

UCL Institute of Child Health

**Haemodynamic instability  
during the intubation of critically-ill children**

Thesis submitted by

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## Dedication

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During a cold night in 2006 I was asked to transfer a sick child from a specialist haematology unit in a Paris teaching hospital to the PICU of another. The eight year old child was suffering from neutropaenia and septic shock following a second failed bone marrow transplant for leukaemia. Although he was conscious at the time of our arrival, he proceeded rapidly to a low output state that required emergency intubation. During induction and intubation his cardiac rhythm changed from sinus tachycardia to asystole and he did not recover after the cardio-pulmonary resuscitation that followed. Before losing consciousness he looked into the eyes of his mother, took her hand and said simply, "C'est fini, Maman...". The circumstances of his death that night, and the birth of my son two years later, led me to embark on this research.

Pour  
Pierre,  
Pierre-loup,  
et Maman

## Declaration

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I conceived of all the studies in this thesis and was responsible for, and participated in, all of the research contained in this thesis. I made the principal contribution to the setting up, supervision and analysis of all of these studies. This work has not been accepted in any previous application for a degree.

However, research is often the product of collaborations, so I would like to list in alphabetical order my principal collaborators and their contributions.

Prof. Alberti	Contributed to the drawing up of the protocol of the ECG study and gave valuable input into the Delphi methodology.
Dr. Benoît	Participated in the setting up of the high-performance liquid chromatography protocol and performed all data collection for the catecholamine analyses.
Dr. Boulkedid	Assisted in the analyses of the arrhythmia ECG and Delphi data.
Prof. Dager	Contributed to the setting up and supervision of the Delphi and ECG study.
Dr. Desbois	Supervised all anaesthetic procedures on all experimental animals.
Mr. Guillaud	Gave valuable technical assistance in the preparation of all experimental animals.
Dr. Kurth	Performed the statistical analysis relating to the propensity score.
Dr. Ovenden	Constructed the algorithm and processed data for Chapter 5.

## Abstract

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Haemodynamic instability is common during critical illness when homeostatic mechanisms are attenuated or already at the limit of their efficacy. Intubation is a crucial life-saving intervention which seeks to stabilize respiratory and cardiovascular function, but itself represents an additional, short-term haemodynamic challenge.

This thesis aimed to investigate changes in heart rate during intubation of critically ill children. Heart rate was chosen as a crude measure of haemodynamic stability because it is most readily available even in time-critical pre-hospital settings. Focusing on heart rate also raised the question of the benefits of atropine pre-medication

The first study was an international survey of Paediatric Intensivists using the Delphi methodology. There was agreement that there is a risk of death during intubation. There was no agreement about the capacity of atropine to reduce the incidence of bradycardia, hypotension or death.

An observational study of 414 intubations in critically ill children was used to provide data for the thesis. Reductions in heart rate were common amongst first intubations in neonates, children between 28 days of age and eight years and further intubations in both groups. The limitations of using the minimum heart rate as a measure of haemodynamic disturbance were considered. An alternative measure of the change in heart rate, or 'lost-beats', was proposed and investigated. Atropine use

was associated with less of a fall in heart rate and fewer lost heart beats during intubation.

There was a strong association between a low heart rate and an increased incidence of arrhythmias and conduction abnormalities during intubation. Arrhythmias and conduction abnormalities were reduced, but not eliminated, by atropine pre-medication. Sinus tachycardia was not observed to convert to ventricular tachycardia or fibrillation when atropine was used.

Mortality during critical care intubation was low (<0.5%). Atropine could not be statistically proven to have an effect on mortality during intubation although was associated with reduced intensive care mortality in children over 28 days of age but not in neonates. The association of atropine pre-medication with reduced PICU mortality in children over one month is unexpected and requires further investigation.

A rabbit model of endotracheal intubation was used to investigate the consequences of vagal activation on blood pressure in hypovolaemia and endotoxaemia. Hypovolaemic rabbits observed a significantly smaller decrease in blood pressure after vagal stimulation than that in control rabbits. The relative change in blood pressure after vagal stimulation was similar between the endotoxaemic rabbits and controls. This finding suggests that different disease states may influence the haemodynamic function during intubation.

## Acknowledgements

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The authors of several Ph.D. theses that I have consulted for style and content have mentioned that the experience was for them 'a journey'. For myself, I would say that it has been more of an adventure, but one that began almost 25 years ago. Before mentioning the names of those who have accompanied me from the start of this adventure I must pay a particular tribute to my brilliant Supervisor, Dr. Mark Peters. I cannot imagine having had a better Supervisor. If this thesis, scientific papers and any future career in medical research that may emerge from it are successful, it is due to Mark and his diligent and cheerful supervision style. Although, I admit that must have been times when Mark's patience was sorely tried, 'You use statistics like a drunk uses a lamp post, for support and not illumination!' (I am sure that this is not an original remark). He once fustigated, 'Don't try to be clever...someone else will always be cleverer than you...'. Thank you for all those precious moments.

Thank you also to Dr. Andy Petros, my Secondary Supervisor, for his support and encouragement throughout the development of this thesis. Fortunately Prof. David Muller and Ms. Stella Fusco overcame their reticence in admitting me to the M.Phil/Ph.D. programme and without their important decision this thesis would never have seen the light of day. They gently supported me in this work and I am greatly indebted to them both. Prof. Janet Stocks and Jana Varma welcomed me warmly into the Portex Unit at ICH and offered me encouragement and generous financial support that enabled me to secure sufficient funding for the animal research. This support was strategic in convincing the Ecole Nationale Vétérinaire d'Alfort that I was serious. I am grateful to my examiners for the time that they have spent reading this thesis. Thank you, also, to the University College London; my first shall be my last.

The start of this adventure was undoubtedly when the exemplary Prof. John Playfair, Emeritus Professor of Immunology at University College London, refused to accept me as his Ph.D. student in 1989. He was right, I needed to 'get on and finish the medicine first'. Nevertheless John, and Dr. Janice Taverne of UCL, were very

formative mentors at an important time in my life. Thanks also to Prof.s Cox and Peters of the University of Cambridge who declined to accept me on the M.B./Ph.D. course in 1990, I wasn't ready and I think that they knew it too.

Prof. John Foreman and the late Prof. John Pegington, both of UCL, and Prof. Thomas Sherwood of Cambridge University gave me a place to read medicine and through their kindness and paternal style ensured that I made it to the end of the course. Similarly, I very am grateful for the support of my parents, particularly in the undergraduate years and particularly for their encouragement to read. In Fort William, Scotland, Dr. Brian Tregaskis offered me his important and unqualified support at a difficult moment in life. Special thanks go to all the Paediatric Consultants, without exception, that I encountered at Nottingham University Hospitals. Their firm belief that there was no future in paediatrics for me gave me the audacity to seek for a different and better life abroad.

Prof. Sir Brian Greenwood of the London School of Hygiene and Tropical Medicine gave me my first real job in research with the Medical Research Council in the Gambia in 1996 and is without doubt one of the greatest physicians of any generation. Without Brian, and his intermittent but generous support over the years, this thesis would never have been written. Thank you to Dr. Alison Wringe, also of the London School of Hygiene and Tropical Medicine, was the first person to suggest that I research for this thesis. Similarly 'Uncle' Dr. Tom Doherty of the Hospital for Tropical Diseases, London ensured that I never got into too much mischief in the Gambia and has always been ready with good advice since, despite the fact that most of it is too colourful to be printed. Not forgetting Prof. Manoj Duraisingh, Professor of Malariology at Harvard, for his generosity of spirit and infectiously positive outlook in life, I only wish that I had contracted more of it.

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Shortly before contracting malaria just south of the front line in Mbandaka during the war in the Democratic Republic of the Congo I was fortunate to meet and be befriended by the remarkable Mme. Claudine André. During my convalescence Claudine introduced me to primatology. Claudine opened my eyes to a different world and was indirectly responsible for the first of my first-author publications. This publication led to the fortuitous contact with Dr. Labib Bakkali at the Ecole Nationale Vétérinaire Alforts, Maison-Alforts and it was due to Labib that I began working with Prof. Hélène Combrisson, one of my two Off-campus Supervisors, M. Laurent Guillaud, and Dr. Christophe Desbois. Without their essential assistance the research described in the final three results chapters of this thesis could not have been accomplished. Dr. Jean-François Benoist of the Hôpital Robert Debré unsparingly gave his time to teach me high-performance liquid chromatography for the analysis of catecholamines.

In 2003 Prof.s Beaufils and Bourillon, both renowned professors of paediatrics in the francophone world, introduced me to Dr. Noëlla Lodé Head of Department of PICU Transport of the Hôpital Robert Debré. Through Noëlla's support I became a Paediatric Consultant in France and then Praticien Hospitalier, the highest grade Hospital Consultant. Noëlla's insistence that I use atropine for all intubations without differentiation, and my natural 'stubbornness', as she would put it, led me to question the usefulness of this most interesting and relatively little understood drug.

Prof. Stéphane Dager, of PICU of the Hôpital Robert Debré, my other Off-campus Supervisor, has for a long time accompanied my research projects and without his firm support none of the chapters of this thesis would ever have been written. Similarly I must thank Dr. Corinne Alberti, Professor of Clinical Epidemiology at the Hôpital Robert Debré for her assistance in the early phases of these projects. Dr. Angie Wade and Miss. Eirini Koutoumanou, both of the ICH, were responsible for turning me from a complete statistical ignoramus into the moderately successful medical researcher that I am today. That they did so against all the odds is a truly extraordinary achievement. Through an informal solicitation Dr. Tobias Kurth made



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### **Publications**

Bradycardia during critical care intubation; mechanisms, significance and atropine  
 An International Delphi Survey of Atropine for Critical Care Intubation  
 by 61 Paediatric Intensivists

## Publications

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### *Publications arising from this thesis*

Jones P, Dauger S, Peters MJ. Bradycardia during critical care intubation: mechanisms, significance and atropine. Arch Dis Child. 2012;97(2):139-44.

Jones P, Boukchedid R, Dauger S, Kisson N, Carcillo J, Alberti C, Peters MJ. An international Delphi survey on the use of atropine for critical care intubation. J Intensive Care Soc. 2012;13(2):2-8.

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Jones P, Peters MJ, PintodaCosta N, Kurth T, Alberti C, Kessous K, Lodé N, Dauger S. Atropine for critical care intubation in a cohort of 264 children and reduced mortality unrelated to effects on bradycardia. PLoSone

### *Papers arising from this thesis in preparation for publication*

Jones P, Ovenden N, Dauger S, Peters MJ. A new definition of heart rate slowing during critical care intubation by estimating 'lost heart beats'

Jones P, Guillard L, Desbois C, Benoît J-F, Combrisson H, Dauger S, Peters MJ Pathology influences changes in blood pressure following vagal stimulation in an animal model of intubation

***Conference abstracts arising from this thesis***

Jones P, Alberti C, Michot C, Neve M, Sachs P, Peters MJ, Dauger S. Incidence des troubles du rythme cardiaque lors de l'intubation en urgence de l'enfant : effets de l'atropine. Société de Réanimation en Langue Française, Paris, France 2010.

Jones P, Peters MJ, Dauger S. How much difference does atropine make to heart rate during emergency intubation? A prospective cohort study of 264 cases. World Congress of Pediatric Intensive Care. Sydney, Australia 2011

***Previous publications related to this thesis***

Jones P, Lodé N. Ventricular fibrillation and defibrillation. Arch Dis Child. 2007;92(10): 916-21.

***Publications during the time of this thesis, unrelated to the thesis***

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## List of Abbreviations

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AbbreviationDescription

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95% CI	95% confidence interval
$\alpha_1$	Alpha-1 catecholamine receptor
$\alpha_2$	Alpha-2 catecholamine receptor
AHA	American Heart Association
AD	Anno domini
ApEn	Appropriate entropy
APLS	Advanced paediatric life support
$\beta_1$	Beta-1 catecholamine receptor
$\beta_2$	Beta-2 catecholamine receptor
BC	Before Christ
BNP	Brain natriuretic peptide
cAMP	Cyclic adenosine monophosphate or 3'-5'-cyclic adenosine monophosphate
$\Delta V$	change in volume
$\Delta P$	change in pleural pressure
DHBA	Dihydroxybenzoic acid
FD	Familial Dysautonomia
ECG	Electrocardiogram
ETT	Endo-tracheal tube
EDTA	Ethylenediaminetetraacetic acid
ENVA	Ecole Natrionale Vétérinaire d'Alfort
HSAN	Hereditary and Sensory Autonomic Neuropathies
HPLC	High performance liquid chromatography
ICI	Imperial Chemical Industries
ICT	Paediatric and neonatal intensive care transport service
ICU	Intensive care unit
ISI	Inverse sequence induction
$l$	length

kPa	kilo Pascal
L-DOPA	L-3,4-dihydroxyphenylalanine
LNT	Linear no-threshold model
MAS	Morphine-atropine-suxamethonium
mmHg	Millimetres of mercury
MODS	Multi-organ dysfunction syndrome
<i>n</i>	viscosity
nM	nano Molar
NICU	Neonatal intensive care unit
NMDA	<i>N</i> -methyl-D-aspartic acid
nonNRD	Non neonatal respiratory distress
NRD	Neonatal respiratory distress
NZW	New Zealand White (rabbits)
OR	Odds ratio
PICU	Paediatric intensive care unit
PRISM	Paediatric RISK of Mortality score
PS	Propensity score
<i>r</i>	radius
RCT	Randomised, controlled trial
RDS	Respiratory distress syndrome
RSI	Rapid sequence induction
SpO <sub>2</sub>	Peripheral saturation in oxygen
USA	United States of America

# **PART ONE**

## **INTRODUCTION/BACKGROUND**

# Chapter One

## Introduction

---

*"The time has come when Belladonna drugs should be tailored to circumstance and not given by rote" Eger 1962(1)*

*'...[the] long-term benefits and adverse effects of [atropine] premedication are unknown'. Kumar et al. 2010(2)*

**H**aemodynamic instability is common during critical illness. Patients with reduced cardio-respiratory reserve may deteriorate further during induction of anaesthesia and intubation.(3, 4) This risk of deterioration relates not only to respiratory factors such as loss of lung volume or risk of aspiration but to loss of acute haemodynamic compensatory mechanisms. Myocardial depressant(5) or vasodilatory effects(6) of induction agents and vagally-mediated responses to hypoxia(7) and/or laryngoscopy(8-10) may all add to the risk of haemodynamic decompensation during intubation.

A degree of haemodynamic instability is encountered frequently during routine anaesthesia and is well-tolerated.(11-13) During critical illness many of the haemodynamic homeostatic mechanisms are attenuated or already at the limit of their efficacy. Hence a relatively minor additional insult may have dramatic consequences. It is a paradox that critical care intubation often takes place to support haemodynamic function yet itself represents a haemodynamic challenge. The APLS 'Golden Hour' Handbook lists *'haemodynamic unstable or hypotensive patients'* as



being candidates for intubation.(14) Ironically it also lists '*hypotension, and bradycardia*' as being complications of intubation.(15)

Adult studies of intubation in critical care settings describe a mortality risk of up to 3%, with prior hypotension being an important associated risk factor (3, 16, 17) and intra-intubation bradycardia being a risk for cardiac arrest.(18) In contrast, studies in critically ill children to date have limited themselves to describing bradycardia.(19-21) As such we do not know the incidence of fatal deterioration during intubation of critically ill children or the associated risk factors.

One of the many factors contributing the intubation risk has long been thought to be readily amenable to treatment. Unwanted efferent vagal discharges in response to hypoxia and/or laryngoscopy can effectively be blocked by inhibition of muscarinic acetylcholine action. In the 1950's the use of the 'vagolytic' drug atropine, as part of induction pre-medication, was proposed specifically to attenuate bradycardia which was often associated with the use of suxamethonium or other relatively cardio-toxic inhalation anaesthetic agents, such as halothane.(22, 23) The subsequent transition away from suxamethonium to less toxic drugs, such as sevoflurane and non-depolarising muscle relaxants, led anaesthetists to question the continued usefulness of atropine.(24-27) Today, the use of atropine has been almost entirely abandoned for routine paediatric pre-medication.(28)

In contrast to the reduction in use of atropine for routine anaesthetic intubation, atropine has been recommended in recent years for use during critical care intubations in neonates(29-32), children under five years (31, 33) and for children in

septic shock.(34) These recommendations exist in the absence of studies assessing at the impact of atropine on heart rate, haemodynamic instability, or outcomes in critically-ill children.(35) In 2010, Kumar *et al.* published a review of premedication for non-emergency intubation in the neonate and noted amongst the '*gaps in knowledge*' that, '*...[the] long-term benefits and adverse effects of [atropine] premedication are unknown*'.(2)

## **1.1 Definition of 'Critical Care Intubation'**

The term 'critical care intubation' is used during the extent of this thesis, as opposed to 'emergent' or 'urgent' intubation which deal with the relative rapidity with which the intubation should be performed.(19) The study seeks to demonstrate the effects of intubation on haemodynamic stability during an episode of critical care illness.

## **1.2 Aims of the study**

The general aim of this thesis is to describe the nature and effects of haemodynamic disturbance, with a focus on heart rate and blood pressure, during intubation of critically ill children and to examine the factors that contribute to instability.

Specifically, the aims of this thesis were to

- 1 establish the perceived frequency of haemodynamic disturbances during intubation among a group of peers and the factors that influence the prescription of atropine.

- 2 describe the range of normal and abnormal heart rates during critical care intubation.
- 3 describe the incidence of arrhythmias after atropine administration and during intubation.
- 4 describe the mortality rate during intubation and the association with atropine use.
- 4 test the hypothesis that hypovolaemia and endotoxaemia have no effect on haemodynamic instability during vagal stimulation in an animal model of intubation.

## Chapter Two

### Background

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#### 2.1 A Short History of Critical Care Illness in Neonates and Children

The treatment of premature infants, or '*faibles*', often translated as '*weaklings*', was introduced in 1898 by Pierre-Constant Budin and other centres opened from 1914 onwards in North America and Western Europe.(36) Pierre-Constant Budin's achievement was the insistence of using maternal milk sometimes using a feeding tube. Although pathological specimens of neonatal respiratory distress syndrome (RDS) exist from as early as 1903, the clinical syndrome was not described until 1932.(37) Mechanical ventilation for RDS did not occur until the 1960's. Exchange transfusion was performed for jaundice and erythroblastosis from 1925 and in 1946 canulation of the umbilical vein was performed for the purposes of exchanging blood.(36) A necessary step in the treatment of the smaller newborns was the maintenance of temperature homeostasis using an incubator which appeared in Boston, USA, shortly before the Second World War.(36)

**Figure 2-1;** Dr. Pierre-Constant Budin (1846-1907), obstetrician and paediatrician who pioneered the treatment of premature and small-for-dates newborns. (This image was obtained from <http://www.neonatology.org/pinups/budin.html> on 17.07.2012).

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The advent of specialist units for the treatment of surgical disease in older children occurred in the 1950's when Everett Koop realised that post-operative care in general surgical wards was insufficient to ensure survival.(36) The foundations of paediatric cardiac surgery were laid just before the Second World War following the repair of a patent *ductus arteriosus* by Gross (38) and the relief of Tetralogy of Fallot by the Blalock-Taussig shunt just after the war.(39)

Specialist units for the care of children were established by anaesthetists from the mid-1950's. In Paris the Hôpital St. Vincent de Paul and in England Alder Hey Children's Hospital were amongst the first.(36) The Hôpital St. Vincent de Paul, where some of the children included in this thesis were hospitalised, has just closed. G. Jackson Rees at Alder Hey introduced the concept of 'convalescent' beds and 'resuscitation' beds that were equipped for general anaesthesia.(36)

Today, the treatment of life-threatening illness in an expanded network of intensive care units in developed, and some developing, countries has been one of the major achievements of modern paediatrics. Diseases that were hitherto regarded as incurable are now amenable to therapy with ventilatory, haemodynamic support and 'blood purification'. Survival continues to improve.(40) Overall PICU mortality in the United Kingdom and Ireland was 5.5% in 2003-2004 and 4.2% in 2008-2010.(41)

## **2.2 A Historical Perspective of Intubation**

The use of the trachea for respiration bypassing the upper airway is by no means a recent phenomenon. Tracheotomy was recorded as having been performed to alleviate an acute obstruction of the upper airway *in extremis* in ancient Egyptian writings of around 3500BC.(42) Emergency tracheotomy has also been described in ancient Arabic(43), Indian(44) and Greek literature.(45) Alexander the Great is credited with having saved the life of an injured soldier on the battlefield by performing an emergency tracheotomy with his sword.(46)

**Figure 2-2;** Alexander the Great at the Battle of Issus in when the young Alexander defeated King Darius III of Persia in 330BC in the struggle for power in Asia. (This image was obtained from <http://www.ciolamuse.com/spip.php?article1> on 17.07.2012).

Asclepiads of Bithynia supposedly carried out a non-emergency tracheotomy (45) and Galen of Pergamum performed artificial ventilation, using a bellows on a dead pig.(47) Without doubt the Renaissance played an essential role both in changing attitudes to, and knowledge of the human body. The practice of dissection provided the knowledge regarding the anatomy and often the physiology of the body. Andreas Vesalius (1514-1564AD) was responsible for the first serious textbook of anatomy first published in 1543, *De humani corporis fabrica*.(48) Indeed, it was Vesalius who is credited with the idea of tracheal intubation to facilitate ventilation when he inserted a reed into the trachea through a tracheotomy of a dying pig into which he intermittently blew.(47, 49)

**Figure 2-3;** Andreas Vesalius (1514-1564AD) (left) published the first serious textbook of anatomy in 1543, *De humani corporis fabrica*. On the right is a feature of one of his anatomical studies showing details of the musculature of the torso and neck. (This image was obtained from <https://www.google.fr/search?q=Andreas+Vesalius+image&hl=fr&prmd=imvnso&tbn=isch&tbo=u&source=univ&sa=X&ei=X9YGUP3kLsel0AWzjvzDDQ&ved=0CF4QsAQ&biw=1366&bih=650> on 17.07.2012).

The first serious study of tracheotomy was published by Armand Trousseau who described a series of 169 cases in 1852.(50) Many of the patients from whom data were collected for this thesis were hospitalised at the Hôpital Armand Trousseau in the XII<sup>e</sup> arrondissement in Paris.

Tracheal intubation using the oro-pharyngeal route probably originated in the mid 1700's when the Chelmsford surgeon Benjamin Pugh inserted a leather-covered coiled wire tube, or 'air-tube', into the trachea and performed intermittent insufflation on an asphyxiated new-born. Later, in 1807, Chaussier produced a curved rigid metal



canula for insertion into the trachea into which he blew.(49) Both of these pioneers were unable to see the tracheal orifice.

**Figure 2-4;** Armand Trousseau (1801-1867) is credited, amongst other achievements, with being the first physician in France to perform a tracheotomy. Note the striking resemblance between Armand Trousseau the young Alexander the Great in Figure 2.2. (This image was obtained from [http://en.wikipedia.org/wiki/Armand\\_Trousseau](http://en.wikipedia.org/wiki/Armand_Trousseau) on 17.07.2012).

The creation of a device enabling direct visualisation of the laryngopharynx was essential to allowed oro- or naso-tracheal intubation to be repeated with reliability.(51) However, progress in the techniques of intubation and ventilation would have been insufficient without parallel evolution in the efficacy and delivery of volatile anaesthetics (from the Greek meaning without sensation, **αν-**, *an-*, 'without' and **αἴσθησις**, *aisthēsis*, 'sensation'). Mechanical ventilation using humidified gases at a constant tidal volume was introduced by Prof. Trendelenberg in 1910 in Leipzig, Germany.(36)

Magill advanced the process of intubation by introducing a laryngoscope blade which enabled the passing the endo-tracheal tube alongside the laryngoscope (52-54) The curving the blade of the laryngoscope, which is so well recognised today was made popular by Macintosh in 1943.(55),

The transfer of anaesthetic skills from the operating theatre to the ward for the provision of chronic respiratory support dated from 1940's and 50's. Björn Ibsen made available chronic respiratory support through tracheotomies for suffers of polio by using medical students to give positive ventilation. Negative pressure ventilation using 'iron lungs' was also employed.(36) Ibsen later commented in an interview, *'what we did was just to use the principles and techniques, which served us well in the operating theatre, also on patients with medical diseases'*.(56)

Volatile anaesthetics have several disadvantages that make them unsuitable from the point of view of their use during critical illness. These are principally the equipment entailed in their vaporisation and their flammable nature when eliminated. As such, the act of intubation remained the domain of the operating theatre. It required the development of liquid anaesthetics, metabolised rather than excreted by the body, to enable tracheal intubation to take place outside theatre.

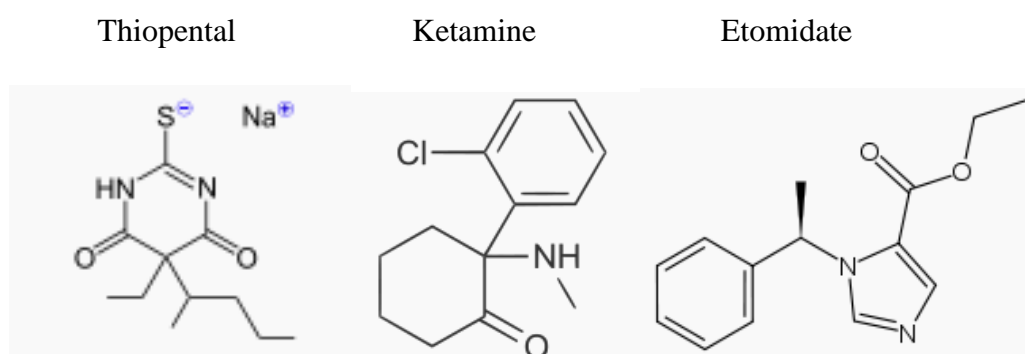
### **2.3           Injectable induction drugs**

The barbiturate thiopental was discovered in the 1930's.(57) Thiopental is an unsatisfactory anaesthetic because of its limited analgesic qualities (57) and negative inotropic properties.(12) It is for this reason that thiopental is frequently administered with a morphine based drug. The NMDA (*N*-methyl-D-aspartic acid) receptor

antagonist ketamine was discovered in 1962.(58) One of the advantages of ketamine is that it is a good analgesic. Ethomidate was discovered in 1960's, and effectively induces amnesia, but again is not a good analgesic.(59) Finally, the powerful hypnotic propofol was first marketed as an emulsion by the then ICI in 1986.

**Figure 2-5;** Molecular structures of A, thiopental, B; ketamine and C; etomidate.

(These images were obtained from [http://en.wikipedia.org/wiki/File:Sodium\\_thiopental.svg](http://en.wikipedia.org/wiki/File:Sodium_thiopental.svg), <http://en.wikipedia.org/wiki/Ketamine> and <http://en.wikipedia.org/wiki/Etomidate> on 17.07.2012).



The combination of anaesthetic agents for 'induction' of anaesthesia and intubation followed by sedation with drugs such as morphine meant that patients could be intubated and ventilated in a pain-free manner.

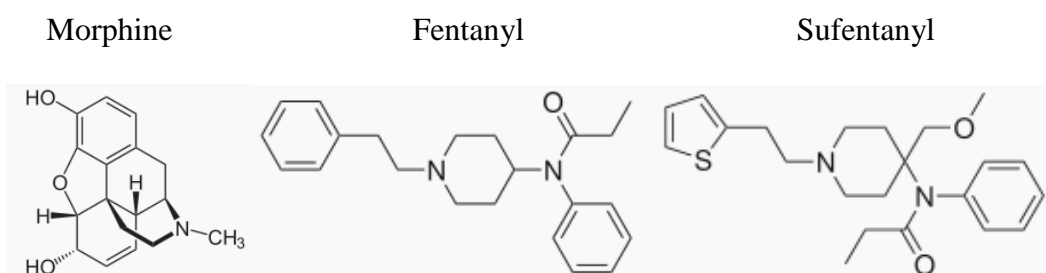
The most widely used sedative agents are the opiates morphine and its modern day fast-acting morphine derivatives (such as sufentanil, fentanyl and remifentanil), all of which are effective analgesics. Morphine (from the Greek god of dreams, Morpheus- **Μορφέας**) is extracted from the latex (opium) derived from the excoriation of poppy seed pods by Friedrich Sertürner in 1804.(60) Morphine is the primary biological constituent of opium and has analgesic properties in relieving the discomfort of the

ETT and inducing a sensation of euphoria, both of which assist coordination with mechanical ventilation.

**Figure 2-6;** Poppy (*Papaver somniferum*) seed pod, left showing the latex containing opium and, right, field of poppy in June 2000, Farah Province, Afghanistan. (The image on the left comes from the Author's collection and that on the right was obtained from [https://www.google.fr/search?q=picture+poppy+seed+pod&hl=fr&prmd=imvns&tbm=isch&tbo=u&source=univ&sa=X&ei=\\_h0JULDmLJSYhQeWjvncQ&ved=0CFMQsAQ&biw=1366&bih=650#hl=fr&tbm=isch&sa=1&q=picture+poppy+seed+pod+opium&oq=picture+poppy+seed+pod+opium&gs\\_l=img.3...64299.65847.0.66123.6.6.0.0.0.173.648.4j2.6.0...0.0...1c.enBZYjF0RvU&bav=on.2,or.r\\_gc.r\\_pw.r\\_qf.,cf.osb&fp=9104bee40e719afc&biw=1366&bih=650](https://www.google.fr/search?q=picture+poppy+seed+pod&hl=fr&prmd=imvns&tbm=isch&tbo=u&source=univ&sa=X&ei=_h0JULDmLJSYhQeWjvncQ&ved=0CFMQsAQ&biw=1366&bih=650#hl=fr&tbm=isch&sa=1&q=picture+poppy+seed+pod+opium&oq=picture+poppy+seed+pod+opium&gs_l=img.3...64299.65847.0.66123.6.6.0.0.0.173.648.4j2.6.0...0.0...1c.enBZYjF0RvU&bav=on.2,or.r_gc.r_pw.r_qf.,cf.osb&fp=9104bee40e719afc&biw=1366&bih=650) on 20.07.2012).



**Figure 2-7;** Molecular structures of morphine and the derivatives fentanyl and sufentanyl. (These images were obtained from <http://en.wikipedia.org/wiki/Morphine>, <http://en.wikipedia.org/wiki/Fentanyl> and <http://en.wikipedia.org/wiki/Sufentanil> on 20.07.2012).



## 2.4 Rapid Sequence Induction

Injectable anaesthetics may insufficiently protect from pain and involuntary muscle tension which may make securing the airway uncomfortable and difficult. The solution was to give a separate paralysing drug in association with the anaesthetic drug. When combined with an injectable anaesthetic outside theatre the phase of ventilation and oxygenation is dispensed with and the intubation becomes one of 'rapid sequence', or rapid sequence induction of anaesthesia for intubation (RSI). Rapid Sequence Induction involves several steps; pre-oxygenation, pre-medication, muscle relaxation and induction, intubation, primary and secondary confirmation and post-intubation patient management.(61) The technique of RSI has been successfully extended to neonates.(32, 62, 63)

### 2.4.1 *Depolarising muscle relaxants*

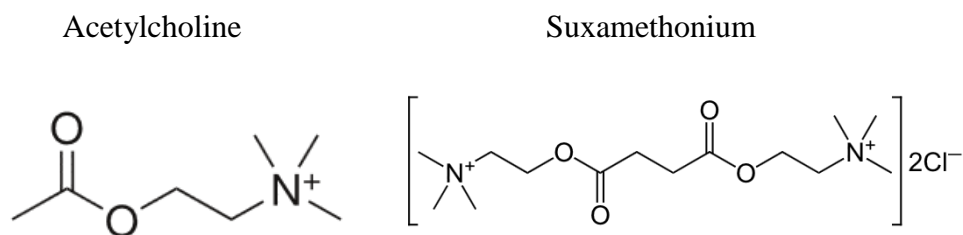
Suxamethonium was derived from the unsatisfactory decamethonium in 1949.(64) Suxamethonium is a non-competitive agonist of acetylcholine on the post-synaptic membrane of nicotinic synapses in muscle which it depolarises before blocking. The structures of acetylcholine and suxamethonium are illustrated in figure 2-8. Acetylcholine is metabolised in fractions of a second whereas the onset of action and elimination of suxamethonium is in the order of 2-4 minutes.(65) Elimination takes place through the activity of the plasma enzyme butyrylcholinesterase and is substantially slower than the metabolism of acetylcholine by acetylcholinesterase.

Suxamethonium was introduced for intubation in theatre. A volatile anaesthetic was administered by manual ventilation with oxygen and then the muscle relaxant

injected prior to intubation. This technique ensured that the patient was both compliant with, and remembered nothing of, the procedure of intubation.

The principal advantage of RSI is that the patient will awaken rapidly. This means that the patient can ensure his own ventilation in case of failure of intubation. Rapid sequence induction is frequently performed in combination with cricothyroid pressure which is supposed to reduce the risk of vomiting and inhalation pneumonitis during intubation, although this last point is disputed.(66)

**Figure 2-8;** Molecular structures of acetylcholine and suxamethonium. (These images were obtained from <http://en.wikipedia.org/wiki/Suxamethonium> and <http://en.wikipedia.org/wiki/Acetylcholine> on 17.07.2012).



