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

Anne-Louise Smith

BSc (Biophys) MEng (Sys Eng)

School of Computer Science, Engineering and Mathematics

Faculty of Science and Engineering

Flinders University of South Australia

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Supervisors: Prof. Karen Reynolds and Prof. Harry Owen
Contents

FIGURES.................................................................................................................................. VII
TABLES ....................................................................................................................................... IX
ABSTRACT .................................................................................................................................. X
DECLARATION ............................................................................................................................. XII
ACKNOWLEDGEMENT ............................................................................................................... XIII
ABBREVIATIONS ...................................................................................................................... XIV
GLOSSARY ................................................................................................................................... XV

CHAPTER 1. OVERVIEW ............................................................................................................. 17

CHAPTER 2. BACKGROUND: OPIOIDS AND THE AIRWAYS .................................................. 20
  2.1 THE PROBLEM: OPIOID-INDUCED RESPIRATORY DEPRESSION ..................................... 20
      2.1.1 Opioid usage .................................................................................................................. 20
      2.1.2 Problems with opioid use ............................................................................................... 22
      2.1.3 Incidence of respiratory depression ................................................................................. 26
      2.1.4 Reducing incidence of respiratory depression in the hospital ....................................... 28
      2.1.5 Summary ......................................................................................................................... 31
      2.2 OPIOID EFFECT ON RESPIRATION ................................................................................. 32
          2.2.1 ANS ............................................................................................................................... 32
          2.2.2 Opioid effect on ANS ..................................................................................................... 32
          2.2.3 Multiple opioid respiratory effects ............................................................................... 34
          2.2.4 Airway form and function ............................................................................................. 35
          2.2.5 Normal respiration ......................................................................................................... 39
          2.2.6 Respiratory pattern in sleep ........................................................................................... 43
          2.2.7 Opioid effects on respiration .......................................................................................... 45
          2.2.8 Summary opioid effect .................................................................................................... 46

CHAPTER 3. BACKGROUND: THE HEART AND HEART RATE VARIABILITY ......................... 47
  3.1 ANATOMY ............................................................................................................................. 47
  3.2 INNERVATION ...................................................................................................................... 47
      3.2.1 Sympathetic ...................................................................................................................... 48
      3.2.2 Parasympathetic ............................................................................................................... 48
      3.2.3 Latency ............................................................................................................................. 49
      3.2.4 Modulation ....................................................................................................................... 49
      3.2.5 Intrinsic heart rate ............................................................................................................ 49
  3.3 RESPIRATORY SINUS ARRHYTHMIA ............................................................................... 51
  3.4 HEART RATE VARIABILITY, HRV ..................................................................................... 52
      3.4.1 HRV basics ...................................................................................................................... 52
      3.4.2 HRV measurement .......................................................................................................... 58
  3.5 EFFECT OF AIRWAY ON HRV .......................................................................................... 59
      3.5.1 Effect of respiration on HRV ............................................................................................ 59
      3.5.2 Effect of respiratory depression on HRV ........................................................................ 60
      3.5.3 Effect of airway on HRV .................................................................................................. 62
  3.6 OPIOID EFFECT ON HRV .................................................................................................. 63
      3.6.1 Direct effect of opioids on the heart .................................................................................. 63
      3.6.2 Effect of opioids with anaesthetic agents on HRV ......................................................... 63
      3.6.3 Effect of fentanyl on HRV ............................................................................................... 67
      3.6.4 Pre-intubation effect of fentanyl on HRV ........................................................................ 68
      3.6.5 Respiration-related fentanyl effects ................................................................................. 70
      3.6.6 Summary of opioid effects on HRV ............................................................................... 71

CHAPTER 4. SELECTION OF VERY SHORT-TERM INDICES ...................................................... 73
  4.1 AIM ........................................................................................................................................ 73
  4.2 BACKGROUND ...................................................................................................................... 73
HRV and opioid-induced loss of airway tone

