

THE MILITARY APPLICATIONS OF NEAR
INFRARED SPECTROSCOPY IN TRAUMA

Tom Barker

*A Thesis Submitted to
The University of Birmingham
for the degree of*
DOCTOR OF MEDICINE

School of Clinical and Experimental Medicine
College of Medical and Dental Sciences
The University of Birmingham
March 2016

UNIVERSITY OF
BIRMINGHAM

University of Birmingham Research Archive

e-theses repository

This unpublished thesis/dissertation is copyright of the author and/or third parties. The intellectual property rights of the author or third parties in respect of this work are as defined by The Copyright Designs and Patents Act 1988 or as modified by any successor legislation.

Any use made of information contained in this thesis/dissertation must be in accordance with that legislation and must be properly acknowledged. Further distribution or reproduction in any format is prohibited without the permission of the copyright holder.

ABSTRACT

This work examines tissue oxygenation (StO_2), as measured by near infrared spectroscopy (NIRS), as tool for assessing trauma patients, with particular emphasis on its use in the deployed military environment.

Resting StO_2 values were examined and found to vary significantly between monitoring sites. Exercise was associated with a significant increase in StO_2 . Comparing the sensitivities of different NIRS monitoring sites in detecting simulated hypovolaemia, the forearm and deltoid were found to be the most sensitive sites. The thenar eminence and brain were not sensitive to mild degrees of hypovolaemia. The administration of morphine was found to attenuate the StO_2 response to hypovolaemia at all sites.

In a porcine trauma model changes in StO_2 recorded from both injured and uninjured muscle sites preceded those of base excess and lactate by 31–37 minutes, and demonstrate that injured monitoring sites can be used to accurately track patients' response to resuscitation.

In the deployed military setting NIRS was found to be a robust, easy to use technique for the initial assessment of patients. Although StO_2 was not demonstrable superior to a combination of pulse rate and blood pressure it has several practical advantages that make it a useful adjunct to contemporary trauma care.

ACKNOWLEDGEMENTS

Firstly I wish to thank my supervisors Dr Thomas Clutton-Brock, Surg Capt Mark Midwinter and Prof Sir Keith Porter, for getting me started on this work and providing the necessary support to bring it to completion.

Thanks to Prof Emrys Kirkman and Dr Sarah Watts of the Defence Science and Technology Laboratory (DSTL), [REDACTED].

Similarly, thanks again to Prof Kirkman and also Lt Col Jeremy Henning for their collaboration on the human simulated hypovolaemia study and allowing me to use the haemodynamic data presented in Chapter 6.

For the exercise study I wish to thank Lt Col Ewen Murchison, Commanding Officer, 42 Commando Royal Marines (42 Cdo RM) Regiment, Plymouth and Lt Col ‘Sharky’ Ward, SO1 Training, Commando Training Centre (CTC), Lympstone, for releasing their men to participate in the study. Thanks Sgt Driscoll, Unit Physical Training Instructor, 42 Cdo RM who provided administrative support and endured long days overseeing the exercise component of the protocol. Finally thanks to all the men of 42 Cdo RM and Hunter Coy 2 & 3 (CTC) who volunteered as subjects for the study.

I should like to recognise the contributions of everyone who provided support during this project and shaped my ideas on NIRS and trauma care. In particular I am grateful to: Miss Phillippa Spencer of DSTL (Porton Down) and Dr Johnathan Bishop of the University of Birmingham, for statistical support; all of the surgical SpRs deployed on Operation Herrick and especially CPO David Roper, Ministry of Defence Hospital Unit Derriford, who provided assistance with the data collection for the NIRS trauma resuscitation study, presented in Chapter 9; finally thanks to Miss Juliana Hendel, Copenhagen Business School, for her meticulous proof reading of the finished manuscript.

This work was produced entirely using free/open source software and I am grateful to all contributors to the free software movement, but especially those who contribute to the projects I depended upon during the course of this work: L^AT_EX; Emacs; Inkscape; the GNU Image Manipulation Program; the R Project; gnuplot; LibreOffice; GNU core utilities; the BASH shell; and Gawk.

CONTENTS

LIST OF FIGURES [vii](#)

LIST OF TABLES [ix](#)

ABBREVIATIONS [xi](#)

I INTRODUCTION

1	THE PROBLEM OF TRAUMA	2
1.1	Epidemiology of Major Trauma	2
1.2	Distribution and Causes of Death Associated with Major Trauma	4
1.2.1	The Tri-modal Distribution of Trauma Deaths	4
1.2.2	Causes of Death Following Trauma	6
1.3	Problems with the Management of Trauma Associated Hypovolaemia	7
1.3.1	Fluid Resuscitation in Trauma	8
1.3.2	Conventional Measures of Physiological Status in Trauma	10
1.4	Trauma in the Military Environment	13
2	OXYGEN DYNAMICS AND THE PROPERTIES OF HAEMOGLOBIN	15
2.1	Oxygen Delivery	15
2.2	Oxygen Consumption	18
2.3	The Properties of Haemoglobin	19
2.3.1	The Structure of Haemoglobin	20
2.3.2	Oxygen Carriage by Haemoglobin	20
2.4	Local Tissue Oxygenation	22
3	NEAR INFRARED SPECTROSCOPY	25
3.1	A Brief History of the Development of NIRS	25
3.1.1	The Discovery of the NIR Range	25
3.1.2	The Early Development of Spectroscopy	26
3.1.3	The Development of Oximetry and Medical NIRS	28
3.2	Principles of Spectroscopy	30
3.2.1	Transmission/absorption Spectroscopy	30
3.2.2	Reflectance Spectroscopy	31
3.2.3	Dual Beam NIRS Algorithms	34
3.3	Measuring Haemoglobin Concentrations in Mammalian Tissues	35
3.3.1	The Problems of Other Chromophores	37
3.4	Comparison to Pulse Oximetry	39
4	CURRENT STATE OF NIRS AS APPLIED TO TRAUMA RESUSCITATION	41
4.1	The Range of StO ₂ Measurements in Normal Subjects	41

4.2	Non-Trauma Human Hypovolaemia Studies	43
4.2.1	Lower Body Negative Pressure as Model for Simulating Hypovolaemia	46
4.2.2	Lower Body Negative Pressure Hypovolaemia Studies	47
4.3	Animal Hypovolaemia Models	49
4.4	Human Clinical Studies of NIRS in Trauma Resuscitation	52
4.5	Effect of Exercise on NIRS Measurements	55
 II EXPERIMENTAL STUDIES		
5	GENERAL METHODS	59
5.1	Selection of NIRS Device	59
5.2	Data Export From the INVOS® System	60
5.3	Work flow for INVOS® System Data Management	61
5.4	Monitoring Sites	63
6	NIRS HUMAN VOLUNTEER SIMULATED HAEMORRHAGE STUDY	65
6.1	Introduction	65
6.2	Aim	67
6.3	Materials and Methods	67
6.3.1	Study Population	68
6.3.2	Monitoring and Protocol	68
6.3.3	Lower Body Negative Pressure Protocol	71
6.3.4	Data Analysis	71
6.4	Results	72
6.4.1	Demographics of Study Population	72
6.4.2	Baseline Physiological Measurements and Effect of Morphine	73
6.4.3	Effect of the Simulated Hypovolaemia Protocol	76
6.4.4	Effect of Morphine on LBNP Tolerance	79
6.5	Discussion	80
6.6	Conclusion	84
7	NORMAL NIRS VALUES AND RESPONSE TO EXERCISE STUDY	86
7.1	Introduction	86
7.2	Aim	87
7.3	Materials and Methods	87
7.3.1	Study Population	87
7.3.2	NIRS Monitoring Protocol	89
7.3.3	Exercise Protocol	90
7.3.4	Data Collection	91
7.3.5	Data Analysis	91
7.4	Results	92

7.4.1	Demographics of Study Population	92
7.4.2	Exercise Performance	92
7.4.3	NIRS Values at Rest	92
7.4.4	Response of NIRS Values to Exercise	95
7.5	Discussion	100
7.6	Conclusion	106
8	NIRS ANIMAL TRAUMA AND HAEMORRHAGE MODEL	107
8.1	Introduction	107
8.2	Aim	109
8.3	Materials and Methods	110
8.3.1	Preparation of the Animal Model	110
8.3.2	Experimental Protocol	111
8.3.3	Physiological Measurements and NIRS Monitoring	113
8.3.4	Data Acquisition and Collection	113
8.3.5	Data Analysis	114
8.4	Results	115
8.4.1	Baseline Measurements	115
8.4.2	Effect of the Hypovolaemia Protocol	115
8.4.3	Correlation Between Physiological Parameters	120
8.4.4	Effect of Limb Injury on StO ₂	122
8.4.5	Phase Relationship Between Physiological Parameters	123
8.5	Discussion	124
8.6	Conclusion	128
9	NIRS TRAUMA RESUSCITATION STUDY	129
9.1	Introduction	129
9.2	Aim	130
9.3	Materials and Methods	130
9.3.1	Study Population	131
9.3.2	Materials	131
9.3.3	Monitoring Protocol	132
9.3.4	Data Collection	133
9.3.5	Data Analysis	134
9.4	Results	134
9.4.1	Demographics of Study Population and Injury Burden	135
9.4.2	StO ₂ and Physiological Parameter Response to Resuscitation	135
9.4.3	Correlation Between Physiological Parameters	142
9.4.4	Phase Relationship Between StO ₂ and ABG Parameters	142
9.5	Discussion	144
9.6	Conclusion	148

10	CONCLUSION	149
----	------------	-----

APPENDICES

A	INVOS® 5100C SYSTEM SPECIFICATIONS	157
B	BASH SCRIPT FOR CLEANING INVOS® SYSTEM DATA FILES	158
C	US MARINE CORPS PHYSICAL FITNESS TEST PROTOCOL	162
D	JOINT MEDICAL EMPLOYMENT STANDARD	163
	D.1 Medical Deployment Standard	163
	D.2 Medical Employment Standard	163
E	NATO TRIAGE TREATMENT CATEGORIES	165