Suxamethonium has rapid onset and rapid inactivation but it is not without its disadvantages. The most notable side effects are related to the massive depolarisation of skeletal muscle synapses prior to their inactivation. This provokes an acute rise in plasma potassium concentration, which may have effects on myocardial function and can cause muscle pain following awakening.(67) Malignant hyperthermia is a serious secondary effect and is related to a group of autosomal dominant genes.(67) A separate class of neuromuscular blocking drugs was being developed over the same

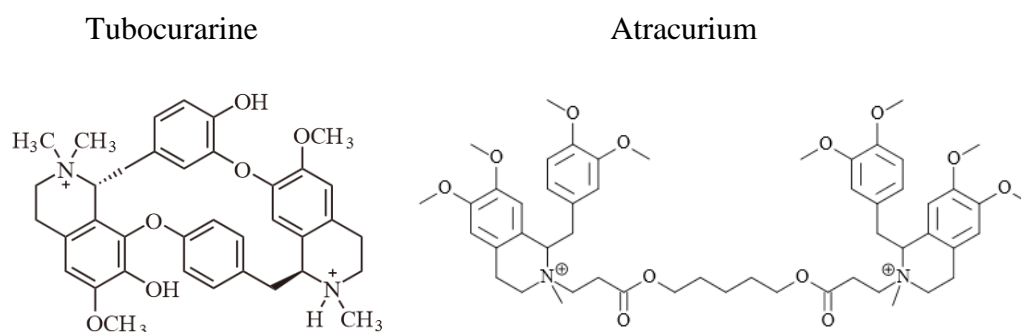
time which would not possess the side-effects of the depolarising muscle relaxants; the curares.

#### 2.4.2 *Non-depolarising muscle relaxants*

The curares are a mixture of alkaloids that were initially derived from *Chondodendron tomentosum*, a South American plant used by Indians when hunting to paralyse their prey.(68) D-tubocurarine was isolated in 1935 with the synthetic atracurium being produced later.(69) All of the curares are quaternary compounds which means that they are poorly absorbed and rapidly excreted. They compete at the post-synaptic acetylcholine receptor, as does suxamethonium, but are non-depolarising. Their secondary effects are that of ganglion blocking and occasional hypersensitivity reactions.(70, 71) Both of which potentially reduce blood pressure.(68) Nevertheless, hypersensitivity reactions to suxamethonium remain more frequent than for the curares.(71) Some disadvantages of the curares are that their onset and duration of action are relatively longer than that of suxamethonium.(68) Another disadvantage of the curares compared to suxamethonium is that the onset of paralysis with suxamethonium is accompanied by visible muscle fasciculation at the end of which the muscles will be in a state of paralysis. Despite this, atracurium is of relatively short action and the technique of Inverse Sequence Induction (ISI) has been developed as an alternative to RSI. In ISI, atracurium is given before the anaesthetic which means that the onset of action of the two drugs is coordinated.(72, 73) The structures of tubocurarine and atracurium are illustrated in figure 2-9.

A recent Cochrane Review noted that both suxamethonium and rocuronium provided excellent intubating conditions; suxamethonium was slightly preferable to rocuronium.(74)

**Figure 2-9;** Molecular structures of tubocurarine and atracurium. (This image was obtained from <http://en.wikipedia.org/wiki/Tubocurarine> and <http://en.wikipedia.org/wiki/Atracurium> on 20.07.2012).



## 2.5 Intubation in Specific Critical Care Scenarios

Individuals with a variety of pathologies can benefit from intubation and ventilation. Globally these can be divided into the following organ systems; respiratory tract, nervous system and circulation. Sometimes the failure of several organ systems, multi-organ dysfunction syndrome (MODS) may require ventilation. Ventilation for neurologic impairment aims to protect the airway and ensure constant respiration, whereas ventilation for respiratory and circulatory failure aims to optimise gaseous transfer and minimise the work of breathing.

### 2.5.1 Nervous system: Central Nervous System Failure

Coma (from the Greek meaning deep sleep, *koma-κῶμα*) is a state of severely depressed consciousness arising from inhibition of brain activity. Any reduction in



the activity of the mesencephalic portion of the reticular activating system of the mid-brain is capable of inducing coma. Diverse types of pathology can induce coma; metabolic derangements such as hypoglycaemia, hypothermia, global brain insults such as cerebral oedema or specific lesions such as stroke, intoxication, prolonged hypoxia and inflammation such as encephalitis. Intubation and ventilation is carried out for three separate reasons. Firstly, the same pathophysiologic processes that are responsible for the coma may provoke respiratory depression by inhibiting the respiratory centre that is located in the brain stem. Secondly, inhibition of laryngeal reflexes may allow inhalation of the stomach contents during regurgitation.(75) Thirdly, there is a risk of severe acute respiratory depression as a result of herniation from increases in intra-cerebral pressure.

## 2.5.2 *Respiratory tract*

### 2.5.2.1 *Reduced lung compliance*

Pathologies that reduce lung compliance increase the work of breathing by exaggerating the effort required to expand the lungs. This is above and beyond the work normally necessary to overcome the natural elastic forces of the parenchyma and is expressed in the equation below;

$$\text{Compliance} = \frac{\Delta V}{\Delta P}$$

,...where  $\Delta V$  is a change in volume and  $\Delta P$  a change in pleural pressure.

Artificial ventilation reduces the work of breathing which increases efficiency of exchange of respiratory gases. Examples of which include respiratory distress syndrome (RDS - previously known as hyaline membrane disease due to its

histopathological appearance) of the newborn infant where surfactant is deficient,(76) infection, pulmonary oedema and lower airway obstruction such as in asthma.

#### 2.5.2.2 *Airway resistance*

The work required to overcome airway resistance can be increased by any narrowing of the airway or airways whether these be in the upper airway. Relatively small constrictions may produce large disturbances in flow even when turbulent flow is not precipitated. Resistance in the airways is governed by Poiseuille's law.

### 2.5.4 *Circulation*

#### 2.5.4.1 *Cardiogenic Shock*

Pump failure may occur due to a variety of reasons whether they are related to muscle malfunction, interruption of the conduction system or abnormalities of the valves or pericardium. Heart failure can be divided into dilated and hypertrophic causes. The most frequent causes of dilated heart failure in a recent North American study are idiopathic, myocarditis, malformation syndromes and inborn errors of metabolism. The principal causes of hypertrophic heart failure are inborn errors of metabolism and malformation syndromes.(77) Geographical variation may have an important influence on epidemiology of heart failure with Kawasaki disease being more common in Japan (78) and typhus in India.(79)

Anatomical defects may create the conditions necessary for a hyperdynamic circulation whereby rapid transfer of blood occurs between the venous and arterial compartments.

The most frequent initial treatment of heart failure is off-loading of the left ventricle by the use of diuretic. Thereafter digoxin and/or inotropic support may be necessary.(77) The long term survival of children with acute fulminating myocarditis has been associated with the left ventricular ejection fraction on arrival at hospital.(80)

#### 2.5.4.2 *Septic Shock*

Septic shock occurs due to disseminated infection in the vasculature. Septic shock causes widespread depletion of anti-oxidants and mitochondrial dysfunction which is a risk for multi-organ dysfunction syndrome.(81, 82) The classical description of septic shock involves the production of endotoxin by gram-negative bacteria which can bring about agglutination of platelets, fever, high cardiac output and particularly prolonged capillary refill time and hypotension due to vasodilatation.(34, 83, 84) The physiological deficits present in septic shock are a reduction in pre-load, and a reduction in left ventricular stroke volume.(85) Early septic shock in the USA is associated with 5-7% mortality with those in established shock having a mortality is as high as 30%.(86) Established haemodynamic disturbance during bacterial meningitis is a risk factor for early mortality.(87) The treatment is through early volume boluses and noradrenaline which correct pre-load and myocardial contractility deficiencies.(88)

#### 2.5.4.3 *Hypovolaemic Shock*

Several diverse conditions can be responsible for hypovolaemic shock. There may be loss of volume as during haemorrhage of blood, loss of water due to vomiting or excessive sweating or loss of plasma as a result of burns. The haemodynamic

response to hypovolaemia depends on the rate of loss of volume. During acute haemorrhage the haemodynamic response is biphasic and asymmetric with the early phase consisting of maintenance of blood pressure in the face of a decrease in cardiac output due to a reduction in left ventricular ejection volume. This can only be achieved by an increase in systemic vascular resistance.(89) The second phase is characterised by falling blood pressure despite a maintenance of cardiac output and is a result of a decrease in systemic vascular resistance.(90, 91)

## **2.6 A very brief Introduction to Haemodynamics**

The heart acts as a pump by its force of contraction. The rate of contraction and volume of blood ejected during each cycle (stroke volume) are equal to the cardiac output (ml/min).

$$\text{Cardiac output} = \text{stroke volume} * \text{heart rate}$$

The vascular resistance to the blood injected into the arterial compartment of the circulation generates blood pressure (mmHg). Both resistance ( $\text{dyn}/\text{cm}^2$ ) and pressure are proportional to one another.

$$\text{Blood pressure} = \text{Cardiac output} * \text{Resistance}$$

Pressure is only a potential for movement of blood. Flow is permitted by a pressure gradient, as is described in Ohm's law. Resistance is the principal factor influencing differential pressure and therefore flow, assuming equal viscosity.

$$\text{Flow} = \frac{\text{Change in pressure}}{\text{Resistance}}$$

The circulation of blood can be described in two manners; linear, equivalent to velocity (cm/s) or flow, which is a specified volume over a period of time (cm<sup>3</sup>/s). Velocity is dependent on the physical properties of the fluid, pressure gradient and the dimensions of the system in which flow is occurring. There is an inverse relationship between flow and the cross sectional area of the tube in which blood is passing. According to Poiseuille's law (the hydraulic resistance equation) the rate of flow is inversely proportion to the power of four of the radius of the airway, and assuming unchanged viscosity.(92)

$$\text{Resistance to flow} = \frac{8nl}{\pi r^4}$$

...,where  $n$  = viscosity,  $l$  = length and  $r$  = radius.

It is important to note that an increase in heart rate or ejection volume will have a linear effect on cardiac output, whereas, according to Poiseuille's law, any change in the radius of the vessels will have an exponential effect on blood flow (assuming that viscosity remains constant).

There are several means by which the body modifies blood flow; by variation in ejection volume, heart rate and/or vascular resistance. The regulation of all three is dependent on the dynamic relationship between the autonomic nervous system and humeral influences. The reaction of the body to hypotension is to attempt to increase cardiac output by increasing vascular resistance, ejection volume and heart rate. These changes are in part mediated by the secretion of catecholamine hormones (principally adrenaline and to a lesser extent noradrenaline) from the adrenal medulla

which can act on the vasculature and heart. An increase in vascular resistance is also mediated by the sympathetic nervous system which acts locally using noradrenaline as a neurotransmitter.

## **2.7 Control of the Circulation**

The autonomic nervous system (ANS) is divided into sympathetic and parasympathetic branches. The ANS effectuates the communication between the vasomotor centre situated in the midbrain and the nervous and humeral mechanisms that regulate blood flow.

### **2.7.1 *The vasomotor centre***

The vasomotor centre consists of an area which controls vascular constriction and dilatation and a sensory area. It is to be found in the reticular substance of the medulla and lower third of the pons.(93) Continuous firing of the vasoconstrictor area is responsible for vascular tone. Hypothalamic and cortical influences are integrated in the vasomotor centre. Heart rate is controlled by the parallel influences of the lateral portions of the vasomotor centre via sympathetic nerves to the heart. These increase heart rate and contractility whilst the medial portions, in immediate juxtaposition to the dorsal motor nucleus, control the parasympathetic Vagus nerve.(93)

### 2.7.2 *The parasympathetic nervous system control of the heart; the Vagus nerve*

The Vagus is the X<sup>th</sup> cranial nerve whose name is derived from the Latin for 'wandering'. Activation of the Vagus nerve reduces the heart rate by reducing the periodical discharge of the sino-atrial node (SAN) which is responsible for the control of heart rate. The SAN is the phylogenic remnant of the *sinus venosus* of lower vertebrate hearts and is situated in the right atrial wall near the insertion of the superior vena cava. Regular spontaneous depolarisations of the cell membranes of the SAN trigger an action potential when an electrophysiological threshold is passed. This activity has often been described as a pacemaker.(94) These depolarisations are conducted through the atrioventricular node along the Purkinje fibres to the apex of the ventricles and ensure rhythmic, coordinated contraction of the heart.

The Vagus also transmits afferent sensory fibres from the aortic bodies that are activated by decreases in oxygen tension and tactile stimulation from the larynx by the superior laryngeal nerve. Particular amongst the cranial nerves the Vagus has both afferent and efferent fibres. It is this quality whereby sensory information and motor responses are transmitted by the same nerve which allows the vagal activation to be described as 'reflex'.

**Figure 2-10;** The anatomy of the Vagus nerve showing afferent sensory fibres from the superior laryngeal nerve and efferent fibres of the cardiac branch which innervate the sino-atrial node. (This image was obtained from [https://www.google.fr/search?q=image+anatomy+vagus+nerve&hl=fr&prmd=imvns&tbm=isch&tbo=u&source=univ&sa=X&ei=CFsJUP6pGcOR0AWMwJWuCg&ved=0CFoQsAQ&biw=1366&bih=650#hl=fr&tbm=isch&sa=1&q=image+vagus+nerve&oq=image+vagus+nerve&gs\\_l=img.3...302178.302178.0.302363.1.1.0.0.0.150.150.0j1.1.0...0.0...1c.t8yE9XAnG3U&bav=on.2,or.r\\_gc.r\\_pw.r\\_qf.,cf.osb&fp=9104bee40e719afc&biw=1366&bih=650](https://www.google.fr/search?q=image+anatomy+vagus+nerve&hl=fr&prmd=imvns&tbm=isch&tbo=u&source=univ&sa=X&ei=CFsJUP6pGcOR0AWMwJWuCg&ved=0CFoQsAQ&biw=1366&bih=650#hl=fr&tbm=isch&sa=1&q=image+vagus+nerve&oq=image+vagus+nerve&gs_l=img.3...302178.302178.0.302363.1.1.0.0.0.150.150.0j1.1.0...0.0...1c.t8yE9XAnG3U&bav=on.2,or.r_gc.r_pw.r_qf.,cf.osb&fp=9104bee40e719afc&biw=1366&bih=650) on 20.07.2012).

### 2.7.3 *Reflex bradycardia : hypoxia.*

Hypoxia in the aortic bodies provokes reflex bradycardia which probably developed as a survival mechanism by early aquatic organisms that needed to cope with currents of hypo-oxygenated water. Primitive organisms which were dependent on oxygen for cellular respiration were obliged to match metabolism to oxygen supply. Later in evolution the same reflex bradycardia protected fish from oxygen deprivation during the temporary collapse of their gills during terrestrial



exploration.(95) Reflex bradycardia is strongly conserved in many animal species and persists in crabs,(96) trout,(97) carp,(98) sturgeons(99) and is enhanced to deal with a return to water by amphibious and diving animals such as frogs(100, 101), turtles(102), ducks(103, 104), elephant seals (105) including armadillos experimentally covered in soil.(106)

We find the same reflex again exploited by certain mammals to adapt circulatory and metabolic needs during the early euthermic stage of hibernation.(107) It is also interesting to note that both tubocurarine and atropine, a selective antagonist of acetylcholine in muscarinic receptors, are both produced by plants. Acetylcholine is also used in non-neuronal cell transmission and these two observations demonstrate the usefulness of acetylcholine in diverse biological systems.(108)

The capacity to induce reflex bradycardia is retained by terrestrial mammals (109) including human children (7) and adults during diving (110, 111) and sleep apnoea (112) probably as an evolutionary vestige. Prior to birth and during the first three to six months of life humans possess an autonomic imbalance due to the dense Vagal innervation of the sino-atrial node and poor sympathetic innervation of the ventricles and conduction bundles.(113) This disequilibrium allows the fetus to mount a defence against the hypo-oxygenation due to the placental hypoperfusion which accompanies contractions during birth. A further manifestation of this is the higher frequency of reflex bradycardia in the young during routine anaesthetic intubation.(4)

Vagally mediated bradycardia is 'compensated' by the selective vasoconstriction of non-vital organs by the vasomotor centre.(95, 114-118) The overall effect is one of

redistribution of blood flow to maintain availability of oxygen to the brain (119) and other vital organs whilst generally reducing metabolite consumption in general (120, 121) and cerebral metabolism in particular.(122)

Free divers exploit the Vagus nerve to depress their heart rate, increase peripheral vasoconstriction and decrease cardiac output all of which aid conservation of oxygen during prolonged submersion.(110, 111, 123, 124) Ventricular escape beats have been observed during episodes of severe bradycardia.(111, 125) It is interesting that there may be a component of neuro-humeral adaptation to repeated episodes of prolonged hypoxia.(110)

Individuals with high cervical cord lesions, generally acquired through injury, have exaggerated bradycardia when sensory afferent vagal fibres are stimulated. This is because unbalanced parasympathetic activity is exerted on the heart by the interruption of transmission between the vasomotor centre and the sympathetic ganglia. During tracheal aspiration or hypoxia severe bradycardia occurs that can sometimes stop the heart.(126, 127) When both the Vagus and sympathetic innervations to the heart are abolished following heart transplant, the bradycardia associated with desaturation during sleep apnoea is abolished.(128)

It is possible that certain individuals may have an innate, exaggerated vagal reflex, or perhaps in sufficient sympathetic tone, due to a genetic predisposition. The result is that the presence of reflux acid around the vocal cords in some infants may be responsible for intense and prolonged bradycardia.(129) It has been suggested that any

such genetic pre-disposition may be associated with sudden infant death syndrome (130, 131) or acute life-threatening events.(132)

The vagal reflex arc has also been postulated to have control over inflammation.(133) Several experimental models have suggested that the immune response may be modulate by cholinergic neurones in such a way that vagal activation may reduce inflammation.

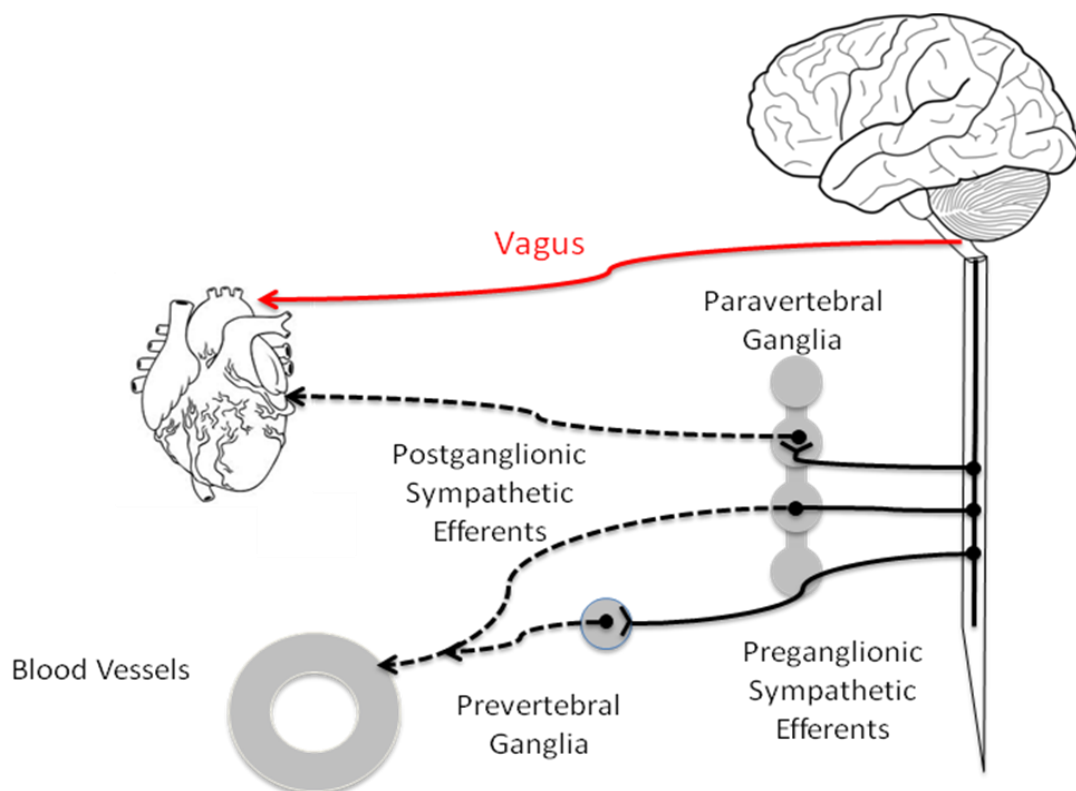
#### **2.7.4        *The sympathetic nervous system control of the heart and vasculature***

Unlike the parasympathetic nervous system, which innervates only the heart, the sympathetic nervous system has vasomotor fibres in the heart and vessels. These are supplied from the upper five or six thoracic and lower one or two cervical segments of the spinal cord.(134) Synapses are situated in the paravertebral chains of ganglia the middle of which joins a plexus with the Vagus nerve in the mediastinum before entering the heart.(134) Fibres from the sympathetic fibres penetrate the heart along the coronary vessels before reaching their insertions in the myocardium. Elsewhere in the body, all the vessels with the exception of the capillaries, pre-capillary sphincters and meta-arterioles are sympathetically innervated.(135) Innervation of the arteries is generally responsible for the phenomenon of resistance to flow and innervation of the veins is responsible for regulating volume and thus right atrial pressure.

The carotid bodies sense changes in blood pressure and transmit impulses by the Glossopharyngeal nerve (the IX<sup>th</sup> cranial nerve) to the vasomotor centre. These have an important influence on sympathetic nervous activity which acts so as to increase blood pressure. The actions on the heart include an increase in heart rate and an

increase in contractility. In parallel, there is an increase in vascular tone. Both of these effects are mediated by the action of noradrenaline on  $\alpha_1$  and  $\alpha_2$  adrenergic receptors situated in post-synaptic membranes of the vasculature and  $\beta_1$  adrenergic receptors situated in the heart.

**Figure 2-11;** Autonomic nervous system control of the circulation showing sympathetic innervation of the heart and vessels. The Vagus nerve efferent innervation of the heart is also shown.



### 2.7.5 *Disease processes may influence autonomic haemodynamic control*

The influence of age on the maturation of the autonomic balance is a feature of the normal development of control on the circulation and has been discussed in 2.7.3.(113) Subsequent autonomic disequilibrium of the autonomic nervous system, or dysautonomia, may develop secondarily or as a result of an inherited genetic

disorder.(136) Secondary dysautonomia may equally arise from the effects of certain diseases. For instance, RDS and prematurity can affect the process of autonomic maturation.(137, 138) Generalized brain injury (139) or specifically to the sympathetic trunk in the thorax (140) can also generate autonomic imbalance. In experimental situations sepsis has been shown to affect baroreceptor activity (141) which may be linked to the direct effect of inflammatory cytokines.(142) Deleterious clinical outcome has been associated with dysautonomia due to brain injury of several causes.(139, 143, 144)

### **2.7.6            *Heart rate variability***

Background heart rate variability results from the dynamic equilibrium of the activation of the SAN by the Vagus nerve, which is almost instantaneous, and by the relative slowness of the sympathetic nervous control, which is in the order of a few seconds. Efferent vasomotor fibres are contained in the Vagus nerve, which uses acetylcholine as a neurotransmitter, and the sympathetic nerves of the autonomic system, that uses noradrenaline as a neurotransmitter. There are very different response times built into the two systems. Acetylcholine is stored in vesicles and is released in sufficient quantities to stop the heart within one cardiac cycle. The metabolism of acetylcholine in the synaptic left is by the enzyme acetylcholinesterase and proceeds in the order of milliseconds. Whereas, the release of noradrenaline is mediated by the secondary messenger cAMP (cyclic adenosine monophosphate) and largely taken up by the pre-synaptic membrane after release from the adrenoceptors.(134) This latter process is in the order of a few seconds. The two systems act differently but synergistically to stabilise the circulation. The

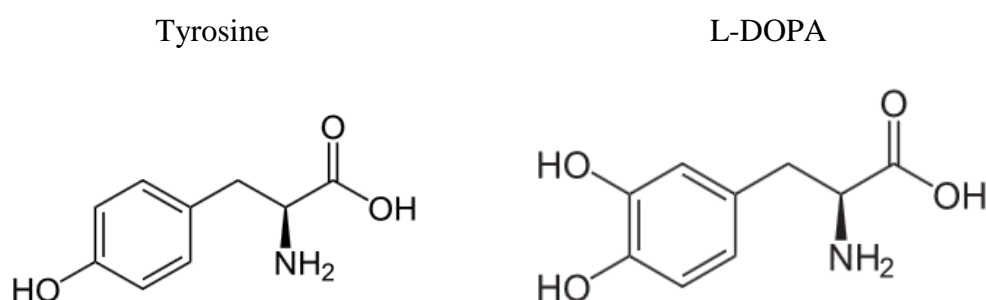
relative differences in the delay of release-metabolism/uptake are responsible for a subtle competition in the control of heart rate whose by-product is variability.

### 2.7.7 *Humeral control of the circulation*

The finding that aqueous extracts from the adrenal glands could induce increases in blood pressure was noted as far back as 1895 by Oliver and Schafer.(145) Indeed, adrenaline was the first chemically identified hormone.(146) Dopamine and noradrenaline were isolated and synthesised later.(147) All three are chemically characterised as catecholamines due to the presence of a catechol nucleus, see figures 2-12 and 2-13.

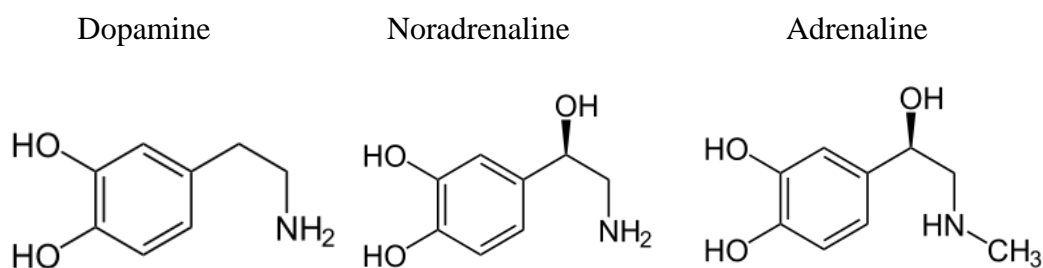
Catecholamines are all derived from the amino acid tyrosine which contains a catechol nucleus (a benzene ring with two hydroxyl groups [1,2-dihydroxybenzene]) with an ethyl side-chain to which is attached a terminal amine (Figure 2-12). Tyrosine is hydroxylated to form L-DOPA (L-3,4-dihydroxyphenylalanine) which is subsequently decarboxylated to dopamine and transported into vesicles in the synapses of the sympathetic nervous system where it is hydroxylated to form noradrenaline.(148)

**Figure 2-12;** Molecular structures of tyrosine and L-DOPA. (This image was obtained from <http://en.wikipedia.org/wiki/Tyrosine> and [http://en.wikipedia.org/wiki/L\\_Dopa](http://en.wikipedia.org/wiki/L_Dopa) on 20.07.2012).



In the adrenal medulla noradrenaline is methylated to form adrenaline for secretion into the blood.(147, 148) Only small quantities of noradrenaline are secreted into the blood from the adrenal medulla.(147) Dopamine and noradrenaline differ from adrenaline in that they are important central nervous system transmitters.

**Figure 2-13;** Molecular structure of dopamine, noradrenaline and adrenaline. (This image was obtained from <http://en.wikipedia.org/wiki/Dopamine>, <http://en.wikipedia.org/wiki/Noradrenaline> and <http://en.wikipedia.org/wiki/Adrenaline> on 20.07.2012).



There are three possible outcomes for noradrenaline molecules following secretion. They may be actively reabsorbed by synapses for recycling (which is the fate of 50 to 80%), they may be destroyed or conjugated locally by tissue enzymes such as *monoamine oxidase* and *catechol-O-methyl transferase* or they may diffuse into the interstitial fluid and from there into the blood.(147-149)

The plasma half-life of plasma catecholamines is of the order of 30 seconds to a few minutes. Metabolism by *monoamine oxidase* and *catechol-O-methyl transferase* taking place principally in the liver.(148)

Catecholamines are responsible for the 'fight-or-flight' reaction that is associated with an increase in blood pressure, heart rate and blood glucose. The actions of

noradrenaline and adrenaline are summarised in Table 2-1. Generally, adrenaline acts upon the heart to increase contractile force and heart rate. Adrenaline also has a vasoconstrictive influence on most vascular beds, skeletal muscle being the principal exception. Noradrenaline has a similar action on the heart but is also vasoconstrictive in skeletal muscle. The effect elicited by adrenoreceptors depends on the type and concentration in any one tissue. Catecholamines are important humeral and nervous mediators in the defence against shock.(150) The actions of noradrenaline and adrenaline in particular serve to maintain perfusion pressure to the vital organs (heart, brain and kidneys). They do this by increasing peripheral vascular resistance, heart rate and cardiac contractile force.(151)

**Table 2-1;** The actions of noradrenaline and adrenaline on adrenergic receptors.(152)

	$\alpha_1$	$\alpha_2$	$\beta_1$	$\beta_2$
Heart rate			increase	
Cardiac contractile force			increase	
Vascular smooth muscle	constrict	constrict		dilate
Noradrenaline	+++	+++	++	+
Adrenaline	++	++	+++	+++

The process of intubation may have a destabilising effect on haemodynamic function by interfering with one or more of the controlling processes outlined above.

### 2.7.8 *Catecholamine analysis methodologies*

Several different methodologies have been used for the determination of plasma catecholamines. Bioassays measure physiological responses, an example of which is



a modification in blood pressure following the injection of adrenal gland extract. These assays are associated with a high level of sensitivity but are not specific.(153) Colorimetry exploits the capacity of plasma to give a carmine colour when exposed to a variety of oxidising agents. This assay not only lacks sensitivity but also specificity.(154) Fluorimetry relies on the property of fluorescence of a phenolic group when adrenaline or noradrenaline solutions are treated with strong alkali.(155) The specificity of this assay is superior to colorimetry with only dopamine interfering and only in large amounts.(156) The disadvantage of fluorimetry is the instability of the reactants which means that the interval between addition of the reactants, completion of the reaction and measurement is critical.(147)

Other possible methodologies for the detection and quantification of catecholamines include gas-liquid chromatography.(147) This is because catecholamines are strongly polar, non-volatile and relatively insoluble in most solvents. An alternative is to use a radiochemical technique but this is time-consuming and the sensitivity has been questioned.(147)

Chromatography, or "colour writing", was developed in the early 1900s by the Russian scientist Tsvet to separate plant pigments. Chromatography can either be used as a purification method on an industrial scale, as is the case in the extraction of petrol from crude oil, or for the analysis of small quantities of molecules in solution. The solution to be analysed, or analyte, is dissolved in what is known as the '*mobile phase*' and is forced at high pressure across a porous '*stationary phase*', which is usually contained in a column. In analytical chromatography reverse-phase systems, ion pairs are formed between appropriate counter ions on the stationary phase and the

ionized catecholamines present in the mobile phase.(147) Differentiation of the constituents to be analysed occurs due to the relative speed through the column. The coefficient of separation is the characteristic that determines the time taken for the analytes to leave the column. During of HPLC analysis, noradrenaline is released from the stationary phase before adrenaline and before dopamine. A mass spectrometer is employed to detect the mass-to-charge-ratio of the mobile phase as it leaves the stationary phase.

High-performance liquid chromatography is the principal method for the determination of catecholamines since the beginning of the 1990s.(157) High-performance liquid chromatography makes use of micro-particulate supports for the separation and quantification of catecholamines.(147) The use of shorter columns has enhanced the concentration of solutes which has improved sensitivity.(147)

Anecdotal evidence from the testing of plasma catecholamines in the Hôpital Robert Debré has indicated that they are rarely found either in normal or shocked children (personal communication, Dr. Jean-François Benoist). However, there are some published studies that have used high-performance liquid chromatography (HPLC) for the analysis of plasma catecholamines with success.(158)

## Chapter Three

### Haemodynamic Instability during Intubation and Anticholinergic Drugs

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#### 3.1 Haemodynamic instability during intubation

The modification of any one of the haemodynamic parameters of ejection volume, heart rate, cardiac output, blood pressure or blood flow during *and as a result of* the process of intubation is considered to be 'haemodynamic instability'.

##### 3.1.1 Heart rate

Electrocardiogram monitoring in normal children has demonstrated that spontaneous variations in heart rate occur occasionally in infants,(159) young children,(160) and boys aged 10-13 years.(161) Regulatory mechanisms promptly re-establish normal heart rate and the individual is unaware of the episode.

Prolonged heart rate slowing, bradycardia (from the Greek 'heart slowness', *brædɪ'kɑrdiə-bradykardía-βραδυκαρδία*), is considered to be abnormal. When bradycardia persists, several consequences may arise. Firstly, the regulatory mechanisms that re-establish heart rate may be inadequate, secondly, a positive feedback loop of bradycardia and coronary hypoperfusion may be set-up and finally, widespread tissue damage may occur from hypoperfusion. The simultaneous presence of pathology may be important in setting the threshold at which these events occur.

