypotension and the severity of myelopathy as determined by the Japanese Orthopaedic Association score. Non-parametric HRV within group data will be analysed with the Wilcoxon matched pairs test. Comparisons of non-parametric HRV data between groups will be performed using the Mann–Whitney test. Student t test will be used for parametric data.

Definitions:

1. *Heart rate variability*

The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology has standardized guidelines for the measurement of heart rate variability (14). These recordings will be analysed and power spectrum densities will be calculated for total power (TP) which is a measure of heart rate variability. Low frequencies (LF), high frequencies (HF) and LF: HF ratio will also be analysed. Based on HRV values, two groups will be designated: group L (low HRV) and group N (normal HRV) based on the normal range for total power i.e. 3466 ms^2 ± 1018 ms^2.

2. *Blood Pressure*

Hypotension will be defined as a mean arterial blood pressure less than 70 mmHg lasting more than 1 min as measured using arterial line. Non-invasive measurement will be taken if arterial line is not available. Based on the blood pressure, patients will be classified into 3 groups

Group 1: no episodes of hypotension i.e. mean blood pressures at or above 70 mmHg

Group 2: hypotension i.e. means blood pressures below 70 mmHg with minimal intervention (<5 interventions)

Group 3: severe hypotension i.e. means blood pressures below 60 mmHg or MAP<70 mmHg needing multiple interventions or infusions of ionotropes.

All interventions for the treatment of hypotension will be recorded. The interventions include phenylephrine 40 mcg, Ephedrine 5 mg, fluid bolus and decrease the anesthetic level (inhalational or intravenous). Infusion of vasopressors and also total vasopressor dose will be recorded separately.

3. Severity of myelopathy

The Modified Japanese Orthopaedic Association score for severity of myelopathy will be used to determine the severity of myelopathy i.e.

Mild (Modified Japanese Association Score - MJOA) ≥ 15

Moderate (MJOA = 12)

Severe (MJOA < 12).

Sample size

There is only one previous study that has looked at the autonomic dysfunction in patients with cervical myelopathy. They had a sample size of 30 patients and majority of patients had either moderate or severe myelopathy. Currently there is no data on the incidence of low HRV in patients with varying severities of cervical myelopathy. We plan to recruit around 100 patients with various degrees of cervical myelopathy for this study. Around 25 % of patients will be mild to moderate myelopathy and rest will be moderate to severe. Hence this sample size will provide us the useful information on the true incidence of autonomic dysfunction across different severities of myelopathy.

Ethical Aspects

Regulatory approval

Regulatory approval will be sought from the local research ethics board and the study will not commence until it is obtained.

Informed Consent

Prior to enrolment potential participants will receive written and verbal information regarding the nature and purpose of the study, what participation involves and potential benefit and risks. They will be given time to ask questions and it will be emphasized that participation is voluntary, that they are free to withdraw from the study at any time and that any decision to do so will not affect any treatment they would otherwise receive. Where the participant understands and accepts these terms, they will be asked to sign the consent form.

Privacy and Confidentiality

The laptop used in the study will contain only de-identified data and that it will be encrypted as per UHN policy 1.40.006 Storage, Transport & Destruction of Confidential Information.