BIBLIOGRAPHY

	BIBLIOGRAPHY	168
--	--------------	-----

LIST OF FIGURES

1.1	The classic tri-modal distribution of trauma deaths	5
1.2	Distribution and causes of trauma deaths	6
2.1	The oxygen cascade	16
2.2	The structure of haemoglobin	20
2.3	The oxygen-haemoglobin dissociation curve	22
3.1	Herschel's experiment demonstrating energy associated with the NIR spectrum	26
3.2	Bunsen and Kirchhoff's spectroscope	27
3.3	A diagrammatic representation of the Beer-Lambert Law	32
3.4	A diagrammatic representation of reflectance spectroscopy	33
3.5	A diagrammatic representation of dual beam reflectance NIRS	35
3.6	The absorption spectra of pure water	36
3.7	The absorption spectra of HbO ₂ , HHb and CtOx	37
4.1	Histogram of thenar StO ₂ values in normal human volunteers	42
4.2	A diagrammatic representation of the threshold area over the curve (TAOC) calculation	51
5.1	The INVOS® 5100C System monitor	60
5.2	An example of data output from the INVOS® System	62
5.3	Positions of NIRS probes used in the human studies	64
6.1	A subject undergoing experimentation in the lower body negative pressure chamber.	69
6.2	Lower body negative pressure study timeline	71
6.3	Box plot of pre-infusion StO ₂ values at each site	74
6.4	Box plots of StO ₂ data over the course of the LBNP protocol for the placebo group	78
6.5	Box plots of StO ₂ data over the course of the hypovolaemia protocol in the morphine group	79
7.1	Histograms of raw pre-exercise StO ₂ data	94
7.2	StO ₂ measurements over time for each monitoring site	96
7.3	Histograms of raw post-exercise StO ₂ data	97
7.4	Box plot and summary statistics for pre and post exercise NIRS data	99
7.5	Examples of tattoos which interfered with NIRS recordings	105

8.1	A Large White Sow	110
8.2	Animal haemorrhage and trauma model experimental timeline	112
8.3	Site of application of shots with the penetrating captive bolt pistol	113
8.4	StO ₂ in each limb by animal	117
8.5	Mean StO ₂ for all animals during the course of the protocol	118
8.6	Mean values for blood pressure measurements during the course of the protocol	118
8.7	Mean values for the main ABG parameters over the course of the protocol	120
8.8	An example of raw and smoothed StO ₂ data	127
9.1	Deltoid and cerebral StO ₂ data in trauma patients	139
9.2	Box plot of StO ₂ values during each phase of the study	140
9.3	A scatterplot of deltoid against cerebral StO ₂	141
9.4	StO ₂ and base excess data from patient 2	147

LIST OF TABLES

4.1	LBNP and their estimated blood loss equivalent	47
4.2	Comparison of physiological responses to LBNP and haemorrhage	48
5.1	Column descriptors from the INVOS® System file data output	63
6.1	Summary statistics for the baseline StO ₂ values in the placebo and morphine groups	73
6.2	Summary statistics for the baseline physiological measurements in the placebo and morphine groups	75
6.3	Mean values for physiological parameters during the LBNP protocol	77
6.4	Increments of LBNP completed by subject in each arm of the study	80
7.1	Data fields used in the NIRS exercise study	91
7.2	Data for tobacco consumption in smokers	93
7.3	Exercise performance data	93
7.4	Descriptive statistics for pre-exercise raw and median StO ₂ data	95
7.5	Results for Wilcoxon rank-sum tests comparing the pre-exercise data recorded from the first and fifth minutes to that from the 6-10 time period	96
7.6	Results for Wilcoxon rank sum tests comparing the post-exercise data from minutes one and five to the data from the 6-10 time period	98
8.1	Timing of ABG samples in the animal haemorrhage and trauma model study	114
8.2	Descriptive statistics for baseline values in the animal trauma study	116
8.3	Mean values for the key physiological parameters at the ABG sampling points	119
8.4	Correlation matrix of main physiological parameters	121
8.5	Summary statistics for all StO ₂ values	123
8.6	Results of a cross-correlation analysis comparing haemodynamic and StO ₂ data to the principle ABG measurements	124
9.1	The proposed ideal protocol for frequency of ABG measurements	133
9.2	Data field used in the trauma resuscitation study	134
9.3	Summary of the major injuries in patients 1-10 by anatomical location	136
9.4	Summary of the major injuries in patients 11-20 by anatomical location	137
9.5	ISS and TRISS predicted mortality values for patients.	138

- 9.6 Mean values for physiological parameters during each of the study phases [142](#)
- 9.7 A correlation matrix for the main physiological variables during the combined ED and theatre phases [143](#)
- D.1 Joint Medical Employment Standard (JMES) codes [164](#)

ABBREVIATIONS

µm	Micrometer
1RM	One repetition maximum
2,3-DPG	2,3-diphosphoglyceric acid
A	Amps
ABG	Arterial blood gas
AC	Alternating current
AKA(s)	Above knee amputation(s)
ASCII	American Standard Code for Information Interchange
ASA	American Society of Anesthesiologists
ATLS®	Advanced Trauma Life Support
BKA(s)	Below knee Amputation(s)
bpm	Beats per minute
CaO ₂	Concentration of oxygen in arterial blood
CE	Conformité Européenne
CI	Confidence interval
CO	Cardiac output
CO ₂	Carbon dioxide
CRLF	Carriage return line feed
CT	Computed tomography
CTC	Commando Training Centre
CvO ₂	Concentration of oxygen in venous blood
CNS	Central nervous system
DALY(s)	Disability adjusted life year(s)
DC	Direct current
DPF	Differential pathlength factor
ḐO ₂	Oxygen delivery
DSTL	Defence Science and Technology Laboratory
ED	Emergency Department
ER	Extraction ratio
FDA	Food and Drugs Administration
FiO ₂	Fraction of inspired oxygen
FRS	Fellow of the Royal Society
GMT	Greenwich Mean Time
GSW(s)	Gun shot wound(s)
Hb	Haemoglobin (concentration of)
HbO ₂	Oxyhaemoglobin (concentration of)
IED(s)	Improvised explosive device(s)

INR	International normalised ratio
IR	Infrared
ISS	Injury Severity Score
JMES	Joint Medical Employment Standard
LED(s)	Light emitting diode(s)
LBNP	Lower body negative pressure
MES	Medical employment standard
ml	Millilitres
mm	Millimetres
mmHg	Millimetres of mercury
MAP	Mean arterial pressure
MoDREC	Ministry of Defence Research Ethics Committee
MODS	Multiple organ dysfunction syndrome
na	Not applicable
NATO	North Atlantic Treaty Organisation
NIR	Near infrared
NIRS	Near infrared spectroscopy
O ₂	Oxygen
ODP	Operating department practitioner
P ₅₀	Partial pressure of oxygen at which haemoglobin is 50% saturated
PaO ₂	Partial pressure of oxygen in arterial blood
PRS	President of the Royal Society
PTI	Physical Training Instructor
RCDM	Royal Centre for Defence Medicine
SaO ₂	Percentage oxygen saturation of haemoglobin in arterial blood
SpO ₂	Peripheral oxygen saturation
SpR(s)	Specialist Registrar(s)
StO ₂	Tissue haemoglobin oxygen saturation
SV	Stroke volume
SvO ₂	Mixed venous oxygen saturation
TAOC	Threshold area over the curve
TIVA	Total intravenous anaesthesia
TKA(s)	Through knee amputation(s)
V	Volts
VBG	Venous blood gas
$\dot{V}O_2$	Oxygen consumption
$\dot{V}O_{2Max}$	Maximal oxygen consumption
USB	Universal serial bus
WHO	World Health Organisation

Part I

INTRODUCTION

1. THE PROBLEM OF TRAUMA

Globally major trauma is one of the leading causes of morbidity and mortality, presenting significant challenges to the delivery of medical care and social policy in both the Western and Developing World. When assessing the literature on the causes and prevalence of trauma it should be appreciated that most descriptions are confined to a single centre/population or are based on datasets which are inconsistent, incomplete or fragmented. Even national databases fail to capture all of their relevant population: the National Trauma Data Bank® in the USA represents only two-thirds of the population while the Trauma Audit and Research Network (TARN) in the UK covers less than half of its respective population (Søreide, 2009). With these limitations understood, this chapter will introduce the problem of trauma in modern society and outline the need for better methods of assessing and managing the trauma patient.

1.1 EPIDEMIOLOGY OF MAJOR TRAUMA

The accepted definition of major trauma is that where the individual's Injury Severity Score (ISS) exceeds 15 (Søreide, 2009). While there are many criticisms of ISS as an approach to defining and categorising trauma, as exemplified by the number of other scoring systems that have evolved in an attempt to address its perceived deficiencies, it remains a useful standard, not least for allowing comparisons of trauma outcomes between different datasets and with historical standards.

In clinical practice trauma is most commonly considered as an individual affliction, but seen from a public health perspective it is a pandemic disease with a unique capacity to suddenly strike anyone regardless of age, sex, race, or socioeconomic status. Despite advances in medical practice and improved safety legislation, trauma retains its position as one of the leading global causes of morbidity and mortality in both developed and developing nations (Sherry, 2003).

In the western world major trauma is currently the most common cause of death in individuals below the age of 35 years, with the burden of disease being particularly high in males between the ages of 15–24 years (Polinder et al., 2007). This preponderance for a young population, particularly men, i.e. a major eco-

nomic productive population, combined with the frequently complex long term care/rehabilitation needs of survivors results in disproportionately high cost burden on society compared to most other disease processes.

Internationally unintended injury is ranked as the sixth leading cause of death and the fifth leading cause of moderate to severe disability (World Health Organization, 2008). Considered another way, injury accounts for 9% of worldwide deaths and 12% of the global burden of disease (Peden et al., 2002). In 2004 this equated to over 45 million individuals, more than 2000 people every hour, suffering moderate to severe injuries as a result of trauma, and there are few signs that this pattern is going to change. In 2004 road traffic collisions and conflict were ranked as the ninth and sixteenth leading causes of disability adjusted life years (DALYs), respectively (World Health Organization, 2008). With increasing numbers of motor vehicles, population and conflict, these are projected to rise to the third and eighth positions by 2020 (Murray and Lopez, 1997), producing an even greater demand on civilian and military medical resources and on the society that must bear the long term cost of caring for and rehabilitating victims of trauma.

Within western civilian practice, certainly within Europe, blunt trauma predominates, as would be expected where falls and motor vehicle collisions are the most common injury mechanisms (Polinder et al., 2007). Penetrating trauma is relatively uncommon, estimated in one European study to account for only 13% of major traumas, with most of these being self-inflicted or suicidal in nature (Søreide et al., 2007). The exceptions to this occur in nations with less strict gun/knife laws, such as parts of the USA and South Africa, where epidemics of penetrating trauma can be found (Søreide, 2009). In patients subject to blunt trauma, severe thoracic and/or abdominal injuries occur in approximately 20% of cases. Where intra-abdominal solid organ damage is present, this is most likely to involve the liver (36%), spleen (32%) or kidneys (24%) (Smith et al., 2005). The significance of these cases is that they are the ones most likely to present with uncontrolled (uncompressible) haemorrhage requiring early operative intervention to salvage. Penetrating injuries have a higher frequency of intra-thoracic/abdominal organ injury and consequently are associated with a high early fatality rate with most deaths occurring within 72 hours of hospital admission (Kauvar and Wade, 2005).