Many arbitrary definitions of bradycardia during intubation have been proposed. These are most frequently based on an absolute change in heart rate (11, 13, 162) but any 'bradycardic event' (4, 163), a fall below two standard deviations of the mean heart rate for age (20), three or more beats at  $<60\text{min}^{-1}$  (164),  $<100\text{min}^{-1}$  (165) or percentage reductions in base rate such as 20% (26) or 25% (21) have also been proposed. Such non-agreement over any definition what constitutes bradycardia during intubation inevitably obscures the true frequency of the event. Carroll *et al.* recently looked at a retrospective cohort of emergency intubations using yet another definition of bradycardia ( $<80\text{min}^{-1}$  for  $<2$  years or  $<60\text{min}^{-1}$   $\geq 2$  years) and found a frequency of 10% for emergent intubation compared to 2% for urgent intubations.(19) The most obvious reason for this extra-ordinary lack of consensus is that none of the above authors have tried to link their particular definition of bradycardia to a specific clinical outcome such as changes in other haemodynamic parameters or the clinical outcome of death or neurological deficit. Sing *et al.* considered that a fall of 25% from baseline was a '*haemodynamically significant event*' without any justification or the establishment of a relationship with a defined clinical outcome.(21)

### **3.1.2        *Drug induced bradycardia***

Leigh *et al.* made the important observation in 1957 when using the newly introduced suxamethonium during routine anaesthesia that severe heart rate slowing could occur during the intubation of children.(22) This observation was perhaps the first to indicate that the haemodynamic consequences of intubation in children might be clinically important.

Induction drugs can induce bradycardia due to their capacity to alter autonomic balance and/or by direct effects on the heart and vasculature. The heart slowing related to the use of suxamethonium has been described as 'vagomimetic' because it is an acetylcholine muscarinic receptor agonist. Second doses have a more prominent effect which can be so severe as to provoke asystole.(166, 167) It is probably the most important drug-induced bradycardia and is a well known complication of suxamethonium.(22, 167) Conversely the use of non-depolarising muscle relaxants, such as vecuronium, and rocuronium has been shown to have a tendency to attenuate oculocardiac vagal reflex bradycardia.(168)

During routine anaesthetic use of propofol, a 12% frequency of bradycardia has been noted in children aged less than four.(169) Propofol slows atrio-ventricular node conduction and has been demonstrated to convert supra-ventricular tachycardia to sinus rhythm.(170, 171) Fast acting morphine-like sedation agents such as sufentanyl, and particularly remifentanyl, can also induce bradycardia in both adults (172) and children.(173) Thiopental does not have a direct effect on heart rate.(12)

Those induction agents which have no effects on heart rate include ketamine in experimental situations (174) and etomidate (175) whose use in the emergency department setting has been shown to increase heart rate in children by 10 beats per minute although this may be due to an insufficient analgesic effect.(175)

Myocardial contractility may also be reduced by some drugs, such as for thiopental and ketamine (5) and propofol.(12, 169) Induction agents can also affect vascular tone, vasodilatation being a feature of propofol,(6, 176, 177) thiopentone,(177)

remifentanyl,(178) sufentanyl (179) and morphine.(180) In contrast etomidate (181) and midazolam (182) are not vasodilators.

### **3.1.3        *Reflex bradycardia : hypoxia***

Desaturation of haemoglobin occurs frequently during intubation and is more rapid in younger children and during upper respiratory tract infections.(7, 19, 183, 184) Hypoxia activates chemoreceptors in the aortic bodies which send afferent signals to the vasomotor centre whose response is to lower the heart rate via the Vagus nerve.

### **3.1.4        *Reflex bradycardia : laryngoscopy***

The second source of reflex bradycardia during intubation is the manipulation of the laryngopharynx. During laryngoscopy,(8-10) bronchoscopy,(185) insertion of a gastric catheter,(186) or during oesophagogastroduodenoscopy(187) mechanical stimulation of the laryngopharynx occurs which activates the superior laryngeal nerve. The superior laryngeal nerve is an afferent branch of the Vagus nerve. The number of attempts at intubation (188) or speed of gastric catheter insertion,(186) which are both indirect measures of vigour of laryngopharyngeal stimulation, are associated with more frequent bradycardia.

### **3.1.5        *Tolerance and intolerance of bradycardia***

Prior to birth there is dense vagal innervation of the sino-atrial node which is associated with poor sympathetic innervation of the ventricles and conduction bundles.(113) Periodic uterine contractions may induce placental hypoperfusion during labour. To resist, fetuses use reflex bradycardia to maintain blood pressure (189) and redistribute flow by selective vasoconstriction.(190, 191) After birth there

is a change from parasympathetic dominance to a state of autonomic co-dominance.(192)

Humans have narrow tolerances for hypoperfusion due to hypoxia and have relatively limited access to the adaptive mechanisms possessed by some other animals. For instance, the common map turtle can hibernate without oxygen for several months and seals can dive aerobically for periods in excess of one hour. Such extreme conditions are compensated by adaptive responses that include a reduced dependence of neuronal oxidative metabolism (193, 194), tolerance of cardiac hypoperfusion,(195, 196) increased oxygen (197, 198) and glycogen (199) storage, post bradycardia tachycardia (118) which plays a role in metabolite washout,(196) tolerance of metabolic acidosis by increased buffering,(200) tolerance of increased lactate levels (201) and cellular hypometabolism.(120)

The important difference between reflex bradycardia and drug-induced bradycardia is that during vagal reflex bradycardia the vasomotor centre is activated by efferent signals in the Vagus nerve. This maintains pre-load by vasoconstriction thus preserving ventricular filling, ejection volume, cardiac output whilst also inducing vascular constriction.(115, 202) The net result of reflex bradycardia is a sustaining flow whereas drug-induced bradycardia presents a risk to flow.

Specific cases may be at particular risk of bradycardia. For instance, the potential for isolated cerebral hypoperfusion to affect neurological function is an important clinical outcome to consider. During raised intra-cranial pressure decreases in blood pressure are translated directly into decreases in brain perfusion pressure.(203) This

is an important risk for secondary ischaemia after cranial trauma.(204) One retrospective study of paramedic intubation, as opposed to transport without intubation for traumatic brain injury using a historical control group indicated an overall increase in mortality and neuromorbidity.(205) Preterm infants experience reductions in cerebral blood flow velocities during spontaneous 'central' non-reflex bradycardia. These have been associated with absent end diastolic flow (206) which may be reduced as much as 80% (207) and reductions in cerebral oxygen saturation.(186, 208)

### **3.1.6            *Changes in cardiac output and blood pressure***

During routine anaesthesia using halothane (13) and isoflurane (209) maintenance and immediately after induction intubation with halothane (11), thiopental and suxamethonium (12) and sevoflurane/remifentanil (162) the cardiac index falls. Blood pressure also diminishes after halothane induction in children.(210) Unfortunately there are no similar studies during critical care intubation in children.

Adult studies of intubation in critical care settings have shown that blood pressure falls during intubation and that hypotension is an important associated risk factor for mortality.(3, 16, 17) Marshall *et al.* studied a group of 10 premature infants during intubation noted that blood pressure increased significantly despite a significant fall in heart rate.(9) This effect was probably due to the absence of sedation but may have been due to the vasoconstriction that accompanies reflex bradycardia and which counter-balances reduction in heart rate to maintain, or increase, blood pressure. Nevertheless, this finding has been confirmed by a randomised trial of propofol *versus* morphine-atropine-suxamethonium which



revealed non-significant increases blood pressure from pre-intubation values for both groups.(211) There is a very important differences between the adult and paediatric studies. The adult intubations were carried out in a population where blood pressure was reduced before intubation whereas the infants were intubated for neonatal respiratory distress and had normal blood pressure.

The stimulation of the Vagus nerve is a potential source of haemodynamic instability during intubation. The secretion of acetylcholine in the SAN was considered an early candidate for pharmacological manipulation. Drugs originally derived from the extracts from plants containing anticholinergic properties were used during intubation from the 1950's as a means of reducing the occurrence of bradycardia.(22)

### **3.1.7            *Induction and intubation in familial dysautonomia***

Familial dysautonomia (FD) is a hereditary condition of clinically heterogeneous but genetically distinct disorders otherwise known as hereditary and sensory autonomic neuropathies (HSAN).(212) Familial dysautonomia predominantly affects the Ashkenazi Jewish population.(212) The clinical manifestations of FD are due to incomplete neuronal development and progressive neuronal degeneration of the peripheral and autonomic nervous system.(213) In particular autonomic crises are responsible for bradycardia and/or tachycardia as well as vomiting and profuse sweating along with other symptoms.(213)

Special consideration is required when considering the choice of induction drugs due to the altered effects of drugs that modify the influence of autonomic innervation in FD, ketamine being preferred to thiopental.(214) In addition, excessive vomiting or

sweating can give rise to metabolic disturbances and hypovolaemia which is a risk for anaesthesia particularly in the presence of bradycardia.(213) Despite the potential for bradycardia and hypotension the use of the anticholinergic atropine has not been recommended for routine anaesthetic induction.(213)

### 3.2 Anticholinergic drugs

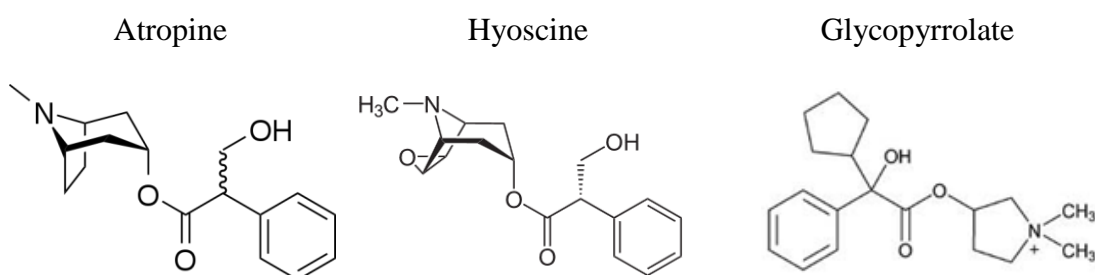
Many plants naturally produce competitive antagonists of acetylcholine. The most frequently exploited derivative is atropine, which is a tropane alkaloid. *Atropa belladonna* (derived from the Italian for beautiful lady because of the effects on pupil dilatation) is the plant that is most frequently associated with the extraction of tropane alkaloids. The common name for *atropa belladonna* is deadly nightshade. Similar plants are to be found in North Africa, Europe and Western Asia. Hyoscine was extracted in 1910 followed by atropine which had a quicker absorption and faster onset of action.(215)

**Figure 3-1;** Deadly nightshade berries source of tropane alkaloids (including atropine), left, and notice indicating the danger involved in ingesting them, right (photos courtesy of Dr. Mark Peters).



Atropine antagonises acetylcholine in muscarinic receptors at the post-synaptic terminal of parasympathetic nerves. As such it prophylactically prevents vagal activation of the sino-atrial node which prevents reflex bradycardia and diminishes non-reflex bradycardia. Alternatives to atropine include glycopyrrolate, better known for its use in sialorrhoea (excessive drooling), and hyoscine.(216, 217) They are equally effective in preventing bradycardia but their side effect profiles differ slightly with atropine having a tendency to induce a higher rate of sinus tachycardia.(217-222) Glycopyrrolate, and particularly hyoscine, have slower onset of action than atropine which is of no significance when used as part of anaesthetic pre-medication but is clearly not conducive to use in the emergency setting where they have not been tested and where no recommendations exist for their use. It is for this reason that this thesis confines itself from here on to looking at atropine exclusively.

**Figure 3-2;** Molecular structures of atropine, hyoscine and glycopyrrolate. (This image was obtained from <http://en.wikipedia.org/wiki/Atropine>, <http://en.wikipedia.org/wiki/Hyoscine> and <http://en.wikipedia.org/wiki/Glycopyrrolate> on 20.07.2012).



### 3.2.1 *Atropine modifies haemodynamic function during intubation*

Prospective electrocardiogram studies during the intubation of infants(210), small (223) and older children and adolescents (26, 164) have shown a general consensus that atropine limits, but does not abolish, falls in base line heart rate. Unfortunately,

the conclusions of these studies are mitigated by their small sample sizes. In intensive care settings a similar trend has been repeated in neonates (224, 225) and one retrospective out-of-hospital study.(21) However, this has not been confirmed by another retrospective study in an emergency department which showed a 4% rate of bradycardia with or without atropine.(20)

Atropine shows a small attenuation of,(210) or no effect on (11, 209) the fall in blood pressure during routine anaesthetic induction with inhalation anaesthetics and has no effect on the reduction in cardiac index caused by remifentanyl.(162) However, atropine does increase cardiac index (13) and blood pressure during maintenance of anaesthesia with halothane (226) or enflurane.(227)

### **3.2.2        *Side effects of atropine***

The side effects on the heart of atropine at normal doses (10 to 20mcg/kg intravenous) in anaesthetic studies are benign in the normal heart and are probably limited to sinus tachycardia. Sinus tachycardia nevertheless increases oxygen consumption (228) and has been shown to reduce ventricular filling and left ventricular end diastolic pressure in normal dogs.(229) This may be of importance in critical care situations.

The true cardiac side effects in a normal heart are best elucidated from the reports of accidental atropine ingestion where dose levels are high. For instance, during the First Gulf War at least 240 children in Israel were poisoned by the injection of adult dose “automatic atropine injector” organophosphorous nerve agent antidotes but no fatalities resulted.(230) Accidental or intentional poisoning of naturally occurring

anticholinergic molecules occurs regularly and cardiac toxicity beyond sinus tachycardia is generally not a feature.(231-235) Similarly, the absence of cardiac toxicity in three children who received more than a thousand times the normal dose illustrates just how safe atropine can be in a normal heart.(236) Both hyoscine and glycopyrrolate induce similar or less tachycardia than atropine.(217, 220, 222)

In an abnormal heart there is one case report which describes a nine year old girl who had spontaneously occurring bigeminism that converted to ventricular tachycardia after administration of atropine (237). The conversion from atropine-induced sinus tachycardia to ventricular tachycardia has not been proven in children or adults.

Non-cardiac, or 'peripheral', side effects in normal children include dilated pupils and dry hands and mouth (238) and pro-hyperthermia (239) are well documented. There exists at least one report of fatal atropine poisoning which was probably related to fever.(240) Other side effects include the inhibition of micturition (233, 241), the relaxation of the oesophageal sphincter (242, 243), a reduction in gastric and colonic motility.(244)

'Central anticholinergic syndrome' occurs more frequently in adults with lethargy or excitatory behaviour, hallucinations and coma.(236) When central effects are encountered in children, hyoscine is classically sedative whereas atropine is excitatory.(217) Stimulation of the Vagus nerve is generally anti-convulsant (245) and atropine possesses pro-convulsant activity.(246) An exception is when the seizures are initiated by hypoxia from breath-holding attacks, in which case atropine is reduces the

frequency of seizures.(247) Glycopyrolate theoretically has little or no CNS activity as it is a quaternary compound and so penetrates the blood-brain barrier poorly.

# **PART TWO**

## **RESULTS**

## Chapter Four

### An International Delphi Survey of Atropine for Critical Care Intubation by 61 Paediatric Intensivists

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#### 4.1 Introduction

Atropine has been recommended to be used as pre-medication for anaesthesia from as early as the 1950s to attenuate vagally-mediated or drug-induced bradycardia during induction and laryngoscopy (22, 164). Later studies showed the advantage of atropine in maintaining cardiac output during halothane induction (11). The subsequent transition to less bradycardia-inducing anaesthetic inhalation agents and non-depolarising muscle relaxants (168) led to the rejection of the routine use of atropine (27).

In contrast, several recent reviews have recommended that neonates (29, 30, 47) and children under five years (33) should receive atropine prior to critical care intubation and the American College of Critical Care Medicine has specifically recommended its use for intubation in septic shock in neonates and children (34). The above recommendations are based on the opinions of a small number of authors, with the exception of that for septic shock, and have appeared without there being any recommended clinical outcome or clinical trials of the efficacy or side effects of atropine in the paediatric intensive care population (248). Currently, the use of pre-intubation atropine is an increasing trend in neonatology as is illustrated by the one recent survey which noted that approximately half of all UK tertiary neonatal units use atropine routinely (32).



Qualitative research methods, such as the Delphi method, are tools for obtaining consensus where scientific evidence is inconclusive or contradictory, as is the case for critical care pre-medication with atropine. The Delphi seeks to establish a quantitative assessment of the level of agreement with a statement amongst a group of experts by a process of ‘Rounds’ of structured questioning regarding a pre-determined statement combined with a system of anonymous, iterative feedback. This feedback enables the participants to modify their opinion with respect to that of the group whilst ensuring that no one participant can dominate the final outcome (249). An advantage of the Delphi Method is that the opinions of a large number of individuals in diverse locations with differing experience and backgrounds can contribute towards enhanced decision making. A disadvantage is that it does not provide quantitative data and so cannot replace the need for clinical trials (250).

Our objective was to use a Delphi approach to determine the qualitative influences on atropine use during critical care intubation by a group of highly experienced and relatively inexperienced Paediatric Intensivists geographically diverse locations. We modified the Delphi to examine atropine prescribing practices to determine whether it was possible to establish recommendations for the use of atropine by means of stratification according to frequency of atropine prescription.

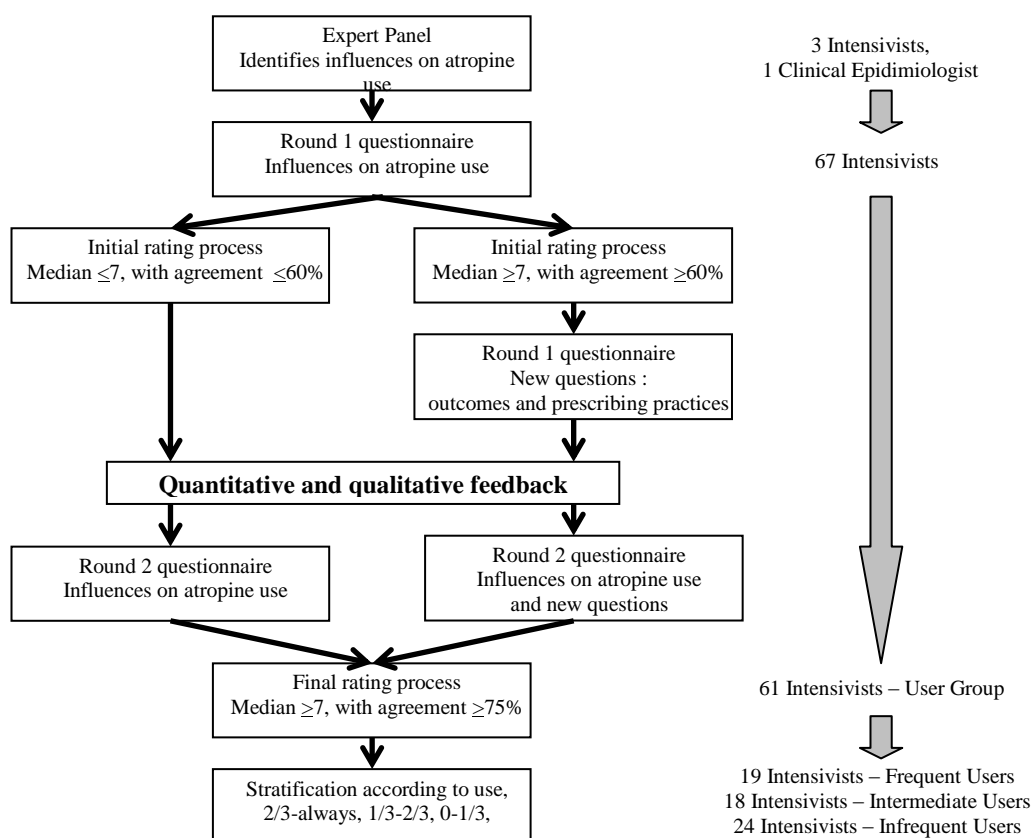
## **4.2 Methods**

### ***4.2.1 Recruitment of the Expert Panel***

An expert panel of three Paediatric Intensivists and a Clinical Epidemiologist was created which examined clinical indicators regarding the influences on atropine prescription, clinical outcome and the influence of atropine on clinical outcomes.

They proposed nine indicators that were formatted into statements contained in the ‘Round 1 questionnaire’ using a Likert-type scale. Independent English and French reverse translations were used to verify accuracy the questionnaire and all other written material. The members of the expert panel were thereafter excluded from participation in the study (Figure 4-1).

**Figure 4-1;** Process of the Delphi survey. The formation of the questionnaire on the influences on atropine prescription was followed by two rounds of questions and structured feedback with a final rating process and stratification for analysis.



#### 4.2.2 Recruitment of the Study Population

An international group of Paediatric Intensivists, or ‘User Group’, was brought together by five Intensivists (Peter Jones, Stéphane Dager, Niranjan Kissoon, Joe

Carcillo, and Mark Peters) who then answered the questionnaires between March 2010 and April 2011. The aim was to include a broad range of age and experience, as has been previously recommended (248, 249). An absolute inclusion criterion was the prerequisite that each Paediatric Intensivist should have two or more years experience in Paediatric Intensive Care and/or Paediatric Intensive Care Transport. Importantly, no information was collected regarding prescribing practices for atropine prior to recruitment. Agreement to participate in the survey was given by all the Paediatric Intensivists when they replied to the Round 1 questionnaire which included a letter explaining the functioning of the Delphi methodology. No financial incentive was offered.

The Paediatric Intensivists were contacted personally or by email and replied to questionnaires principally by email although sometimes by fax. English translations were used by all the UK, USA and Brazilian Paediatric Intensivists and French translations by the French, Swiss and Dutch participants. The Canadian Paediatric Intensivists used either English or French translations according to their preference. The opinions of the Paediatric Intensivists regarding influences on the prescription of atropine were rated according to their level of agreement, or non-agreement the indicators chosen in by the Expert Panel. The Likert Scale rated indicators whereby '1' indicated strong disagreement and '9' strong agreement. In addition, the Paediatric Intensivists were encouraged to provide written comments. Non-responders were motivated to participate through email contacts, in person or by phone by the principal author or the co-author who had recruited them.

### **4.2.3 Process of the study**

An initial rating process rated respondents' answers according to the quantitative level of agreement with the statement at the end of Round 1 (median score) and agreement with each other (percentage of respondents agreeing with a median of 7-9). Three categories of agreement were possible; 1-3 where there was a consensus of non-agreement, 4-6 where there was no consensus and 7-9 where there was a consensus of agreement. Round 1 questionnaires rated above the cut-off with a median score of 7-9 and a consensus of  $\geq 60\%$  agreement could be developed into new statements to examine other influences on atropine prescription. The comments obtained from the User Group were developed into new Round 1 statements. Those Round 1 statements which were rated below the cut-off entered directly into Round 2 (Figure 4-1).

The Round 2 questionnaire included quantitative feedback in the form of the individual's previous response to the Round 1 questionnaire and the median and distribution of the User Group. Qualitative feedback was provided with an anonymised résumé of the longhand comments. The purpose of the feedback contained in the Round 2 questionnaire was two-fold; to enable the Paediatric Intensivist to confirm their previous response and permit them to change their responses with regard to the responses of the other Paediatric Intensivists. A group conversation between the Intensivists was not facilitated, as is sometimes a feature of the Delphi technique, because of the differing time zones which would inevitably be biased by the views of those most freely able to participate.[13] At the end of Phase II a final rating process was used to select indicator/s according to a median score of  $\geq 7$  with a

consensus of  $\geq 75\%$ , as previously used by Shield *et al.* (251). Those statements with a median  $\leq 3$  and a consensus of  $\geq 75\%$  were considered to have obtained a negative consensus. During Round 2 each Paediatric Intensivist was asked to confirm their estimated frequency of atropine use.

The User Group was stratified according to the declared estimated frequency of use of atropine in the following three Stratified Groups; 'Frequent Users' (2/3 to all the time), 'Intermediate Users' (1/3 to 2/3 of the time) and 'Infrequent Users' (0 to 1/3 of the time). For the purposes of analysis, the Frequent Users group was chosen as the reference against which the two other groups' answers were compared.

#### **4.2.4**        *Statistical analysis*

Continuous variables are expressed as a mean (standard deviation) or median [interquartile range] according to their distribution and quantitative variables are expressed as a percentage (%). A Wilcoxon test was used to compare the median score of the User Group answers and a Chi2 test to compare qualitative variables using SAS 9.2 software (Cary, North Carolina, USA).

### **4.3**        **Results**

#### **4.3.1**        *Study population*

Seventy-five Paediatric Intensivists were approached to participate in the User Group of whom 68 completed the Round 1 questionnaire. One was excluded for having been inadvertently included with less than two years experience and 91% (61/67) replied to the Round 2 questionnaire (Figure 4-1). Overall, only three Intensivists (5%) participated with less than five years experience and the distribution of

experience was similar between the three prescribing groups (Table 4-1). The distribution of the 61 according to country is described in descending order; France (34), USA (9), UK (8), Canada (6), Brazil (2), and Switzerland (2).

**Table 4-1;** Characteristics of the 61 Paediatric Intensivists who completed the Round 2 questionnaire. The Frequent Users are used as the reference for comparison of the groups of Intermediate and Infrequent Users. ‘Continental Europe’ countries include France and Switzerland and the ‘Americas and UK’ countries include UK, USA, Brazil and Canada

User Group n=61	Frequent Users (REFERENCE) n=19	Intermediate Users n=18	p	Infrequent Users n=24	p
<b>Sex n= (%)</b>					
Male	14 (74)	15 (83)	0.5	17 (71)	0.8
Female	5 (26)	3 (17)		7 (29)	
<b>Geographical origin n= (%)</b>					
Continental Europe	11 (58)	9 (50)	0.6	15 (63)	0.7
Americas and UK	8 (42)	9 (50)		9 (38)	
<b>Age in years median [IQR]</b>	47[38-52]	43 [40-55]	0.8	44.5 [39-52.5]	0.9
<b>Years of experience median [IQR]</b>	14 [10-23]	15.5 [13-28]	0.5	14.5 [9.5-19]	0.4

#### 4.3.2 Stratification of the Study Population

Forty nine percent (30/61) of the User Group estimated they used atropine for less than half of intubations. Nineteen (31%) were Frequent Users of atropine (2/3 to all the time), 18 (30%) were Intermediate Users (1/3 and 2/3 of the time) and 24 (39%) were Infrequent Users (1/3 to never). There were no significant differences between the three Stratified Groups as regards gender, geographical location (divided into two

groups of countries; Continental Europe or the Americas and UK), age or number of years experience (Table 4-1).

#### **4.3.3 Identification of Influences on Atropine Prescription**

After Round 1, five indicators met the previously determined criteria whereby they could be expanded for development in to new statements, these concerned whether it is the personal decision to prescribe atropine, the age of the patient, the drugs used for induction, the pathology (Q2, 5, 7, 8, Table 4-2) and the influence of atropine on bradycardia (Q9, Table 4-3). The influence of a temperature  $>38.5^{\circ}\text{C}$  achieved a consensus of non-agreement after Round 1 (median 1, 92% agreement, Q6, Table 4-2).

After Round 2, only the statement regarding whether it is the personal decision to use atropine achieved consensus with a median of 7 with 62% agreement in Round 1 compared to median 8 with 81% agreement in Round 2 (Q2, Table 4-2). The indicators of age, induction drug and pathology all retained a median of 7 during Round 2 and slightly increased their levels of agreement; 60 to 64% for age, 61 to 67% for induction drug and 60 to 61% for pathology, none of them achieving final consensus (Q5, 7, 8, Table 4-2).

**Table 4-2;** Results of the Round 2 statements relating to the influences on atropine prescription. The User Group is divided according to the frequency of atropine prescription into the Stratified Groups of Frequent, Intermediate and Infrequent Users. The Intermediate and Infrequent Users are compared against the reference of the Frequent Users.

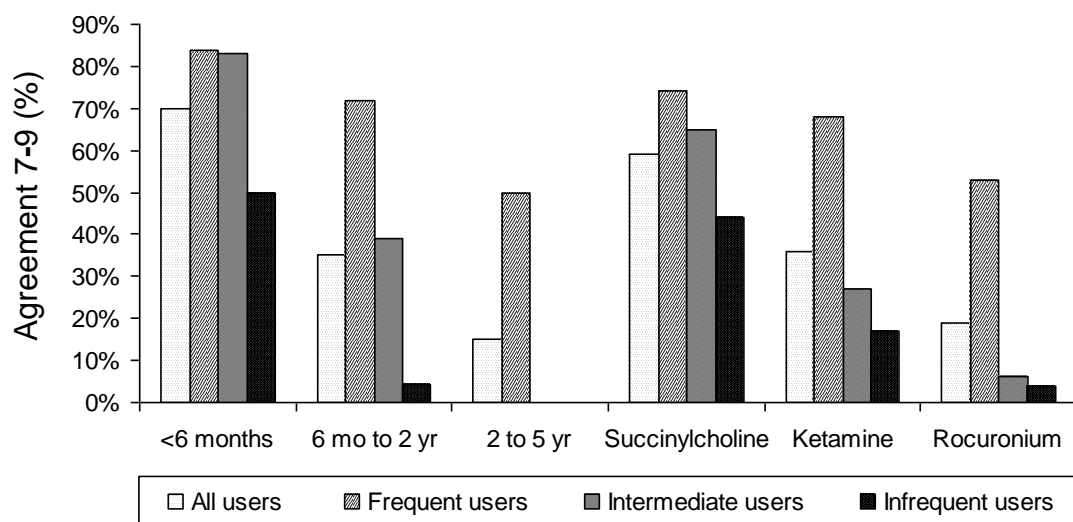
	User Group (n=61) % Agreement between 7-9 Median [IQR]	Frequent Users (n=19) % Agreement between 7-9 Median [IQR] <b>REFERENCE</b>	Intermediate Users (n=18) % Agreement between 7-9 Median [IQR]	Infrequent Users (n=24) % Agreement between 7-9 Med [IQR]
Q1, I routinely respect my unit's protocol regarding atropine administration for induction for emergency intubation §	29% 1.5[1-8]	53% 7 [1-9]	28% 2.5[1-7]	13% 1[1-5]
Q2, It is my personal habit whether I use or do not use atropine during induction for emergency intubation	80% 8[7-9]	84% 8[7-9]	89% 8[7-9]	71% 8[5-9]
Q3, Recommendations from the literature influence my decision to use atropine for induction for emergency	49% 6[3-8]	37% 6[3-7]	78% 7[7-9]*	36% 5[1.5-7.5]
Q4, A high heart rate influences my decision to use atropine for induction for emergency intubation	21% 3[2-6]	21% 4[3-5]	28% 4[3-7]	17% 2[1-5.5]
Q5, The age of the child influences my decision to use atropine for induction for emergency intubation	64% 7[4.5-8]	60% 7[4-8]	78% 8[7-8]	58% 7[1.5-8]
Q6, Fever [ $>38.5^{\circ}\text{C}$ ] influences my decision to use atropine for induction for emergency intubation	0% 1[1-2]	0% 1[1-1]	0% 1[1-2]	0% 1[1-1]
Q7, Certain induction drugs mean I am more likely to use atropine for induction for emergency intubation	61% 7[3-9]	58% 7[3-9]	83% 8[7-9]	46% 4[1-8]
Q8, The pathology influences my decision to use atropine for induction for emergency intubation	67% 7[5-8]	58% 7[5-8]	72% 7[6-8]	71% 7[4-7]

\* -  $p < 0.05$

§ - If there was no unit policy then the Paediatric Intensivists were required to answer '1'.

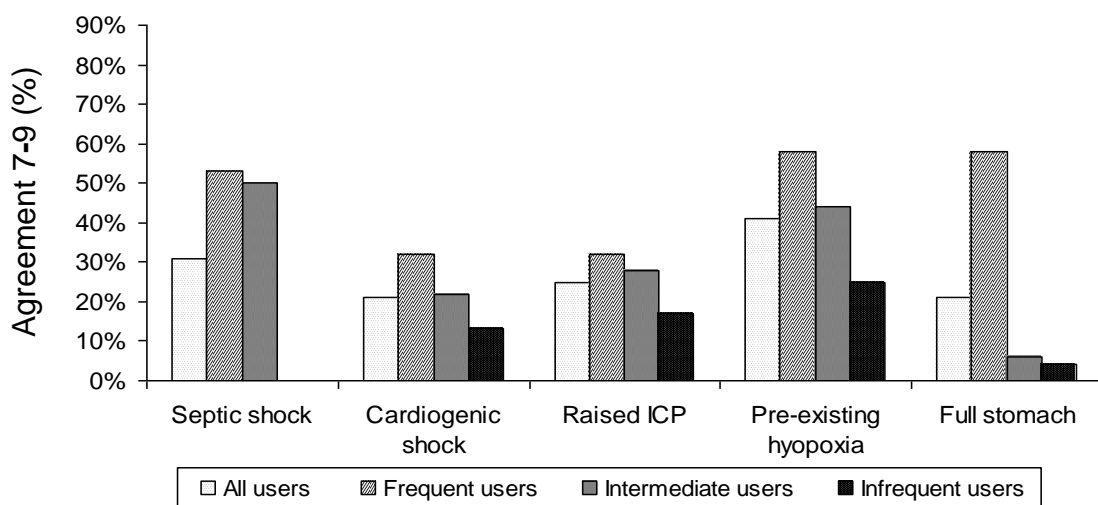


**Figure 4-2;** Results of the Round 2 questionnaire regarding age and induction drugs. The bars represent the percentage of responses in the range of 7 to 9 (meaning that the respondents agreed or agreed strongly with the use of atropine in this scenario). The User Group is divided according to the frequency of atropine prescription into the Stratified Groups of Frequent, Intermediate and Infrequent Users. The Intermediate and Infrequent Users are compared against the reference of the Frequent Users.



