Using very short-term heart rate variability to monitor fentanyl-induced changes in the autonomic nervous system preceding respiratory depression

HRV and opioid-induced loss of airway tone

by

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Abstract

Post-operative opioid analgesia to control pain is complicated by the occurrence of respiratory depression in 0.1-1% of patients with subsequent hypoxia. Timely detection of critical respiratory depression events such as loss of airway tone would be useful in preventing harm to these patients.

The heart and airway have inherent vagal rhythms synchronous with the respiratory cycle; cardiac vagal tone and respiratory sinus arrhythmia can be monitored with heart rate variability (HRV). This study investigated whether a premonitory change in the HRV occurred with opioid-induced changes in airway stability.

The opioid fentanyl was selected for its safe pre-operative use and short action time (5-6 min). This required establishment of HRV analysis over very short-term periods.

The hypothesis was that a measure of short-term, non-stationary HRV could detect a change in vagal or sympathetic activity that may be a reflection of a shift in the stability of airway tone.

The first part of this study identified 70 HRV indices suitable for short-term use from: time and spectral domain, Poincaré plot and heart rate characteristics. The minimum window length of 30 beats was determined by analysis of Lomb-Scargle spectral indices.

The indices were validated over 10x30 beat windows using PhysioNet databases with physiological states: at rest, active, exercising, sleeping, and meditating (N from 12 to 20). Baseline 95% confidence intervals of the median were established with bootstrap resampling (10,000). Statistical significance was assessed using the overlap of 95% confidence intervals. Correlation of subject average was used to remove redundant indices and a minimal set of 31 indices differentiated at least one of the physiological states from resting.

The second part of this study applied the indices in a pilot observational study (N = 10) of the fentanyl effects on upper airway stability of healthy subjects

scheduled for minor surgery. Physiological data (ECG, SpO_2, $ETCO_2$, flow and chest impedance) and clinical observations were recorded. Baseline data (7x30 beat) was compared to 10 consecutive 30-beat periods: a) post-fentanyl and b) peri-critical respiratory depression. Statistical significance was assessed with overlap of 95% confidence intervals for the median.

All subjects had an initial central depression followed by a critical respiratory depression event (no flow). Five subjects developed clinically observed upper airway obstruction: two snoring and three with full sustained UAWO.

The expected decreases in heart rate, total variability or sympathetic activity were not seen, nor was there a change in vagal activity in the post-fentanyl or peri-respiratory depression periods. Some subjects had consistently reactive HRV for many indices, but the changes were not related to the extent of respiratory depression.

One index, **PolVar20**, detected a flurry of sympathetic activity, after fentanyl administration and before the critical respiratory depression in some subjects with sustained trends (statistically insignificant due to the skewed distribution).

PolVar20 may indicate an attempt to restore airway patency after opioid-induced respiratory depression in a small subset of patients in the clinical setting; those not suffering from any cardiac autonomic neuropathy.

Declaration

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

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Abbreviations

ANS	autonomic nervous system
CD	central depression
CNS	central nervous system
CO_2	carbon dioxide
ECG	electrocardiogram
EEG	electroencephalogram
EMG	electromyography
EOA	epidural opiate analgesia
$ETCO_2$	end-tidal carbon dioxide (% or mmHg)
FMC	Flinders Medical Centre
HR	heart rate
HRV	heart rate variability
N_2O	nitrous oxide
O_2	oxygen
PCA	patient-controlled anaesthesia
$PETCO_2$	partial pressure of end-tidal carbon dioxide (mmHg)
RD	respiratory depression
RRI	interval between R-waves on ECG
SpO_2	oxygen saturation
UADM	upper airway dilator muscles
UAWO	upper airway obstruction