1.2 DISTRIBUTION AND CAUSES OF DEATH ASSOCIATED WITH MAJOR TRAUMA

1.2.1 *The Tri-modal Distribution of Trauma Deaths*

The classic tri-modal distribution of trauma deaths was first described by Trunkey (1983), who identified three mortality peaks occurring after trauma (illustrated in Figure 1.1):

1. a first peak corresponding to 'immediate deaths', occurring at scene or within the first 60 minutes, i.e. prehospital or very shortly after admission to hospital. These account for the majority (approximately 50%) of trauma deaths, usually as a result of unsurvivable central nervous system (CNS) injuries or massive haemorrhage (McGwin et al., 2009). Medically there is little that can be done to change the outcome in these patients, although public health measures, changes in social attitudes, legislation and engineering developments, may reduce their incidence.
2. a second peak of 'early deaths', those patients surviving to hospital but dying within the first 1–4 hours. These make up approximately 30% of deaths. Within this time-frame CNS injuries are the most common cause of death, accounting for 40–60% of fatalities, with haemorrhage constituting the next largest group causing 30–40% of deaths (Heckbert et al., 1998). Deaths in this group are generally considered the most preventable and are the main target for medical interventions to reduce mortality.
3. a third lower peak of 'late deaths' occurring sometime after the first week as a result of sepsis or multiple organ dysfunction syndrome (MODS), accounting for the remaining 20% of trauma deaths (McGwin et al., 2009).

Subsequent, more contemporaneous studies have called into question the tri-modal distribution. Most of the current evidence suggests that, at least in mature trauma systems, the pattern tends towards a bimodal distribution with the third peak of late trauma deaths absent in most modern descriptions (Meislin et al., 1997; Søreide et al., 2007; McGwin et al., 2009; Pfeifer et al., 2009; Chalkley et al., 2011). Meislin et al. (1997) performed long term follow up of trauma patients and proposed a 'fourth' peak/phase of trauma deaths occurring up to a year after

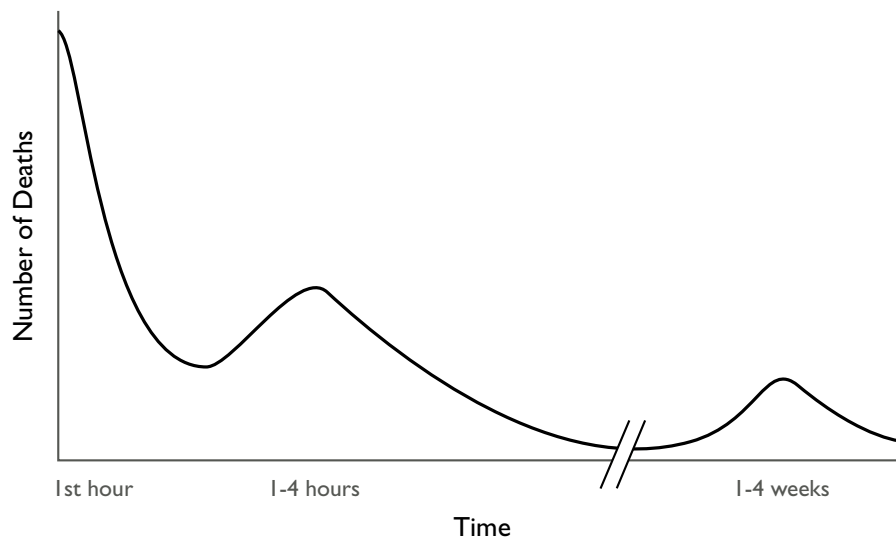


Figure 1.1: The classic tri-modal distribution of trauma deaths described by Trunkey (1983).

hospital discharge, particularly in the over 65 years age group. This would suggest that in the elderly trauma has acute and long term influences on mortality. Søreide et al. (2007) argues, that in fact the survival distribution pattern is a function of the analysis model used, in particular the time interval bin sizes. Their data from a civilian population in Norway showed a bimodal distribution when analysed with the same intervals used by Trunkey, but when deaths were stratified by cause, a weak third peak due to MODS could be seen in the second week (see Figure 1.2). What is confirmed in all studies is that immediate deaths (within the first hour) account for the majority of fatalities, with ‘early deaths’ making up most of the remainder. The exact definition of early deaths varies between reports, but most studies show the second peak shifted to the right, occurring slightly later than Trunkey reported, but still within 48 hours. No single reason for these differences have been identified, although a great deal has changed in trauma care since Trunkey’s original description and common explanatory innovations cited include: the wide spread adoption of the American College of Surgeons’ Advanced Trauma Life Support (ATLS®); 24 hour access to computed tomography (CT) imaging; and the establishment of regional trauma centres. Despite questions as to its validity, the tri-modal distribution remains a conceptually important model for examining trauma deaths and planning the delivery of trauma services.

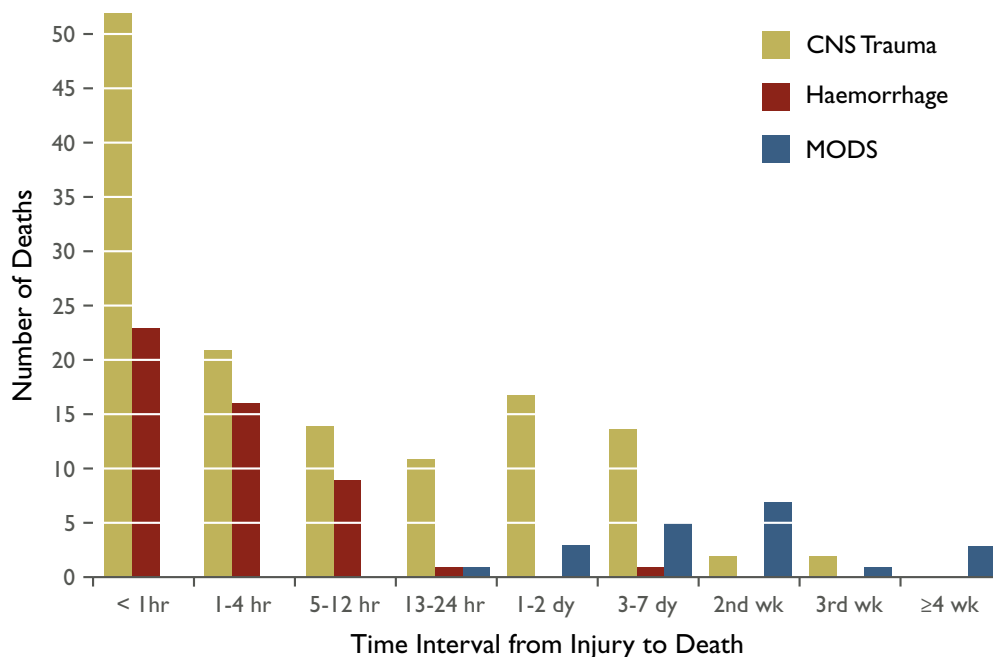


Figure 1.2: Distribution and causes of trauma deaths within a Scandinavian civilian population, demonstrating a bimodal distribution with mortality peaks occurring at <1 hour and 1–2 days. When stratified by cause of death a third peak due to MODS can be seen at 2 weeks, adapted from Søreide et al. (2007).

1.2.2 Causes of Death Following Trauma

Figure 1.2 illustrates the distribution of trauma deaths classified by cause from an evaluation of 260 consecutive trauma autopsies in a Scandinavian civilian population. The trends seen in this dataset are broadly representative of the current global patterns described by Pfeifer et al. (2009) in a review of the global literature published between 1980 and 2008. As can be seen CNS injuries account for the majority of deaths (21.6 – 71.5% in the global literature) — predominately occurring in the immediate and early phases. There has been little change in this figure in the past 30 years. The reasons for this are unclear but are probably in part due to the fact that many of the deaths, particularly those occurring in the first four hours, are as a result unsurvivable CNS injuries, and therefore not amenable to change produced by improvements in trauma care.

Exsanguination is the next most common cause of death (12.5–26.6%). In

1.3. PROBLEMS WITH THE MANAGEMENT OF TRAUMA ASSOCIATED HYPOVOLAEMIA

Søreide et al. (2007) series these individuals had the highest Abbreviated Injury Score in the thoracic and abdominal regions, which would be consistent with exsanguination from uncompressible haemorrhage. Like CNS injuries, at scene deaths probably represent unsurvivable haemorrhage not amenable to intervention other than preventative measures. Deaths from haemorrhage after the first hour represent an important group as these include individuals in whom targeted intervention may change outcome. This premise would appear to be supported by the fact that deaths in the early haemorrhage group have fallen over the last 30 years. It is reasonable to assume that further improvements in the delivery of trauma care would have the biggest impact on mortality in this group.

Although much less significant in terms of absolute numbers, MODS (1.6–9% of deaths) and sepsis (3.1–17% of deaths) remain the leading causes of mortality after the first week following trauma (Pfeifer et al., 2009). Although the incidence of deaths from these causes has been falling in recent decades, they have become an increasing problem in the elderly — the emerging phenomenon of ‘geriatric trauma’ (Søreide, 2009).

In summary the greatest benefit to survival rates in major trauma patients from any single intervention is likely to be achieved from innovations directed towards the management of early hypovolaemia secondary to haemorrhage. Not only would this reduce deaths from exsanguination, but as Jaicks et al. (1997) demonstrated early correction of hypovolaemic shock also improves the clinical outcome in patients with associated severe head injuries, although this does not necessarily translate into improved mortality rates as the historical evidence has shown. Similarly, since prolonged periods of tissue ischaemia are known to result in a number of metabolic disturbances directly associated with increased mortality (Rixen et al., 2001), improvements in the early management of hypovolaemia are also likely to have an impact upon late survival rates.

1.3 PROBLEMS WITH THE MANAGEMENT OF TRAUMA ASSOCIATED HYPOVOLAEMIA

One of the main challenges during trauma resuscitation is the restoration and maintenance of adequate oxygen delivery to tissues. This is of paramount importance since prolonged periods of tissue ischaemia lead to metabolic dysfunction

that manifest in a number of deleterious consequences, for example:

1. individual organ system failure and multiple organ dysfunction syndrome.
2. enhanced inflammatory response, potentially causing damage to organ systems not directly injured by the initial insult, leading to increased post-operative complications and prolonging the requirement for intensive care (Davis et al., 1996; Krishna et al., 1998).
3. coagulopathy due to both activation of protein C (leading to hyperfibrinolysis (Brohi et al., 2007, 2008)) and metabolic acidosis, reducing the effectiveness of clotting enzymes/factors and attenuating clot formation (Cosgriff et al., 1997; Dempfle and Borggrefe, 2007; Lier et al., 2008).

