

**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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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 <i>Opioid usage</i>	20
2.1.2 <i>Problems with opioid use</i>	22
2.1.3 <i>Incidence of respiratory depression</i>	26
2.1.4 <i>Reducing incidence of respiratory depression in the hospital</i>	28
2.1.5 <i>Summary</i>	31
2.2 OPIOID EFFECT ON RESPIRATION.....	32
2.2.1 <i>ANS</i>	32
2.2.2 <i>Opioid effect on ANS</i>	32
2.2.3 <i>Multiple opioid respiratory effects</i>	34
2.2.4 <i>Airway form and function</i>	35
2.2.5 <i>Normal respiration</i>	39
2.2.6 <i>Respiratory pattern in sleep</i>	43
2.2.7 <i>Opioid effects on respiration</i>	45
2.2.8 <i>Summary opioid effect</i>	46
CHAPTER 3. BACKGROUND: THE HEART AND HEART RATE VARIABILITY	47
3.1 ANATOMY	47
3.2 INNERVATION	47
3.2.1 <i>Sympathetic</i>	48
3.2.2 <i>Parasympathetic</i>	48
3.2.3 <i>Latency</i>	48
3.2.4 <i>Modulation</i>	49
3.2.5 <i>Intrinsic heart rate</i>	49
3.3 RESPIRATORY SINUS ARRHYTHMIA	51
3.4 HEART RATE VARIABILITY, HRV	52
3.4.1 <i>HRV basics</i>	52
3.4.2 <i>HRV measurement</i>	58
3.5 EFFECT OF AIRWAY ON HRV	59
3.5.1 <i>Effect of respiration on HRV</i>	59
3.5.2 <i>Effect of respiratory depression on HRV</i>	60
3.5.3 <i>Effect of airway on HRV</i>	62
3.6 OPIOID EFFECT ON HRV.....	63
3.6.1 <i>Direct effect of opioids on the heart</i>	63
3.6.2 <i>Effect of opioids with anaesthetic agents on HRV</i>	63
3.6.3 <i>Effect of fentanyl on HRV</i>	67
3.6.4 <i>Pre-intubation effect of fentanyl on HRV</i>	68
3.6.5 <i>Respiration-related fentanyl effects</i>	70
3.6.6 <i>Summary of opioid effects on HRV</i>	71
CHAPTER 4. SELECTION OF VERY SHORT-TERM INDICES	73
4.1 AIM	73
4.2 BACKGROUND	73

4.2.1 Short-term HRV	73
4.3 METHOD	74
4.3.1 Survey of HRV indices	74
4.3.2 Coding and testing of indices	74
4.4 RESULTS: SURVEY OF INDICES	75
4.4.1 Coding and testing of indices	75
4.4.2 Traditional time domain indices	76
4.4.3 Spectral indices	80
4.4.4 RSA, Respiratory sinus arrhythmia indices	83
4.4.5 Poincaré plot indices	86
4.4.6 Other indices	94
4.5 DISCUSSION	98
4.5.1 Selection of indices	98
4.5.2 Measures of sympathetic and parasympathetic activity	98
4.5.3 RSA indices	98
4.5.4 Poincaré plot issues	99
4.5.5 Other indices	99
4.5.6 Limited use	99
4.5.7 Problems of spectral analysis	99
4.6 SUMMARY	100
CHAPTER 5. DETERMINATION OF MINIMUM WINDOW SIZE FOR SPECTRAL INDICES	101
5.1 AIM	101
5.2 BACKGROUND	101
5.2.1 Spectral analysis requirements	101
5.2.2 Bias, distortion and contamination	102
5.3 METHOD	102
5.3.1 Resolution of outer limit peaks	102
5.3.2 Resolution of outer limit peaks for decreasing RR-intervals	103
5.3.3 Spectral power of outer limits for decreasing mean RR-intervals	104
5.3.4 Validation with realistic synthesised data	104
5.3.5 Noise	107
5.4 RESULTS	108
5.4.1 Resolution of outer limit peaks	108
5.4.2 Resolution of outer limit peaks for decreasing RR-intervals	110
5.4.3 Spectral power of outer limits	111
5.4.4 Validation with realistic synthesised data	112
5.4.5 Addition of linear trend	116
5.5 DISCUSSION	119
5.5.1 Resolution of LF and HF outer limits	119
5.5.2 Outer limit HF contamination with high heart rate	119
5.5.3 Synthesised realistic signals	119
5.5.4 LF limits	120
5.5.5 Low heart rate	120
5.5.6 Contamination by high-frequency components	121
5.5.7 Nonstationarity: trend or VLF noise	121
5.6 SUMMARY	121
CHAPTER 6. VALIDATION OF VERY SHORT-TERM INDICES	123
6.1 AIM	123
6.2 BACKGROUND	123
6.2.1 Correlations between indices	123
6.2.2 Limited use	124
6.3 METHOD	124
6.3.1 Databases	124
6.3.2 Data analysis	125
6.3.3 Correlation between indices	126
6.3.4 Correlation with mean heart rate	126
6.3.5 Stationarity	126