Glossary

Abductor	Muscular action drawing one part away from another [1].
Ach	Acetylcholine (ANS neurotransmitter).
Adductor	Drawing inward or together, as a muscle [1].
Afferent nerve	Nerve that conveys impulses to the central nervous system.
Agonist	A drug or ligand that binds to the same site as the endogenous ligand and produces the same signal. The magnitude of the signal is usually equal to or less than that produced by the endogenous ligand. (Also see antagonist) [2].
Alkaloid	Any of various nitrogenous organic bases founding plants, having specific physiological action.
Anaesthesia	Loss of feeling, insensibility (not capable of emotion, dull, unconscious, imperceptible by the senses), general or local [1].
Analgesia	Loss of pain without loss of consciousness. A state in which no pain is felt despite the presence of normally painful stimuli [2].
Anodyne	A medicine that relieves pain; something that relieves mental distress.
Antagonist	A drug that binds to the site used by the endogenous ligand and acts competitively to diminish or block the signal produced by the endogenous ligand (also see agonist) [2].
Antitussic	Tending to alleviate or suppress coughing.
Apnoea	Cessation of breathing.
Cholinergic	The neurotransmitter acetylcholine used almost exclusively by the parasympathetic nervous system.
CSF	Cerebro-spinal fluid.
Efferent nerve	A nerve carrying impulses away from the central nervous system.
Endogenous opioids	There are three families of opioid peptides originating within the body: endorphins, enkephalins and dynorphins.
Genioglossus	Muscle that runs from the chin to the tongue enabling protrusion of the tongue.
HPV	Heart period variability.
Hypnotic	Relating to a soporific or sleep-like state.
Hypopnea	Breathing that is shallower, and/or slower, than normal.
Hypoxia	Reduction of oxygen supply to tissue below physiological levels despite adequate perfusion of the tissue by blood.
Hypoxaemia	Below-normal oxygen content in arterial blood due to deficient oxygenation of the blood and resulting in hypoxia.
Intrathecal	Drug administration into the cerebrospinal fluid.
Ligand	An atom, molecule, radical or ion which forms a complex with a central atom [1].
MI	Myocardial infarct.
MSNA	Muscle sympathetic nerve activity.

NANC	Non-adrenergic non-cholinergic; the third ANS control.
Narcotic	Producing sleep, torpor (numbness, dullness), or deadness; affecting the central nervous system so as to produce dizziness, euphoria, loss of memory and of neuromuscular co-ordination, and eventually unconsciousness [1]. Narcotic is an imprecise term still used to refer to opioids, but also to drugs that produce a stuporous, sleep-like state and may or may not relieve pain. This came from its use in US Federal Legislation, (1914 Harrison Narcotic Act) [2].
NE	Norepinephrine (ANS neurotransmitter).
Nociceptor	Pain receptor activated by noxious or nociceptive stimuli [2].
nu	Normalised units.
Opiate	Narcotic analgesic, having morphine-like qualities Used to describe any natural or synthetic agent derived from morphine. (Note: The discovery of peptides in the brain that had similar pharmacological actions to morphine prompted a change in nomenclature)[3].
Opioid agonists	All substances, natural or synthetic, with opioid or morphine-like properties that bind specifically to opioid receptors with effects that are reversed by naloxone.
Opioid antagonists	All substances that bind to opioid receptors and block or reverse the effects of opioid agonists.
Opioid receptors	The principal opioid receptors are: mu (μ), delta and kappa.
Parenteral	Not intestinal, not by way of the alimentary tract.
PCA	Patient-controlled analgesia with intravenous delivery of opioids for postoperative pain management.
Phasic	A sensory receptor that adapts rapidly to a stimulus; the response diminishing quickly. It gives information on rapid changes in stimulus intensity and rate.
PPI	Interval between consecutive P-waves of ECG.
REM sleep	Rapid-eye movement.
RF	Respiratory frequency.
RR-interval	Time (in ms) between consecutive R-waves in electrocardiogram.
Sedation	The act of calming, or state of being calmed, by means of sedatives [1].
Sedative	Medicine or agent.
Somatic pain	Pain that is originated in muscle and bone, toothache, headache, arthritic, sprains etc.
Soporific	Inducing sleep, sleep-bringing agent.
Stridor	A harsh, whistling sound of obstructed breathing.
Tonic	A sensory receptor that adapts slowly to a stimulus and continues to produce action potentials over the duration of the stimulus.
Visceral pain	Pain that is originated in non-skeletal parts of the body, gastric pain, intestinal cramps, etc. It is relieved only by opioid analgesics.