The net result of these complications is a higher mortality. These problems can be mitigated by restoration and maintenance of adequate tissue oxygenation via fluid resuscitation. Leaving aside the complex arguments as to what type of resuscitation fluid should be administered, the challenge for clinicians is determining how much fluid should be administered, and how quickly, to adequately restore tissue perfusion.

1.3.1 *Fluid Resuscitation in Trauma*

Severe haemorrhagic shock causes microvascular injury which allows fluid loss into the extracellular space and results in a fluid deficit greater than can be attributed to the volume of blood loss alone (Bacter et al., 1970). Based on this understanding, early proponents for aggressive blind fluid resuscitation of the type epitomised by the previous ATLS® guidelines (Americian College of Surgeons, 1997), argued that the benefits of improved cardiac output and tissue perfusion, and reduced endothelial dysfunction outweighed the risks of inducing further haemorrhage ('popping the clot') produced by restoration of normal blood pressure (Krausz, 2006). This practice has now largely fallen out of favour, with a number of animal models of uncontrolled haemorrhage demonstrating it to be associated with increased bleeding, haemodynamic decompensation and higher mortality (Bickell et al., 1991; Stern et al., 1993; Solomonov et al., 2000), and that better mortality outcomes are achieved with an initial period of hypotensive resuscitation (Kowalenko et al., 1992). Similar findings have also been reported

1.3. PROBLEMS WITH THE MANAGEMENT OF TRAUMA ASSOCIATED HYPOVOLAEMIA

in randomised trials in prehospital trauma patients, where those receiving early aggressive fluid resuscitation were found to have a higher mortality than those receiving no fluid before arrival in hospital (Martin et al., 1992; Bickell et al., 1994). However once in the hospital environment, where definitive means of haemorrhage control are available, there appears to be no survival benefit to continuing hypotensive resuscitation (Dutton et al., 2002). It should be appreciated that these studies relate to patients with uncontrolled haemorrhage, and should not be interpreted as promoting the withholding of fluid resuscitation in those individuals with a controlled source of bleeding, or advocating prolonged hypotensive resuscitation, which recent animal models suggest is associated with a higher mortality (Garner et al., 2010). Rather, fluids should be restricted in those patients with uncontrolled haemorrhage until the source of bleeding can be controlled, at which point the restoration of normal tissue perfusion should be the goal*.

The early recognition and effective management of hypovolaemia is fundamental to preventing the immediate and late complications associated with inadequate tissue perfusion in trauma patient. As simple and obvious as this statement appears, the failure to recognise the magnitude or even the presence of blood loss has long been identified as a significant cause of preventable death in trauma patients (Anderson et al., 1988). Unfortunately this problem cannot be solved by the indiscriminate administration of large volumes of fluid which may precipitate new bleeding and push the patient's cardiac function off the right side of the Frank-Starling curve. Fluid resuscitation must be titrated to the individual needs of the patient and the goal of achieving adequate tissue perfusion. The problem for clinicians at present is that all commonly available tools for assessing resuscitation are either poor proxy indicators of end organ perfusion or have major practical limitations in the trauma setting.

*Most of the evidence for this practice comes from civilian studies of trauma in urban environments, where transport to hospital times were generally under one hour. In the military environment or remote rural civilian practice evacuation timelines may be considerable longer. For this reason British Military operational practice, circa 2011, has been for 'novel-hybrid resuscitation': one hour of hypotensive resuscitation, after which normotensive resuscitation should be attempted regardless of patient location or predicted evacuation timelines.

1.3. PROBLEMS WITH THE MANAGEMENT OF TRAUMA ASSOCIATED HYPOVOLAEMIA

1.3.2 *Conventional Measures of Physiological Status in Trauma*

Traditional clinical signs of hypoperfusion include capillary refill rate, features of elevated sympathetic nervous system activity such as pallor, sweating and assessment of cerebation. While these have value when assessed as part of the whole clinical picture, they are highly subjective and used in isolation lack either specificity or sensitivity.

Pulse rate is the simplest objective clinical sign of volume state in trauma. It is highly reproducible and relatively easy and simple to record continuously in real time, as such it is widely used. Despite its ubiquity, the heart rate response to haemorrhage is widely misunderstood (Secher and Bie, 1985). A small reduction in central blood volume from haemorrhage, but equally as a result of postural changes, causes a modest increase in the pulse rate (<100 bpm). Once the reduction in central blood volume approaches 30% there is a 'paradoxical' drop in pulse rate and blood pressure mediated by a Bezold-Jarish-like* vagal reflex associated with a loss of peripheral (muscle) sympathetic activity (Campagna and Carter, 2003). Only with greater reductions in the central blood volume is there an increase in heart rate and a concomitant drop in the blood pressure, signalling the transition towards irreversible shock. In the young or athletic, of which the military population represents both, this biphasic response may be absent as they compensate very well initially for small volumes of blood loss. The interpretation of heart rate is further complicated by the fact that the initial baroreflex can be over 'overridden' by the sympathetic response associated with pain or tissue damage. Although commonly used, heart rate can be seen to be an unreliable indicator of volume state with significant haemorrhage occurring in the presence of tachycardia, a normal heart rate or even a relative bradycardia.

Along with pulse rate, blood pressure is the other most commonly misunderstood parameter for assessing volume state. Again this demonstrates the biphasic response to blood loss, and has many of the same problems in interpretation as pulse rate. Blood pressure is frequently preserved in young individuals during

*The Bezold-Jarish reflex, originally described by Albert von Bezold (1836–1868) and Ludwig Hirt (1844–1907) and subsequently confirmed by Adolf Jarish (1850–1902), strictly describes the triad response of apnoea, bradycardia and hypotension observed in experimental animals following the administration of veratrum alkaloids (Aviado and Aviado, 2001).

mild to moderate haemorrhage particularly when associated with significant tissue injury, but may drop suddenly in these individuals as they progress to uncompensated shock. Compounding the physiological problems with the interpretation of blood pressure in trauma patients are the practical limitations associated with the most common methods of measuring it. The gold standard for measuring blood pressure is intra-arterial monitoring, however this is invasive and time consuming to establish and calibrate and thus is not typically available during the early stages of resuscitation. As a result non-invasive blood pressure monitoring is often used during the early stages of resuscitation. Measurements are usually taken by an automated blood pressure device, the accuracy of which in the trauma patient have been questioned with one study having shown automated measurement to be significantly higher than those recorded manually (Davis et al., 2003). The technique is further limited by the time taken to obtain a measurement: most automated machines typically provide intermittent recordings on a five minute rolling cycle, which makes accurate interpretation of the patient's response to interventions very difficult. Despite the convenience and widespread availability of non invasive blood pressure monitoring there is often a significant delay in obtaining the first measurement. In a 2009 audit on trauma care in Selly Oak Hospital, Birmingham (a regional trauma centre), the average time from patient arrival in the emergency department (ED) to the first blood pressure measurement was 11 minutes (Prof K Porter, personal communication). There is also wide variation in the limit of agreement between invasive and non-invasive blood pressure monitoring (MacFarlane et al., 2010). This makes interpreting the literature difficult as many major trauma patients will transition from non-invasive to invasive blood pressure measurements as their care progresses, but the distinction as to when this occurs and the potential for differences between the two techniques is rarely made clear.

Central venous pressure (CVP) monitoring and pulmonary artery catheters offer an accurate means of assessing volume state in patients, and can be used to guide fluid replacement in trauma, although pulmonary artery catheters are rarely used for this purpose in the UK. The main limitation of CVP monitoring is that it provides no indication of cardiac output (CO), and a low CVP may be a reflection of low central volume or reduced myocardial contractility, of which

trauma is associated with both (Abou-Khalil et al., 1994; Yang et al., 2004). For this reason it is often suggested that a pulmonary catheter is required to provide the distinction. Unfortunately the insertion and calibration of these lines requires specialist skills and is time consuming, as a result their use is largely confined to the theatre and ITU settings, and they are rarely available to guide the early stages of resuscitation.

Arterial pH, lactate and base excess are indicators of anaerobic metabolism occurring as result of tissue hypoperfusion in shock. Of the three lactate is considered to provide the most accurate reflection of tissue oxygen delivery (Husain et al., 2003). Some authors suggest that lactate can be raised in trauma due to mechanisms other than anaerobic glycolysis secondary to hypoperfusion, and in these circumstances it may be a misleading end point of resuscitation (James et al., 1999). Such theoretical concerns appear to be less of a problem in clinical practice, however lactate is still not commonly used due to a lack of widespread availability when compared to base excess and other arterial blood gas parameters. For this reason the application of base excess in assessing trauma resuscitation has received much more attention in the literature. Attempts to directly compare base excess to lactate have yielded conflicting results (Davis, 1994; Mikulaschek et al., 1996). The principle problem is that base excess can be affected by the administration of large amounts of saline. Base excess appears to be a useful surrogate for lactate as long as its changes are a result of alterations in tissue perfusion. When changes in base excess occur secondary to hyperchloreaemic acidosis associated with saline administration, or lactate is influenced by ketoacidosis or renal dysfunction, this relationship can become discordant (Chawla et al., 2010). Despite these problems, base excess has been shown to correlate better than conventional haemodynamic parameters with other indicators of oxygen delivery and utilisation in trauma models (Davis et al., 1991) and human trauma patients (Kincaid et al., 1998). Moreover venous base excess correlates well with arterial base excess in trauma, making it useful when arterial samples are not available (Davis, 1994). The limitation of all arterial or venous blood gas measurements is that they are invasive, provide intermittent ‘snapshots’ of patients’ resuscitation status and take time to process — due to this practical constraint and the nature of the samples themselves ABG measurements typically lag behind the true clinical picture. In addition, processing

ABGs requires carefully calibrated equipment and a degree of logistical support that may not be available in the military or prehospital environment.

1.4 TRAUMA IN THE MILITARY ENVIRONMENT

Trauma management in the military environment follows many of the same principles as that practiced in the civilian setting, however the nature of war, the injury pattern, evacuation timelines and patient population, all pose additional challenges.

War is characterised by a high volume of multiply injured casualties sustaining massive trauma of a type rarely seen in civilian practice. Penetrating ballistic wounds and blast trauma — the hallmarks of modern warfare occur much more commonly than in civilian practice. The nature of the injuries seen are conventionally associated with the intensity of the conflict. In full-scale war blast injuries are common, while in small scale conflicts penetrating wounds due to gun shots predominate (Ryan, 2000). However, the experience of the early part of the 21st century has seen a reversal of this pattern with patient data from Afghanistan demonstrating a high proportion of injuries occurring due to improvised explosive devices (IEDs) as a consequence of a change in Taliban tactics. The result is an injury pattern composed of a mixture of gun shot wounds (GSWs) and blast injury, often associated with single or multiple traumatic limb amputations (Hodgetts et al., 2007).