Figures

FIGURE 2-1 SUMMARY OF OPIOID EFFECTS ON THE AUTONOMIC NERVOUS SYSTEM ........................................ 33
FIGURE 2-2 UPPER AIRWAY WITH PHARYNX .......................................................... 36
FIGURE 2-3 PHARYNGEAL MUSCLES ........................................................................... 37
FIGURE 2-4 PHARYNGEAL DILATOR MUSCLES .......................................................... 38
FIGURE 2-5 UPPER AIRWAY ANATOMY, ACTION OF DILATOR MUSCLES AND SITES OF OBSTRUCTION 44
FIGURE 3-1 MODEL OF HEART RATE CONTROL BY SYMPATHETIC AND PARASYMPATHETIC EFFECTS ON SINOATRIAL (SA) NODE (MODIFIED FROM [138]) ......................................................... 49
FIGURE 3-2 SIMPLISTIC MODEL OF HEART RATE REGULATION (ADAPTED FROM [Voss, 2009 #3455])
ADDITIONAL FACTORS WITH CONSIDERABLE INFLUENCE ON HR ARE SHOWN WITHIN THE DASHED BOXES. DARKER AND LIGHTER LINES EMPHASIZE THE DIFFERENCE IN SYMPATHETIC AND PARASYMPATHETIC CONTROL OF THE HEART (SHaded BOX). ABBREVIATIONS: P CO2, ARTERIAL CARBON DIOXIDE TENSION; P O2, ARTERIAL OXYGEN TENSION ........................................ 50
FIGURE 3-3 DIAGRAM OF THE INTERRELATIONSHIPS AMONG RESPIRATION AND CARDIOVASCULAR VARIABLES AND HOW THEY CONTRIBUTE TO RR-INTERVAL (ADAPTED FROM [KHOO, 2008 #3767]) .......................................................... 51
FIGURE 3-4 BEAT TO BEAT CHANGES, RR-INTERVALS ............................................. 53
FIGURE 3-5 MEASURING RSA FROM THE TACHOGRAM: PEAK-VALLEY METHOD ........................................ 55
FIGURE 3-6 POINCARé PLOT FOR 10 MIN OF RR-INTERVALS ........................................ 57
FIGURE 4-1 TEST DATA DEVELOPED TO CHECK INDEX CALCULATIONS ................. 76
FIGURE 4-2 TINN CALCULATION EXAMPLE FOR RR-INTERVAL HISTOGRAM ............. 79
FIGURE 4-3 EXAMPLE OF POINCARé PLOT INDEX CALCULATIONS WITH 100 BEATS ........................................................................................................... 86
FIGURE 4-4 EXAMPLE OF POINCARé PLOT INDEX CALCULATIONS WITH 25 BEATS ........................................................................................................... 87
FIGURE 4-5 SYNTHESISED SIGNAL WITH OUTER LIMIT PEAKS AT 0.041 AND 0.37 Hz .... 103
FIGURE 4-6 POINCARé PLOT FOR 10 MIN OF RR-INTERVALS ........................................ 105
FIGURE 4-7 SYNTHESISED SIGNAL WITH MID-RANGE PEAKS AT 0.07 AND 0.24 Hz .... 106
FIGURE 4-8 LINEAR TRENDS FOR 16 SUBJECTS IN THE EXERCISE DATABASE ........ 107
FIGURE 4-9 SYNTHESISED SIGNAL WITH MID-RANGE PEAKS AND LARGE TREND .... 108
FIGURE 4-10 OUTLET LIMIT (0.041 AND 0.37 Hz) RESOLUTION FOR MEAN RR-INTERVAL 975 MS ... 109
FIGURE 4-11 OUTLET LIMIT RESOLUTION FOR MEAN RR-INTERVAL 600MS ............... 110
FIGURE 4-12 OUTLET LIMIT RESOLUTION FOR MEAN RR-INTERVAL 500MS (EXERCISE) .......... 110
FIGURE 4-13 POWER OF OUTER LIMITS (0.041 AND 0.37 Hz) ................................ 111
FIGURE 4-14 MEAN RR-INTERVALS FROM PHYSIONET DATABASES .......................... 112
FIGURE 4-15 ABSOLUTE POWER FOR MID-RANGE PEAKS ...................................... 113
FIGURE 4-16 PERCENT CHANGE IN POWER OF MID-RANGE PEAKS ........................... 114
FIGURE 4-17 RELATIVE POWER, LF/NNU, HF/NNU, AND RATIO LF/HF ..................... 115
FIGURE 4-18 POWER FOR BRADYCARDIA, MEAN RR-INTERVAL 1200 MS ............... 116
FIGURE 4-19 ADDITION OF SMALL LINEAR TREND, 0.00011 T, LF VLF NOISE .......... 117
FIGURE 4-20 ADDITION OF LARGE LINEAR TREND, 0.00066 T, SIMILAR TO EXERCISE .... 118
FIGURE 4-21 FALSE DISCOVERY RATE METHOD FOR MULTIPLE TESTS ................. 130
FIGURE 4-22 SKEW AND KURTOSIS FOR INDICES USING RESTING DATABASE ...... 131
FIGURE 4-23 VISUAL INSPECTION OF CORRELATIONS BETWEEN INDICES, RHO < 0.96 .................. 136
FIGURE 4-24 INDICES AND MEAN RR-INTERVAL WITH HIGHEST CORRELATIONS .......... 138
FIGURE 4-25 RANKED PROPORTION OVERLAP (POL) OF CONFIDENCE INTERVALS .................. 141
FIGURE 4-26 LOMB-SCARGLE SPECTRAL INDICES SHOW PARADOXICAL CHANGE IN MEDITATION ... 146
FIGURE 4-27 PHYSIOLOGICAL DATABASE BASELINE 95% confidence INTERVALS ........ 147
FIGURE 4-28 PATIENT DISTRIBUTION FOR FENtanyl DOSE ................................... 158
FIGURE 5-1 LAYOUT OF ANAESTHETIC PREPARATION ROOM ................................. 160
FIGURE 5-2 FREQUENCY RESPONSE OF ANALOG ECG MONITORS .......................... 162
FIGURE 5-3 RESULTS OF FIRST PASS R-WAVE DETERMINATION ............................. 164
FIGURE 5-4 MANUAL EDITING OF R-WAVE LOCATION ............................................ 165
FIGURE 5-5 ANALYSIS PERIODS RELATIVE TO FENtanYL ADMINISTRATION AND RESPIRATORY DEPRESSION EVENT (RD) ........................................... 168
FIGURE 8-1 SUBJECT ENROLMENT FLOWCHART ..................................................... 171
FIGURE 8-2 RR-INTERVAL TACHOGRAM FOR EACH SUBJECT ................................ 174
FIGURE 8-3 SPO2 (MEAN AND RANGE) FOR EACH SUBJECT DURING 4 STAGES OF THE STUDY ... 175
FIGURE 8-4 ETCO2 (MEAN AND RANGE) FOR EACH SUBJECT DURING 3 STAGES OF THE STUDY ... 175
HRV and opioid-induced loss of airway tone