The influence of age achieved a Round 2 median score of 7 with a 64% agreement (Q5, Table 4-2). When the statement was narrowed as to whether the practice of the Paediatric Intensivists was to use atropine for children aged less than six months the answer achieved the same median score with a 70% agreement (Figure 4-2). The prescribing practices for induction drugs and pathologies are illustrated in Figures 4-2 and 4-3.

**Figure 4-3;** Results of the Round 2 questionnaire regarding age and induction drugs. The bars represent the percentage of responses in the range of 7 to 9 (meaning that the respondents agreed or agreed strongly with the use of atropine in this scenario). The User Group is divided according to the frequency of atropine prescription into the Stratified Groups of Frequent, Intermediate and Infrequent Users. The Intermediate and Infrequent Users are compared against the reference of the Frequent Users.



#### 4.3.4 *Effect of Atropine on Clinical Outcomes*

The risk of death during intubation achieved consensus when it was first put in Round 1, median 8 with 80% agreement compared to median 8 with 82% in Round 2 although very surprisingly not that for hypotension which had a median 8 with 72% agreement *versus* Round 2 median 8 with 74% agreement (Q10, 12, Table 4-3). There was no consensus that atropine reduces the risk of death (median 4 with 41% agreement) or hypotension at the end of Round 2 (median 3 with 52% agreement) (Q11, 13, Table 4-3).

**Table 4-3;** Results of the Round 2 questionnaire relating to the potential clinical outcomes of intubation and influences on atropine prescription on clinical outcomes. The User Group is divided according to the frequency of atropine prescription into the Stratified Groups of Frequent, Intermediate and Infrequent Users. The Intermediate and Infrequent Users are compared against the reference of the Frequent Users.

	All Users (n=61) % Agreement between 7-9	Frequent Users (n=19) % Agreement between 7-9 Median [IQR] REFERENCE	Intermediate Users (n=18) % Agreement between 7-9 Median [IQR]	Infrequent Users (n=24) % Agreement between 7-9 Med [IQR]
Q9, I believe that atropine prevents bradycardia	52% 7[4.5-8]	68% 8[5-9]	61% 7[4-8]	33% 5[3.5-8]*
Q10, I believe that children are at risk of hypotension (according to your definition) during emergency intubation	74% 8[6-9]	79% 8[7-9]	61% 7.5[6-9]	79% 9[7-9]
Q11, The use of atropine during emergency intubation reduces the risk of hypotension (according to your definition) during the procedure	13% 3[1.5-5]	21% 5[3-6]	17% 5[3-6]	4% 2[1-2.5]*
Q12, I believe that children are at risk dying during emergency intubation	82% 8[7-9]	84% 8[7-9]	83% 7.5[7-9]	87% 8.5[7-9]
Q13, The use of atropine during emergency intubation reduces the risk of dying during the procedure	10% 4[2-6]	26% 5[4-7]	0% 4.5[3-6]	4% 2[1-4.5]*

\* p<0.05

#### 4.4 Discussion

Our study revealed a clear consensus for three indicators. The Paediatric Intensivists agreed that it is their personal decision whether to use atropine (Q2, Table 4-2), that there is a risk of death during critical care intubation (Q12, Table 4-3) and there is a consensus that fever should not influence the decision to use atropine (Q6, Table 4-2). Seventy-four percent of the Intensivists agreed that children are at risk of haemodynamic disturbance (Q10, Table 4-3). Importantly, there was no consensus amongst the User Group as a whole, or in any of the Stratified Groups, that atropine

prevents either bradycardia (Q9, Table 4-3) or reduces the risk of hypotension (Q11, Table 4-3) or death (Q13, Table 4-3).

#### **4.4.1 *Bias in the Study Population***

A recent survey of the Delphi method noted that only 13% of published articles included participants from more than one country.(252) Despite having recruited a relatively large number of Paediatric Intensivists from six countries there was an over-representation of French Intensivists. This was due to the ease of recruitment of this population and potentially limits the general application of the results. We achieved an even distribution of age and experience by group of country for the three Stratified Groups and additionally managed to sustain a high level of participation (91%) which is somewhat above average.(248) We deliberately modified the technique from that using only the very experienced to include the views of a few relatively junior Intensivists with less than five years PICU experience who have a high presence at the bedside.

#### **4.4.2 *The Delphi Methodology***

Quantitative methodologies have the advantage of being able to provide information regarding potential differences when one therapy is employed rather than another. One of their disadvantages is that their conclusions are drawn from populations that may be heterogeneous. Subsequent meta-analyses can be used to enhance their impact. The difference with a qualitative methodology is that the non-trivial importance of years of individual practice, local teaching, discussion, non-scientific bedside testing *as well as* opinion of scientific literature can be assigned a quantitative value.(249) The Delphi methodology is well established but, like other

quantitative methodologies, may fail to give clear results either because of the structure of the questionnaire or anomalies in the selection of the participants or because consensus does not genuinely exist.(250)

It is only possible to speculate as to why so little agreement was forthcoming from our results, particularly with regard to the use of atropine with specific pathologies or drugs. Perhaps there is a critical threshold of literature required for a body of opinion to be formed and this is not the case for our subject. The overall deficiency in convergence of opinion may be related to intransigently held views of Intensivists as a population, as opposed to other specialties, although this should not be taken as a comment on the general applicability of the Delphi methodology in ICU.

The most important bias in the survey is undoubtedly the relationship between influence on prescribing and prescribing itself. Both are subjective judgements and there is no way of separating their influence on each other. There are several reasons why we did not to achieve consensus after Round 2 for more of the indicators. Firstly, and most importantly, whilst the inclusion of heterogeneous opinions is of benefit in generating validity of the results in our survey the Infrequent Users responded almost universally with low scores to all statements.(248, 249) This is ironically both a strength and a weakness as it reduced the possibility of obtaining consensus. The second reason is that there was very little drift towards consensus between the two rounds. On the other hand, that the Paediatric Intensivists did not change their responses between Rounds 1 and 2 is proof of the 'stability' of their opinions. A third reason is linked to the methodology, whereby the statements regarding the 'influences' of, for example induction drugs on atropine prescription,

can be interpreted positively but when the statement is rephrased to determine associations between atropine prescription and, for example ketamine, some Paediatric Intensivists may be positively influenced to prescribe atropine with ketamine whereas others may be negatively influenced.

The most sensitive methodological issue with the Delphi is what is the correct level of consensus should be.(248) The level of consensus is chosen *a priori* by the Investigators and may vary according to study methodologies with inevitable consequences for the conclusions of the study. There is currently there is no quantitative evidence of what should constitute a general level of agreement (218). Our *a priori* use of the 60% agreement cut off during the initial rating process meant that the uniform agreement of the Frequent Users and the Intermediate Users was just able to assure the development of an indicator by virtue of their relative proportion in the study population (37/61, 60%). In practice, however, the selection of an indicator required a high level of agreement among the Frequent and Intermediate Users with the participation of at least some of the Infrequent Users. The use of a cut off of 75% for the final rating process meant that any final consensus needed the substantial participation of all three Stratified Groups including the Infrequent Users.

#### **4.4.3            *Influences on Atropine Prescription***

It is not unexpected that the age of the child influences the administration of atropine even if there was no over-all consensus achieved (Figure 4-2 and Q5, Table 4-2). In the early months after birth there is a predominant parasympathetic autonomic activity due to dense innervation of the sino-atrial node associated with poor innervation of the ventricles and conduction bundles (113) which increases the

likelihood of vagally mediated reflex bradycardia during intubation.(4) Overall, the User Group poorly complied with the 2002 PALS guidelines that all children <1 year and children 1-5 years receiving suxamethonium should also receive atropine (Figure 4-2).(253) Recent guidelines do not give specific recommendations for drugs for rapid sequence induction.

The one consensus of non-agreement that came out of the survey concerns the influence of fever (Q6, Table 4-2). The pro-hyperthermic activity of atropine is due to its ability to diminish sweating and this is a well known complication in the tropics where high ambient temperatures and humidity can raise body temperature during anaesthesia.(239) This is unlikely to be a problem where ambient temperatures are more moderate and so it is unsurprising that the Intensivists' did not see this as a contra-indication to prescription.

The only pathology for which atropine has been specifically recommended is septic shock which failed to achieve a 75% consensus among the practice of any of the three groups of prescribers (Figure 4-2).(34) Indeed, a consensus was not achieved for any of the other pre-existing pathologies or induction drugs that were mentioned by the Paediatric Intensivists in Round 1 (Figures 4-2 and 4-3). Suxamethonium remains one area of practice where anaesthetists use atropine routinely, at least for repeat doses (28) and several published articles clearly indicate the risk severe 'vagomimetic' bradycardia and/or cardiac arrest due to suxamethonium.(22, 167) In contrast, non-depolarising muscle relaxants have been associated with an attenuation of vagal bradycardia so the use of atropine is probably not indicated.(168) Although the use of ketamine has been described during anaesthetic premedication (254) and

Emergency Department sedation (255) the methodology of these studies does not enable a decision to be made as to the value of combining ketamine with atropine.

The Intermediate Users could perhaps be better described as the 'Discerning Users' because they attained 78% agreement (Q3, Table 4-2) regarding whether 'recommendations from the literature' influence their decision to use atropine, much higher than the Frequent (37%) and Infrequent Users (36%). They esteem that the age (78%), pathology (72%) and use of induction drugs (83%) influence their prescribing habits, again more often than the Frequent and Infrequent Users. When they were questioned regarding their practices they tended to agree with one or other of the groups (Figures 4-2 and 4-3). As such, this group and potentially is the best guide as regards practice.

#### **4.4.4. *Effect of Atropine on Clinical Outcomes***

The outcome measures for intubation in paediatric critical care (19, 20) or routine anaesthetic (223) intubation have classically been regarded as change in heart rate because of the high frequency of vagal bradycardia. As such it is perhaps surprising that none of the Stratified Groups achieved a consensus after Round 2 that atropine prevents bradycardia (Q9, Table 43). One retrospective study in a paediatric population has noted a 4% incidence with and without atropine (20) although neonatal studies have been more clear in demonstrating the preventative effect of atropine on bradycardia during critical care intubation.(224) No suggestions were made as to the preferred treatment for bradycardias encountered during intubation. This is a limitation of the Delphi methodology whereby new statements are dependent on free comments arising from previous rounds.



In contrast, the outcomes of studies in adults have focussed on the risk of death or hypotension.(3, 16) Clear consensus was achieved by all three Stratified Groups that there is a risk of death and consensus was nearly achieved that there is a risk of hypotension during critical care intubation (Q10, 12, Table 4-3). However, none of the three Stratified Groups considered that atropine had an effect on either of these two outcomes, not even the Frequent Users, which is perhaps our most important finding (Q11, 13, Table 4-3).

#### **4.5 Conclusion**

In conclusion, despite our demonstration of consensus with regards to some indicators, our survey exposes that the widespread variation in atropine prescription is dependent on personal opinion rather than scientific literature. The Delphi was unable to distinguish clear areas of consensus for prescribing atropine in combination with induction drugs and in certain disease states. In addition, the methodology employed diminished the capacity to achieve positive consensus because the Infrequent Users responded regularly with low scores to all statements. The Intermediate Users are perhaps the most discerning users who generally prescribe atropine for children aged less than 6 months and when using suxamethonium, as did the Frequent Users. Whereas the Intermediate Users did not prescribe atropine when using ketamine or rocuronium and when intubating older children or those with a full stomach, as did the Infrequent Users. Importantly, no consensus was achieved by any of the Stratified Groups regarding the potential benefit of using atropine in reducing the risk of hypotension or death.

## Chapter Five

### A New Definition of Change in Heart Rate during Critical Care Intubation by Estimating 'Lost Heart Beats'

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#### 5.1 Introduction

Bradycardia is the most frequently reported parameter reflecting haemodynamic disturbance during paediatric critical care intubation (CCI).(19, 20, 224, 225) As reviewed above, bradycardia occurs by two mechanisms. Firstly hypoxia in the aortic bodies(7) and/or mechanical stimulation (10) of the laryngopharynx activate the Vagus nerve which reflexly slows the heart due to secretion of acetylcholine in the sino-atrial node. Secondly, some induction drugs, such as propofol,(169) fast-acting morphine compounds(173) and suxamethonium (22) can slow the heart either by direct action on the myocardium or through stimulation of the sino-atrial node. Atropine, reduces activation of the sino-atrial node by antagonising the binding of acetylcholine on the post-synaptic receptor. This attenuates the reduction in heart rate during both routine anaesthetic intubations(22) and those undertaken in the context of critical illness.(30)

When defining heart rate a series of measurements, or point estimates, is made from which a mean value can be calculated. Centiles can be estimated using the variation, or dispersion, from the mean and in children these are often accompanied by an age-adjusted mean.(256) The 95th centile is frequently used to define the limit of 'normal' and 'abnormal'. In the period preceding CCI, age-adjusted normal values are not appropriate to define what a normal heart rate is. This because the presence of critical

illness often with associated systemic inflammation and fever(257), means that demand for metabolites is high so tachycardia is typically present.

Anaesthetic studies commonly describe the change in heart rate from baseline as a measure of cardiovascular impact of intubation.(11, 12, 162, 225) Critical care studies of intubation have generally used threshold values below which the heart rate is considered to be abnormal. In several studies these have been related to normal range for age(19) and include <60beats/min(19, 225), <80beats/min(19) or <100beats/min.(225) Percentage changes from baseline heart rates have also been employed.(21, 209, 210, 223, 258) One study simply used a subjective description of '*clinical significant bradycardia*', which may be specific but is unlikely to be very sensitive.(4)

Our objective was to describe the distribution of in pre-intubation heart rate in the presence of paediatric critical illness in a prospective, observational study. We then aimed to establish a lower 95% confidence interval (95%CI) of heart rate that could be used as a reference. With these we propose a new approach to characterising CCI change in heart rate by calculating the number of 'lost heart beats'. Finally we test this approach by describing the impact of atropine pre-medication on numbers of lost heart beats during CCI.

## **5.2 Methods**

### **5.2.1 Common clinical study methodology for chapters 5, 6 and 7**

Chapters 5, 6 and 7 draw data from a prospective, observational clinical study that was conducted at the Hôpital Robert Debré. The study was approved by the Comité

d'Ethique et d'Evaluation en Recherche Biomédicale of the Groupe Hospitalo-Universitaire-Paris Nord.

All children undergoing intubation, who were not in asystole and were aged less than eight years, were eligible for inclusion. ECG recordings were made in the Paediatric Intensive Care Unit (PICU) and by the Paediatric/Neonatal Intensive Care Transport Service (ICT) of the l'Hôpital Robert Debré, Paris, France, between September 2007 and September 2009. A cut-off of eight years above which children were not included was used as the hospital protocol was not to administer atropine routinely over that age. The prescription of atropine, and other induction drugs, was at the discretion of the attending Intensivist. The hospital dose protocols were as follows; atropine was  $20\mu\text{g}/\text{kg}^{-1}$ , etomidate  $0.4\text{mg}/\text{kg}$ , propofol  $2\text{-}4\text{mg}/\text{kg}$ , ketamine  $1\text{-}2\text{mg}/\text{kg}$ , thiopental  $5\text{mg}/\text{kg}$ , morphine  $0.1\text{mg}/\text{kg}$ , midazolam  $0.1\text{mg}/\text{kg}$ , sufentanyl  $0.2\text{mcg}/\text{kg}$ , suxamethonium  $2\text{mg}/\text{kg}$  less than 18 months and  $1\text{mg}/\text{kg}$  more than 18 months and vecuronium  $0.1\text{mg}/\text{kg}$ .

The following data were prospectively recorded: age, sex, pathology (neonatal respiratory distress [NRD], non-neonatal respiratory distress [non-NRD], cardiac, neurological, ear nose and throat [ENT], sepsis and 'other'), principal sedation drug, adrenaline use and atropine administration.

Those who received atropine were considered as the 'atropine' group and those who did not were considered as the 'non-atropine' group. Children who received atropine after the start of the intubation were included in the non-atropine group on the basis of the intention-*not*-to-treat. The number of attempts at intubation was recorded on

the ECG by the Intensivist. Intermittent SpO<sub>2</sub> values were printed on the ECGs by the monitoring equipment.

During the 24 month recruitment period 414 intubations were performed in the PICU and by the ICT Team. Of these, ECG data were collected during 354 intubations. The three chapters describing change in heart rate during the first intubation (Chapter 5), the incidence of arrhythmia in first and further intubations (Chapter 6) and finally the association between atropine use and mortality during first intubations (Chapter 7) all drew data exclusively from this clinical study. Due to the requirements for the separate objectives in each chapter the number of intubations included in the analysis for each chapter varies.

### **5.2.2      *Process of the study***

Prior to intubation, a one-minute baseline ECG strip (25mm/s) was recorded. Two paediatric intensivists independently estimated the lowest and highest heart rate from the longest and shortest two R-R intervals. The lowest heart rate was subtracted from the highest heart rate, which gave a value for the variation in baseline heart rate. The standard deviation of these variations in baseline heart rate was calculated, divided by two (as above and below the mean) and multiplied by 1.96 to give a 95% confidence interval (C). The baseline heart rate was calculated from the average of the two point estimates.

During intubation, continuous ECG recording started from the moment of insertion of the laryngoscope until the endo-tracheal tube had been positioned in the trachea with a SpO<sub>2</sub> of >95% or connection to a ventilator. Continuous heart rates during intubation

were determined by the measurement of two consecutive R-R intervals every 5.5seconds ( $dt$ ) from the beginning to the end of any episode where the heart rate fell below the lower 95%CI. An interval of 5.5seconds was used because there was a regular break in the PICU ECG recordings between 7-11seconds. The potential loss of beats during any 5.5 second interval was considered to be without clinical consequences. So as not to record an infinite number of lost beats, the heart rate any children who became asystolic was considered to have returned to normal at the moment of the start of asystole. Missing data in the ECG recordings were averaged between the previous and next heart rate for no more than one 5.5second interval every five periods of 5.5seconds. Where data were missing for two consecutive intervals of 5.5 seconds the intubation was excluded. Those ECGs where more than 10% of data were missing were also excluded.

### 5.2.3 *Algorithm for Calculation of Lost Beats*

The number of lost heart beats was calculated by a two-step algorithm;

When  $C$  was subtracted from the mean of the baseline heart rate for any individual, a fall in heart rate below this number was defined as 'abnormal' and resulted in beats being 'lost'.

The second step involved the estimation of the number of lost beats according to the following formula; a total number of readings  $N$  (meaning that the total time interval measured was  $T=(N -1) dt$  seconds) and a series of ECG values  $e_i = e(t_i)$  at each time interval  $i = 1, \dots, N$  gave the total area below the lower 95% confidence interval. The integral represents the number of 'lost heart beats' by,...

$$\mathcal{LB} = \int_0^T \frac{1}{60} \max(0, C - \epsilon(t)) dt$$

...where  $t$  and  $T$  are measured in seconds. A numerical trapezoidal approximation is used to calculate this interval.

Finally, the means and medians of the changes in heart rate from baseline and lost beats, with and without atropine, were compared.

#### **5.2.4**      *Statistical analysis*

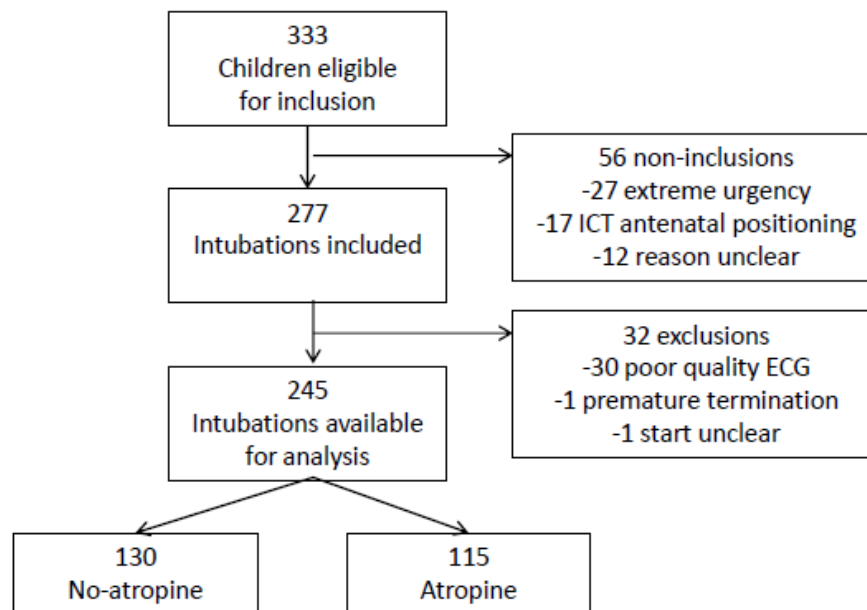
Qualitative variables are described as numbers and percentages (%) and quantitative variables as median [quartiles] or mean (standard deviation) according to their Gaussian distribution. Independent t-tests or a Wilcoxon test were used for continuous data and Fisher's exact test for categorical data. All statistical tests were 2-sided and the probability of a type 1 error ( $\alpha$ ) was determined at  $<0.05$ . All statistical tests were carried out using SPSS (version 19).

### **5.3**            **Results**

#### **5.3.1**          *Study Population*

A total of 333 first intubations in children were eligible for inclusion, 277 intubations were included and 245 available for analysis (74%), see Figure 5-1 for the details for non-inclusions and exclusions. Ninety-eight children were included from PICU and 147 from ICT. Atropine was prescribed for 115 (47%) of intubations. One child died during intubation.

**Figure 5-1;** Flow chart of inclusions, non-inclusions and exclusions with the number of intubations available for analysis according to atropine use.



The children who received atropine were significantly younger and had slower baseline heart rates. Children who were intubated for non-NRD and those who were intubated with propofol or ketamine received significantly less atropine (Table 5-1).



**Table 5-1;** Population characteristics of the 245 children intubated.

	245 first intubations		
	No-atropine n=130 (%)	Atropine n=115 (%)	P
Age (days, IQR)	19 [0-188]	1 [0-67]	0.047*
Mean baseline heart rate, beats/min ( $\pm$ SD)	156 (123-179)	150 (124-176)	0.03*
Median variation in baseline heart rate, beats/min [ $\pm$ IQR]	9 [5-15]	10 [6-16]	0.40
Sex (boys)	72 (55)	78 (68)	0.06
Neonatal respiratory distress	55 (42)	59 (51)	0.20
Non-Neonatal respiratory distress	36 (28)	16 (14)	0.01*
Cardiac	9 (7)	4 (3)	0.27
Ear nose and throat	8 (6)	8 (7)	0.80
Neurologic	10 (8)	18 (16)	0.07
Sepsis	9 (7)	7 (6)	1.00
Other	3 (2)	3 (3)	1.00
No drugs	34 (26)	35 (30)	0.48
Ethomidate	5 (4)	5 (4)	1.00
Propofol	38 (29)	20 (17)	0.04*
Ketamine	10 (8)	1 (1)	0.01*
Sufentanyl	14 (11)	19 (17)	0.20
Morphine	17 (13)	12 (10)	0.56
Midazolam	11 (8)	20 (17)	0.06
Other	1 (1)	3 (2)	0.63
Suxamethonium	4 (3)	6 (5)	0.52
Vecuronium	4 (3)	0	0.13

\* Signifies a statistically significant difference,  $p < 0.05$

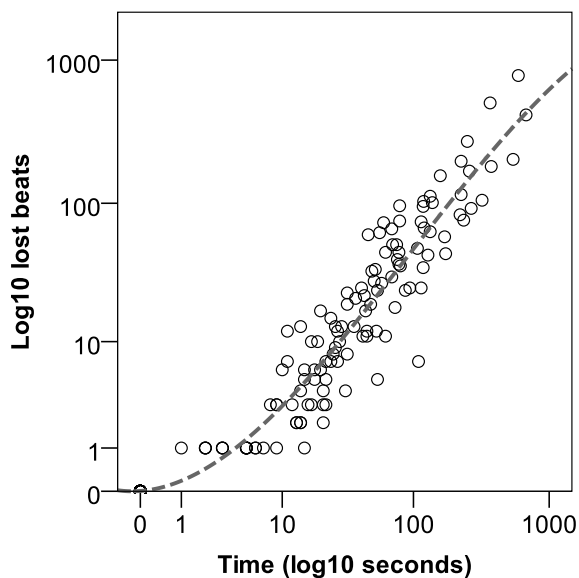
### 5.3.2 Calculation of Lost Beats

Mean baseline heart rate was 153.3beats/min (128.8-177.8) for all patients. The standard deviation of the variation in individual baseline heart rate was

14.5beats/min, which when multiplied by 1.96 gave the 95%CI of the variability in baseline heart rate (28.4beats/min). The 95%CI was divided by two to account for variation above and below the mean (14.2 beats/min). The variation in heart rate was not modified by age (results not shown).

There was a close linear relationship between the number of lost beats and the time spent below the lower limit of normal (Figure 5-2). The slope of the best fit line is approximately  $45^\circ$  which means that for every one second spent below the 95%CI one heart beat is lost.

**Figure 5-2;** Relationship between the time and the number of beats lost during intubation. There is a close linear relationship with an  $r^2$  of 0.93.

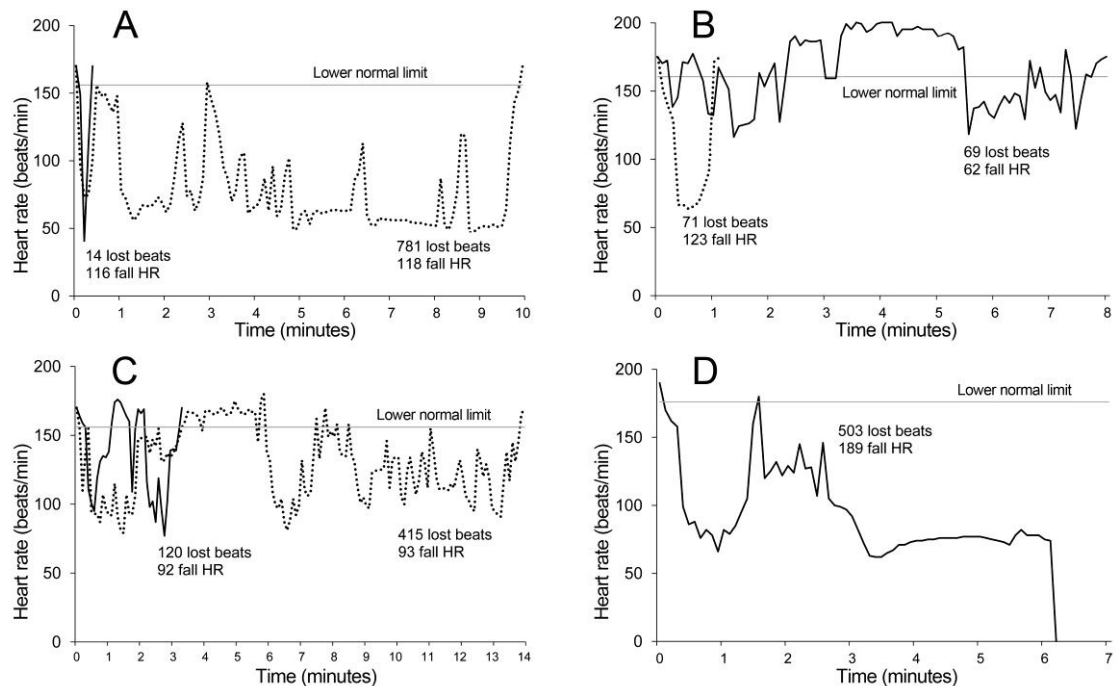


### 5.3.3 *Comparison of Fall in Heart Rate and Lost Beats*

Several examples of intubations where the fall in heart rate was more than 50 beats/min are illustrated in Figure 5-3. Similar falls in heart rate could produce very different numbers of lost beats; from three-fold to 56 fold (Figure 5-3 A and C).

Another example shows intubations with very similar loss of beats but with a two-fold difference in fall in heart rate (Figure 5-3 B). One child died during intubation with septic shock, severe chronic pulmonary hypertension with a lethal chromosomal disorder (figure 5-3[D]).

**Figure 5-3;** Changes in heart rate during several different intubations. These are extreme examples where the heart rate fell from baseline by more than 50 beats/min; A, shows two intubations with similar fall in heart rate (fall HR) and more than 50 fold differences in lost beats (lost beats), B, shows two examples where the number of lost beats was similar but the fall in heart rate 50% greater, C, shows two examples where the fall in heart rate was less but there remained more than a three-fold difference in lost beats and D, is the one child who died in the study having lost 503 beats before an asystolic arrest. Inter-bradycardia tachycardia is also apparent in B. Note that the scales on the *x*-axes are different for each graph.



Using the administration of atropine and/or adrenaline during the intubation process as a marker of haemodynamic instability the lowest heart rate during intubation and accumulation of lost beats is compared in Table 5-2. Only six children received atropine after the start of intubation of which two also received adrenaline. No children received adrenaline without having received atropine. Both the lowest heart rate and the accumulation of lost beats were significantly associated with this definition of haemodynamic disturbance during intubation.

**Table 5-2;** The association between change in heart rate or numbers of lost beats and the use of atropine and/or adrenaline for bradycardia after the start of intubation.

	Odds Ratio	95% confidence interval	p
Change in heart rate	0.95	0.93-0.98	0.003*
Lost beats	1.01	1.00-1.02	0.001*

#### 5.3.4 *The Association between Atropine use and Losing Beats*

Atropine had a significant influence on change in heart rate as assessed by difference from baseline to the lowest heart rate. In comparison, the number of lost beats was not significantly affected by the use of atropine (Table 5-2).

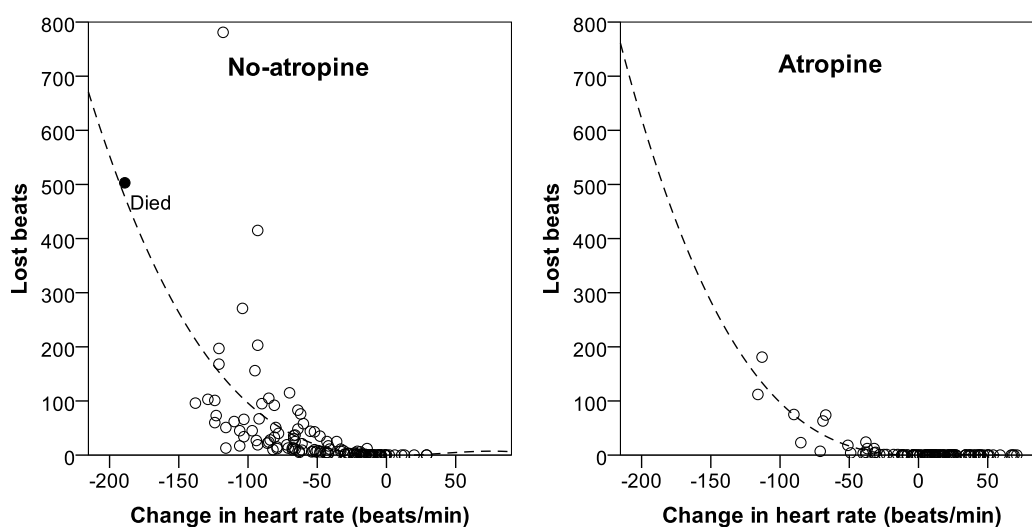
**Table 5-3;** Comparison of change in heart rate from baseline and number of lost beats showing the association with atropine use.

	245 first intubations		
	No-atropine n=130 (%)	Atropine n=115 (%)	P
Mean change in heart rate change from baseline (beats/min)	-49.4 (-90.5- -8.3)	5.8 (-29.3-40.9)	<0.0001*
Median number of lost heart beats	1 [0-18.3]	0 [0-11.0]	0.054

\*Signifies a statistically significant difference,  $p < 0.05$

When the heart rate fell by more than 50 beats/min there was a linear relationship between fall in heart rate and lost beats (Figure 5-4) with the median number of lost beats being 0[0-1] (n=175 with and without atropine). One intubation, with a fall in heart rate of 48 beats/min, registered 35 lost beats. Otherwise, all intubations where the fall in heart rate was less than 50beats/min were of less than 25 lost beats. The progression of lost beats after a fall in heart rate of more than 50beats/min was exponential showing a wide dispersion with a median of 42 lost beats [15-83] (n=70). When no atropine was used, 76% (99/130) of intubations involved lost beats whereas 19% (22/115) involved lost beats when atropine was used.

**Figure 5-4;** Distribution of the lost beats with and without atropine (n=130 for no-atropine and n= 115 for with atropine). The  $r^2$  for no-atropine is 0.41 and 0.85 with atropine. Note the similarity between the two best-fit curves (dotted lines) both in terms of take off and slope. All children survived intubation except the labelled that labelled 'Died'



## 5.4 Discussion

The 95% confidence interval around the mean baseline heart rate for an individual is plus-or-minus 14.2beats/min. During intubation there was a linear increase in lost heart beats until the heart rate had fallen by 50beats/min. Thereafter there was an exponential increase in loss of beats with a poor correlation between fall in heart rate with numbers of lost beats. Atropine pre-medication before CCI was associated with a reduced change in heart rate from baseline and reduced number of lost beats.