6.3.6 Confidence intervals.....	127
6.3.7 Non-useful indices.....	128
6.3.8 Statistical considerations and significance.....	128
6.4 RESULTS	131
6.4.1 Correlations between indices.....	131
6.4.2 Correlation with mean heart rate.....	138
6.4.3 Stationarity of data.....	139
6.4.4 Establishment of CI.....	141
6.4.5 Correction for multiple tests.....	141
6.4.6 Comparison of baselines with literature.....	143
6.4.7 Usefulness of indices.....	146
6.5 DISCUSSION.....	148
6.5.1 Correlations of indices.....	148
6.5.2 Stationarity.....	148
6.5.3 Establishment of CI.....	149
6.5.4 Usefulness of short-term indices.....	149
6.5.5 Spectral analysis.....	152
6.5.6 Statistics.....	153
6.5.7 Limitations.....	153
6.6 SUMMARY.....	154
CHAPTER 7. METHOD FOR STUDYING HRV OF FENTANYL-INDUCED LOSS OF AIRWAY TONE.....	155
7.1 INTRODUCTION.....	155
7.2 AIMS.....	155
7.3 DESIGN OF STUDY.....	155
7.3.1 Use of fentanyl.....	156
7.3.2 Fentanyl dose.....	157
7.3.3 Fentanyl and midazolam.....	158
7.4 SUBJECTS.....	158
7.4.1 Number of subjects.....	159
7.4.2 Inclusion criteria.....	159
7.4.3 Exclusion criteria.....	159
7.5 PROCEDURE.....	159
7.5.1 Pillow.....	160
7.5.2 Oxygen.....	160
7.5.3 Noise.....	161
7.6 DATA COLLECTION.....	161
7.6.1 Physiological data.....	161
7.6.2 Analog ECG.....	161
7.6.3 Clinical notes and data synchronisation.....	163
7.7 DATA PROCESSING.....	163
7.7.1 Analog ECG.....	163
7.7.2 Physiological data.....	165
7.8 DATA ANALYSIS.....	166
7.8.1 HRV indices.....	166
7.8.2 Analysis strategies.....	167
7.9 STATISTICAL CONSIDERATIONS.....	168
7.9.1 Confidence intervals.....	168
7.9.2 Statistical significance.....	168
7.9.3 Correction for multiple tests.....	169
7.9.4 Significance of endpoint.....	169
7.9.5 Sample size and power.....	169
7.10 SUMMARY.....	170
CHAPTER 8. RESULTS FOR HRV OF FENTANYL-INDUCED LOSS OF AIRWAY TONE.....	171
8.1 INTRODUCTION.....	171
8.2 PROCEDURE DETAILS.....	171
8.2.1 Subject enrolment.....	171