Figure 8-5 A)-D) Subjects 1-4 Identification of Respiratory Depression Events .... 177
Figure 8-6 A)-D) Subjects 5-8 Identification of Respiratory Depression Events .... 178
Figure 8-7 A)-B) Subjects 9-10 Identification of Respiratory Depression Events .... 179
Figure 8-8 Relative Timing of Events for Each Subject ........................................... 184
Figure 8-9 O₂ Mask (F) Indices Compared to Other Physiological States (A-E) .... 187
Figure 8-10 Effect of Fentanyl and Midazolam Dose on Extent of Respiratory Depression .......................................................... 188
Figure 8-11 Ranked POL for 310 Post-Fentanyl Tests .............................................. 189
Figure 8-12 HRV Response to Fentanyl Administration ........................................... 190
Figure 8-13 HRV Response for peri-CD ................................................................. 191
Figure 8-14 HRV Response for peri-UAWO .......................................................... 193
Figure 8-15 Ranked POL A) peri-CD and B) peri-UAWO ...................................... 195
Figure 8-16 Individual Responses to Fentanyl for Time Domain Indices ............. 197
Figure 8-17 Individual Responses for Lomb Scargle Spectral Indices ............... 198
Figure 8-18 Individual Responses for Significant Indices .................................... 200
Figure 8-19 Individual Responses for Indices with Spikes ................................. 201
Figure 8-20 Individual Responses to Fentanyl for PolVar20 ............................... 202
Figure 8-21 Plot of Subject RR-Interval Parameters Affecting Baseline PolVar20 .. 203
Figure 8-22 PolVarXX for Subjects with High and Low Baseline SDNN ............. 204
Figure 9-1 Anxiety Effect on Confidence Interval Range for O₂ Mask Baseline .... 213
Figure 9-2 Autonomic Imbalance Identification .................................................. 218
**HRV and opioid-induced loss of airway tone**

### Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1</td>
<td>Clinical Uses of Morphine</td>
<td>20</td>
</tr>
<tr>
<td>2-2</td>
<td>Opiates Used for Inducing Analgesia or Anaesthesia</td>
<td>21</td>
</tr>
<tr>
<td>2-3</td>
<td>Clinical Problems with Therapeutic Doses of Morphine</td>
<td>23</td>
</tr>
<tr>
<td>2-4</td>
<td>Respiratory Depression Definitions</td>
<td>24</td>
</tr>
<tr>
<td>2-5</td>
<td>Incidence of Severe Respiratory Depression Complications with Opioid</td>
<td>26</td>
</tr>
<tr>
<td>2-6</td>
<td>Relationship Between Measurement Method and Respiratory Depression</td>
<td>28</td>
</tr>
<tr>
<td>2-7</td>
<td>Opioid Effects with Nerve Actions</td>
<td>33</td>
</tr>
<tr>
<td>2-8</td>
<td>Opioid Effects on Respiratory System and Mechanism</td>
<td>35</td>
</tr>
<tr>
<td>2-9</td>
<td>Innervation of Soft Palate and Glossus with Cranial Nerves X and XI</td>
<td>40</td>
</tr>
<tr>
<td>2-10</td>
<td>Innervation of Pharynx and Larynx with Cranial Nerves IX, X and XI</td>
<td>41</td>
</tr>
<tr>
<td>2-11</td>
<td>Innervation of Soft Palate (Velum), Suprahyoid, Infrahyoid and Glossus...</td>
<td>42</td>
</tr>
<tr>
<td>3-1</td>
<td>HRV Studies of Anaesthetic Agents with Opioids Part 1: Anaesthetic Agents</td>
<td>63</td>
</tr>
<tr>
<td>3-2</td>
<td>HRV Studies of Anaesthetic Agents with Opioids Part 2: HRV Effects, Post-</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Intubation</td>
<td></td>
</tr>
<tr>
<td>3-3</td>
<td>HRV Studies with Fentanyl Part 1: Anaesthetic Agents Used</td>
<td>69</td>
</tr>
<tr>
<td>3-4</td>
<td>HRV Studies with Fentanyl Part 2: HRV Effects, Pre-Intubation</td>
<td>70</td>
</tr>
<tr>
<td>4-1</td>
<td>Traditional Time Domain Indices</td>
<td>77</td>
</tr>
<tr>
<td>4-2</td>
<td>Spectral Power Indices based on Lomb-Scargle Algorithm</td>
<td>81</td>
</tr>
<tr>
<td>4-3</td>
<td>RSA Indices</td>
<td>83</td>
</tr>
<tr>
<td>4-4</td>
<td>Poincaré Indices</td>
<td>91</td>
</tr>
<tr>
<td>4-5</td>
<td>Other Indices</td>
<td>97</td>
</tr>
<tr>
<td>5-1</td>
<td>Frequency Characteristics for Spectral Density Analysis</td>
<td>102</td>
</tr>
<tr>
<td>5-2</td>
<td>HRV Characteristics Determined from Physiological Data</td>
<td>105</td>
</tr>
<tr>
<td>5-3</td>
<td>Sine Wave Parameters for Synthetic Signals</td>
<td>106</td>
</tr>
<tr>
<td>6-1</td>
<td>Descriptions of PhysiONet Databases</td>
<td>125</td>
</tr>
<tr>
<td>6-2</td>
<td>Normality of Indices with Shapiro-Wilk or Shapiro-Francia Tests</td>
<td>132</td>
</tr>
<tr>
<td>6-3</td>
<td>Minimum Set of Indices Not Correlated with Each Other</td>
<td>134</td>
</tr>
<tr>
<td>6-4</td>
<td>Indices Correlated with Others Spearman’s rho &gt; 0.9</td>
<td>135</td>
</tr>
<tr>
<td>6-5</td>
<td>Correlations Between Indices: Comparison with Literature</td>
<td>137</td>
</tr>
<tr>
<td>6-6</td>
<td>Stationarity Test</td>
<td>139</td>
</tr>
<tr>
<td>6-7</td>
<td>Database Stationarity Examples</td>
<td>140</td>
</tr>
<tr>
<td>6-8</td>
<td>Bootstrap 95% Confidence Intervals for Median of Indices</td>
<td>142</td>
</tr>
<tr>
<td>6-9</td>
<td>Comparison of Resting Data with Normative Values</td>
<td>143</td>
</tr>
<tr>
<td>6-10</td>
<td>Summary of Minimum Period (S) for Short-Term Indices</td>
<td>152</td>
</tr>
<tr>
<td>7-1</td>
<td>Fentanyl Dose Range for Clinical Use</td>
<td>157</td>
</tr>
<tr>
<td>7-2</td>
<td>Exclusion Criteria for Fentanyl Study</td>
<td>159</td>
</tr>
<tr>
<td>8-1</td>
<td>Summary of Patient Data</td>
<td>172</td>
</tr>
<tr>
<td>8-2</td>
<td>Subject Details: Age, Fentanyl and Midazolam Dose, and Procedure Time....</td>
<td>172</td>
</tr>
<tr>
<td>8-3</td>
<td>ECG Quality and Processing Comments</td>
<td>173</td>
</tr>
<tr>
<td>8-4</td>
<td>Summary of Respiratory Depression Events for Each Subject</td>
<td>179</td>
</tr>
<tr>
<td>8-5</td>
<td>Details of Key Study Events for Subjects</td>
<td>180</td>
</tr>
<tr>
<td>8-6</td>
<td>Number of Beats Between Key Events</td>
<td>183</td>
</tr>
<tr>
<td>8-7</td>
<td>Post-Fentanyl 95% Confidence Intervals for Median</td>
<td>186</td>
</tr>
<tr>
<td>8-8</td>
<td>Peri-CD 95% Confidence Intervals of Indices</td>
<td>192</td>
</tr>
<tr>
<td>8-9</td>
<td>Peri-UAWO 95% Confidence Intervals of Indices</td>
<td>194</td>
</tr>
<tr>
<td>8-10</td>
<td>Individual Subject HRV Parameters Affecting PolVar20</td>
<td>203</td>
</tr>
<tr>
<td>8-11</td>
<td>Summary of Individual Responses to Selected Indices</td>
<td>205</td>
</tr>
<tr>
<td>9-1</td>
<td>Summary of Effects Known to Impact Fentanyl Results</td>
<td>219</td>
</tr>
</tbody>
</table>
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, SpO₂, ETCO₂, 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.
Acknowledgement