Chapter 1. Overview

Opioids are provided as sedatives after surgery and after trauma to reduce pain. They are often given in hospital wards where physiological patient monitors are not a requirement. Opioids are important analgesic drugs that continue to be the mainstay of perioperative anaesthesia; with morphine by far the most commonly administered opioid.

The provision of effective sedation is difficult as its efficacy is dependent on a number of factors including the relative intensity of non-pain-related, external and internal stimulation. Examples of non-pain-related stimuli are ambient noise and light, and patient discomfort (e.g. full bladder, peripheral trauma requiring a nerve block). If too much sedative is given, or the non-pain-related (and non-opioid affecting) stimulation is reduced, the sedation predominates and, if present in sufficient quantity, can lead to respiratory depression or loss of airway tone or both, leading to hypoxia and brain injury. While there is low prevalence of this condition in the hospital, the possible effect on the patient is significant.

Opioids produce the sedative effect by action on the central nervous system. The cardiac and respiratory systems are closely linked and appear to have some synchronicity from either the central nervous system through parasympathetic and sympathetic activity, or direct physical action of respiration on the autonomic nervous system.

Heart rate variability (HRV) analysis, based on indices of the cardiac beat-to-beat interval, has been used to study the effect of the autonomic nervous system on the heart, in particular, the different contributions from the parasympathetic and sympathetic systems. HRV is also sensitive to respiration (respiratory sinus arrhythmia) such that regular changes in respiration can be identified in the heart rate, acceleration occurring with inspiration. With the knowledge that the airway stiffens with each inspiration, there is the possibility of some concurrence with respiratory sinus arrhythmia.

Although morphine is the most common opioid prescribed, this research studied the effect of the faster acting opioid, fentanyl, in the well-monitored environment of the operating theatre.

If opioid-induced loss of airway tone could be detected with HRV, there is a possible application for monitoring patients receiving opioids that may be at risk of airway collapse.

The following hypothesis was investigated:

> *That a measure of short-term, non-stationary HRV could predict a change in vagal or sympathetic activity that may be a reflection of a shift in the stability of airway tone.*

The background knowledge necessary to understand the problem of opioid-induced respiratory depression is covered in Chapter 2 including the structure and physiology of the airway, innervation of the airway, and changes causing loss of airway tone. In Chapter 3, the background knowledge is extended to cover the heart and its innervation. The theory of heart rate variability is introduced with commonly used indices and their usage, along with the known effects of opioids on these indices.

In Chapter 4 indices suitable for very short-term use are identified and tested. This chapter includes a survey of the literature, identification of indices able to be used over < 60 s windows, coding and testing of the index calculations. The concern with spectral analysis is that it will not provide useful information in window lengths less than 2 min. This minimum window length for spectral indices using the Lomb-Scargle algorithm is investigated in Chapter 5.

The indices selected for short-term use are validated with the very short window in Chapter 6 to determine if the indices can differentiate four physiological states from resting. As part of this process, normality of the indices was determined, correlation analysis identified redundant indices, stationarity was inspected, and confidence intervals established index baselines. The chapter defines a minimum set of useful indices and concludes with a discussion of the very short-term results in comparison to the data for longer windows in the literature.

Chapter 7 describes the method for the clinical trial investigating fentanyl-induced loss of airway tone, data collection (hardware and software), patient selection and operating theatre logistics, end-point definitions, and statistical considerations. The pre-processing of the data is an important step and includes the method of ECG R-wave detection, editing and artifact removal to produce the series of time intervals used by the index calculations.

The results are tabled in Chapter 8 which covers subject details, data analysis problems and outcomes, statistical analysis comparing baseline to a) resting data from Chapter 3, b) post-fentanyl period, c) peri-central depression, and d) peri-upper airway obstruction. Further investigation is done on individual subject results with indices that were found to be significant in the previous analyses.

In the discussion, Chapter 9, the post-fentanyl results are compared to literature, problems in the method analysed and results put in context with respect to monitoring heart rate variability to identify loss of airway tone. Finally in Chapter 10 the findings are examined with respect to future work.