8.2.2 Fentanyl and midazolam dose	172
8.2.3 Procedure timing	172
8.3 DATA PROCESSING	173
8.3.1 ECG	173
8.3.2 SpO ₂ and ETCO ₂	174
8.3.3 Respiratory depression	176
8.3.4 Relative timing of events	182
8.4 EFFECT OF OXYGEN MASK ON HRV BASELINE	185
8.5 EFFECT OF FENTANYL DOSE ON EXTENT OF RESPIRATORY DEPRESSION	188
8.6 EFFECT OF FENTANYL ON HRV	188
8.7 PERI-RESPIRATORY DEPRESSION	191
8.7.1 Peri-CD	191
8.7.2 Peri-UAWO	193
8.8 INDIVIDUAL DIFFERENCES IN RESPONSE TO RESPIRATORY DEPRESSION EVENTS	195
8.8.1 Time domain indices	196
8.8.2 Spectral indices	196
8.8.3 Significant indices	199
8.8.4 Spikes near UAWO	199
8.8.5 Sustained peaks or dips	202
8.8.6 Consistency of individual responses	205
8.9 STUDENT T-TEST	205
8.10 RESULTS SUMMARY	206
CHAPTER 9. DISCUSSION FOR HRV OF FENTANYL-INDUCED LOSS OF AIRWAY TONE	209
9.1 STUDY DESIGN	209
9.2 FENTANYL EFFECT ON HRV	209
9.2.1 Peak effect of fentanyl	210
9.2.2 Contradictory effects of fentanyl	210
9.2.3 Low-dose midazolam	211
9.2.4 Concomitant midazolam and opioids	211
9.2.5 Anxious subject group	212
9.2.6 Baseline - oxygen mask	213
9.2.7 Respiratory depression	215
9.2.8 Use of HRV over short term periods	216
9.2.9 Pre-existing conditions	217
9.2.10 Summary fentanyl-induced changes on HRV	219
9.3 HRV PRECEDING RESPIRATORY DEPRESSION	220
9.3.1 PolVar20	220
9.3.2 Statistics	221
9.3.3 Endpoint determination	221
9.3.4 Magnitude of respiratory depression	222
9.3.5 Effects of critical respiratory depression	222
9.3.6 Sleep apnoea	223
9.3.7 Implications of pre-existing autonomic neuropathy	225
9.3.8 Other uses for measuring autonomic neuropathy	225
9.4 SUMMARY OF DISCUSSION	226
CHAPTER 10. CONCLUSION	228
10.1 MAIN FINDINGS OVERALL	229
10.2 CONSIDERATIONS FOR FUTURE WORK	230
10.2.1 Use of short-term HRV	230
10.2.2 Sleep apnoea	230
10.2.3 Defining the end-point	230
10.2.4 Morphine	231
10.2.5 Index improvement	231
10.2.6 Screening autonomic activity	232
10.2.7 Critical care applications	232
APPENDIX A IDENTIFIED INDICES	233

A.1 TRADITIONAL TIME DOMAIN INDICES	233
A.2 SPECTRAL POWER INDICES BASED ON LOMB-SCARGLE ALGORITHM.....	234
A.3 RSA INDICES.....	234
A.4 POINCARÉ INDICES.....	234
A.5 OTHER INDICES	237
APPENDIX B MATLAB CODE FOR INDICES	238
B.1 INDEX CODING	238
B.2 FUNCTION ENTRY.....	238
B.3 INDICES.....	240
<i>B.3.1 Time domain indices.....</i>	<i>240</i>
<i>B.3.2 Frequency domain indices.....</i>	<i>242</i>
<i>B.3.3 RSA indices</i>	<i>244</i>
<i>B.3.4 Other indices, a-f.....</i>	<i>245</i>
<i>B.3.5 Other indices, g-n.....</i>	<i>247</i>
<i>B.3.6 Other indices, p-v.....</i>	<i>248</i>
B.4 LONG FUNCTIONS	253
<i>B.4.1 Ataci</i>	<i>253</i>
<i>B.4.2 log_dRR.....</i>	<i>253</i>
<i>B.4.3 polvarxx.....</i>	<i>254</i>
<i>B.4.4 rRRlag0x.....</i>	<i>254</i>
<i>B.4.5 RSA_pv.....</i>	<i>255</i>
<i>B.4.6 TINN.....</i>	<i>256</i>
<i>B.4.7 TRIANG</i>	<i>257</i>
<i>B.4.8 Testdata</i>	<i>258</i>
B.5 LOMB-SCARGLE.....	258
<i>B.5.1 Lomb-Scargle function.....</i>	<i>258</i>
<i>B.5.2 Lomb-Scargle outer limits resolution test function.....</i>	<i>261</i>
<i>B.5.3 Lomb-Scargle synthesised HRV test function</i>	<i>261</i>
B.6 TEST DATA FOR CHECKING INDICES.....	262
APPENDIX C TINN DETAILS	266
APPENDIX D ETHICS APPLICATION	267
REFERENCES.....	277