In addition to the problems of managing one or more potentially multiply injured casualties, the delivery of medical care in the military setting is further complicated by the often austere and resource constrained nature of the environment, particularly in the forward role. Initial care may have to be performed in the presence of a persistent threat and under tactical conditions, e.g. minimal noise and limited artificial light. Even in the field hospital logistical constraints limit the resources and expertise available for care. There is often delayed access to definitive care, and where evacuation does take place this will be under forward operating constraints. When transporting casualties by helicopter the problems of noise and vibration severely limit the type and extent of care that can be undertaken, although this problem is not unique to the military. The net result, certainly for conflicts in the 20th century for which accurate data exists, is a higher mortality

for haemorrhagic shock when compared to civilian settings, 65% vs 50% and a high mortality before reaching care at Role 2* or above (Champion et al., 2003).

Military trauma practice does have one major advantage over its civilian counterpart: the vast majority of the population are young, physical fit males, who have been medically screened to exclude significant comorbidities and are up-to-date with their vaccinations. Hence the population tends to have much greater physiological reserves, will tolerate a greater injury burden and has better rehabilitation potential. The problem working with such a group is that it can make translation of research from the civilian world to military environment, or vice versa, difficult. The exception to dealing with young healthy individuals occurs when the military is required to manage allied forces, the local civilian population, or expatriates/contractors who enter the medical evacuation chain. Under these circumstances the population will more closely resemble that seen in civilian practice. However this can present different management issues, particularly in the case of local civilian populations in third world nations, where problems with chronic malnutrition, unmanaged major/advanced comorbidities, or opiate use are much more common than that seen in western medical practice.

In summary, the constraints of the military environment present many additional challenges to the management of trauma patients. New techniques introduced to improve care need to be robust, able to survive the logistical chain and preferably simple to use or interpret with the minimum of specialist support.

*Role 2 is one of the four tiers in which medical support is organised, as defined by NATO. Role 2 is the smallest facility at which a surgical capability is provided, usually of a damage control nature. Above this would be Role 3, typically provided by a field hospital, and Role 4 a facility capable of providing definitive care across the full range of specialities, most commonly this refers to health care facilities located in the country of origin.

2. OXYGEN DYNAMICS AND THE PROPERTIES OF HAEMOGLOBIN

The previous chapter discussed the limitations of current techniques used to guide resuscitation in the trauma patient — mainly that they are all only surrogate markers of end organ/tissue perfusion. This chapter outlines some of the physiology of tissue oxygen delivery and examines the role of goal directed therapy in trauma resuscitation.

2.1 OXYGEN DELIVERY

Oxygen is an essential substrate for oxidative cellular metabolism. Although some tissues are capable of anaerobic respiration in the face of inadequate oxygen delivery, the process is inefficient and produces toxic byproducts such as lactate. Increased concentrations of such compounds have deleterious effects in the trauma patient, e.g. lactic acidosis and coagulopathy, compounding the physiological disturbance that gave rise to their production in the first place.

Oxygen delivery to end organs is described as ‘flowing down’ an oxygen cascade from high concentrations of oxygen in the atmosphere along a series of physiological transport steps to the relatively low partial pressures found in peripheral tissues (see Figure 2.1). This process of oxygen diffusion can be broken down into five simple stages, with movement between each stage occurring in accordance with basic physical laws (Bersten and Soni, 2009):

1. Ventilation
2. Oxygen uptake from the lungs
3. Reversible binding of oxygen to haemoglobin
4. Convective transport of oxygen to the tissues
5. Diffusion of oxygen into cells

Step 1: Ventilation

This describes the mechanical process of moving air by convection into the alveoli of the lungs where gaseous exchange can take place. At sea level the partial pressure of oxygen in arterial blood (PaO_2) is around 21 kPa. During inspiration it is

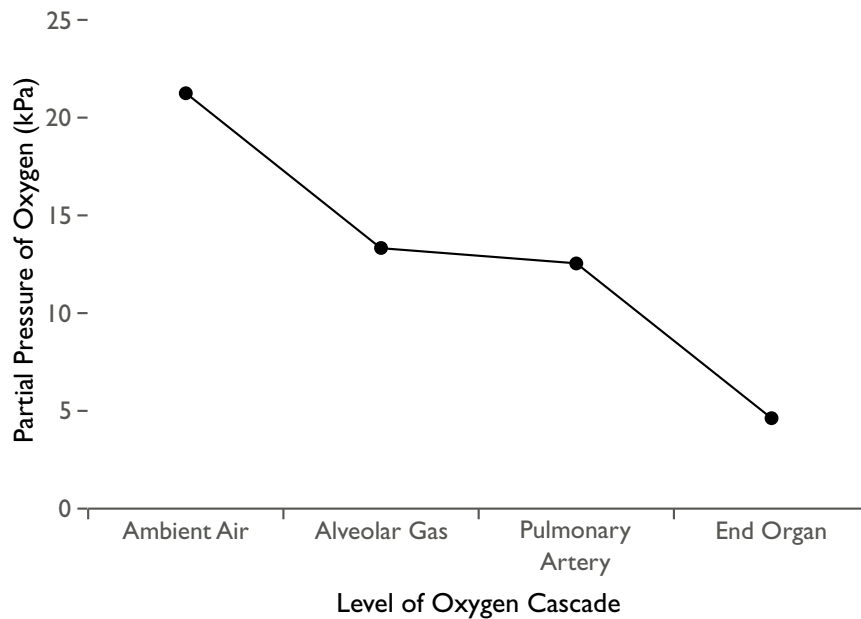


Figure 2.1: The oxygen cascade. Oxygen diffuses ‘downhill’ along the transport chain, with each step existing at a lower partial pressure of oxygen than the one before. Disruption of one or more of the steps will result in a reduction in oxygen delivery to end organs, adapted from Martin and Windsor (2008).

humidified and mixed with CO_2 such that the partial pressure at the alveolar level is reduced to around 13 kPa.

Step 2: Oxygen uptake

Oxygen diffuses from the alveoli, across the alveolar-capillary membrane into the blood in accordance with Fick’s Law:

$$\text{Rate of gas transfer} \propto \frac{kA\Delta P}{D}$$

where k is the diffusion constant for oxygen, A is the surface area over which diffusion takes place, ΔP is the partial pressure gradient and D is the thickness of the alveolar-capillary membrane. The net result of each of these factors on oxygen diffusion results in a typical pulmonary capillary PaO_2 being around 12 kPa. For diffusion to occur effectively there must be adequate oxygen present in the alveoli (delivered in step one) and sufficient capillary perfusion to maintain the diffusion gradient. Critically these two processes have to occur in the same place

at the alveolar level. Failure to achieve this is referred to a ventilation-perfusion (V/Q) mismatch. Trauma patients have several challenges at this level: global hypovolaemia results in inadequate perfusion of the lung parenchyma; in addition reduced ventilation secondary to chest wall trauma, a supine position, or positive pressure ventilation all serve to exacerbate the V/Q mismatch.

Step 3: Reversible binding of oxygen to haemoglobin

Oxygen is poorly soluble in plasma and only around 3% is carried in this way, the rest being transported bound to haemoglobin. The properties of haemoglobin and its role in oxygen carriage are discussed in Section 2.3. The concentration of oxygen in the blood (CaO_2) is the sum of the quantities of oxygen bound to haemoglobin and that dissolved in plasma. This can be expressed as:

$$CaO_2 = \underbrace{([Hb] \times 1.34 \times SaO_2)}_{\text{O}_2 \text{ bound to Hb}} + \underbrace{(0.003 \times PaO_2)}_{\text{O}_2 \text{ dissolved in plasma}}$$

where $[Hb]$ is the concentration of haemoglobin in g/dl, 1.34 is a constant expressing the quantity of oxygen in mls bound by 1 g of haemoglobin and SaO_2 is the percentage saturation of haemoglobin. It can therefore be seen that the next major constraint on oxygen delivery in the trauma patient is the haemoglobin concentration, which will be reduced in any patient suffering moderate to severe haemorrhage.

Step 4: Convective transport of oxygen to tissues

Tissues have a limited capacity for storing oxygen and depend upon on a continuous supply being delivered by the cardiovascular system. Oxygen delivery ($\dot{D}O_2$) to tissues is dependant upon two factors:

1. the cardiac output (CO)
2. local controls on regional blood flow to tissues

Mathematically $\dot{D}O_2$ can be expressed as:

$$\dot{D}O_2 = 10 \times CO \times CaO_2$$

where $\dot{D}O_2$ is expressed in ml/min and CO as l/min (a conversion factor of 10 is used to balance the units). In a normal adult at rest $\dot{D}O_2$ is approximately

1000 ml/min. In the trauma patient CO will be reduced in accordance with Ohm's Law* which, as can be seen from the equation above, will be associated with a proportionate reduction in $\dot{V}O_2$.

Step 5: Diffusion of oxygen into cells

Over 90% of aerobic metabolism takes place in the mitochondria. At the point of utilisation in mitochondria the partial pressure of oxygen can be as low as 0.1 kPa. This creates a diffusion gradient down which oxygen will move into the cell in accordance with the principles of Fick's Law and the state of the oxygen haemoglobin dissociation curve. Assuming that oxygen supply exceeds demand, the amount of oxygen taken up by a cell will be determined by its metabolic needs and not amount of oxygen available.

Examining the five steps above it can be appreciated that there are several potential challenges to oxygen delivery in the trauma patient. Ventilation is not usually a problem, unless there is tracheobronchial disruption or other significant chest injury, but at every step after that problems can occur. Hypovolaemia, a supine position and positive pressure ventilation will all contribute to a V/Q mismatch. Low concentrations of haemoglobin (as a result of haemorrhage) and the effects of acidosis and hypothermia will reduce oxygen carriage in the blood. Low arterial pressure is associated with a concomitant reduction in CO, which ultimately results in a narrowing of the oxygen diffusion gradient at the end organ level.

2.2 OXYGEN CONSUMPTION

Oxygen consumption ($\dot{V}O_2$) is often used synonymously with whole body oxygen demand, although the two are not the same. Demand is related to need, and the two terms are only equivalent when demand for oxygen exceeds supply. $\dot{V}O_2$ can be expressed in terms of CO and the difference between the oxygen content of

*Ohm's Law describes the relationship between flow and pressure. In terms of cardiovascular physiology it can be expressed as: $CO = \text{arterial pressure} / \text{total peripheral resistance}$. CO is directly proportionally to arterial pressure therefore a reduction in arterial pressure, associated with hypovolaemia, will lead to commensurate reduction in CO.

arterial (CaO_2) and venous blood (CvO_2):

$$\dot{V}O_2 = CO \times (CaO_2 - CvO_2)$$

where CvO_2 can be expressed as:

$$CvO_2 = \underbrace{([Hb] \times 1.34 \times SvO_2)}_{O_2 \text{ bound to Hb}} + \underbrace{(0.003 \times PvO_2)}_{O_2 \text{ dissolved in plasma}}$$

where SvO_2 is the haemoglobin-oxygen saturation of mixed venous blood and the PvO_2 is the partial pressure of oxygen in the venous blood. Since the quantity of oxygen dissolved in the plasma is negligible, the major determinants of CvO_2 are SvO_2 and the concentration of haemoglobin ($[Hb]$).