#### **5.4.1**        *Possible Sources of Bias*

Several methodologies have been used to determine heart rate; a clinical measurement without further description(257), a single pulse oximeter reading,(259) apical heart rate measured over 15 seconds multiplied by four,(260) one R-R interval on an ECG (261) or during automatic blood pressure measurement.(262) We recorded baseline heart rate for one minute and averaged the two extremes of heart rate. It is possible that if a longer recording had been made more variation would have been registered and this would have increased both the standard deviation and therefore the 95%CI. The effect of these changes would have been to reduce the numbers of lost beats for any one individual. Case-mix differences also exist in the sample population. In this respect the population would have benefited from recruitment with prospective randomisation.

#### **5.4.2**        *Clinical Significance*

Neither the use of absolute changes (11-13, 162) nor the use of percentage changes (209, 210, 258) from baseline are indicators of risk of haemodynamic decompensation (defined as use of adrenaline, cardiac massage or death) during intubation. The application of the lost beat score introduces the concept of what is normal and abnormal heart rate and integrates the dimension of time. This may give a better estimate of risk but further studies will need to be performed to validate this. When the heart rate falls by more than 50beats/min, the possibility of a 50 fold difference between the numbers of lost beats for the same fall in heart rate may give an indication that loss of beats may be a preferable measure of risk of haemodynamic decompensation. (Figure 5-4). This represents the clinical situation where fall in heart rate is a frequent event but haemodynamic decompensation is infrequent. This

suggests that fall in heart rate is a selective indicator for haemodynamic instability whereas loss of beats may be a more specific indicator for haemodynamic decompensation.

The lost beat algorithm defined a 95% confidence interval whereby 95% of children prior to intubation would have a heart rate in the range. Pincus *et al.*(263, 264) used a calculation to quantify regularity in serial data, which they defined as '*appropriate entropy*' (ApEn). An important difference between our two methodologies is that we use only two data points per individual, whereas ApEn requires at least 50 data points, and ApEn does not exclude data within a defined set of limits, which counting lost beats does. Another difference is that we do not measure regularity, as does ApEn, but we define normality and measure heart rate that falls outside our definition.

#### **5.4.3      *Algorithms in other Biological Systems***

Biological risk is often described as a degree of exposure over time. For instance, underwater divers who experience short dives at deep depths can be of equal risk of the decompression sickness as longer dives at shallower depth.(265) And ionizing radiation exposure is measured by intensity and as a factor of time.(266) Both of these risks are characterised in linear no-threshold models (LNT) whereby any increase in exposure equates to an increase in risk. LNT models don't apply for the risk of haemodynamic decompensation because of compensatory changes in ejection volume and vascular resistance. For instance, heart rate in healthy,(267) premature (268) and shocked (269) neonates is poorly correlated with cardiac output whereas it is highly correlated with stroke volume and systemic vascular resistance. One article has already proposed that the risk of haemodynamic instability during intubation is



related not to the presence of bradycardia but the absence of accompanying vasoconstriction.(270) Any threshold for haemodynamic decompensation that exists for an individual during CCI will be determined by the interaction between physiology and pathology. Pre-intubation parameters such as low blood pressure, tachycardia and the need for inotropes, have been identified as risks for mortality during adult studies (3, 16) and give an indication that the threshold is low. If the loss of beats is calculated and displayed in real-time this may also give an indication of risk of haemodynamic decompensation.

## **5.5 Conclusions**

A variability of 14.2 beats/min above and below the baseline heart rate (or perhaps 15 as an *aide memoire*) is typical of critical illness. Fall in heart rate is a very poor indicator of loss of beats and should not be used as a performance indicator of a successful intubation, certainly when the fall in heart rate is greater than 50beats/min. Atropine was significantly associated with change in heart rate but not loss of beats. Monitoring equipment at the bedside could be equipped with an algorithm that would calculate numbers of lost beats in real-time during intubation. Further studies are needed to validate whether this would be a reliable indicator of risk of haemodynamic disturbance.

## Chapter Six

### The Association of Atropine with Reduced Rhythm and Conduction Disturbances during 322 Critical Care Intubations

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#### 6.1 Introduction

Paediatric critical care (19, 224) and anaesthetic intubation (223) may result in slowing of the heart. The causes of this are two-fold. Firstly, stimulation of afferent fibres of the Vagus nerve occurs due to the hypoxia and/or mechanical stimulation of the laryngopharynx with terminal efferent fibres secreting acetylcholine in the sinoatrial node(270). And secondly, the use of various induction drugs such as halothane (271), rapidly-acting morphine analogues, sufentanyl and remifentanyl (172, 173), propofol (163) or suxamethonium (22, 23) also tend to slow heart rate. The overall effect may be to expose the circulation to the risk of bradycardia related arrhythmias. Certain drugs, such as halothane and may also increase the frequency of arrhythmias.(271)

Atropine was proposed in the 1950s to limit bradycardia due to its antagonistic action on the post-synaptic acetylcholine receptor.(22) In normal children atropine toxicity is benign and is related to changes in pupil size, reduction in glandular secretions with cardiac toxicity limited to sinus tachycardia.(230, 232, 270) But in routine anaesthesia atropine has been shown facilitate the progression to ventricular extrasystoles and unusually ventricular tachycardia (237) and fibrillation.(272) Indeed, one study concluded that the incidence of ventricular arrhythmias was so high with atropine that its use during routine anaesthesia should be

'reconsidered'.(221) By the 1990's the wide-spread use of non-cardiotoxic sevoflurane and non-depolarizing muscle relaxants led to the discontinuation of atropine for routine anaesthetic induction.(28)

Recently however, atropine has been recommended for the maintenance of haemodynamic integrity in intensive care populations by several authors but without knowing the frequency or importance of atropine's efficacy in stabilising the circulation and potential side-effects.(30, 34) This is in spite of the increased risk during critical care intubation of arrhythmias due to the complex amalgam of rapid changes in heart rate, electrolyte abnormalities, hypoxia, perfusion abnormalities, acidosis and hypercarbia, and the effects of induction drugs. All of these effects may be exaggerated in the presence of myocardial dysfunction or congenital abnormalities.

Our objectives were to describe the prevalence of arrhythmia before critical care intubation and test the hypothesis that atropine was not associated with a change in incidence of new arrhythmias or conduction abnormalities either after its administration or during intubation.

## **6.2 Methods**

### **6.2.1 Study design**

Data for analysis in this chapter are drawn from the common methodology of the clinical study that is described in Chapter 5 (5.2.1).

### 6.2.2 *Study procedures*

Two Paediatric Intensivists reviewed the ECGs independently. An average was made of their readings of the baseline heart rate, two minutes after atropine administration and the lowest two R-R complexes during intubation (not necessarily at the time of the arrhythmia). All potential episodes of arrhythmia were recorded for review by an Electrophysiologist. A random sample of 10% of the ECG recordings that were considered to be normal by the two intensivists was also examined by the Electrophysiologist to control for false negatives.

Sinus brady/tachycardia was regarded as a normal rhythm. Abnormal rhythms were considered to be atrial or ventricular extra-systoles, ectopic rhythm, ventricular tachycardia or fibrillation. Abnormalities of conduction were also noted

Patients who were not in sinus rhythm at baseline were excluded from the atropine analysis. The remaining cases were divided into the two groups of 'atropine' and 'non-atropine'. Intubations were classified according to the 'intention-to-treat' with atropine or not as prophylaxis. Atropine given as rescue treatment for established bradycardia was not considered in this classification.

Sub-groups were defined of neonatal ( $\leq 28$  days post-natal age), older children ( $> 28$  days post-natal age) and 'further' intubations (of all ages). Further intubations were derived from the patients who were re-intubated during the same or a subsequent illness after planned extubation and/or for change of endo-tracheal tube. Further intubations were treated as new events so as to restrict bias in the groups of primary intubations by not replicating data from the same children. The rationale of dividing

the group at 28 days was due to the physiological transition in autonomic innervation from predominant parasympathetic to co-dominance that occurs during early extra-uterine life (113).

### **6.2.3**        *Statistical analysis*

Qualitative variables are described as numbers and percentages and quantitative variables as median [inter-quartile range] or mean (standard deviation) according to their Gaussian distribution. Independent and paired t-tests were used for continuous data, a Chi<sup>2</sup> test for categorical data where there were three or more variables and Fisher's exact test where there were two variables. All statistical tests were 2-sided and the probability of a type 1 error ( $\alpha$ ) was determined at <0.05. Univariate and stepwise multivariable logistic regression models were constructed to test the association of atropine and other pre-intubation variables on the occurrence of new arrhythmias using a maximum of one co-variate per 10 new arrhythmias or conduction disturbances. Only variables that were significant  $p < 0.20$  in the univariate analysis were entered into the multivariable model. Effect estimates were calculated for numerical variables and odds ratios (OR) for categorical variables with their corresponding 95% confidence intervals (95%CI). All statistical tests were carried out using SAS V.9.2 software (SAS, Cary, NC).

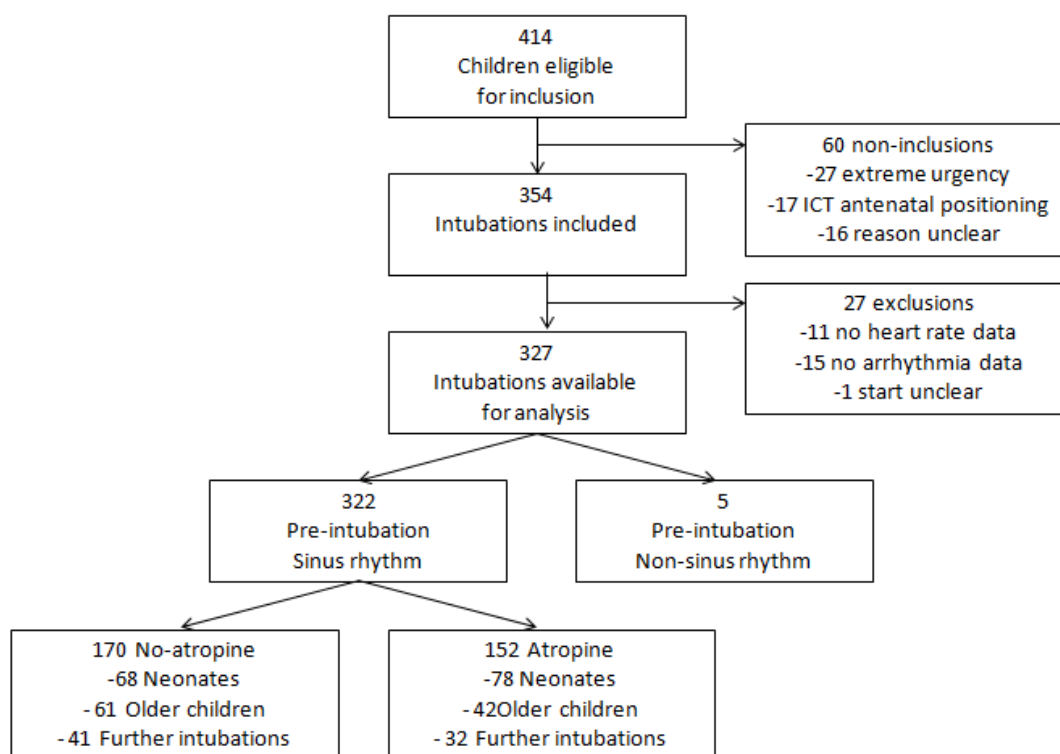
## **6.3**        **Results**

### **6.3.1**        *Study Population*

Four hundred and fourteen intubations were eligible for inclusion. Sixty intubations were not included, generally due to urgency or high work-load conditions, and twenty-seven intubations were subsequently excluded, generally due to poor quality

recordings (Figure 6-1). Three hundred and twenty seven intubations (79%) were available for analysis. A total of 185 intubations were performed in PICU (115 first intubations and 70 further intubations) and 142 by the ICT team (with 140 first intubations and two further intubations). The ICT team's activity was predominantly neonatal (118/142 intubations, 83%). Eleven ICT intubations were performed out-of-hospital. Seventy-two further intubations were performed on 42 children (40 in PICU and two by ICT) with a median of 2[2-3] intubations per child who were re-intubated.

**Figure 6-1;** Flow-chart of inclusions, non-inclusions and exclusions. The five intubations where normal sinus rhythm was not present before intubation were excluded from the atropine analysis. Neonates are  $\leq 28$  days, older children  $>28$  days and less than 8 years and further intubations are any age below 8 years.



\* ICT antenatal positioning refers to the presence of the ICT team prior to high-risk deliveries, generally these were extremely premature births.

There was no significant difference between the median number of attempts at intubation with and without atropine (1[1-2] *versus* 1[1-2],  $p=0.46$ ) or the median trough SpO<sub>2</sub> (74% [49-88] no-atropine *versus* 75% [50-89] atropine,  $p=0.95$ ). Data were missing for 24 intubations for the attempts at intubation and 10 intubations for the SpO<sub>2</sub>.

### **6.3.2      *Pre-intubation Arrhythmias***

The prevalence of baseline arrhythmia before the start of intubation was 1.5% (5/327). These intubations were excluded from the subsequent analysis. One intubation had frequent bursts of ventricular tachycardia interspersed by junctional rhythm in a patient with leukemic infiltration of the heart. This child died some hours after intubation. Another was intubated for ventricular fibrillation in the context of *Shigella* septicaemia and multiple organ failure and died during intubation. Two cases had long-standing left bundle branch block from a cardiac malformations and one other an atrial ectopic beat.

**Table 6-1:** Population characteristics of the intubations. The groups of 'All' non-atropine and atropine intubations are composed of the three subgroups of first intubations for neonates and older children and further intubations. Neonates are  $\leq 28$  days and older children  $> 28$  days and less than 8 years, there is no age differentiation for further intubations.

	No-atropine (n=170)					Atropine (n=152)					p value for All intubations
	All no-atropine intubations (n=170)	First intubation, neonate (n=68)	First intubation, Older children (n=61)	Further intubation, PICU (n=41)	All atropine intubations (n=152)	First intubation, neonate (n=78)	First intubation, Older children (n=42)	Further intubation, PICU (n=32)			
Median age days [IQR]	48* [0-222]	0 [0-2]	227 [148-180]	91 [34-284]	17* [0-92]	0 [0-1]	132 [61-160]	86 [48-160]	0.01*		
Boys	100	36	36	28	106	60	23	23	0.08		
Mean baseline heart rate (SD)	159* (137-183)	154 (132-176)	161 (135-187)	161 (138-184)	153* (127-179)	148 (127-169)	153 (132-174)	158 (130-186)	0.01*		
NRD	50	49	-	1	60	59	-	1	0.06		
NonNRD	62*	8	31	23	35*	7	13	15	0.01*		
Cardiac	9	5	4	0	7	2	1	4	0.80		
ENT	20	1	8	11	20	2	9	8	0.74		
Neurologic	15	1	10	4	21	5	13	3	0.16		
Sepsis	10	1	8	1	7	3	4	0	0.63		
Other	4	3	0	1	3	1	1	1	1.00		



**Table 6-2;** Population characteristics of the intubations. The groups of 'All' non-atropine and atropine intubations are composed of the three subgroups of first intubations for neonates and older children and further intubations. Neonates are  $\leq 28$  days and older children  $>28$  days and less than 8 years, there is no age differentiation for further intubations.

	No-atropine (n=170)				Atropine (n=152)				p value for All intubations
	All no-atropine intubations (n=170)	First intubation, neonate (n=68)	First intubation, Older children (n=61)	Further intubation, PICU (n=41)	All atropine intubations (n=152)	First intubation, neonate (n=78)	First intubation, Older children (n=42)	Further intubation, PICU (n=32)	
No sedation drugs	33	26	4	3	36	33	2	1	0.59
Ethomidate	4	0	4	0	6	1	4	1	0.53
Propofol	69*	11	33	25	40*	3	17	20	0.02*
Ketamine	15*	0	12	3	4*	0	3	1	0.01*
Morphine	19	15	2	1	15	11	1	3	0.72
Midazolam	15*	6	5	4	28*	14	8	6	0.01*
Sufentanyl	14	10	0	4	20	16	4	0	0.20
Other	1	0	1	0	3	0	3	0	0.35
Suxamethonium	8	0	7	1	6	0	3	3	0.79
Vecuronium	7	1	3	3	2	0	0	2	0.18

\* significant difference ( $p < 0.05$ )

### **6.3.3      *Atropine Use***

A total of 322 intubations were analysed for the association between atropine and the emergence of new arrhythmias and conduction disturbances during intubation. Atropine was used in 47% (152/322) intubations and 53% (170/322) were without atropine (Figure 6-1). Atropine was used in a similar proportion ( $p=0.12$ ) of cases in each of the three sub-groups (neonatal, >28 days to <8years and further intubations). The baseline characteristics of the cases in the sub-groups are presented in Table 6-1 and 6-2.

### **6.3.4      *Changes in Heart Rate and Rhythm after Atropine before Intubation***

A total of 55 ECGs were identified by the Intensivists as being abnormal of which 48 were confirmed by the Electrophysiologist as being abnormal. None of the ECGs considered to be normal by the Intensivists were considered to be abnormal by the Electrophysiologist giving 100% sensitivity and 87% specificity.

After the administration of atropine the mean baseline heart rate of all patients rose from 153 beats/min (127-179) to 171 beats/min (148-194) ( $p<0.001$ ). This was seen across all sub-groups. The mean heart rate after atropine administration before intubation was significantly higher than baseline in the neonatal group ( $p<0.001$ , 166beats/min [147-185]), the older children ( $p<0.001$ , 176beats/min [146-206]) and the further intubations ( $p=0.003$ , 177beats/min [157-197]). No arrhythmias were detected in the minute of ECG recording following atropine injection but before intubation.

**Table 6-3:** All intubations with new arrhythmias/conduction abnormality, *only one arrhythmia is counted per intubation*. Description of arrhythmias; *several types of arrhythmia/conduction abnormality may be present for each intubation*. The groups of 'All' non-atropine and atropine intubations are composed of the three subgroups of first intubations for neonates and older children and further intubations. Neonates are  $\leq 28$  days and older children  $> 28$  days and less than 8 years, there is no age differentiation for further intubations.

	No-atropine (n=170)				Atropine (n=152)				p value
	All no-atropine intubations (n=170)	First intubation, neonate (n=68)	First intubation, Older children (n=61)	Further intubation, PICU (n=41)	All atropine intubations (n=152)	First intubation, neonate (n=78)	First intubation, Older children (n=42)	Further intubation, PICU (n=32)	
Lowest intubation heart rate (SD)	109* (68-150)	107 (67-147)	103 (62-144)	123 (83-163)	149* (112-186)	159 (132-186)	138 (94-182)	139 (100-178)	<0.001*
All intubations with new arrhythmias/conduction abnormalities	45*				7*				<0.001*
<b>Arrhythmias/conduction disturbances - Some intubations involved more than one type of arrhythmia/conduction abnormality</b>									
Atrial extra-systole	9*	1	7	1	1*	0	0	1	0.02*
Atrial ectopic rhythm	3	0	2	1	0	0	0	0	NA
Junctional rhythm	29*	6	14	9	6*	1	3	2	<0.001*
Mobitz type II	1	0	0	1	0	0	0	0	NA
Ventricular escape rhythm	5	1	4	0	1	0	0	1	0.38
Bundle branch block	3	0	2	1	0	0	0	0	NA

\* significant difference (p<0.05) NA not analyzed

### **6.3.5        *Atropine and New Arrhythmias***

The mean heart rate fell significantly for all patients when atropine was not used ( $p<0.001$ ). Junctional and atrial ectopic rhythms were significantly more frequent when atropine was not used (Table 6-3). Other new arrhythmias and conduction disturbances are presented in Table 6-3. Overall, the new arrhythmias are related to heart slowing and their frequency was higher for those intubations where atropine was not used ( $p<0.001$ ) (Tables 6-3 and 6-4). Three cases of acute bundle branch block and five cases of sinus pause with ventricular escape were noted when atropine was not used. No new cases of acute bundle branch block were recorded with atropine used.

**Table 6-4;** Univariate and multivariable regression analysis for new episodes of arrhythmia and conduction disturbances compared to age, baseline heart rate, sex, atropine and sedation drugs for all intubations irrespective of age or further intubation. One co-variate was entered into the model per 10 new arrhythmias or conduction disturbances. Only variables with p values of  $p < 0.20$  in the univariate analysis were entered into the multivariable model.

	Univariate analysis		Multivariable analysis	
	OR (IC95%)	p value	OR (IC95%)	p value
Age (months)	1.02 (1.00-1.03)	0.02*	NS	
Baseline heart rate (beats/min)	1.00 (0.99-1.02)	0.51	NS	
Sex (girls)	0.86 (0.44-1.7)	0.65	NS	
Atropine	0.17 (0.07-0.39)	<.0001*	0.14 (0.06-0.34)	<.0001*
No drugs	Reference			
<i>Ethomidate</i>	3.5 (0.85-14.5)	0.08	5.29 (1.07-26.2)	0.04*
<i>Propofol</i>	0.59 (0.24-1.5)	0.25	0.44 (0.17-1.1)	0.09
<i>Ketamine</i>	3.1 (0.99-9.6)	0.05	2.0 (0.62-6.7)	0.24
<i>Sufentanyl</i>	0.33 (0.07-1.6)	0.16	0.34 (0.0-1.7)	0.19
<i>Morphine</i>	0.51 (0.13-2.0)	0.33	0.42 (0.11-1.7)	0.22
<i>Midazolam</i>	1.0 (0.36-2.9)	0.96	1.35 (0.45-4.1)	0.60

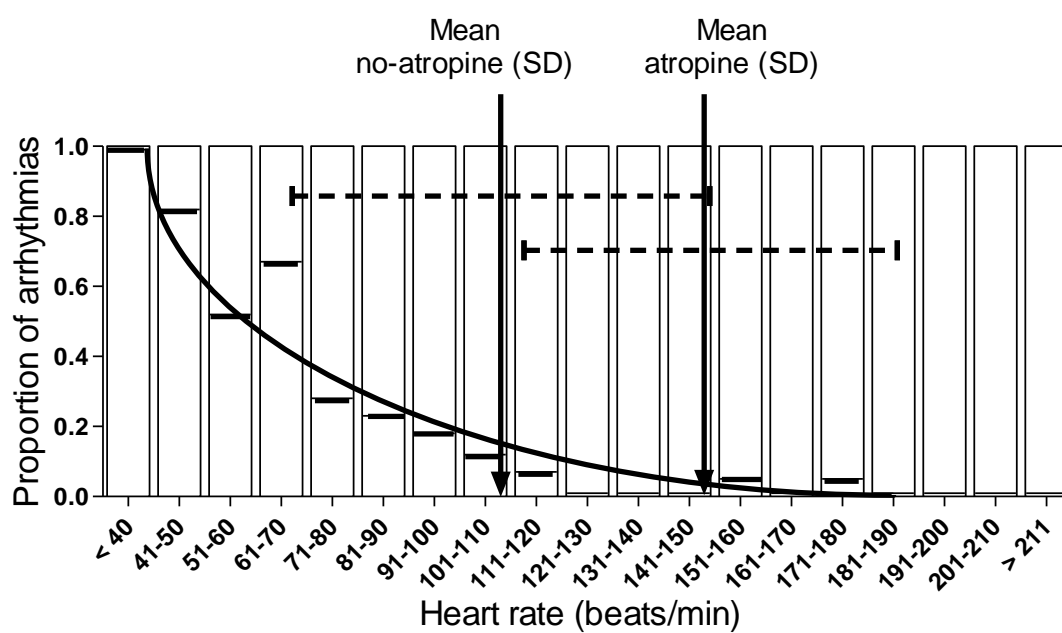
\* indicates a statistically significant result,  $p < 0.05$

NS variables that were eliminated during stepwise multivariable regression for  $p \geq 0.05$

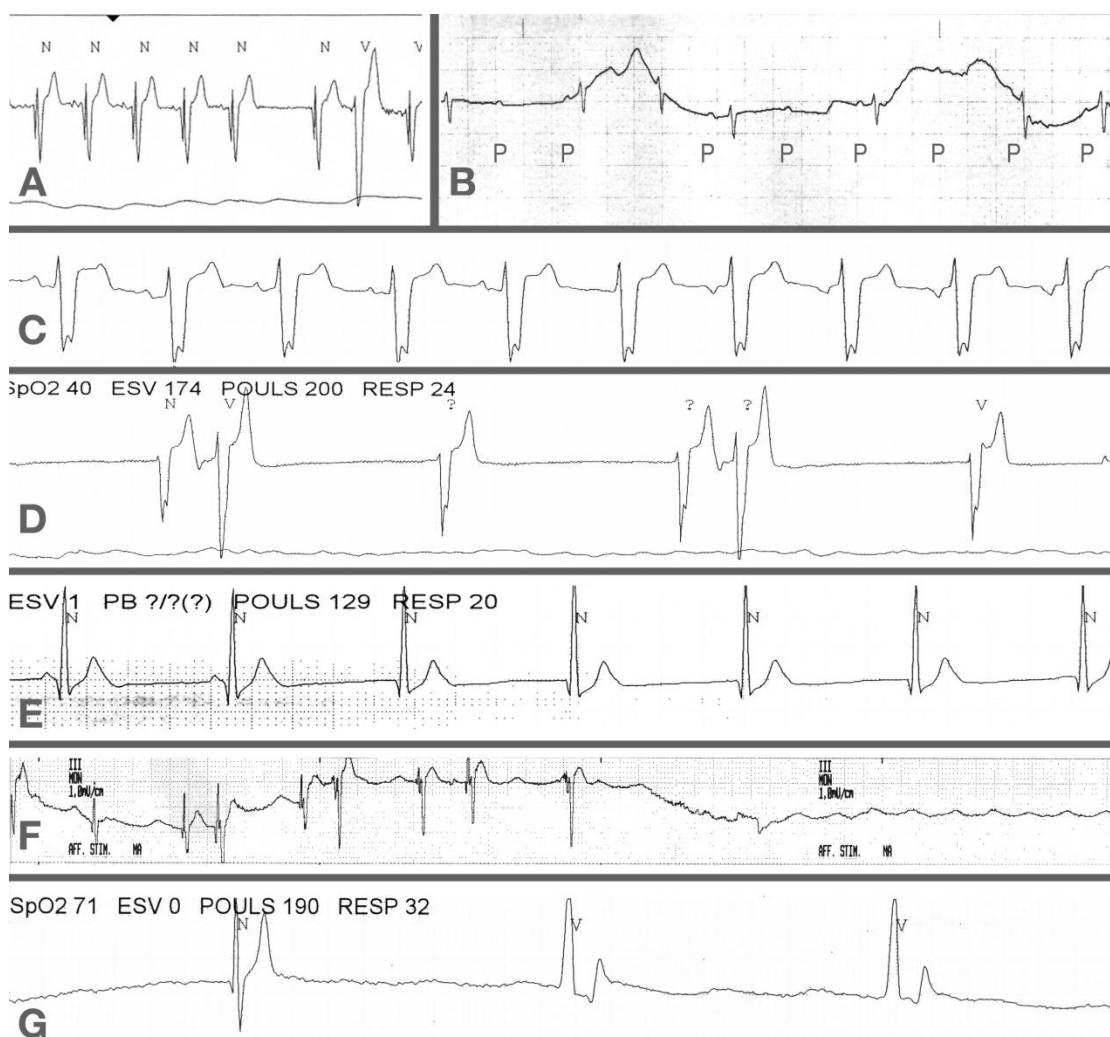
The multivariable regression model revealed that atropine was associated with a significant decrease in new abnormal rhythms and conduction disturbances (Table 6-4). To test for the interference of the further intubations, a *post hoc* analysis for only the first intubations of neonates and older children which revealed a more important association with atropine use in reducing new arrhythmias or conduction

disturbances (OR 0.10, 95%CI 0.03-0.35,  $p < 0.001$ ). Similar tendencies were observed for the other co-variables (results not presented).

**Figure 6-2;** Distribution of arrhythmias according to groups of lowest heart rate during intubation showing increasing frequency of arrhythmia and conduction abnormalities as the heart rates falls. The mean heart rates for those who did and did not receive atropine are shown with standard deviation bars.



**Figure 6-3;** Examples of some arrhythmias and conduction abnormalities recorded during intubation. With the exception of chronic bundle branch block in C, all ECGs were in normal sinus rhythm before the start of intubation.; A, acute bundle branch block, sinus pause followed by ventricular extra-systole; B, infranodal block, Mobitz type II; C, chronic bundle branch block with atrial ectopic pacemaker; D, sinus pause with ventricular escape rhythm and atrial trigeminism; E, sinus bradycardia followed by junctional rhythm; F, sinus pause with ventricular escape rhythm followed by asystole; G, sinus pause with junctional extrasystole followed by ventricular escape rhythm.



## 6.4 Discussion

Arrhythmias and conduction disturbances were prevalent in 1.5% (5/327) of children prior to intubation. No new arrhythmias were documented in the minute of recording post-atropine and pre-intubation in the 152 intubations where atropine was administered. We disproved our hypothesis and showed that there was a significantly higher frequency of abnormal rhythms and conduction abnormalities when atropine was not used during intubation (43[25%] without atropine *versus* 7[4.5%] with atropine, OR 0.14, 95%CI 0.06-0.35,  $p < 0.001$ ).

### 6.4.1 Population Bias

Several possible sources of bias are present in our study. A disharmony in the case-mix of the two groups exists with those with higher heart rates and younger children receiving more atropine (Table 1). Children in the first few months of life have predominant parasympathetic innervation (113) and so have an increased propensity to bradycardia when the Vagus nerve is stimulated.(4) Nevertheless, this is not confirmed by our results wherein the older children had the lowest mean heart rate during intubation (Table 6-1 and 6-2).

Other imbalances between the two groups include the use of propofol which was more frequently used in the older children and has been previously associated with bradyarrhythmia.(169) Overall the use of muscle relaxants was low. This is due to three reasons. Firstly, the relatively high number of neonates (practice in the Hospital, and Paris Region, was not to include paralysis during the study years), secondly, the relatively frequent use of propofol which gives good intubation



conditions without muscle relaxants (273) and finally the PICU practice which has traditionally had a high-case load of ENT patients.

The inclusion of a 'further' intubation group increased the frequency of inclusion of some children with longer illnesses and it is for this reason that these results are presented as a subgroup to avoid introducing bias. The advantage of examining the re-intubations is that they represent real-life practice and this is also featured in other intubation studies.(19) The fact that our study was not randomised is inevitably a limitation in the validity of the results. Randomisation in some circumstances may be so difficult that it may result in unbalanced populations which can create bias. Obtaining the written consent from both parents would probably have lowered our high inclusion rate (79%).

The intubation conditions as regards number of attempts at intubation were similar for the groups with and without atropine and these were similar to those previously described in neonatal (211, 224, 225) and paediatric studies.(19, 20) An exception is the median trough saturation in our group of older children which was lower than in two other studies.(19, 20) However, these studies mention that the retrospective nature of their methodologies was a cause of possible bias in this respect.

The older children (19/61, 31%) and further intubations (11/41, 27%) had a tendency to receive less atropine and experienced proportionately more new arrhythmias than the neonates (8/68, 12%). This is at variance with the opinions of McAllister and Gnauck (274), when discussing arrhythmia during intubation, who concluded that

*'infants are at greater risk than older children for bradycardia-induced haemodynamic compromise'.*

#### **6.4.2        *Atropine and the incidence of new Arrhythmias***

The prevalence of pre-existing arrhythmia was low (1.5%). Two of the five intubations were undertaken as part of the therapy for the arrhythmia, two were related to congenital heart disease and one was inconsequential.

The absence of cardiac toxicity using therapeutic and above-therapeutic doses of atropine in a normal heart, beyond sinus tachycardia, has been rarely reported in the literature and is evidence of its innocuous nature.(230, 232, 270) Of the 154 intubations which concerned atropine on our study, we demonstrated that pre-existing sinus tachycardia progressed only to faster sinus tachycardia and not ventricular arrhythmias. Given the relatively high frequency of ventricular extrasystoles and other ventricular escape rhythms that have been described in anaesthetic studies with atropine and the relative absence of such rhythms in our intubations, the most likely conclusion is the interaction of atropine with the inhalational anaesthetic agents was responsible.(271) Of the seven intubations which were performed with atropine when the child had a previously detected abnormal heart, and normal pre-intubation ECG, only one demonstrated sinus pause rhythm and ventricular extrasystole during intubation.

The absence of atropine was associated with low absolute heart rate which was associated with new arrhythmias (Figure 6-2). Indeed, of the 21 intubations where the heart rate fell below 60beats/min as many as 76% exhibited new arrhythmias.

The highly statistically significant association of atropine and reduced frequency of new arrhythmias was probably due to its inhibition of vagal pressure on the sino-atrial node which generally maintained pre-intubation heart rates and therefore normal rhythmicity (Tables 6-3 and 6-4).