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 SINUATRIAL (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 5-1 SYNTHESISED SIGNAL WITH OUTER LIMIT PEAKS AT 0.041 AND 0.37 Hz	103
FIGURE 5-2 LOCATION OF FREQUENCY PEAKS IN VLF, LF AND HF	105
FIGURE 5-3 SYNTHESISED SIGNAL WITH MID-RANGE PEAKS AT 0.07 AND 0.24 Hz	106
FIGURE 5-4 LINEAR TRENDS FOR 16 SUBJECTS IN THE EXERCISE DATABASE	107
FIGURE 5-5 SYNTHESISED SIGNAL WITH MID-RANGE PEAKS AND LARGE TREND	108
FIGURE 5-6 OUTER LIMIT (0.041 AND 0.37 Hz) RESOLUTION FOR MEAN RR-INTERVAL 975 MS... ..	109
FIGURE 5-7 OUTER LIMIT RESOLUTION FOR MEAN RR-INTERVAL 600MS.....	110
FIGURE 5-8 OUTER LIMIT RESOLUTION FOR MEAN RR-INTERVAL 500MS (EXERCISE).....	110
FIGURE 5-9 POWER OF OUTER LIMITS (0.041 AND 0.37 Hz)	111
FIGURE 5-10 MEAN RR-INTERVALS FROM PHYSIONET DATABASES.....	112
FIGURE 5-11 ABSOLUTE POWER FOR MID-RANGE PEAKS	113
FIGURE 5-12 PERCENT CHANGE IN POWER OF MID-RANGE PEAKS	114
FIGURE 5-13 RELATIVE POWER, LFNU, HFNU, AND RATIO LF/HF	115
FIGURE 5-14 POWER FOR BRADYCARDIA, MEAN RR-INTERVAL 1200 MS	116
FIGURE 5-15 ADDITION OF SMALL LINEAR TREND, 0.0001T, VLF NOISE.....	117
FIGURE 5-16 ADDITION OF LARGE LINEAR TREND, 0.00066T, SIMILAR TO EXERCISE.....	118
FIGURE 6-1 FALSE DISCOVERY RATE METHOD FOR MULTIPLE TESTS.....	130
FIGURE 6-2 SKEW AND KURTOSIS FOR INDICES USING RESTING DATABASE.....	131
FIGURE 6-3 VISUAL INSPECTION OF CORRELATIONS BETWEEN INDICES, $\rho < 0.96$	136
FIGURE 6-4 INDICES AND MEAN RR-INTERVAL WITH HIGHEST CORRELATIONS	138
FIGURE 6-5 RANKED PROPORTION OVERLAP (POL) OF CONFIDENCE INTERVALS	141
FIGURE 6-6 LOMB-SCARGLE SPECTRAL INDICES SHOW PARADOXICAL CHANGE IN MEDITATION ...	146
FIGURE 6-7 PHYSIOLOGICAL DATABASE BASELINE 95% CONFIDENCE INTERVALS.....	147
FIGURE 7-1 PATIENT DISTRIBUTION FOR FENTANYL DOSE	158
FIGURE 7-2 LAYOUT OF ANAESTHETIC PREPARATION ROOM.....	160
FIGURE 7-3 FREQUENCY RESPONSE OF ANALOG ECG MONITORS.....	162
FIGURE 7-4 RESULTS OF FIRST PASS R-WAVE DETERMINATION.....	164
FIGURE 7-5 MANUAL EDITING OF R-WAVE LOCATION	165
FIGURE 7-6 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 SPO ₂ (MEAN AND RANGE) FOR EACH SUBJECT DURING 4 STAGES OF THE STUDY	175
FIGURE 8-4 ETCO ₂ (MEAN AND RANGE) FOR EACH SUBJECT DURING 3 STAGES OF THE STUDY... ..	175

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 O ₂ 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 O ₂ MASK BASELINE	213
FIGURE 9-2 AUTONOMIC IMBALANCE IDENTIFICATION	218