The ratio of oxygen delivery to consumption is referred to as the oxygen extraction ratio (ER):

$$ER = \frac{\dot{V}O_2}{\dot{D}O_2}$$

In a normal individual at rest the ER is around 25%, which means that 25% of the oxygen delivered in arterial blood is taken up by the tissues and the remaining 75% remains in the venous blood. Under these condition $\dot{V}O_2$ and $\dot{D}O_2$ are independant. However as the extraction ratio increases (in the trauma patient this would be as a result of a reduction in CO and haemoglobin concentrations), a critical $\dot{D}O_2$ is reached. $\dot{V}O_2$ becomes dependant upon $\dot{D}O_2$ and anaerobic metabolism occurs (Žaja, 2007).

2.3 THE PROPERTIES OF HAEMOGLOBIN

Haemoglobin is the principle oxygen carrying compound in most vertebrates (others being myoglobin and neuroglobin). Except when in the presence of haemolytic disease, haemoglobin is contained almost exclusively within red blood cells (erythrocytes). Human red cells take the shape of a biconcave disc with a diameter of 6–8 μm . At maturity red cells possess no nucleus or other intracellular organelles, the intracellular volume being largely taken up by haemoglobin, as such red cells incapable of repair and have a typical life span of around 120 days.

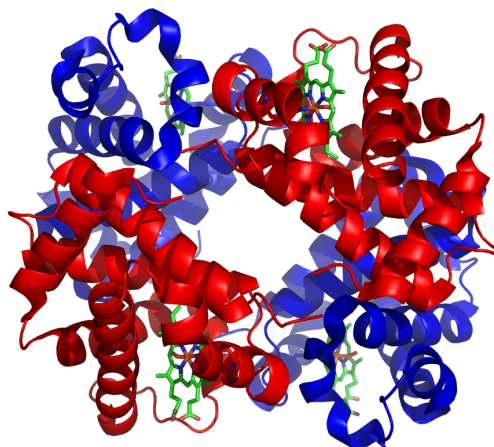


Figure 2.2: The structure of haemoglobin A. Demonstrating the tetramer structure with four globin subunits (α shown in red and β shown in blue). Their associated iron containing haem groups are shown in green.

2.3.1 *The Structure of Haemoglobin*

Haemoglobin is a complex metalloprotein, composed of an iron containing haem group associated with a globin protein chain. Haemoglobin exists as tetramer with a molecule weight of 64,458 (for HbA) composed of four protein subunits, each with molecular weight of approximately 16,000 (see Figure 2.2). Each subunit consist of one of four possible globin chains (α , β , δ and γ). Each globulin chain contains a hydrophobic pocket into which one iron containing haem group is inserted, which is the part that actually binds oxygen. In adults, approximately 97% of haemoglobin exists in the HbA form, which is composed of two α and two β subunits. Up to 2.5% of haemoglobin is HbA₂ (composed of α and δ chains), and the remainder HbF or foetal haemoglobin (composed of α and γ chains), so named because this is the predominant form of haemoglobin in late foetal and early neonatal life.

2.3.2 *Oxygen Carriage by Haemoglobin*

The main function of haemoglobin is to carry oxygen, although it is also involved in several other processes such as the transport of CO₂ and the buffering of acid-base

changes in the blood. Each haem unit in the active ferrous (Fe^{2+}) form is capable of reversibly binding a single molecule of oxygen, therefore the haemoglobin tetramer is capable of binding *up to* four molecules of oxygen. This is not an all or nothing process, and there is no requirement that every haem unit be simultaneously bound to an oxygen molecule. Oxygen carriage by haemoglobin is usually expressed in terms of percentage saturation (SpO_2):

$$\text{SpO}_2 = \frac{\text{HbO}_2}{\text{Hb} + \text{HbO}_2}$$

where HbO_2 is concentration of oxyhaemoglobin and Hb the concentration of deoxyhaemoglobin.

SpO_2 is governed by many factors, the most important of which is the partial pressure of oxygen. SpO_2 and the partial pressure of oxygen demonstrate a sigmoidal relationship, as expressed in the oxygen-haemoglobin dissociation curve shown in Figure 2.3. At low oxygen tensions the SpO_2 is also low, however the binding of oxygen to haemoglobin produces a conformational change in the protein structure facilitating the binding of further oxygen molecules. This is known as cooperative binding and accounts for the difference between the early and middle portions of the curve. At high oxygen concentrations haemoglobin approaches full saturation, and it becomes increasingly difficult for further oxygen binding to take place, accounting for the plateauing of the curve. Under normal conditions the saturation of haemoglobin in arterial blood will be in excess of 97%.

The partial pressure of oxygen at which haemoglobin is 50% saturated is referred to as the P_{50} , which is a conventional measure of the affinity of haemoglobin for oxygen. A shift in the P_{50} to the right is associated with a decreased affinity of haemoglobin for oxygen, and occurs in association with a fall in pH (when this is due a rise in CO_2 it is referred to as the Bohr Effect), a rise in temperature or the concentration, of 2,3-diphosphoglyceric acid (2,3-DPG) an anionic organic phosphate found in red blood cells. Conversely a shift to the left is associated with a higher affinity for oxygen and occurs with a rise in pH/ CO_2 , a fall in temperature, or the concentration of 2,3-DPG.

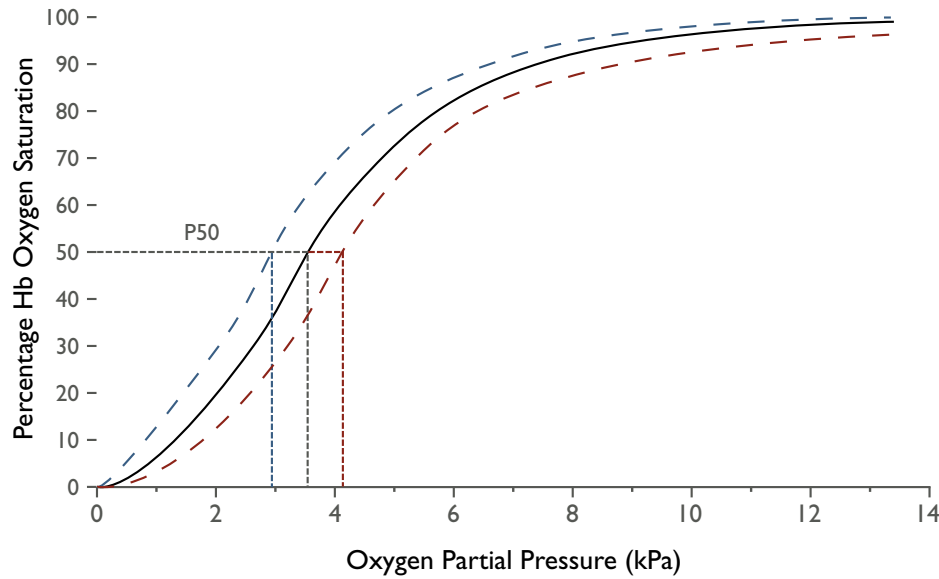


Figure 2.3: The oxygen-haemoglobin dissociation curve. The dashed curves represent shifts in the affinity of haemoglobin for oxygen associated with changes in pH, temperature, or 2,3-DPG concentrations (see text for details). A shift in the curve to right indicates a lower affinity of haemoglobin for oxygen and a shift to the left a higher affinity. The P50 is a partial pressure of oxygen at which haemoglobin is 50% saturated, it provides a conventional measurement for comparing the affinity of haemoglobin for oxygen under different conditions.

2.4 LOCAL TISSUE OXYGENATION

As discussed in Chapter 1 the goal of trauma resuscitation is to achieve adequate end organ perfusion, or for all practical purposes an adequate local tissue oxygenation (StO_2) in the target organ. StO_2 can be derived from the ratio of HbO_2 to total haemoglobin in the target tissue, expressed as:

$$StO_2 = \frac{HbO_2}{Hb + HbO_2}$$

This is the same equation as that for calculating SpO_2 presented on page 21, except here the haemoglobin concentration relates to the combined concentrations in the arterial, capillary and venous compartments. StO_2 can be considered analogous to a mixed venous saturation taken at a microcirculatory level. In reality the redox state of several other oxygen carrying compounds (such as myoglobin) may also influence StO_2 . Fortunately the contributions of such compounds to the NIRS signal are usually small, and they are often ignored. A more detailed consideration

of the influence of other oxygen carrying compounds on StO_2 is presented in Section 3.3.

From the previous discussion regarding oxygen delivery, it can be appreciated that StO_2 in the trauma patient will be influenced by three factors:

1. *Haemoglobin-oxygen saturation of arterial blood*

In most patients the partial pressure of oxygen in alveoli, if breathing room air, is around 13 kPa. From the oxygen-haemoglobin dissociation curve presented in Figure 2.3 it can be seen that this is associated with a haemoglobin saturation in excess of 97%. In reality all trauma patients receive oxygen therapy as a first line treatment resulting in much higher oxygen partial pressures and a near constant 100% haemoglobin saturation, unless there is significant airway or pulmonary injury. Therefore the oxygen saturation of arterial blood can usually be considered a constant and does not contribute to changes in StO_2 in the tertiary/Role 3 environment.

2. *Haemoglobin-oxygen saturation of capillary/venous blood*

Haemoglobin saturation in capillary/venous blood is dependant upon two factors:

- a) The saturation of arterial blood delivered to the capillary bed. In the trauma patient receiving oxygen therapy this will typically be 100% and is not usually a determinant unless there are significant ventilatory problems.
- b) The oxygen extraction ratio. Low CvO_2 , associated with a reduced haemoglobin and low CO, results in an increase in the oxygen extraction ratio reducing the haemoglobin oxygen saturation in the venous compartment.

3. *Ratio of blood volume in the arterial, capillary and venous compartments*

It is believed that in most tissues the blood volume is distributed between the arteriolar, capillary and venular compartments in a ratio of 10:20:70 (Wiedeman, 1963). Therefore StO_2 is predominantly a reflection of oxygen saturations in the venous compartment. Since there are significant differences in the oxygen saturations of the arterial (typically around 100%) and venous

systems (typically 60–80%) a change in the ratios of blood volume between these two compartments will affect StO_2 .