All the new intubation abnormalities observed were related to bradycardia and fall into three categories; atrial ectopic rhythms, sino-atrial pause accompanied by ventricular escape rhythm and impulse conduction abnormalities (Figure 6-3). Ectopic atrial and junctional pacemakers have previously been shown to be relatively frequent in paediatric anaesthetic studies.(221, 275, 276) Ventricular filling is little compromised by atrial ectopic pacemakers at rest because 70 to 80% of ventricular filling is passive(25). This may not be the case for hyper-dynamic circulation during shock. Those ectopic atrial contractions that are transmitted through the AV junction are generally blocked from inducing ventricular contractions by the relatively long refractory period of the Purkinje fibres.(277) But, when the ventricular myocardium is deprived of coordinated impulses from the atria, ventricular escape rhythms may develop (Figure 6-3). Ectopic ventricular contractions may additionally reduce contractile efficiency by the propagation of sub-optimal action potentials between ventricular myocytes. This may generate a negative feedback loop of poor cardiac output and myocardial ischaemia above and over and above the hypoperfusion of severe sinus bradycardia.(278)

#### **6.4.3            *Conduction Disturbances***

Acute bundle branch block is an important finding which was noted in three patients all of whom were intubated for septic shock. One of the three had a pre-existing

cardiac abnormality (pulmonary hypertension) and died during intubation. Acute bundle branch block is a risk for progression to sudden and complete heart block which can be fatal.(279) The occurrence of a second degree 2:1 atrioventricular block (Mobitz type II) during one re-intubation represents an abrupt failure of atrioventricular conduction and is also a potential risk for complete heart block and asystole (Figure 6-3).(280) These episodes had self corrected by the end of intubation. None of the children involved in these intubations had received atropine.

The relative contributions of induction drugs to the creation of new arrhythmias shows that etomidate (multivariate analysis) and ketamine (univariate analysis) have a tendency to induce arrhythmias when compared to 'no drugs' and propofol tends to be protective (Table 6-4). These results should be interpreted with caution for two reasons. Firstly, etomidate and ketamine were used predominantly in septic shock and propofol for non-NRD and secondly because the majority of children intubated without drugs were neonates (Table 6-2). Sufentanyl and morphine tended to be protective whereas midazolam was not which is perhaps due to the superior intubation conditions when sedation is used (Table 6-4).

## **6.5 Conclusions**

The prevalence of pre-intubation arrhythmias was low (1.5%). Atropine did not provoke any new arrhythmias during the minute of recording after administration before intubation. Intubation without atropine was more frequently accompanied by bradycardia and arrhythmia than when atropine was used. Five intubations without atropine, compared to one with atropine, exhibited bradycardia that involved sinus pause with ventricular escape. One of these intubations, without atropine, culminated

to the death of the child. The relative safety of intubation with atropine is probably superior to that when atropine is not used. A randomised study would enable the association observed to be validated.

## Chapter Seven

### Atropine for Critical Care Intubation in a Cohort of 264 Children and Reduced Mortality unrelated to Effects on Bradycardia

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#### 7.1 Introduction

Critical care intubation (CCI) of young children in critical care situations represents a crucial moment in an episode of critical illness and may be associated with cardiorespiratory decompensation. In critically-ill adults the risk of death during CCI has been estimated at 1- 3% with pre-existing hypotension greatly increasing this risk.(3, 16) In children intubation mortality is probably substantially lower. No deaths were observed in either of two retrospective studies of 137 intubations in 103 children outside the Operating Room (19) and or 143 children in the Emergency Department.(20)

Paediatric anaesthetists and intensivists have used slowing of the heart rate in children as a measure of haemodynamic stability during CCI for more than 50 years. Two distinct mechanisms contribute to falls in heart rate during intubation; the direct effects of some induction drugs, and vagally-mediated parasympathetic cholinergic inhibition of sino-atrial node activity as a reflex response to hypoxaemia and/or laryngeal stimulation.(270)

Atropine was proposed in the 1950s to overcome the anti-cholinergic effects of suxamethonium during induction and intubation.(22) Its efficacy in attenuating falls in heart rate during anaesthetic intubation in children is proven.(164, 223) Following

the introduction of non-depolarising muscle relaxants and less cardio-depressant anaesthetics, such as sevoflurane, there has been a decline in atropine use.(28)

Atropine is currently recommended to optimise haemodynamic stability during CCI.(30) The 2007 American College of Critical Care Medicine clinical practice parameters for hemodynamic support in paediatric septic shock provide a level III (expert opinion) recommendation for “*Ketamine and atropine pretreatment ...[to] be used as a ...induction regimen of choice to promote cardiovascular integrity*”.(34) The lack of prospective data on the impact of atropine on heart rate and outcome in critically ill children prompted this study.

Our objective was to measure the association between atropine use and mortality and heart rate in a prospectively-recruited population of children undergoing their first critical care intubation. We assumed the null hypothesis that atropine was not associated with either outcome. A propensity score was used to adjust for patient specific prognostic characteristics that might have influenced atropine prescription.

## **7.2 Methods**

### ***7.2.1 Study design and population***

Data for analysis in this chapter are drawn from the common methodology of the clinical study that is described in Chapter 5 (5.2.1).

### 7.2.2 *Study procedures*

Children were retrieved intubated and transported to three other PICUs (Kremlin-Bicêtre, Necker, and Trousseau) and five Neonatal ICUs (Creteil, Institut de Puériculture, Montreuil, Port Royal, Robert Debré) in the Paris Region which participated in the study.

All children who were undergoing their first non-planned intubation and were not asystolic were eligible for inclusion. The PRISM III-24 (281) (Paediatric RISK of Mortality) score was recorded. Mortality prior to intensive care discharge was recorded.

The study population was divided *a priori* into two age sub-groups, neonatal ( $\leq 28$  days post-natal age) and older children ( $> 28$  days post-natal age and  $< 8$  years), for the purposes of analysis. The rationale to divide the group at this age was due to the physiological transition in autonomic innervation that occurs during early extra-uterine life (113) and due to the different distribution of pathologies in the two groups.

A one-minute ECG control strip (25mm/s) was recorded prior to the start of intubation, two minutes after atropine if administered, and used to calculate the mean pre-intubation heart rate by averaging the lowest and highest heart rate.

### 7.2.3 *Propensity score construction*

The propensity score (PS) is a one-dimensional summary of multidimensional covariates that is used to make causal inferences in observational studies by dealing



with confounding patient-specific prognostic characteristics that could have an effect on both treatment assignment and outcome. This allows a statistical balancing of the two treatment groups by adjusting for a series of pre-treatment confounding variables. The PS for a group of patients is the sum of the probabilities for having received a particular treatment according to a specified set of pre-treatment covariates that might plausibly have affected treatment assignment.(282, 283)

We constructed a PS for atropine prescription using the pre-prescription variables (Table 7-1, with the exception of the PRISM score) which included 10 or more children that had been identified by a group of 61 Paediatric Intensivists in eight countries on three continents as influencing their decision to prescribe atropine.(248) Linearity in the log odds of continuous variables was assessed visually and by using likelihood ratio testing.

Our primary end points were changes in mortality and a fall in heart rate from baseline to the lowest two R-R complexes during intubation. The secondary end point was the number of days from intubation to death.

#### **7.2.4**        *Statistical analysis*

Qualitative variables are described as numbers and percentages and quantitative variables as median [quartiles] or mean (standard deviation) according to their Gaussian distribution. Independent t-tests or a Mann-Whitney test were used for continuous data according to their distribution and Fisher's exact test was used for categorical data. All statistical tests were 2-sided and the probability of a type 1 error ( $\alpha$ ) was determined at <0.05. Univariate and/or multivariable linear or logistic

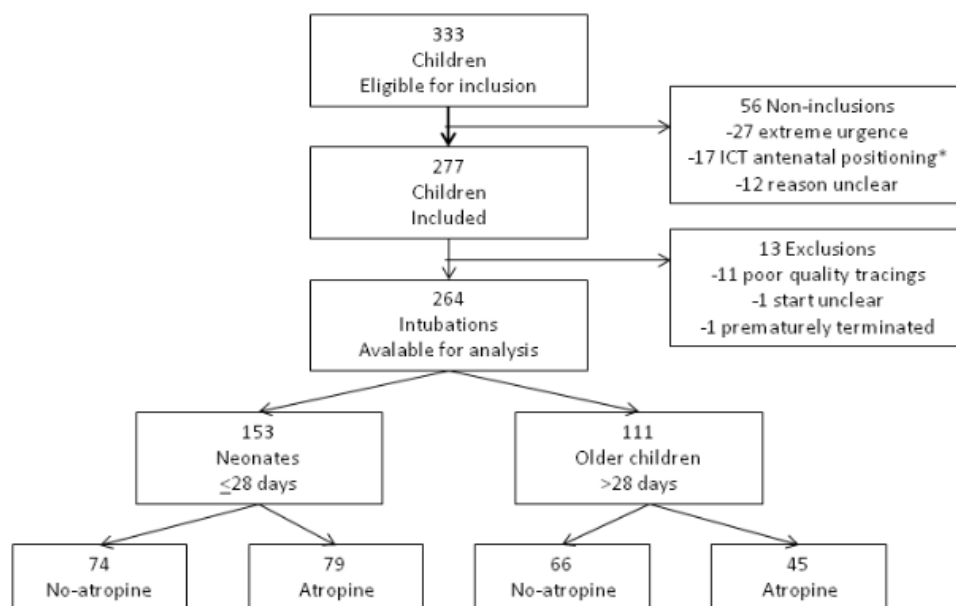
regression models were constructed to test the influence of atropine using the PS. Effect estimates were calculated for numerical variables and odds ratios (OR) for categorical variables with their corresponding 95% confidence intervals (95%CI). Pearson correlation was used to compare quantitative variables. Kaplan-Meier plots and Log-rank tests were used for survival analysis. Missing data were excluded list-wise. All statistical tests were carried out using SPSS (version 19) with the exception of those concerning the PS which was performed using SAS V.9.2 software (SAS, Cary, NC).

### **7.3 Results**

#### **7.3.1 Study patients**

A total of 333 children were eligible for inclusion of which 277 were included. Fifty-six children were not included and 13 children were excluded (Figure 7-1). A total of 264 study patients were available for analysis (264/333, 79%) of which 114 from PICU and 150 from ICT. Twenty three Intensivists included a median of 5 [1-16] children each.

**Figure 7-1;** Flow-chart of inclusions, non-inclusions and exclusions. Neonates are  $\leq 28$  days and older children  $>28$  days and less than 8 years.



\*ICT - Intensive Care Transport team positioned antenatally for premature births.

### 7.3.2 *Atropine use*

Atropine was prescribed in 124 of the 264 (47%) intubations and more frequently prescribed, although not significantly ( $p=0.08$ ), during the intubations of neonates (79/153, 52%) than older children (45/111, 41%) (Table 7-1 and Figure 7-1). Atropine was prescribed significantly more frequently ( $p=0.01$ ) by the ICT intensivists (81/150, 54%) than in PICU (43/114, 38%). The median frequency of atropine prescription per intensivist was 2 [1-8]. Two ICT intensivists with similar case loads were responsible for an important number of inclusions and had diametrically opposed but balanced practices. One used atropine for 44 of 48 inclusions (92%) and the other for 5 of 49 inclusions (10%). The ante-natal positioning of the ICT team for extremely premature births, who were almost exclusively intubated without venous access, meant that the median gestational age of neonates without atropine was 32 [IQR 30-37] compared to 38 [IQR 35-39] weeks for those given atropine ( $p<0.001$ ).

**Table 7-1;** Population characteristics for all patients and the two age sub-groups of neonates and older children. All of the variables from the columns ‘All Patients’ were entered into the propensity score. The PRISM score was not included in the propensity score. Neonates are  $\leq 28$  days and older children  $> 28$  days and less than 8 years.

	All Patients (n=264)		Neonates (n=153)		Older children (n=111)	
	No-atropine n=140(%)	Atropine n=124(%)	No-atropine n=74(%)	Atropine n=79(%)	No-atropine n=66(%)	Atropine n=45(%)
Median age days [IQR]	21* [0-220]	1* [0-71]	0 [0-2]	0 [0-1]	225 [78-861]	134 [67-325]
Boys	94 (67)	85 (69)	56 (76)	60 (76)	38 (58)	25 (56)
Mean baseline heart rate, min-1 (SD)	157* (133-181)	150* (125-175)	154 (132-176)	148 (126-170)	161 (135-187)	154 (124-184)
NRD	56 (40)	61 (49)	56 (76)	61 (77)	-	-
NonNRD	40 (29)	18 (15)	8 (11)	4 (5)	32 (48)	14 (31)
Cardiac	9 (6)	4 (3)	4 (5)	3 (4)	5 (8)	1 (2)
ENT	9 (6)	11 (9)	1 (1)	1 (1)	8 (12)	10 (22)
Neurologic	13 (9)	20 (16)	1 (1)	5 (6)	12 (18)	15 (33)
Sepsis	10 (7)	7 (6)	1 (1)	3 (4)	9 (14)	4 (9)
Other	3 (2)	3 (2)	3 (4)	2 (3)	0 (0)	1 (2)
No sedation drugs	35 (25)	37 (30)	30 (41)	35 (44)	5 (8)	2 (4)
Ethomidate	5 (4)	5 (4)	0 (0)	1 (1)	5 (8)	4 (9)
Propofol	44 (31)	23 (19)	10 (14)	2 (3)	34 (52)	21 (47)
Ketamine	12 (9)	3 (2)	0 (0)	0 (0)	12 (18)	3 (7)
Morphine	17 (12)	12 (10)	15 (20)	11 (14)	2 (3)	1 (2)
Midazolam	12 (9)	22 (18)	6 (8)	15 (19)	6 (9)	7 (16)
Sufentanyl	14 (10)	19 (15)	13 (18)	15 (19)	1 (2)	4 (9)
Other	1 (1)	3 (2)	0 (0)	0 (0)	1 (2)	3 (7)
Suxamethonium	8 (6)	3 (2)	0 (0)	0 (0)	8 (12)	3 (7)
Vecuronium	1 (1)	3 (2)	1 (1)	0 (0)	3 (5)	0 (0)
					No-atropine (n=57/66)	Atropine (n=37/45)
PRISM n=93	-	-	-	-	10.5 [7-19]	9 [5-13.5]

\* p value  $< 0.05$  for the difference between the atropine and non-atropine groups

NRD - neonatal respiratory distress, Non-NRD - non-neonatal respiratory distress,

ENT - ear nose and throat, PRISM - Paediatric RISK of Mortality score.

### 7.3.3 *Baseline characteristics and construction of the propensity score*

Only two of the variables of baseline pre-atropine prescription characteristics were significantly different between the atropine and no-atropine groups, these were the median age of patients ( $p=0.02$ ) and the mean baseline heart rate ( $p=0.02$ ). Three variables were not used in the construction of the PS because they featured in less than ten cases: fentanyl ( $n=1$ ), thiopental ( $n=4$ ) and vecuronium ( $n=4$ ). The c-statistic of the PS was 0.72. When the two sub-groups were further subdivided into neonatal and older children age subgroups there was no significant difference between any of the variables. The PRISM score was retrospectively available for 94 of 111 older children and was not significantly ( $p=0.09$ ) different between the atropine and non-atropine groups (Table 7-1). The predicted risk of death of the older children, calculated from the PRISM scores, was 8% [3-30%] for the no-atropine group and 5% [2-12%] for the atropine group ( $p=0.08$ ).

### 7.3.4 *Mortality during intubation and during ICU stay*

Thirty-one children died during ICT/ICU care (11.7%, 31/264). There was significantly lower mortality in the neonatal group 6.5% (10/153) than for the older children 18.9% (21/111) ( $p=0.003$ ). One child died during intubation giving an overall 0.4% mortality for the immediate intubation period (16 months old with a lethal chromosomal disorder, pulmonary hypertension and septic shock). No children were lost to follow up.

The unadjusted mortality was 7.2% (9/124) for those who received atropine compared to 15.7% (22/140) for those who did not (OR 0.42, 95%CI 0.19-0.95  $p=0.04$ ). When the association between atropine use and mortality was examined in

the age subgroups, there was a significant reduction of mortality in the older children, but not in the neonates (Table 7-3). The excess mortality in the older children who had not received atropine and had been intubated for non-neonatal/cardiac/septic shock pathologies. The repartition according to pathology is presented in Table 7-2.

**Table 7-2;** Breakdown of the causes of death by pathology. Neonates are  $\leq 28$  days and older children  $>28$  days and less than 8 years.

	Neonates (n=153, deaths/cases)		Older children (n=111, deaths/cases)	
	Non-atropine (n=74)	Atropine (n=79)	Non-atropine (n=66)	Atropine (n=45)
Neonatal respiratory distress	1/56	2/61	-	-
Non-neonatal respiratory distress	2/8	0/4	9/32	0/14
Cardiac	0/4	0/3	2/5	0/1
Ear, nose and throat	1/1	0/1	1/8	0/10
Neurologic	0/1	3/5	3/12	3/15
Sepsis	0/1	1/3	3/9	0/4
Other	0/3	0/2	0/0	0/1
<b>Total</b>	<b>4</b>	<b>6</b>	<b>18</b>	<b>3</b>

**Table 7-3;** The association between ICU mortality related to atropine use corrected by the propensity score (PS) in the two age subgroups. Neonates are  $\leq 28$  days and older children  $>28$  days and less than 8 years.

	Neonates (n=153)			Older children (n=111)		
	Odds ratio	P	CI 95%	Odds ratio	p	CI 95%
Atropine PS corrected	1.3	0.74	0.31-5.1	0.22	0.028	0.06-0.85

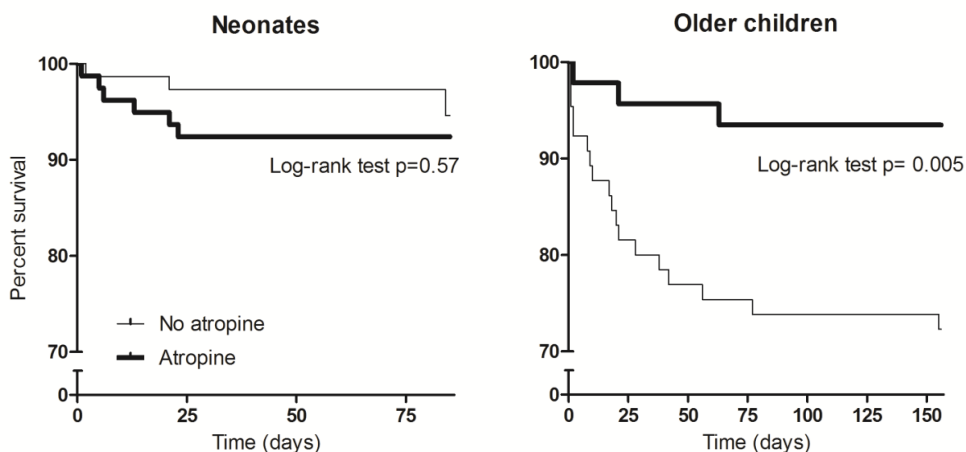
We conducted a *post hoc* analysis to consider the apparent association of absence of atropine treatment with death by using two PS constructed from the variables for

each age group. This was done to test the possibility that the construction of the PS from data from all children would be different if the PS was constructed using data from children of each age group. The association of atropine use with death remained relatively unchanged: *post hoc* PS adjusted OR in neonates of 2.4, (95%CI 0.56-10.4,  $p=0.23$ ) and *post hoc* PS adjusted OR 0.24 (95%CI 0.06-0.96,  $p=0.043$ ) for the older children.

### 7.3.5 Survival analysis

When atropine was used there was a significant difference in the survival distribution of the older children ( $p=0.005$ ) but not the neonates ( $p=0.57$ ) (Figure 7-2).

**Figure 7-2;** Kaplan-Meier plots for mortality in the two age sub-groups of neonates and older children (7-2).



### 7.3.6 Change in heart rate during intubation

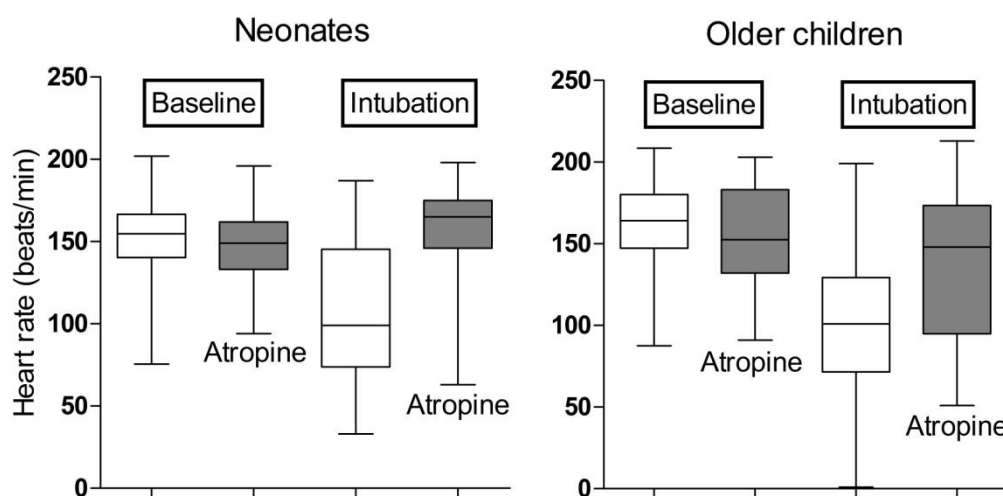
When atropine was used, the heart rate was a mean of 50 (45-55) beats/min ( $p<0.001$ ) higher during intubation than when atropine was not used. After the administration of atropine the mean heart rate rose from 148 (126-170) beats/min to

166 (SD 147-185) beats/min ( $p < 0.001$ ) for the neonates and from 154 (124-184) beats/min to 174 (145-203) beats/min ( $p < 0.001$ ) for the older children (Figure 7-3).

**Table 7-4;** Multivariable analysis of the change in heart rate during intubation following fall in peripheral oxygen saturation ( $SpO_2$ ) and after the use of atropine (corrected by the propensity score [PS]). Neonates are  $\leq 28$  days and older children  $> 28$  days and less than 8 years.

	Neonates (n=153)			Older children (n=111)		
	Heart rate change (beats/min)	P	CI 95%	Heart rate change (beats/min)	p	CI 95%
Fall in $SpO_2$ by 10 % points	-4.1	0.005	-1.3 - -7.0	-5.4	$< 0.001$	-2.6 - -8.4
Difference with and without atropine (PS corrected)	-45.9	$< 0.001$	-34.3 - -57.5	-43.5	$< 0.001$	-25.5 - -61.5

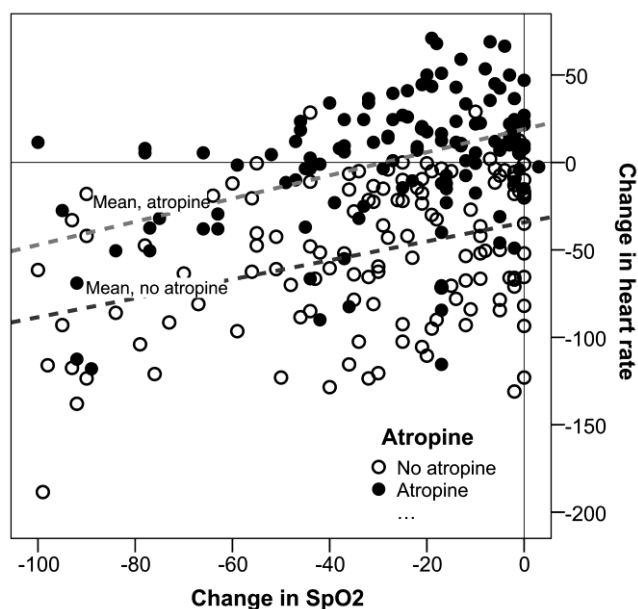
**Figure 7-3.;** Change in heart rate during intubation according to atropine use of the two age sub-groups. The central bar is the mean, the box represents the inter-quartile range and the whiskers the range.





Measured oxygen saturations were similar between atropine and non-atropine groups. Median fall in SpO<sub>2</sub> was 25% [8-44] in the non-atropine group and 19% [6-44] in the atropine group (p=0.31). There was a significant correlation between a fall in SpO<sub>2</sub> and a fall in heart rate (p<0.0001) (Figure 7-4 and Table 7-4). The median number of attempts at intubation was also comparable between non-atropine (1 [1-2]) and atropine (1 [1-2]) (p=0.20) cases. One attempt at intubation significantly reduced mean heart rate in the neonates by 9.6 beats/min (95%CI 2.3-16.9, p=0.01) but not in the older children (6.1 beats/min per intubation attempt, 95%CI 1.5-13.8, p=0.12). In multivariable analysis the number of attempts at intubation was not significantly different for either age group. Eleven children were excluded from the saturation analysis and 16 from the number of attempts at intubation because of missing data.

**Figure 7-4;** Change in heart rate related to a change in peripheral oxygen saturation (SpO<sub>2</sub>) during intubation. The coefficient of determination is (r<sup>2</sup>) 0.10.



The use of the PS had little effect on the crude estimates of the mean change in heart rates which were 58.7 beats/min without the PS *versus* 53.4 beats/min with the PS for the neonates and 41.5 beats/min without the PS *versus* 40.8 beats/min with the PS for the older children. When the SpO<sub>2</sub> and number of intubation attempts and atropine corrected by the PS were entered into a multivariable model only atropine and a fall in SpO<sub>2</sub> remained significant (Table 7-4).

## **7.4 Discussion**

We disproved our hypothesis and showed that the use of atropine was associated with less frequent ICU mortality but only in the older children. The decrease in ICU mortality was not a consequence of the reduction in intubation bradycardia which occurred in a similar measure in both age groups when atropine was not used.

### **7.4.1 Study Population Bias**

Our population was diverse, with 57% of children being intubated and hospitalised outside the PICU of Robert Debré. This is similar to a 2004 survey in 204 French PICUs (165) and a 2010 report from UK neonatal units.(225) A recent survey of influences on atropine use and atropine prescribing habits among 61 paediatric intensivists in 8 countries noted that 49% prescribed atropine for half of their intubations.(16) One area where our practise differs from others is the relatively infrequent use of muscle relaxants including suxamethonium. This is due to the important proportion of neonates where hospital protocol does not recommend muscle paralysis, a relatively large proportion of ENT intubations and propofol use which is associated with good intubation conditions without relaxants.(273)

#### **7.4.2            *Frequency of Atropine Prescription***

The measured the frequency of atropine use in our population was 47% which is similar to that of one previous survey of activity in 204 French ICU units published in 2004 whereby that atropine was prescribed for 30% of neonatal intubations (<28 days), 63% for infants (28 days to 23 months) and 18% for older children (165). Venkatesh *et al.* (225) recorded a 29% use of atropine in 93 neonatal units in the UK in 2010. A more recent survey of influences on atropine use and atropine prescribing habits among 61 paediatric intensivists in 8 countries noted that 49% prescribed atropine for half of their intubations.(248)

#### **7.4.3            *Desaturation and Numbers of Intubation Attempts***

In our neonatal group of the median number of intubation attempts was 1 [1-2]. These results are analogous two other RCTs of neonatal intubation comparing a Morphine-Atropine-Suxamethonium (MAS) group and a propofol group (2, [1-3] *versus* 1, [1-2]) (211) and another study for a MAS pre-medicated group (1, [1-3]) *versus* a non-pre-medicated group (1, [1-6]) (224). Median trough oxygen saturation in our study was 76% which compares favourably to two neonatal RCTs which noted 60% to 80% (211, 224) and in a prospective cohort of 58% to 65% (225).

In one paediatric intubation study the mean number of attempts at intubation in a retrospective study was 1.6 per patient (20) compared to a mean of 1.9 in our study population. Carroll *et al.* (19) recorded a 23% prevalence of three or more attempts at intubation compared to our 7% frequency. The same study noted that desaturation below 90% occurred in 29% (40/137) of intubations (19). If we use an identical definition for our study population as many as 75% of the children were desaturated.

Fastle recorded a 22% (31/143) prevalence in hypoxaemia (without giving its definition) and noted that younger children were more susceptible to hypoxia (20). One previous anaesthetic study has also mentioned that age is an important risk factor for desaturation (4). There are two reasons to explain the difference in trough saturations between these studies and ours. Firstly, both Carroll (19) and Fastle (20) both highlight that their retrospective methodologies relied on accurate and honest recording in the intubation log and that this was a limitation. Secondly, our over one month population had a median age of 5.4 months, considerably lower than that of Fastle (12 months) (20) or Carroll (2.8 years) (19).

#### **7.4.4 Use of the Propensity Score**

We agree with Gayat *et al.* that emergency situations are a good example where recruitment patterns in RCTs may distort treatment effect and PS controlled cohorts may be preferable (284). However, we disagree with Gayat *et al.* when they recommend that matching on the PS should be the preferred method of using the PS (284). Matching assumes that the effect of treatment on the outcome is not different in those participants, treated or untreated, that could not be matched. The advantage of our choice of using a multivariable regression based model incorporating a PS is that all of the individuals can contribute to the final result. We chose a multivariable regression based model which provides more statistical power.(285) Our study design produced treatment groups of neonates and older children where there were no significant differences between pre-treatment variables (Table 7-1). This validates the use of the PS for which a considerable overlap in the distribution of variables is an *a priori* condition. In addition, our result for the crude OR for the mortality in the older children (0.21) remained stable when adjusted using the PS for the whole group

at 0.22 and was 0.24 for the *post hoc* divided PS. The effect of residual unidentified variables that were not entered into the PS could potentially have influenced the final result. Despite our result remaining significant when using a PS for all patients and divided for the two age groups, our result needs to be confirmed in a study using randomised methodology.

There are three possible explanations for the unexpected significant difference in ICU mortality with and without atropine that we found both with and without case-mix adjustment for atropine prescription using the PS. Firstly, the PS has not dealt with atropine prescription bias because not all prescription-influencing co-variables were included in its construction, which is a condition of its use (282), leaving residual confounders linking atropine prescription to death. A possible indication of this could be the non-significant difference in the PRISM scores of the atropine and non-atropine groups, which showed a trend towards an increased risk of death for the non-atropine group. The significant difference in the baseline heart rate between the two groups is integrated in the PRISM score and was also included in the PS before adjusting the final result. Secondly, that chance has produced a statistically significant result and finally that atropine may reduce mortality.

The excess mortality we observed was not related to mortality during intubation because this was rare with only a single death observed. This rate is similar to previous series.(19, 20) Neither can the excess post-intubation mortality be ascribed to a late effect of bradycardia because this occurred with similar frequency in both the neonates and older children, yet the ICU mortality difference was only seen in the

older children. The pathologies that were associated with fewer deaths with atropine were principally Non-NRD and sepsis (Table 7-2).

#### **7.4.5 R-R Beat-to-Beat Variability**

One possible explanation for the observed association of atropine on mortality may be related the uncoupling of real-time feedback of measurements of blood pressure in the baroreceptors in the carotid bodies, which has the effect of reducing R-R beat-to-beat variability (RRBBV). Vagal impulses are rapid by nature of the rapid hydrolysis of acetylcholine in postganglionic parasympathetic receptors contrary to sympathetic stimulation of the heart and vessels which is of the order of 2-5 seconds.(286) Reductions in RRBBV following atropine administration have been measured in premature neonates awaiting intubation for respiratory distress (287) and normal children undergoing routine anaesthesia.(173) In small children, reductions in RRBBV could be achieved by a single dose of atropine due to its long half-life (288) which is a consequence of the extended elimination phase resulting from its increased distribution volume (289).

Pre-terminal haemodynamic decompensation is frequently accompanied by bradycardia in children.(290) It results from a 'two-hit' process whereby the first step is often exaggerated RRBBV before the second step of entry into a negative feedback loop of arrhythmia and hypoperfusion, as has been demonstrated experimentally in dogs.(291) The short-lived intubation bradycardia commonly observed in our non-atropinised patients is an example of severe RRBBV, yet intubation mortality was rare because the children were still self-protecting from the second stop of bradycardia-hypoperfusion. Atropine is ineffective against hypo-perfusion and non-

vagally mediated bradycardia when they are already established, indeed atropine is no longer recommended by the AHA for resuscitation.(292) However, when atropine is prophylactically administered before bradycardia-hypoperfusion, as happened to our atropinised older patients, some of whom later became vulnerable to haemodynamic decompensation, atropine could protect against the first step of spontaneously occurring exaggerated RRBBV.

## **7.5 Conclusions**

Atropine was associated with a reduction in ICU mortality outside the immediate period of the intubation only in children aged over one month. This effect is independent of its capacity to reduce heart slowing during intubation. The association between atropine use during CCI and reduced ICU mortality should be investigated in other populations using prospective randomisation.

## Chapter Eight

### An Animal Intubation Model of Vagally Induced Changes in Blood Pressure during Hypovolaemia and Endotoxaemia

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#### 8.1 Introduction

The intubation of children during critical illnesses can provoke alterations in both heart rate (19, 20) and blood pressure.(9, 224) The physiological stimulation of the Vagus nerve by hypoxaemia in the aortic bodies (7) and manipulation of the laryngopharynx during laryngoscopy releases acetylcholine in the sino-atrial node.(8) Intubation-related vagal stimulation is accompanied by selective vasoconstriction which conserves atrial pre-load and therefore ventricular filling.(114-117). In 1984 Marshall *et al.*(9) noted a rise in blood pressure in a group of newborns who experienced significant bradycardia during intubation.