Tables

TABLE 2-1 CLINICAL USES OF MORPHINE	20
TABLE 2-2 OPIATES USED FOR INDUCING ANALGESIA OR ANAESTHESIA	21
TABLE 2-3 CLINICAL PROBLEMS WITH THERAPEUTIC DOSES OF MORPHINE.....	23
TABLE 2-4 RESPIRATORY DEPRESSION DEFINITIONS.....	24
TABLE 2-5 INCIDENCE OF SEVERE RESPIRATORY DEPRESSION COMPLICATIONS WITH OPIOID ADMINISTRATION.....	26
TABLE 2-6 RELATIONSHIP BETWEEN MEASUREMENT METHOD AND RESPIRATORY DEPRESSION DEFINITION	28
TABLE 2-7 OPIOID EFFECTS WITH NERVE ACTIONS	33
TABLE 2-8 OPIOID EFFECTS ON RESPIRATORY SYSTEM AND MECHANISM	35
TABLE 2-9 INNERVATION OF SOFT PALATE AND GLOSSUS WITH CRANIAL NERVES X AND XI	40
TABLE 2-10 INNERVATION OF PHARYNX AND LARYNX WITH CRANIAL NERVES IX, X AND XI.....	41
TABLE 2-11 INNERVATION OF SOFT PALATE (VELUM), SUPRAHYOID, INFRAHYOID AND GLOSSUS....	42
TABLE 3-1 HRV STUDIES OF ANAESTHETIC AGENTS WITH OPIOIDS PART 1: ANAESTHETIC AGENTS USED.....	63
TABLE 3-2 HRV STUDIES OF ANAESTHETIC AGENTS WITH OPIOIDS PART 2: HRV EFFECTS, POST- INTUBATION	65
TABLE 3-3 HRV STUDIES WITH FENTANYL PART 1: ANAESTHETIC AGENTS USED.....	69
TABLE 3-4 HRV STUDIES WITH FENTANYL PART 2: HRV EFFECTS, PRE-INTUBATION.....	70
TABLE 4-1 TRADITIONAL TIME DOMAIN INDICES:.....	77
TABLE 4-2 SPECTRAL POWER INDICES BASED ON LOMB-SCARGLE ALGORITHM	81
TABLE 4-3 RSA INDICES.....	83
TABLE 4-4 POINCARÉ INDICES.....	91
TABLE 4-5 OTHER INDICES.....	97
TABLE 5-1 FREQUENCY CHARACTERISTICS FOR SPECTRAL DENSITY ANALYSIS.....	102
TABLE 5-2 HRV CHARACTERISTICS DETERMINED FROM PHYSIOLOGICAL DATA.....	105
TABLE 5-3 SINE WAVE PARAMETERS FOR SYNTHETIC SIGNALS	106
TABLE 6-1 DESCRIPTIONS OF PHYSIONET DATABASES	125
TABLE 6-2 NORMALITY OF INDICES WITH SHAPIRO-WILK OR SHAPIRO-FRANCIA TESTS	132
TABLE 6-3 MINIMUM SET OF INDICES NOT CORRELATED WITH EACH OTHER.....	134
TABLE 6-4 INDICES CORRELATED WITH OTHERS SPEARMAN'S RHO>0.9	135
TABLE 6-5 CORRELATIONS BETWEEN INDICES: COMPARISON WITH LITERATURE	137
TABLE 6-6 STATIONARITY TEST	139
TABLE 6-7 DATABASE STATIONARITY EXAMPLES.....	140
TABLE 6-8 BOOTSTRAP 95% CONFIDENCE INTERVALS FOR MEDIAN OF INDICES	142
TABLE 6-9 COMPARISON OF RESTING DATA WITH NORMATIVE VALUES	143
TABLE 6-10 SUMMARY OF MINIMUM PERIOD (S) FOR SHORT-TERM INDICES.....	152
TABLE 7-1 FENTANYL DOSE RANGE FOR CLINICAL USE.....	157
TABLE 7-2 EXCLUSION CRITERIA FOR FENTANYL STUDY.....	159
TABLE 8-1 SUMMARY OF PATIENT DATA	172
TABLE 8-2 SUBJECT DETAILS: AGE, FENTANYL AND MIDAZOLAM DOSE, AND PROCEDURE TIME	172
TABLE 8-3 ECG QUALITY AND PROCESSING COMMENTS	173
TABLE 8-4 SUMMARY OF RESPIRATORY DEPRESSION EVENTS FOR EACH SUBJECT	179
TABLE 8-5 DETAILS OF KEY STUDY EVENTS FOR SUBJECTS.....	180
TABLE 8-6 NUMBER OF BEATS BETWEEN KEY EVENTS	183
TABLE 8-7 POST-FENTANYL 95% CONFIDENCE INTERVALS FOR MEDIAN	186
TABLE 8-8 PERI-CD 95% CONFIDENCE INTERVALS OF INDICES.....	192
TABLE 8-9 PERI-UAWO 95% CONFIDENCE INTERVALS OF INDICES.....	194
TABLE 8-10 INDIVIDUAL SUBJECT HRV PARAMETERS AFFECTING POLVAR20	203
TABLE 8-11 SUMMARY OF INDIVIDUAL RESPONSES TO SELECTED INDICES	205
TABLE 9-1 SUMMARY OF EFFECTS KNOWN TO IMPACT FENTANYL RESULTS	219

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, **PoIVar20**, 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).

PoIVar20 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

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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 ₂ O	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.