3. NEAR INFRARED SPECTROSCOPY

Near infrared spectroscopy (NIRS) is a technique that can be applied in clinical medicine to provide a non-invasive, real-time continuous estimate of local tissue oxygenation (StO₂). This chapter describes some of the background to the technique and discusses the theory of its application in medical practice. Parts of this chapter, in particular Section 3.2, include material previously published in the Journal Trauma under the title ‘The Diagnosis of Acute Lower Limb Compartment Syndrome: Applications of Near Infrared Spectroscopy’ (Barker et al., 2011).

3.1 A BRIEF HISTORY OF THE DEVELOPMENT OF NIRS

The history of NIRS for measuring StO₂ is one encompassing innovations from the fields of astronomy, physics, chemistry, physiology, and only relatively recently that of clinical medicine. Its development spans nearly 350 years, from Newton’s early work on optics to current day medical practice.

3.1.1 *The Discovery of the NIR Range*

In 1665 Newton’s* work on optics demonstrated that white light was not the homogeneous matter previously thought, but a composite of the all visible colours of the electromagnetic spectrum. However it was William Herschel†, with the presentation of his seminal work ‘Experiences on the Refrangibility of the Invisible Rays of the Sun’ (Herschel, 1800) to the Royal Society in 1800, who is credited with the discovery of the infrared range.

In an elegant experiment Herschel projected the visible spectrum onto a bench with the aid of a prism and proceeded to measure the heating effect of different parts of it. He found that the temperature increased as the thermometer was moved from violet to red and reached a maximum beyond the range of the visible spectrum (see Figure 3.1). Herschel correctly surmised that sunlight must contain more than just the visible spectrum, referring to his new discovery as ‘radiant heat’ and the ‘thermometrical spectrum’, but mistakenly believed that this energy

*Sir Isaac Newton PRS (1642–1727), English physicist and mathematician, Lucasian Professor of Mathematics at the University of Cambridge.

†Sir Fredrick William Herschel FRS (1738–1822), German born English Astronomer and Composer.

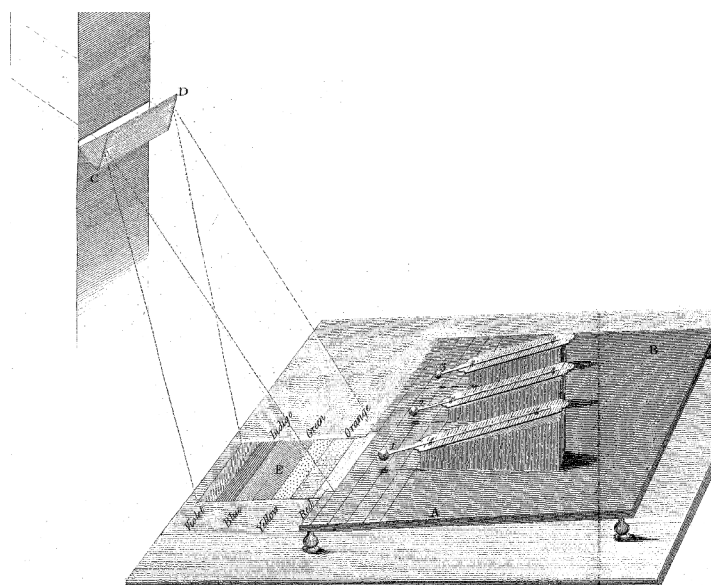


Figure 3.1: An illustration taken from Herschel's original description of his experiments identifying energy associated with the infrared range of the electromagnetic spectrum. Sunlight is diffracted through a prism so as to project a rainbow on the bench. Three thermometers are positioned such that the first records the temperature of a band of radiation, while the other two lie outside of the spectrum intended to act as controls.

was fundamentally different to visible light. It was Ampère* who, in 1835 using the recently developed thermocouple, demonstrated that near infrared (NIR) waves had the same properties as visible light, and that they were in fact part of the same phenomenon (Hindle, 2007). But it would take over a century more before the technology would be available to allow the acquisition of spectra outside of the visible spectrum.

3.1.2 *The Early Development of Spectroscopy*

The first spectroscope was constructed by the German optician Joseph von Fraunhofer† in 1814. By replacing the mirror of a theodolite with a hollow prism, he was able to use this equipment to observe dark lines appearing in the solar spectrum, subsequently shown to be atomic absorption lines which still bear his name today. Fraunhofer also developed a wire diffraction grating that allowed the separation

* André-Marie Ampère (1775–1936), French mathematician and physicist.

† Joseph Ritter von Fraunhofer (1787–1826), German optician.

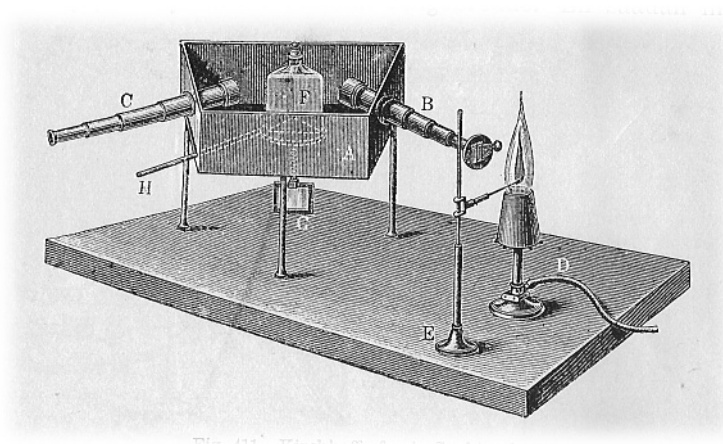


Figure 3.2: Bunsen and Kirchhoff's spectroscope.

of light of different wavelengths with high resolution, transforming spectroscopy from a qualitative art to a quantitative science (Stepanov, 1977).

In 1859 Bunsen* and Kirchhoff† began studying the emission spectra of heated elements (the design of their spectroscope is shown in Figure 3.2). Together they discovered caesium in 1861, and shortly afterwards radium (Weeks, 1932). The techniques they pioneered would be responsible for the direct discovery of several other elements. Although not the first to use spectroscopy, Bunsen and Kirchhoff's collaboration is arguably the most famous and their work led to an explosion of interest in the new field, however the lack of suitable detection equipment limited progress outside of the visible spectrum.

In the early 1880s an important step was made when it was realised that the photographic plate, invented in 1829 by Niépce‡ and Daguerre§, had some NIR sensitivity. Abney¶ and Festing|| exploited this discovery early on and from 1881 began recording spectra of organic liquids in the range of 1–1.2 μm (Abney and Festing, 1881). Their work was significant in that not only did it represent the first serious measurements in the NIR range, but also that they were the first to realise

*Robert Bunsen (1811–1899), German Chemist, recipient of the Copley Medal.

†Gustav Robert Kirchhoff (1824–1887), German Physicist, recipient of the Rumford Medal.

‡Nicéphore Niépce (1765–1833), French inventor and photographer.

§Louis-Jacques-Mandé Daguerre (1787–1851), French designer and photographer.

¶William de Wiveleslie Abney FRS (1843–1920), English army officer, chemist, and photographer.

||Major-General Edward Robert Festing FRS (1839–1912), English army officer and chemist.

the importance of hydrogen bonds in the NIRS spectrum (Hindle, 2007).

Building on the work of Abney and Festing the American Physicist William Coblentz* constructed a spectrometer highly sensitive to vibration and thermal disturbances. Taking measurements with this device was a laborious process, the equipment being so sensitive that Coblentz would have to leave the room to allow it to settle, and it would take an entire day to acquire a single spectrum (Hindle, 2007). Nevertheless by 1905 he had recorded the spectra of several hundreds compounds in the 1–15 μm wavelength range. Coblentz recognised that no two compounds share the same spectra and that certain molecular groupings absorbed specific and characteristic IR wavelengths. In time this discovery would provide a tool by which chemists could obtain structural information about compounds based on their spectra. Through his spectroscopy work Coblentz was also probably among the first, if not the first person, to verify Planck's Law[†] (Plyler, 1962).

3.1.3 *The Development of Oximetry and Medical NIRS*

Shortly after Bunsen and Kirchhoff's publications, the German physiologist and chemist Ernst Felix Hoppe-Seyler[‡] began studying the absorption patterns of coloured substances in solution. His work on the absorption spectrum of haemoglobin, was further developed by George Gabriel Stokes[§], an experimental physicist occupying Newton's old chair at Cambridge. Stokes was the first to appreciate the significance of the different absorption spectra between arterial and venous blood. Reproducing these changes in vitro, he demonstrated that reducing haemoglobin in the test tube altered its absorption spectrum, and that these changes could be reversed by shaking the sample in air (Stokes, 1864).

The first person to actually measure human blood oxygenation in vivo was the German physiologist Karl von Vierordt[¶]. From 1874 he began using what was probably the first true spectrophotometer, recording measurements from haemoglobin as well as bile and urine. In 1876 he observed changes in the solar

*William Weber Coblentz (1873–1962), American physicist.

[†]Planck's Law describes the spectral radiance of electromagnetic radiation at all wavelengths from a black body at a specified temperature.

[‡]Ernst Felix Immanuel Hoppe-Seyler (1825–1895).

[§]Sir George Gabriel Stokes, 1st Baronet FRS (1819–1903), English mathematician and physicist.

[¶]Karl von Vierordt (1818–1884), Professor of theoretical medicine and later professor of physiology at the University of Tübingen.

spectrum transmitted through the fingers of his hand, noting that the amount of red light transmitted decreased when the hand was made ischaemic. Unfortunately complexity of Vierordt equipment and skill required to obtain measurements meant that much of this pioneering work went largely undeveloped until the 1930s.

The 1930s saw several innovations. Lead sulphide (PbS) compound semiconductors were developed, which allowed the production of highly sensitive detectors in the 1–2 μm wavelength, i.e. the infrared and near infrared ranges. Kurt Kramer* built a spectrometer using tiny flat photocells, resulting in a significant reduction in the size of the equipment required to acquire spectra. Using this equipment he demonstrated it was possible to monitor oxygen saturation to within a 1% accuracy (Severinghaus, 2002), however his equipment was not able to compensate for changes in haemoglobin concentration. Karl Matthes† overcame this problem by using two wavelengths of light — one red and one green. The green wavelength, being oxygen independent, compensating for variations in the transmission of red light other than those caused by haemoglobin.

The onset of the Second World War produced an acceleration in the development of non-invasive oximetry associated with the war effort, in particular the requirement to monitor pilots flying at high altitude in unpressurised cabins. Glen Millikan‡ developed the first portable ear oximeter at the University of Pennsylvania, and also coined the term ‘oximetry’ (Cohn, 2007). Ultimately his device was to prove impractical for aviation use due to the requirement for a motion sensitive galvanometer to measure the current, but subsequent improvements led to one of the first commercial successful products — the Hewlett Packard Ear Oximeter (Severinghaus, 2002).