There are two other influences on haemodynamic instability during intubation; drugs and pathology. Induction drugs, such as propofol(6, 177), thiopental(177), morphine(180), sufentanyl(179) and remifentanyl(178), may also induce bradycardia. Unlike vagal bradycardia this is typically accompanied by vasodilatation. Vasodilatation is potentially detrimental because it lowers atrial pre-load with a negative impact on ejection volume and therefore cardiac output. Septic shock in adults (84, 293) is typically associated with vasodilatation. In contrast early hypovolaemic is associated with vasoconstriction.(90)



The consequences of the above effects on haemodynamic stability during routine anaesthetic intubation are almost always insignificant. However the interactions between these pharmacological and physiological mechanisms producing bradycardia and the physiology of acute critical illness mean that intubation presents a significant risk of death in critically ill adults (3, 16, 18) and children.(4) Mean blood pressure has a tendency to fall by 30mmHg during intubation in adults and those who start the procedure with hypotension are particularly at risk of haemodynamic deterioration.(3) One recent review has suggested that bradycardia in the presence of vasodilatation during intubation may destabilise haemodynamic homeostasis.(270)

The animal model was used to test the hypothesis that blood pressure changes after vagal stimulation are not modified by hypovolaemia or endotoxaemia. Preliminary animal experimentation at the national veterinary school near Paris established a model of intubation in rabbits. Mechanical stimulation of the laryngopharynx was unable to reliably induce changes in blood pressure even in the presence of severe hypoxia. However, electrical stimulation of the laryngopharynx of a rabbit using a modified ETT did produce changes in blood pressure but only at an intensity of electric current whereby the muscles of the whole of the upper body contracted. When the Vagus nerve was dissected out and stimulated directly using an electrical current changes in blood pressure were consistently produced (results not shown). The rabbits were anaesthetised with intra-venous urethane because of its single dose regimen, good analgesic and anaesthetic properties and previously established minimal effects on haemodynamic function in the experimental situation.(294) Direct measurement of the blood pressure in the right carotid artery using an iWorx 214 monitor was favoured because of its reliability in measuring changes in blood

pressure at low and rapidly changing pressures and in combination with rapidly changing heart rate (results not shown).

In addition we examined the levels of circulating catecholamines and their relationship to blood pressure in response to during the two pathological states.

## **8.2 Methods**

### **8.2.1 *Experimental Protocol***

The study was approved by the ComEth Anses/ENVA/UPEC (Comité d’Ethique pour l’Expérimentation Animale, Maison-Alforts, FRANCE). Male New Zealand White (NZW) rabbits were obtained from Hypharm, La Corbière, 49450, Roussay. A maximum of 15 rabbits were maintained in a pen of 3m wide by 4m long and of a height of 3m with a dense layer of straw and hay, which is in excess of animal husbandry recommendations.(295) The pen was situated in a room of 15m by 12m with several large windows giving access to daylight and at least one window continually open to ensure aeration. Food and water was provided *ad libitum*.

Male New Zealand White rabbits were anaesthetised by the injection urethane in a marginal vein of an ear. A midline incision was made in the anterior aspect of the neck and the trachea opened before being intubated. The right carotid artery was cannulated with a 22gauge canula and the left Vagus nerve exposed. Continuous mean blood pressure readings and intermittent blood gas measurements were made. The rabbits were entered into the experiment when blood pressure had been stable for at least 15 minutes. The arterial pH was required to be between  $\geq 7.35$  and  $\leq 7.45$  (normal limits of rabbit pH 7.2-7.5(296, 297)).

The rabbits were randomly assigned into four groups; control (11 rabbits), endotoxaemia 1mg/kg (LPS from E.Coli B:055, Sigma-Aldrich, France) (11 rabbits), hypovolaemia 20% reduction in blood volume (8 rabbits) and hypovolaemia reduction in blood volume of 40% (8 rabbits).

Rabbits in the hypovolaemia groups were bled over a period of five minutes from the carotid artery catheter 20 minutes after baseline according to an estimation of the blood volume of 5.5ml of blood per 100g of body weight.(298, 299) The rabbits assigned to the endotoxaemia group were injected with 1mg/kg of endotoxin diluted at 1mg/ml in 0.9% saline solution at a rate of 2mg/5minutes.

### **8.2.2        *Blood Sampling and Biochemical Analysis***

Sampling was performed at the following times; baseline, 30, 60, 90, 120, 150, 180, 240 and 300 minutes, hypovolaemic shock baseline 30, 60, 90, 120 and 150 minutes, endotoxic shock baseline, 30, 60, 90, 120, 150, 180, 240 and 300 minutes (Figure 8-1). The samples taken from the endotoxaemic rabbits at 30, 90 and 150 minutes were not analysed, as according to protocol, so as to ensure identical experimental conditions for all groups.

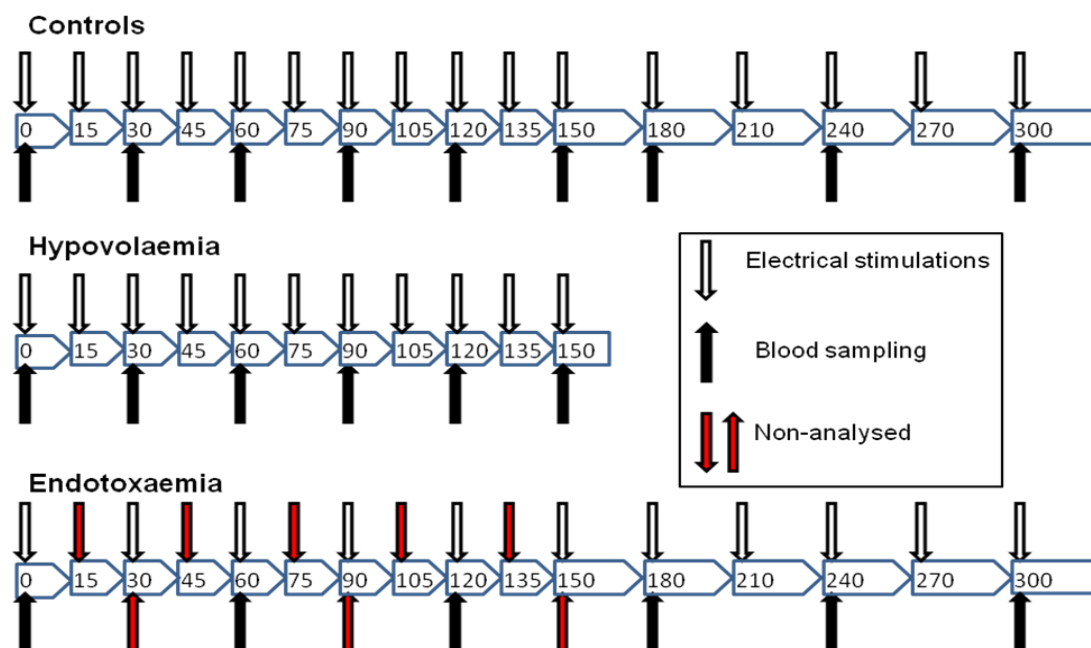
Samples of 1.3ml of blood were drawn from the carotid artery of the anaesthetised rabbits. Seventy microlitres were separated for blood gas (pH, PCO<sub>2</sub>, base excess, bicarbonates) and serum lactate analysis using an i-STAT® (Abbott Point of Care Inc., 400 College Road East, Princeton, NJ 08540, USA). Normal ranges were as follows; lactate (normal range 1.0mmol/l (0.5-1.5)](300), haematocrit (NZW normal range 31.3-43.3% [mean weight of rabbit 3.6kg [3.0-4.2kg]](301). A haematocrit

was determined by placing 0.1ml of whole blood in a heparin coated plastic tube (100µl safeCLINITUBES, Radiometer Medical AsP, Akandevvej 21, 2700 Bronshoj, Denmark), centrifuged at 2000 revolutions/minutes for two minutes and the relative proportion of serum and compacted cells compared. The remaining 1.1 ml was transferred into an EDTA tube of 1.3ml, shaken gently before centrifugation at 4000rpm at a temperature of 4°C for 5 minutes. Thereafter, the plasma was drawn off and transferred directly for storage at -20°C in the dark for later catecholamine analysis.(302, 303)

### **8.2.3            *Stimulation of the Vagus Nerve***

The Vagus nerve was lifted free from other structures in the neck, laid across two steel electrodes 5mm apart and electrically stimulated using a 3.0mA current, 250 pulsations of 10milliseconds at 10Hz (duration of stimulation 25 seconds). Stimulations were made at baseline, 30, 45, 60, 75, 90, 115, 120, 135, 150, 165, 180, 210, 240, 270 and 300 minutes for the controls and endotoxaemia models and baseline, 30, 45, 60, 75, 90, 115, 120, 135, 150 minutes for the hypovolaemic model (Figure 8-1). This allowed the control rabbits to serve for the hypovolaemic and endotoxaemic rabbits but meant that the endotoxaemic rabbits received five more stimulations and three more blood samplings than would otherwise have been necessary. A three-minute interval was left after taking blood before a vagal stimulation.

**Figure 8-1;** Gant chart showing schema of blood sampling. Control rabbits and the experimental groups all received the same number of stimulations and blood samples. Endotoxaemic rabbits had five stimulations and three blood samples that were not analysed, as according to protocol, so as to ensure identical experimental conditions for all groups.



#### 8.2.4 Catecholamine analysis

All catecholamine analysis was performed at the Hôpital Robert Debré. The process of catecholamine analysis takes place in four discrete stages; sampling, purification, chromatography and quantification of the analyte and was carried out in accordance with the reverse-phase ion-pairing liquid chromatography methodology described by Candito *et al.* in 2002.(157)

Preparation of solution buffer solution. Buffer EDTA pH8.6 (2M, EDTA2%). 12.11g of tris base was added to 1g of EDTA and brought to a volume of 50ml using sodium hydroxide to maintain a pH of 8.6.

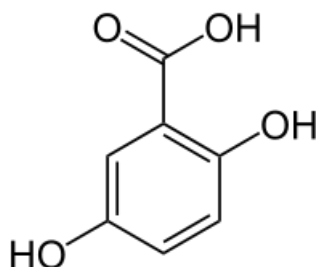
Preparation of washing solution. Buffer EDTA pH 8.1 (0.33M, EDTA 2%). 2g of tris base was added to 20g of EDTA and brought to a volume of 1000ml using sodium hydroxide to maintain a pH of 8.1.

Preparation of eluate (mobile phase). One millilitre of glacial acetic acid concentration 175mM (approximately pH2.0) with 50 $\mu$ L of 5%EDTA solution was added to make a volume of distilled water to bring to a volume of 100ml.

Preparation of control standards. Ten ampoules of 2.5ml CP Plasma Calibration External standard were obtained from Chromosystems (Chromosystems Instruments and Chemicals GmbH, Heimbürgerstrasse 3, 81243 München, Germany). Each 2.5ml ampoule was reconstituted with 2.5ml of distilled water, aliquotted into 500 $\mu$ l quantities in 2ml eppendorf containers and frozen at -40°C. The relative concentrations of catecholamines were; noradrenaline 6.86nM, adrenaline 1.59nM and dopamine 2.80nM.

Preparation of internal control. 50 $\mu$ l of dihydroxybenzoic acid (DHBA) derived from urinary catecholamines diluted was diluted in 1/100 in tris EDTA pH8.6. Dihydroxybenzoic acid is manufactured from a catechol ring and has the property of not interfering with plasma derived catecholamines in the mobile phase (Figure 8-2).

**Figure 8-2;** 2,5-Dihydroxybenzoic acid is used as the internal control during high-performance liquid chromatography for the detection of catecholamines as it does not interfere with the mobile phase. ([http://en.wikipedia.org/wiki/2,5-Dihydroxybenzoic\\_acid](http://en.wikipedia.org/wiki/2,5-Dihydroxybenzoic_acid))



The plasma was removed from  $-40^{\circ}\text{C}$  storage and thawed at room temperature. Six hundred microlitres was drawn from the plasma samples and 20mg of alumina (aluminium oxide,  $\text{Al}_2\text{O}_3$ ) and 100 $\mu\text{l}$  of the internal standard were added to the 600 $\mu\text{l}$  of plasma. The mixture was gently agitated for 5 minutes by hand before sedimentation of the alumina by centrifugation at 5000rpm for 2minutes. The supernatant was drawn off and discarded.

The samples were washed by the addition of 1ml of the washing solution. The mixture was gently agitated by hand for 3 minutes before being centrifuged at 5000rpm for 2minutes. The supernatant was drawn off and discarded. The process as repeated two more times.

A total of 100 $\mu\text{l}$  of buffer solution was added to the alumina in an eppendorf container, which was agitated by hand for 5min to liberate the catecholamines. The mixture was centrifuged at 5000rpm for 5 minutes. Fifty microlitres of the supernatant were removed and added to 100 $\mu\text{l}$  glass microtubes for injection through

a 717 Waters auto-sampler onto a C18 Purospher (Merck) column (150x4 mm, 4 $\mu$ m) equipped with a guard column. The aqueous isocratic mobile phase adjusted to pH 3.9 consisted of citric acid 20mM, sodium acetate 50mM, sodium heptane sulfonate 0.4mM in methanol 10%. Mobile phase was pumped at a flow rate of 1ml/min by a Waters Model 550 pump.

Quantification of the catecholamines was carried out by electrochemical detection. The catecholamines were eluted from the column using an amperometric 2465 Waters detector set at 0.5V. An external control of known concentrations of noradrenaline, adrenaline and dopamine was used to calibrate the internal control against the samples tested. The area under the curve of each peak detected by the chromatograph is used to compare the area under the internal control. In turn the area under the internal control was compared to the area under the curves of the standard of known concentration. Millennium Waters Empower Chromatography software was used for all calculations. Fifteen to 25 samples were batched for analysis. A negative control (acid), internal control (urine catecholamine) and standard control (plasma catecholamine) were analysed in sequence before each batch.

The severity of pathology was determined by the time to the first death in each group. The readings immediately prior to the first death in each group were used *post hoc* as the start point and the end of experimentation was one hour later.

### **8.2.5**      *Statistical analysis*

Qualitative variables are described as numbers and percentages and quantitative variables as median [quartiles] or mean (standard deviation) according to their



Gaussian distribution. An independent t-test, or a Mann-Whitney test, was used for continuous data according to their distribution. All statistical tests were 2-sided and the probability of a type 1 error ( $\alpha$ ) was determined at  $<0.05$ . All statistical tests were carried out using SPSS (version 19).

## **8.3 Results**

### **8.3.1 Baseline Characteristics**

There were no significant differences between the weights of the rabbits in the control group (mean 1.96kg) compared to the endotoxin (mean 1.93kg,  $p=0.62$ ), 20% hypovolaemia (mean 1.91kg,  $p=0.55$ ) and 40% hypovolaemia (mean 1.87kg,  $p=0.28$ ) groups. Nor were there differences in the baseline characteristics of pH, CO<sub>2</sub>, HCO<sub>3</sub>, base excess, lactates, haematocrit and the baseline haemodynamic parameters of mean blood pressure, heart rate, pulse pressure and change in mean blood pressure following vagal stimulation for the control group compared to the other three groups (Table 8-1).

Whilst there was no significant difference in the baseline adrenaline, noradrenaline and dopamine between the control groups and the two hypovolaemia groups, the baseline levels of adrenaline and noradrenaline were significantly higher in the endotoxin group (median control adrenaline 2.0nM[0-5.2] *versus* median endotoxin adrenaline 7.9nM[4.3-9.0],  $p=0.005$ ; median control noradrenaline 0.nM3[0-1.6] *versus* median endotoxin noradrenaline 1.5nM[0.6-2.4],  $p=0.04$ ) (Table 8-1).

**Table 8-1;** Median baseline biochemical, haematologic and hormonal characteristics of the four groups of rabbits; control; endotoxin, and the two hypovolaemia groups (20% and 40%).

	Control (n=11) (reference)	Endotoxaemia (n=11)	Hypovolaemia 20% (n=8)	Hypovolaemia 40% (n=7)
pH	7.39 [7.37 - 7.42]	7.39 [7.37 - 7.40]	7.39 [7.37 - 7.41]	7.38 [7.36 - 7.42]
Lactates (mmol/l)	2.9 [1.8 - 5.5]	2.3 [1.7 - 3.3]	3.6 [1.7 - 5.5]	3.0 [2.6 - 4.5]
Bicarbonates (mmol/l)	25.4 [22.6 - 28.0]	24.0 [21.7 - 24.5]	24.8 [24.5 - 27.3]	23.4 [22.5 - 24.3]
Base excess	0 [-2 - 4]	-1 [-3 - 1]	0 [-1 - 3]	-2 [-3 - 0]
pCO <sub>2</sub> (kPa)	5.5 [5.2 - 6.2]	5.1 [5.0 - 5.4]	5.5 [5.1 - 6.0]	5.4 [5.0 - 5.7]
Haematocrit (%)	42 [37 - 45]	45 [42 - 46]	43 [40 - 48]	42 [39 - 47]
Heart rate (beats/min)	310 [278 - 323]	279 [267 - 303]	289 [270 - 297]	294 [264 - 311]
Pulse pressure (mmHg)	27 [20 - 31]	27 [23 - 29]	24 [19 - 28]	29 [19 - 32]
Blood pressure (mmHg)	77 [58 - 92]	72 [64 - 79]	63 [54 - 80]	73 [64 - 80]
Fall in blood pressure(mmHg)	28 [21 - 37]	28 [18 - 31]	23 [14 - 29]	22 [17 - 30]
Adrenaline (nM)	2.0 [0 - 5.2]	7.9 [4.3 - 9.0] $\alpha$	1.8 [0.6 - 5.8]	0.7 [0.5 - 2.6]
Noradrenaline (nM)	0.3 [0 - 1.6]	1.5 [0.6 - 2.4] *	0.4 [0 - 1.4]	0.4 [0 - 0.5]
Dopamine (nM)	0 [0 - 2.1]	0 [0 - 1.4]	1.0 [0 - 1.6]	0 [0 - 0.5]

\* p<0.05,  $\alpha$  p<0.01

One rabbit from the 40% hypovolaemia group died after bleeding and before stimulation and was excluded. The first death after vagal stimulation after the start of experimentation in the HV40% group occurred between +15 and +30 minutes from bleeding and between +240 and +270 minutes from injection in the endotoxin group. As such the comparison of the biochemical, haematological and change in mean

blood pressure following vagal stimulation was from +15minutes in the hypovolaemia groups and +240 minutes for the endotoxin group. There were two deaths in the HV40% group (2/7, 29%) and three in the endotoxin group (3/11, 27%) in the 60 minutes of experimentation. No rabbits died in the HV20% group.

**Table 8-2;** Median changes in biochemistry and haematocrit in the hypovolaemic rabbits.

	Group	Time t=+15	Time t=+45	Time t=+75
Number of rabbits	Control	11	11	11
	HV 20%	8	8	8
	HV 40%	7	6	5
pH	Control (ref)	7.39 [7.37-7.41]	7.40 [7.37-7.41]	7.39 [7.37-7.41]
	HV 20%	7.34 [7.29-7.38]	7.35 [7.28-7.39]	7.34 [7.29-7.38]
	HV 40%	7.40 [7.33-7.43]	7.25 [7.1-7.3] ∞	7.30 [7.12-7.3] ∞
Lactates (mmol/l)	Control (ref)	3.3 [1.8-5.5]	3.5 [1.5-5.6]	4.2 [1.5-5.6]
	HV 20%	4.3 [1.3-6.7]	5.5 [2.0-8.8]	5.9 [2.0-9.8]
	HV 40%	5.5 [4.1-5.9]	9.2 [5.7-11.7] ∞	8.7 [6.0-16.1] *
HCO <sub>3</sub> (mmol/l)	Control (ref)	26.6 [23.6-28.1]	25.3 [24.6-28.4]	25.4 [24.5-28.1]
	HV 20%	24.8 [21.4-26.4]	22.6 [21.6-23.9] ∞	22.2 [20.6-26.6]
	HV 40%	18.6 [17.9-22.1] ∞	16.5 [12.9-19.2] ∞	16.2 [12.2-18.4] ∞
Base excess	Control (ref)	1 [-1- 4]	0 [0-4]	0 [-1-3]
	HV 20%	-1 [-4- 2]	-3 [-1- -5] ∞	-3 [2- -6] *
	HV 40%	-6 [-2- -8] ∞	-12 [-9- -15] ∞	-10 [-8- -17] ∞
CO <sub>2</sub> (kPa)	Control (ref)	6.0 [5.5-6.2]	5.8 [5.4-6.2]	5.8 [5.5-6.0]
	HV 20%	5.2 [5.0-6.2]	5.2 [4.9-6.0]	5.5 [5.1-6.4]
	HV 40%	4.5 [4.1-4.6] ∞	4.6 [4.4-7.3] *	4.5 [4.0-5.6]
Haematocrit (%)	Control (ref)	41 [37-47]	41 [37-45]	41 [36-44]
	HV 20%	38 [36-40]	37 [35-39]	36 [33-38] *
	HV 40%	36 [28-38] *	32 [28-34] ∞	32 [26-34] ∞

\* p<0.05, ∞ p<0.01

### 8.3.2 *Changes in Biochemical and Haematological Parameters in Hypovolaemia*

The hypovolaemia groups showed significant decreases in pH, CO<sub>2</sub>, HCO<sub>3</sub>, base excess, lactates and haematocrit compared to the control group (Table 8-2). These changes were proportional to severity of hypovolaemia.

A significant increase in adrenaline was observed in the 40%, but not the 20%, hypovolaemia group at time t=+45minues compared to the controls (Table 8-3). There was a non-significant trend for the 20% group to have higher levels of noradrenaline than the 40% group (Table 8-3).

**Table 8-3;** Median changes in catecholamines for the control and hypovolaemia groups.

	Group	Time t=+15	Time t=+45	Time t=+75
Number of rabbits	Control	11	11	11
	HV 20%	8	8	8
	HV 40%	7	6	5
Adrenaline (nM)	Control (ref)	0.45 [0-2.4]	0 [0-0.55]	0 [0-0.55]
	HV 20%	0.83 [0.32-1.2]	0.14 [0-1.1]	0.62 [0.7-1.5]
	HV 40%	2.45 [0.43-13.9]	1.3 [0.36-22.4] *	1.34 [0-3.7]
Noradrenaline (nM)	Control (ref)	1.00 [0-3.2]	0.40 [0-2.1]	0 [0-1.9]
	HV 20%	2.42 [0.55-3.8]	1.50 [0.10-3.9]	1.79 [0.11-3.2]
	HV 40%	0.39 [0-1.9]	0.56 [0.37-7.7]	0.88 [0.38-3.6]
Dopamine (nM)	Control (ref)	0 [0-0.6]	0 [0-1.3]	0 [0-1.2]
	HV 20%	0.62 [0-1.2]	0.86 [0-1.1]	0.63 [0-1.3]
	HV 40%	0 [0-0.91]	1.35 [0.6-2.5]	1.60 [0.71-1.8]

\* p<0.05, α p<0.01

### 8.3.3 *Changes in Biochemical and Haematological Parameters in Endotoxaemia*

In the endotoxin group there were significant decreases in CO<sub>2</sub>, HCO<sub>3</sub> and base excess, no change in pH, lactates and haematocrit and significant increases in noradrenaline (Table 8-3).

**Table 8-4;** Median changes in biochemistry and haematocrit in the endotoxin group.

		Time t=+240	Time t=+300
Number of rabbits	Control	11	11
	Endotoxin	11	8
pH	Control (ref)	7.35 [7.34-7.40]	7.36 [7.35-7.39]
	Endotoxin	7.35 [7.33-7.40]	7.33 [7.28-7.36]
Lactates (mmol/l)	Control (ref)	4.2 [2.0-5.7]	3.3 [1.8-5.6]
	Endotoxin	3.5 [2.1-5.1]	4.2 [1.8-5.1]
HCO <sub>3</sub> (mmol/l)	Control (ref)	24.9 [23.9-26.4]	25.2 [23.5-27.4]
	Endotoxin	21.7 [18.4-22.4] *	21.0 [20.1-22.4] *
Base excess	Control (ref)	0 [-2- 1]	0 [-2- 2]
	Endotoxin	-5 [-3- -7] *	-5.5 [-4- -6] *
CO <sub>2</sub> (kPa)	Control (ref)	6.1 [5.7-6.5]	5.9 [5.6-6.2]
	Endotoxin	4.9 [4.6-5.4] *	5.2 [4.7-6.3]
Haematocrit (%)	Control (ref)	39 [37-43]	40 [37-43]
	Endotoxin	43 [39-44]	38 [38-41]

\* p<0.05, \* p<0.01

The levels of noradrenaline were significantly higher in the endotoxin group at +240 and +300 minutes and although levels of adrenaline were higher there was no significant difference from the control group (Table 8-5).

**Table 8-5;** Median changes in plasma catecholamines in the endotoxin group.

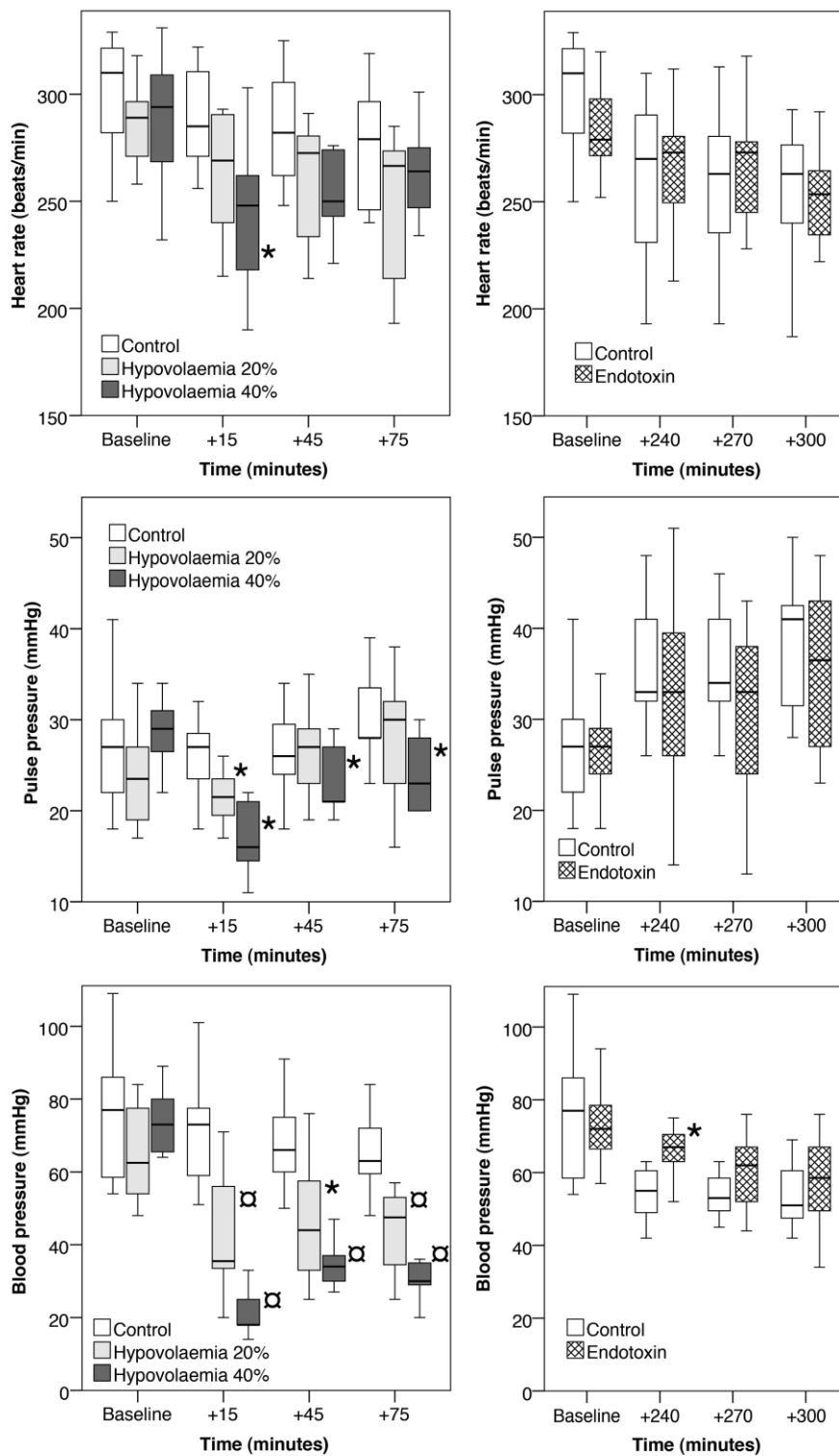
		Time t=+240	Time t=+300
Number of rabbits	Control	11	11
	Endotoxin	11	8
Adrenaline (nM)	Control (ref)	0.29 [0-0.73]	0.31 [0-1.1]
	Endotoxin	1.13 [0-3.5]	0.66 [0-2.8]
Noradrenaline (nM)	Control (ref)	0.75 [0-3.2]	0.36 [0-3.7]
	Endotoxin	3.45 [2.3-6.0] *	3.55 [2.4-5.0] α
Dopamine (nM)	Control (ref)	0 [0-0.64]	0 [0-0.60]
	Endotoxin	0.82 [0.45-1.4] *	0 [0-1.5]

\* p<0.05, α p<0.01

#### 8.3.4 *Changes in Haemodynamic Parameters*

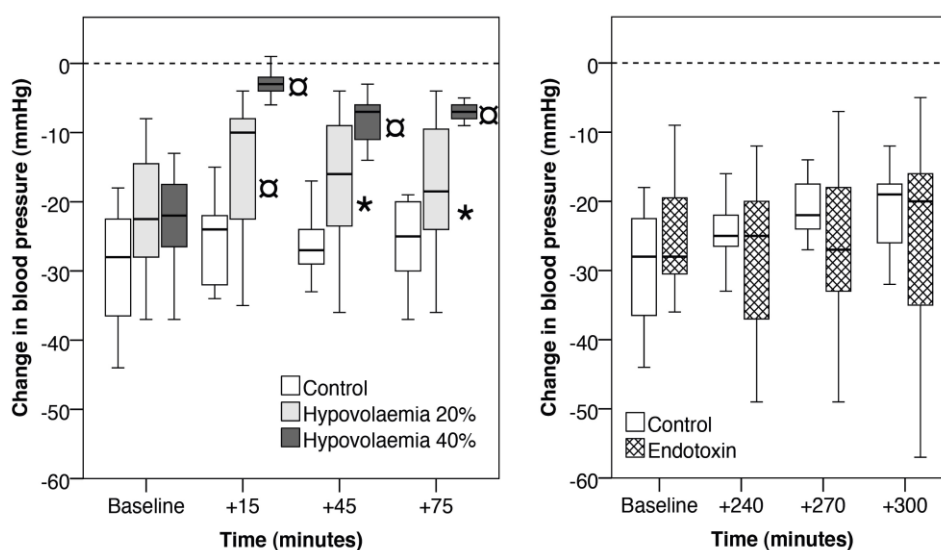
The haemodynamic parameters of pulse pressure, mean blood pressure and heart rate all fell significantly and in proportion with blood loss in the hypovolaemic groups (Figure 8-3). There were no significant changes in any of these vital signs in the endotoxin group (Figure 8-3).

**Figure 8-3;** Changes in haemodynamic parameters for the control; hypovolaemia and endotoxaemia rabbits. The central bar is the mean, the box represents the inter-quartile range and the whiskers the range. Significant differences between the control and experimental groups of  $p < 0.05$  are noted by an '\*' and  $p < 0.01$  by an 'α'.



Mean blood pressure fell in control rabbits with vagal stimulation. Mean blood pressure fell less in rabbits with hypovolaemia (Figure 8-4). There was a dose effect for the two levels of severity of hypovolaemia. There was a trend for mean blood pressure to fall in a similar manner in endotoxaemic rabbits compared to controls (Figure 8-4).

**Figure 8-4;** Fall in mean blood pressure following vagal stimulation prior to the first death. Note, the times from the start of experimentation are different for the hypovolaemia (+15, +60 and +75 minutes) and endotoxin (+240 and +300 minutes) groups. The central bar is the mean, the box represents the inter-quartile range and the whiskers the range. Significant differences between the control and experimental groups of  $p < 0.05$  are noted by an '\*' and  $p < 0.01$  by an 'α'.