Thanks to the following for their support with resources, technical assistance, clinical and academic advice: Prof. Karen Reynolds for academic support, mentoring and friendship throughout; Prof. Harry Owen for clinical advice and expert anaesthesiology support; John Robson, Robin Woolford and all the staff of the Biomedical Engineering Dept. at Flinders Medical Centre for technical resources, infrastructure support and draft editing; Cormac Fahy for additional anaesthesiology services; John Plummer and Pawel Skuza for advice on all statistical matters; and last but not least, the ever present daily support and reality checks from Daryl and his three children, Nick, Erin and Pat, who allowed me the time and space to complete this undertaking.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANS</td>
<td>autonomic nervous system</td>
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<tr>
<td>CD</td>
<td>central depression</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CO₂</td>
<td>carbon dioxide</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<td>EEG</td>
<td>electroencephalogram</td>
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<td>EMG</td>
<td>electromyography</td>
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<tr>
<td>EOA</td>
<td>epidural opiate analgesia</td>
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<tr>
<td>ETCO₂</td>
<td>end-tidal carbon dioxide (% or mmHg)</td>
</tr>
<tr>
<td>FMC</td>
<td>Flinders Medical Centre</td>
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<tr>
<td>HR</td>
<td>heart rate</td>
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<tr>
<td>HRV</td>
<td>heart rate variability</td>
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<tr>
<td>N₂O</td>
<td>nitrous oxide</td>
</tr>
<tr>
<td>O₂</td>
<td>oxygen</td>
</tr>
<tr>
<td>PCA</td>
<td>patient-controlled anaesthesia</td>
</tr>
<tr>
<td>PETCO₂</td>
<td>partial pressure of end-tidal carbon dioxide (mmHg)</td>
</tr>
<tr>
<td>RD</td>
<td>respiratory depression</td>
</tr>
<tr>
<td>RRI</td>
<td>interval between R-waves on ECG</td>
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<tr>
<td>SpO₂</td>
<td>oxygen saturation</td>
</tr>
<tr>
<td>UADM</td>
<td>upper airway dilator muscles</td>
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<tr>
<td>UAWO</td>
<td>upper airway obstruction</td>
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</tbody>
</table>
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.