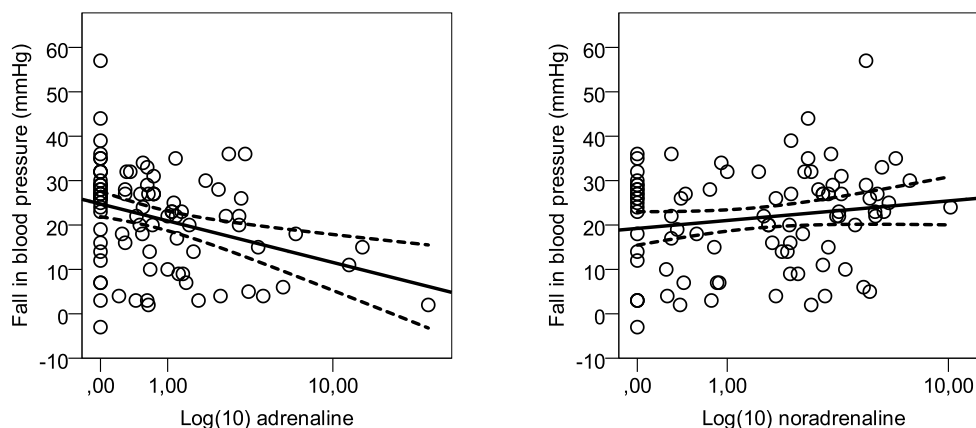


### 8.3.5 *Relationship between Catecholamines and Fall in Mean Blood Pressure*

In pooled results of all rabbits there was an inverse relationship between adrenaline concentration and the absolute value of the fall in mean blood pressure in response to stimulation. No such association was detected with noradrenaline (Figure 8-5).



**Figure 8-5;** Levels of  $\log^{10}$  adrenaline and noradrenaline compared to fall in mean blood pressure following vagal stimulation. 95% confidence intervals are shown as dotted lines. The coefficients of determination ( $r^2$ ) were 0.11 for adrenaline and 0.03 for noradrenaline.



## 8.4 Discussion

We disproved our hypothesis and determined that vagal stimulation during hypovolaemia in our model was significantly associated with a protection from fall in mean blood pressure when compared to controls. There was no significant difference the fall in mean blood pressure in endotoxaemic rabbits compared to controls

### 8.4.1 *Experimental Bias*

All four experimental groups witnessed raised levels of circulating baseline catecholamines which were probably due to the stress of anaesthetic induction and surgical preparation. In particular, the levels of circulating adrenaline and noradrenaline were significantly higher in the endotoxin group at baseline than for the controls (Table 8-5). It has previously been established that conditions of stress increase catecholamine production and this may be a sign that the rabbits were improperly anaesthetised despite each being tested for paw and corneal

reflexes.(303) However, the preparation was identical in all cases. In addition, the plasma samples were analysed in the same order that the rabbits were entered into the experiment. This finding was probably due to chance but is an important bias for the comparison of the endotoxin and control groups during the course of the experiment. Nevertheless, it should be noted that, despite the higher levels of circulating catecholamines the baseline, the heart rate, mean blood pressure and lactates were generally lower in the endotoxin group which is contrary what might have been expected (Figure 8-3 and Table 8-4).

We deliberately chose young animals to ensure that they resembled, in as much as possible, the level of immaturity of the autonomic nervous system in human children whilst not complicating the surgical preparation.(113) Although it is probable that the rabbits reached a stage of autonomic maturity at an earlier age.(304)

We sampled 11-14% of blood volume in our experiment and this was probably responsible for the decline in median haematocrit from 42[37-45] to 40[37-43]. This may have had an influence on haemodynamic homeostasis but was identical for all groups (Table 8-2 and 8-4).

#### **8.4.2      *Anaesthetic Considerations***

Because our experimental protocol involved important surgical intervention the animals were maintained in a state of general anaesthesia throughout. Unfortunately, anaesthetics have effects on haemodynamic and biochemical parameters.(294, 305) We chose urethane as an anaesthetic because of its effective analgesia, its single dose regimen and because it has previously been established to have minimal effect on

haemodynamic parameters in anaesthetised rats.(294) Another advantage of using urethane is that the animals remained spontaneously breathing which resembles the clinical situation when children are first diagnosed with hypovolaemic, although to a lesser extent, for septic shock.

When using urethane in the control rabbits, pH, pCO<sub>2</sub>, base excess, lactates and haematocrit remained constant or relatively little changed. However, despite mean blood pressure being sustained during the course of the experiment heart rate fell progressively notwithstanding the accompanying increases in noradrenaline and adrenaline. This result has been previously observed in rats when using urethane.(294)

#### **8.4.3        *Models of Critical Illness***

Our model of hypovolaemia demonstrated changes in both biochemical and haemodynamic parameters, with the exception of heart rate which decreased (Table 8-2 and Figure 8-3). Normally tachycardia is present during hypovolaemia but bradycardia is also observed in human models where reduced pre-load is compensated for by a prolongation of diastole which allows better ventricular filling.(306)

Classically the effect of hypovolaemic shock on haemodynamic integrity is biphasic and asymmetric. Mean blood pressure is maintained during the early compensatory (Phase I) and heart rate rises due to baroreceptor induced vasoconstriction.(90, 91) This is followed by a decompensatory (Phase II) which sees a fall in mean blood pressure and heart rate associated with a fall in vascular resistance.(90, 91) Phase I is

accompanied by a fall in cardiac output during the maintenance of mean blood pressure whereas Phase II is accompanied by maintenance of cardiac output and fall in mean blood pressure. Initially myocontractile force is maintained or slightly improved but diminishes as shock persists.(307) In our experiment, mean blood pressure fell markedly after bleeding in the 40%HV model, then increased (vasoconstrictive Phase I) before reaching a plateau and then falling (vasodilatory Phase II) (Figure 8-3).

The situation of the endotoxaemic rabbits was more complex. A metabolic acidosis, as exhibited by significant decreases in bicarbonates and base excess, was induced. A normal pH was maintained through compensating by hyperventilation which reduced pCO<sub>2</sub>. Whilst there were no significant differences in heart rate and pulse pressure the mean blood pressure of the endotoxic rabbits compared to the controls (Figure 8-3) and the lactate levels did not increase, which is an effect that has been previously observed by Lobo *et al.*.(308) The baseline higher levels of adrenaline and noradrenaline may be in part an explanation for this. The baseline level of adrenaline fell rapidly in the control group whereas that for noradrenaline remained significantly higher and this may be a true manifestation of endotoxic shock. Despite the relative paucity of biochemical and haemodynamic changes in the endotoxin group three of the 11 rabbits died. There were no deaths among the controls.

Brierley *et al.* used physical characteristics of perfusion in children to characterize septic shock which would not have been pertinent to our model.(34) The most appropriate animal model of human septic shock is subject to conjecture.(309) That so many models have been proposed indicates that no one model clearly reproduces

human septic shock. Our aim by using an intravenous dose of endotoxin was to obtain maximum harmonisation of experimental conditions. In the clinical situation there is rarely an explosive release of cytokines, as intended in our model, but a more gradual inflammatory response. The dose of endotoxin (1mg/kg) was intended to be rapidly lethal within the time period of the experimental protocol whilst producing similar changes in biochemical, hormonal and physiological parameters to other studies.(310) Other studies have described statistically significant falls in mean blood pressure and heart rate from as early as 1-2hr after injection in rabbits (1mg/kg)(308) and dogs (1.5mg/kg).(311)

#### **8.4.4        *Mean Blood Pressure in the Models after Vagal Stimulation***

Our principal objective was to ascertain whether there was a differential reaction in blood pressure to vagal stimulation in the two models of pathology and in this we were successful. The reaction of the hypovolaemic rabbits compared to the control rabbits was to maintain, and sometimes, increase blood pressure during vagal stimulation. The reaction to vagal stimulation of the endotoxic rabbits was similar to controls (Figure 8-5).

Serum levels of noradrenaline were higher in the endotoxic rabbits (Table 8-5) but were unable to protect their blood pressure during vagal stimulation (Figure 8-4). This is surprising because noradrenaline has an action that is both vasoconstrictive and inotropic.(152) This is indicative of a failure of the action of noradrenaline. In contrast, higher levels of adrenaline were associated with protection from vagal stimulation (Figure 8-5).

## **8.5 Conclusions**

Hypovolaemia protected rabbits from fall in mean blood pressure during vagal stimulation. This effect was proportional on the degree of hypovolaemia. The endotoxin group had a similar mortality rate as that for the HV40% group. Higher levels of baseline catecholamines in the endotoxin group introduced bias. Mean blood pressure fell during vagal stimulation in the endotoxin to a similar degree than in the control group. Pathology can have an effect on blood pressure change during vagal stimulation in this model of intubation.

# **PART THREE**

## **DISCUSSION**

## Chapter Nine

### Discussion

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Intubation during critical care illness can be regarded as a 'challenge' to survival with bradycardia and low blood pressure being associated with reduced survival in adults.(3, 17) This general aim of this thesis is to examine instability in these two haemodynamic parameters during the intubation of critically ill children.

#### **9.1 Principal Sources of Bias**

The Delphi survey revealed a striking lack of consensus regarding several indicators of atropine prescription and was moreover unable to generate consensus. The Delphi survey achieved a good mix of experience in all three users groups and was successful in recruiting Intensivists from eight different countries on three continents, which is in excess of that habitually encountered.(252) Set against this is the relatively high proportion of French Intensivists. Had a more exhaustive recruitment been concentrated on three countries, perhaps France, the United Kingdom and the United States, it possible that differences between influences on atropine prescription and opinions would have been generated. Opinions regarding atropine prescription are not only firmly held but are very little modified by the opinions of others. This is paradoxal in that relatively little information has been published concerning the use of atropine for CCI.

The ECG study, Chapters 5-7, furnished a large quantity of data from a critical care setting where few data are available. An important source of bias was created by pool of Intensivists having been drawn exclusively from one centre. This allowed



unrepresentative prescription practices, such as the infrequent use of muscle relaxants, to mitigate against the generalisability of the results. Although the author can confirm that this is a practice that is general in the Paris Region this cannot be said of other countries such as the United States and the United Kingdom. Another example of bias is the relatively low number of children with cardiac disease who were included, the Hôpital Robert Debré being without a cardiac surgery unit.

No adjustments were made for case-mix bias in the ECG study during the estimation of the number of lost beats or incidence of arrhythmias and conduction disturbances. The propensity score is a valuable tool to retrospectively adjust for differences in the study groups but may be insufficiently convincing to Intensivists for them to decide on the potential merits of atropine. Prospective randomisation would have improved external validity but may have had important effects on recruitment patterns. A randomised, placebo-controlled trial is needed to resolve the question of atropine use and intubation/ICU mortality.

The use of direct electrical stimulation to the Vagus nerve in the animal model involved a number of compromises. The approach was necessary because of the failure to achieve reliable changes in blood pressure by mechanical stimulation of the laryngopharynx even in the presence of hypoxaemia. A residual effect on blood pressure was noted when the lower portion of the Vagus nerve was stimulated in rabbits pre-treated with atropine (results not shown). This indicated that not all of the effect of the electrical stimulation on blood pressure was mediated by the Vagus nerve. In addition, the significant surgical preparation of the rabbits induced the production of adrenaline and noradrenaline. The differences in baseline production of

catecholamines in the hypovolaemia group of rabbits compared to the controls and endotoxin group make the interpretation of the blood pressure results complex. It is possible that blood pressure was artificially maintained during vagal stimulation in the endotoxin group due to the elevated baseline production of catecholamines.

## **9.2 The Clinical Outcome of Death**

Although the collective opinion of the 61 intensivists who participated in the Delphi survey was unequivocal that there is a risk of death during CCI (82%, median 8[7-9]) we found intubation mortality to be comparatively low (0.4%). Indeed, two other paediatric studies involving 280 intubations did not report any deaths.(19, 20) When contrasted to the frequency of death reported in adult studies we could have anticipated 3-9 deaths during intubation.(3, 16) Such low intubation mortality, even in studies with relatively large sample sizes as ours, does not allow deductions to be made regarding possible risk factors.

Despite severe reductions in blood pressure prior due to hypovolaemia and severe reductions in blood pressure during vagal stimulation, none of the rabbits died during vagal stimulation. As such the experimental model would not be a valuable tool to investigate intra-intubation mortality.

Our finding that atropine may protect from ICU mortality in children aged over one month but not in neonates is difficult to explain. The difference between the ICU mortality cannot be ascribed to intubation bradycardia because this occurred at the same frequency in the neonates and older children although death occurred rarely during intubation. Despite the PS being validated exactly for this our methodology

the PS can only adjust for bias when the variables that are responsible for the bias are included in the PS. As such our surprising result will need to be investigated by a randomised controlled trial.

### **9.3 Heart Rate**

Whether heart rate falls or not during intubation was not asked during the Delphi survey, Chapter 4, because numerous anaesthetic (4, 7, 8, 10, 12, 13, 22, 162) and critical care (9, 19-21, 224, 225) articles effectively deal with the subject.

Our ECG study confirmed previous findings that bradycardia occurs in a similar manner in neonates, children over one month and during further intubations. Previous articles have not differentiated between age groups using the same cut-off of more or less than four weeks. The transition from a dominant parasympathetic system to autonomic co-dominance in the first few months of life should theoretically result in higher levels of bradycardia in the neonates.(113) This was reflected by the Delphi survey which revealed that the age of the children did have an influence on atropine prescription. As such it was surprising that the fall in heart rate was very similar between the age groups. The distribution of the age of the children meant that although the median age of the children over four weeks of between 134 and 225 days. As such, even the older children could be considered to be influenced by predominant parasympathetic activity. The data do not allow us to separate the influences of vagal activation and drugs but it is possible that the bradycardia witnessed in the younger children was mostly induced by vagal stimulation and that observed in the older children was due to the effects of the anaesthetic drugs used for intubation.

The message from the lost beat algorithm is that whilst heart rate falls frequently during intubations and is unlikely to be of consequence if less than 50beats/min. A fall in heart rate of less than 50beats/min is reassuring but if the heart rate falls by more than 50beats/min it is no longer possible to extrapolate possible risk of haemodynamic decompensation (as defined by use of adrenaline, cardiac massage, fluid boluses or death). This is an important finding for clinical practice and could guide clinicians. Although no evidence has been presented in this thesis to say that a loss of 781 beats compared to 14 beats is of greater risk for haemodynamic decompensation, it would be counter-intuitive to assert that the risks are equal. Intubation records that note that the lowest heart rate fell by more than 50 beats/min from baseline are unlikely to be unable to demonstrate the risk to haemodynamic function. The addition of an algorithm to monitoring equipment may enable better prediction between loss of heart beats and haemodynamic decompensation.

#### **9.4 Arrhythmias and Conduction Abnormalities**

Bradycardia has been shown to be associated with arrhythmias and conduction disturbances. The overall frequency of arrhythmia and conduction abnormalities was higher for the older children despite similar levels of bradycardia being observed. There were two important differences between the two groups which may account for this observation. Firstly, the arrhythmogenic properties of the anaesthetics that were most frequently used in the older children and secondly, that the pathologies of the older children which are a potentially greater risk for instability of the pacemaker and conducting systems of the heart.

The results presented in this thesis do not enable deductions to be made regarding changes in blood flow during these episodes. However, any dys-coordination of myocardial conduction and/or depolarisation of myocytes will have effects on flow would be above and beyond those related to simple bradycardia at the same heart rate. In addition, acute bundle branch block, Mobitz type II conduction abnormalities and/or sinus pause with ventricular escape are risks for cardiac arrest.(280)

## **9.5 Hypotension**

Studies of adult intubations demonstrate that blood pressure falls during intubation.(3, 17) Pre-intubation shock increases the risk of death during intubation.(3) In contrast, studies in neonates have reported increases in blood pressure during intubation.(9, 211) Caution must be exercised when comparing these studies as several important differences are apparent. Firstly, the neonates in these studies received proportionately less hypotension-inducing drugs and secondly, the neonates were intubated for neonatal respiratory distress and not for shock. For instance, Griesdale *et al.*(17) recorded 21% of cases as having a low systolic blood pressure (<90mmHg) prior to intubation and 23% of cases already being maintained on vasopressors.

The Delphi survey was unable to reach a consensus that hypotension occurs during intubation (74%, median 8[6-9]) principally because the intermediate users were not in agreement (61%, median 7,5[6-9]). This is perhaps surprising when viewed in the context of the Infrequent Users, who replied negatively to most the statements but were in agreement over this statement (79%, median 9[7-9]). It is possible that the Intermediate Users, who were described as being 'Discerning Users' in Chapter 4,

interpreted the statement as being ambiguous. Whilst neonates may not experience a fall in blood pressure during intubation, the pathologies for which the older children were intubated resemble much more closely adult type pathologies.

The animal model unexpectedly showed that stimulation of the Vagus nerve in the presence of severe hypovolaemia in rabbits may paradoxically induce a rise in blood pressure. This interpretation is supported by the dose-effect of differing levels of hypovolaemia. Haemodynamic decompensation in the presence of bradycardia is dependent on vascular reactivity.(312) The findings of Marshall *et al.*(9) and Oei *et al.*(224) that blood pressure increases despite bradycardia signify that increases in vascular resistance or ejection volume, or both, occur during intubation for neonatal respiratory distress.

Animal experimentation suggested that blood pressure responses to electrical stimulation of the Vagus nerve in hypovolaemia and endotoxaemia models were different. This is for two reasons, firstly because the baseline levels of catecholamines in the endotoxin group were in excess of those in either the control or the hypovolaemia groups and secondly the hypovolaemic rabbits had spent a shorter time under anaesthetic. What can be said is that despite significantly higher levels of noradrenaline, which should theoretically have facilitated vasoconstriction, the fall in blood pressure of the endotoxaemic rabbits was similar to that of the controls. This is a new finding that suggests that the different pathologies may have different influences on haemodynamic compensation during intubation.

An alternative methodology to the estimation of changes in blood pressure after vagal stimulation would have been to measure biological markers of poor perfusion *a posteriori*. This would have involved before-and-after intubation sampling of blood either in a clinical or an experimental setting. Brain natriuretic peptide (BNP) has been used to predict neurologic outcome at six months and survival following cardiac arrest and would be a possible candidate for investigation. However, this retrospective study of 155 patients recorded a median no-flow time of 2 minutes [IQR 2-5minutes] and a low-flow time of 16 minutes [IQR 10-25] which is in excess of the majority of our patients.(313)

Another option would be to test for troponin I levels which are sensitive and specific for myocardial injury.(314-316) Cecchia *et al.*(315) looked at rises in troponin I in a prospective cohort of 24 children all of whom had had a cardiac arrest including 12 children who had drowned or nearly-drowned. Seven of the children did not survive and had significantly higher levels of troponin I than those that survived. The median arrest time of the survivors was six minutes [IQR 3-63] compared to median 34 minutes [IQR 4-70] for the non-survivors which is again considerably in excess of our patients. Also, sampling relatively large populations prior to intubation would have posed important ethical questions as to the benefit *versus* the discomfort involved. This methodology was not used in the experimental setting for two reasons. Firstly, the reductions in blood pressure typically were rarely greater than one half of pre-stimulation values and generally lasted two to three minutes. Secondly, there was considerable experimental 'noise' from repeated stimulations so the accuracy of any one reading related at any one stimulation would have been

severely compromised because clinical studies have looked production of these markers over time periods of hours rather than minutes.(317)

## 9.6 The Usefulness of Atropine

The fact that 80% (median 8[7-9]) of the Delphi participants used atropine according to their personal preference whereas only 49% (median 6[3-8]) base their decision on scientific literature is illustrative of how far we have (not) progressed in the 50 years from the opinion of Eger(1) in 1962 to Kumar in 2010.(2)

*"The time has come when Belladonna drugs should be tailored to circumstance and not given by rote" Eger 1962(1)*

*'...[the] long-term benefits and adverse effects of [atropine] premedication are unknown'. Kumar et al. 2010(2)*

Atropine was associated with a reduction in fall in heart rate, arrhythmia and/or conduction disturbances. Atropine favoured progression from sinus tachycardia to faster sinus tachycardia without progression to ventricular tachycardia and/or fibrillation. In fact, we recorded no detrimental effects of atropine on the circulation.

Perhaps atropine can be regarded in the same light as a vaccination; it protects from an event that probably will never occur. But the impact of atropine is more complex. Some children who received atropine continued to show bradycardia and arrhythmia, although at a reduced frequency. This may be as a result of insufficient time being left from the moment injection of atropine and the start of intubation. Alternatively,



the pressure on the activation of the Vagus nerve may be so intense that atropine is unable to overcome the stimulation or the haemodynamic state so unstable that small signals from the Vagus nerve may have large haemodynamic effects.

The results presented in this thesis do not support the recommendations that atropine should be routinely used for CCI in neonates.(29, 30, 32) This is because although they frequently experience bradycardia, they infrequently exhibit arrhythmias and conduction disturbances and did not die during intubation in our ECG study. Neither have they been shown to occur during intubation in other studies.(224, 225) Neonates generally suffer from neonatal respiratory pathologies that are not vasoplegic and should be able to protect themselves from bradycardia by increases in vascular resistance and ejection volume. An important caveat to this is the group of extremely premature newborns. The precocious stage of neurodevelopment in this group means that they are possibly at risk of cranial hypertension rather than systemic hypotension. Both hypotension and tachycardia may be a risk for this important group.

The situation is different in children over four weeks of age. In this group atropine did reduce the incidence of arrhythmias and conduction disturbances. Atropine was not shown to induce conversion of sinus tachycardia to ventricular tachycardia or fibrillation. Importantly, vasoplegic pathologies are more frequently encountered in this group where increasing ejection volume may be insufficient to compensate for bradycardia in the face of vasodilatation. Atropine may also have an influence on ICU mortality that is not related to its action in maintaining heart rate during intubation.

## 9.7 Summary of findings

The Delphi group agreed that there is a risk of death during intubation but was not in agreement that atropine could modify this risk. Intubation mortality during first intubations was 0.4%, which is lower than that published for similar adult studies. Atropine diminished ICU mortality only in the group of children over 28 days and in a manner that was independent on its capacity to reduce heart rate during intubation. The observation may be related to beat-to-beat stabilisation of the heart rate.

Hypotension occurred when the Vagus nerve was electrically stimulated under experimental conditions in rabbits. The degree of hypotension was reduced when the animals were hypovolaemic. This occurred in a dose dependent manner. Endotoxaemia did not change blood pressure reductions during vagal stimulation. The Delphi group was unable to agree that hypotension is a risk during intubation or that atropine reduced this risk. The Intensivists were furthermore unable to agree as to whether atropine should be recommended for intubations in children with septic shock.

Sinus pause was not infrequent in both neonates and children aged over four weeks but the progression to the more severe conduction disturbances and ventricular arrhythmias was more frequent in the children aged over four weeks. Atropine was associated with a reduced frequency ventricular arrhythmias and conduction disturbances and did not induce the progression from sinus tachycardia to ventricular tachycardia and/or fibrillation.

Reductions in heart rate occur to a similar degree during critical care intubation in children above and below one month of age. When considering the potential for lost heart beats during intubation bradycardia, a fall in heart rate of less than 50 beats/min resulted in the loss of 25 beats or less with the exception of one child who lost 35 beats. When the heart rate falls below 50 beats/min there is a wide variation in loss of beats (as much as 50 fold). Atropine was associated with reduced bradycardia in both age groups and numbers of lost beats but not for all children. The opinion of the group of Intensivists who participated in the Delphi study was that atropine did not prevent bradycardia.

## **9.8 Future Directions**

We discovered that the frequency of death during intubation is low. If the number of deaths recorded in the studies of Carroll *et al.*(19) and Fastle and Roback (20) is added to the number of deaths during the two years of study we come to one death for 502 intubations. As such prospective cohort studies using the outcome of death during intubation would require very large sample sizes to investigate the risk factors. An alternative could be to use a case-control methodology to examine associated risk factors.

The association between lost heart beats and haemodynamic decompensation could be investigated by regarding the use of adrenaline, fluid boluses, cardiac massage or death during intubation as 'event triggers' and the intubation ECG printed. The ECGs of the next five intubations could be printed as controls.

This thesis tries to investigate the potential effect of pathology on haemodynamic stability during intubation. We were frustrated by the close relationship between atropine prescription of attitudes to prescription in the Delphi survey, the low intubation mortality and raised levels of catecholamines in the endotoxaemic rabbits. An alternative methodology to attempt to eliminate baseline catecholamine bias would be to manufacture an electrode that could be surgically implanted around the Vagus nerve (using non-urethane anaesthesia). The tissues would be closed and the animal left for 48h before intubation and ventilation. Without re-opening the tissues, electrical stimulation of the Vagus nerve would be initiated and monitoring of haemodynamic parameters carried out using Doppler technology. The advantage of such an approach would be that the vascular resistance and cardiac output could be measured using an algorithm that would not be affected by simultaneous changes in blood pressure and heart rate.

Finally, the bias that we encountered regarding low frequency of use of muscle relaxants and the relatively small group of Intensivists needs to be eliminated in any future study of ICU mortality. Our surprising result that atropine may have an influence on ICU mortality should be investigated by a, randomised, controlled trial.

# **PART FOUR**

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# **ANNEX**



**e**



























**ANNEXE**

























## Annexe 2,

## ETUDE DES TROUBLES DU RYTHME-FEUILLE DE DONNEES

No d'étude	<b>Réa</b>	<b>1</b>			
Catégorie d'âge, 1= 0 à 24h, 2= 1 à 3 jours, 3= 3 à 7 jours, 4= 1 à 4 semaines, 5= 1 à 3 mois, 6= 3 à 6 mois, 7= 6 à 12 mois, 8= 1 à 3 ans, 9= 3 à 5 ans, 10= 5 à 8 ans					
Sexe, masculin= 1, féminin= 2					
Si nouveau-né (moins de 48h), quel terme (en semaines)?					
Dose médicaments avant ET pour intubation		Lésions traumatique, empoisonnements... ICD 10 S00-T98			
Atropine		...maladies infectieuses... ICD 10 A00-A99			
Hypnomidate/ Ethomidate		Maladies de l'appareil circulatoire ICD 10 I00-I99	Insuffisance		
Diprivan/ Propofol			Myocardite		
Ketalar/ Ketamine		Maladies du système nerveux ICD 10 G00-G99	Malformation		
Célocurine/ Suxamethonium			Convulsion		
Norcuron/ vecuronium			Myopathie		
Pavulon/ pancuronium			Encéphalopathie		
Morphine			Méningite		
Fentanyl			Hémorragie		
Sufentanyl			Maladies de l'appareil respiratoire ICD 10 J00-J99	Asthme	
Hypnovel/ Midazolam		Bronchiolite			
ADR/		Pneumonie/SDRA			
NOR/		DR nouveau-né			
Dobu/		Maladies... métaboliques ICD 10 E00-E90			
Dopa/		...accouchement... ICD 10 O00-O99			
Autre(s), à spécifier					
Au moment quand la saturation est la plus basse lors de l'intubation, le chiffre de la fréquence cardiaque ?		Sat		FC	
Au moment quand la fréquence cardiaque est la plus basse lors de l'intubation, le chiffre de la saturation ?		Sat		FC	
Nombre d'essais à l'intubation (repris au ballon entre chaque essai)					
Evénements indésirables et/ou mort dans l'heure qui a suivi l'intubation ?					

**Constantes avant l'intubation**

PR		BAV <sub>2</sub> (Wenkebach)		BAV <sub>2</sub> (Mobitz II)	
BAV <sub>1</sub>		ESA/min		ESV/min	
Rythme jonctionnel		BdB droit		BdB gauche	
Fréquence cardiaque la plus basse				Et à ce moment-là...	
QT		RR		QTc	
Saturation la plus basse				Et à ce moment-là...	
QT		RR		QTc	
Fréquence cardiaque la plus élevée				Et à ce moment-là...	
QT		RR		QTc	
Saturation la plus élevée				Et à ce moment-là...	
QT		RR		QTc	
Autre					

**Constantes APRES l'atropine (si utilisée) AVANT l'intubation**

PR		BAV <sub>2</sub> (Wenkebach)		BAV <sub>2</sub> (Mobitz II)	
BAV <sub>1</sub>		ESA/min		ESV/min	
Rythme jonctionnel		BdB droit		BdB gauche	
Fréquence cardiaque la plus basse				Et à ce moment-là...	
QT		RR		QTc	
Saturation la plus basse				Et à ce moment-là...	
QT		RR		QTc	
Fréquence cardiaque la plus élevée				Et à ce moment-là...	
QT		RR		QTc	
Saturation la plus élevée				Et à ce moment-là...	
QT		RR		QTc	
Autre					

**Constantes lors de l'intubation**

PR		BAV <sub>2</sub> (Wenkebach)		BAV <sub>2</sub> (Mobitz II)	
BAV <sub>1</sub>		ESA/min		ESV/min	
Rythme jonctionnel		BdB droit		BdB gauche	
Fréquence cardiaque la plus basse				Et à ce moment-là...	
QT		RR		QTc	
Saturation la plus basse				Et à ce moment-là...	
QT		RR		QTc	
Fréquence cardiaque la plus élevée				Et à ce moment-là...	
QT		RR		QTc	
Autre					

**Annexe 3,****INFORMATION AUX PARENTS**

Madame, Monsieur,

Lors de sa réanimation dans l'Unité de Réanimation de Robert Debré ou par le SMUR pédiatrique, votre enfant a nécessité une assistance ventilatoire intra-trachéale. Cette technique consiste à intuber votre enfant, c'est-à-dire à placer une sonde dans la gorge (trachée) afin de ventiler directement les poumons. Lors de ce geste, la procédure habituelle consiste à surveiller systématiquement et en continu le taux d'oxygène dans le sang et la fréquence des battements du cœur (fréquence cardiaque) afin d'assurer les conditions optimales de sécurité. Ces deux paramètres sont enregistrés automatiquement sur les appareils de surveillance du service de Réanimation et du SMUR.

Nous réalisons actuellement une étude concernant les variations de la fréquence cardiaque pendant la pose de la sonde d'intubation. Ainsi, nous recueillons les enregistrements de fréquence cardiaque de tous les enfants de moins de neuf ans intubés par les médecins de Réanimation ou du SMUR, ce qui ne modifie en aucun cas la prise en charge habituelle de votre enfant dans une telle situation. Nous rendons ces enregistrements entièrement anonymes. Puis nous les sauvegardons dans une banque de données informatiques interne au service afin de les analyser.

Le droit d'accès et de rectification prévu par la loi « Informatique et Liberté » s'exerce à tout moment auprès des responsables de l'étude. Les données sont protégées par les dispositions article 40 de la loi 78.17 du 6 janvier 1978 et art. L.111-7 du Code de Santé Publique, relative à l'informatique, aux fichiers et aux libertés. Elles ne pourront en aucun cas être utilisées à des fins commerciales ou de publicité. Le fichier de données sera détruit au terme du délai prévu à l'article R.1124-7 du Code de la Santé Publique.

Néanmoins, vous avez le droit d'accès et de rectification des données concernant votre enfant. Ce droit peut être exercé à tout moment soit directement par vous-même, soit par l'intermédiaire du médecin de votre choix, en prenant contact avec un des deux investigateurs ci-dessous.

Avec nos remerciements pour votre collaboration, nous vous prions d'agréer, Madame, Monsieur, l'assurance de notre considération distinguée.

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**Responsable de l'étude :** Docteur Peter JONES  
SMUR Pédiatrique de l'Hôpital Robert Debré  
**Chef de service :** Professeur Stéphane DAUGER  
Service de Réanimation Pédiatriques  
SMUR Pédiatrique de l'Hôpital Robert Debré

Pôle de Pédiatrie Aiguë et Médecine Interne  
Hôpital Robert Debré  
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**INSTITUTIONAL REVIEW BOARD (N° IRB00006477)  
COMITE D'EVALUATION DE L'ETHIQUE  
DES PROJETS DE RECHERCHE BIOMEDICALE  
(CEERB) DU GHU NORD**

***Dr Peter JONES  
SMUR  
Hôpital ROBERT DEBRE***

***Courriel : peter.jones@rdb.aphp.fr***

JMD/MDM/539-08

December 3, 2008.

**Subject : The incidence of cardiac arrhythmias during the emergency intubation of children of less than eight years.**

Dear Colleague,

The « **Comité d'Evaluation de l'Ethique des projets de Recherche Biomédicale (CEERB) du GHU Nord** » (Institutional Review Board (IRB) of Paris North Hospitals, Paris 7 University, AP-HP), has reviewed and approved the research project entitled « **The incidence of cardiac arrhythmias during the emergency intubation of children of less than nine years** » (Dr Peter JONES, principal investigator) in 2008. This approval covers the entire period during which the project will be developed until its completion.

With my best regards,

Yours sincerely

Professor J.M. DESMONTS,  
Chair of the Institutional Review Board (IRB)

---

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**Comité d'éthique  
pour l'expérimentation animale**  
Comité d'éthique ComEth Anses/ENVA/UPEC



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UNIVERSITÉ  
PARIS-EST  
CRÉTEIL  
VAL DE MARNE

Enregistré auprès du Comité National de Réflexion  
Éthique sur l'Expérimentation Animale  
sous le numéro 16

**Monsieur Peter JONES**  
Réanimation Polyvalente  
Hôpital Robert Debré  
48 Bd Sérurier  
75019 PARIS

N° du Dossier : 10-0072

N° de l'Avis : 10/12/14-09

Maisons-Alfort, le 14 décembre 2010

**Objet :** Avis du ComEth Anses/ENVA/UPEC

Monsieur,

Le ComEth Anses/ENVA/UPEC a procédé à l'examen de votre projet de recherche intitulé « Un modèle animal de l'intubation en urgence du jeune enfant », et vous informe que votre projet a reçu un **Avis Favorable**.

L'avis du ComEth sur votre projet est donné pour une durée maximale de 3 ans.

Je vous prie d'agréer, Monsieur, l'expression de mes sincères salutations.



**Bernard Andrieux**

Vice-Président du ComEth Anses/ENVA/UPEC

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