At this point the development of oximetry diverged. In 1972 Takuo Aoyagi’s§ discovery that arterial oxygen saturation was a direct function of the absorbency ratios of red and infrared light led directly to the development of modern pulse oximetry (Tremper, 1989). The origins of StO_2 monitoring began in 1977 with the work of Frans Jöbis¶. Jöbis, had originally set out to study redox centres

*Kurt Kramer (1906–1985), German physiologist.

†Karl Matthes (1905–1962), German physician.

‡Glenn Allan Millikan (1906–1947), American physiologist.

§Takuo Aoyagi (1936–), Japanese engineer.

¶Frans Jöbis-vanderVliet (1929–2006), American physician and physiologist.

of cytochrome oxidase in the open heart, but the realisation that NIR photons would penetrate much more deeply than those of visible light and may in effect provide an optical window to study the deep tissues of the body led him to pursue a different line of enquiry. In a landmark paper he described how light in the near infrared range could be transmitted through the intact head of a cat, and noted the differential spectral absorption of haemoglobin and the mitochondrial enzyme cytochrome oxidase (CtOx) (Jöbsis, 1977). Subsequent work by his group improved their algorithm enabling the resolution of the respective spectra of haemoglobin and CtOx, although only as ratios of their respective signal and not absolute values, as this would have required knowledge of the pathlength which was not possible to establish with the technology of the time (Jöbsis-vanderVliet, 1999).

Since Jöbsis' early work, algorithms have continued to improve, the use of 'time of flight' analysis has allowed the determination to effective optical pathlength, and the development of reflectance techniques have allowed the study of tissues where transmission spectroscopy was not possible. But ultimately it was advances in micro-processing that finally allowed the miniaturisation of monitoring devices to the extent that bedside commercial NIRS devices became a reality in the last decade of the twentieth century.

3.2 PRINCIPLES OF SPECTROSCOPY

Spectroscopy (or more strictly spectrometry) is a technique used to identify unknown substances in a compound, or the concentration of known substances in a compound, based upon their absorbed or emitted spectra. For the purposes of this discussion only absorption spectroscopy will be considered, i.e. that technique which measures the absorption pattern of a chromophore* when exposed to parts of the electromagnetic spectrum.

3.2.1 *Transmission/absorption Spectroscopy*

The physical basis for spectroscopy is provided by the Beer-Lambert Law, which states that for a non-scattering medium there is a logarithmic dependence between

*A chromophore is that part of a compound which absorbs light and is therefore responsible for its spectra, in the visible spectrum this would be interpreted as the compound's colour. In the context of spectroscopy the term is often loosely applied to a compound of interest in its entirety rather than the specific part that accounts for its spectrum.

the transmission (T) of light through a substance and the product of the molar absorptivity of the chromophore (ϵ), the chromophore concentration (c) and the thickness of the substance (i.e. the optical path length, ℓ). The molar absorptivity, also known as the molar extinction coefficient, is a measure of how strongly a chromophore absorbs light at a given wavelength. The product of the molar absorptivity and the chromophore concentration ($c\ell$) is the absorption coefficient of the substance being investigated. Mathematically the Beer-Lambert law is expressed as:

$$T = \frac{I}{I_0} = 10^{-\epsilon c \ell}$$

where I_0 is the intensity of the incident light and I the intensity of the emergent light. More usually this relationship is expressed in terms of absorbance (A) for the substance being examined where $A = -\log_{10} T$ so that:

$$A = \log_{10} \left(\frac{I_0}{I} \right) = \epsilon c \ell$$

In a medium containing several different chromophores the overall extinction coefficient of the compound is merely the sum of the contributions of each chromophore:

$$A = \log_{10} \left(\frac{I_0}{I} \right) = (\epsilon_1 c_1 \ell + \epsilon_2 c_2 \ell + \epsilon_3 c_3 \ell + \dots)$$

or

$$A = \sum \epsilon c \ell$$

This relationship holds true for conventional transmission/absorption spectroscopy where the light travels in straight lines and completely traverses the substance being investigated, as shown in Figure 3.3. Unfortunately in the human body, where light frequently cannot pass completely through the structure being investigated and must traverse tissues of difference densities, the situation is a little more complex.

3.2.2 Reflectance Spectroscopy

Human tissue acts as a scattering media. This is in part due to the fact that photons have to traverse several different tissue interfaces in the optical path, each with differing propensities to absorb or scatter photons. The net result is that photons do not pass through tissues in straight lines, but instead are repeatedly

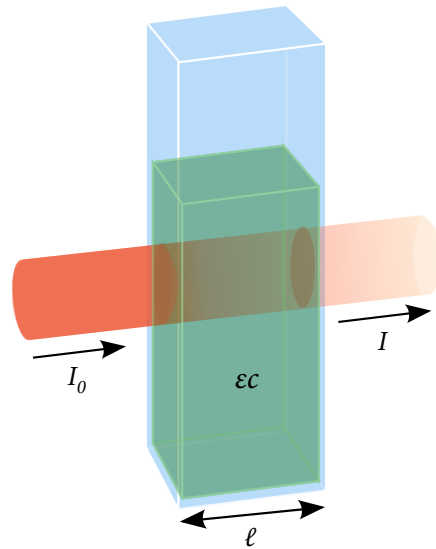


Figure 3.3: A diagrammatic representation of the elements of the Beer-Lambert Law. I_0 is the intensity of incident light, I the intensity of emergent light, ϵ the chromophore molar absorptivity, c the chromophore concentration, ℓ the effective optical pathlength.

reflected, resulting in the effective optical path length being considerably greater than the tissue thickness traversed. This situation is further complicated by the fact that transmission spectroscopy is not practical for many medical monitoring applications. Although near infrared light can penetrate to a depth of several centimetres, it is unable to completely traverse many sites likely to be of interest to the clinician. Even if transmission spectroscopy was possible, the emergent spectra would be an amalgamation of all the structures along the optical path, meaning that spectral features of ischaemia in the tissues of interest could be easily masked by a non-ischaemia signal from other structures. To get around this problem the technique of reflectance spectroscopy is used.

In reflectance spectroscopy the light source and receptor lie in the same plane and the optical path approximates a parabolic, or banana-shaped, course through the tissues (see Figure 3.4). The effective optical pathlength and depth of tissues from which spectra are recorded is a function of the interoptode distance. To quantify the optical pathlength in reflectance spectroscopy, a number of theoretical mathematical models describing light transport in tissues have been developed.

One of the most widely used models describing light transport in tissues, is

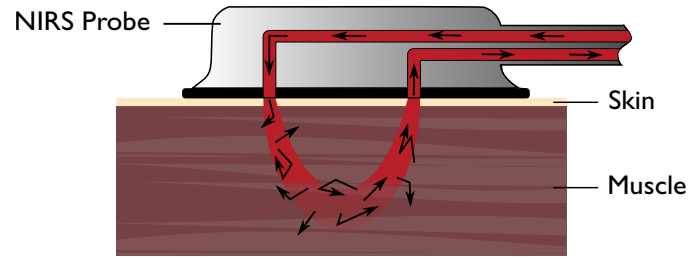


Figure 3.4: A diagrammatic representation of reflectance spectroscopy, showing a NIRS probe attached to the skin overlying a section of muscle. Note that once light enters the tissue it is repeatedly reflected and scattered, the vast majority being dissipated throughout the muscle and never reaching the receiver. Those photons that do reach the receiver follow an often convoluted course several times greater than the interoptode distance, although the overall optical path approximates to a parabola.

the differential pathlength factor (DPF) method. The DPF model assumes that for any single recording site the tissue structure, and hence the effective optical pathlength, remains constant. Thus changes in the light signal at the detector will be a reflection of changes in chromophore concentration. An obvious problem with this assumption is that any change in the tissue geometry or structure, such as movement, may affect the effective optical pathlength and consequently be misinterpreted as a change in chromophore concentration. A further limitation is that without knowledge of the pathlength, the model as described so far only allows a qualitative measurement of chromophore concentrations. To obtain quantitative recordings the DPF (a value >1) correcting for the difference between the interoptode spacing and the effective optical pathlength must be known (van der Zee et al., 1992). Once this has been established the relationship between the sum of all the chromophores contributing to the signal and the tissue absorbance can be calculated from a modification of the Beer-Lambert Law:

$$A = \sum \epsilon c d DPF$$

where d is the interoptode distance and DPF represents the differential pathlength factor, the product of these two variables therefore describe the effective optical pathlength.

The DPF is dependant upon the interoptode distance and the scattering properties of tissues along the optical path. In human tissues DPF values typically fall

between 4–7.50 (muscle usually having a DPF at the lower end of this range and brain at the higher end) (Duncan et al., 1995; Zhao et al., 2002). The DPF requires recalculating for each interoptode and tissue combination, and there are number of approaches for achieving this including time of flight analysis and spatially resolved spectroscopy. It is not necessary that the end user of NIRS devices understand the details of these techniques, as the DPF will have already been established and incorporated into the interpretation algorithm by equipment manufacturers. It should be realised however, that different manufacturers/investigators use different techniques for NIRS monitoring and establishing the assumptions upon which their algorithms are based, the validity of some of which are still open to debate (Ward et al., 2006). The end result is that absolute NIRS recording from different devices are unlikely to be immediately comparable, and even trends recorded in the same individual may show slight variation (Matcher et al., 1995).

3.2.3 *Dual Beam NIRS Algorithms*

One of the clinical problems with spectroscopy techniques is that the recorded StO_2 is an amalgamation of values from all of the tissues traversed in the optical path, e.g. skin, fat and muscle. Adipose tissue is relatively avascular, and demonstrates limited changes in perfusion in response to an alteration in clinical condition. Hence recordings taken from the body surface of obese individuals may be a poor reflection of the underlying muscle perfusion. This problem can be partially circumvented by a good choice of monitoring site, which is one of the principal reasons the thenar eminence has become a popular site for StO_2 monitoring in trauma patients. However in many trauma subjects the thenar eminence may be injured (the effects of monitoring from an injured site in trauma are at present unknown and thus best avoided) or amputated, and the clinician may be forced to monitor at a more proximal site with a greater quantity of subcutaneous fat. Equally clinicians monitoring tissues for specific local changes in StO_2 , such as the anterior compartment of the leg in compartment syndrome, are limited in their choice of probe position. To attempt to correct for this problem researchers and manufacturers have developed dual beam, or superficial extraction, algorithms where the light is passed in two paths through the tissue: one superficial and the other deep. The superficial reading is then subtracted from the deep reading to isol-

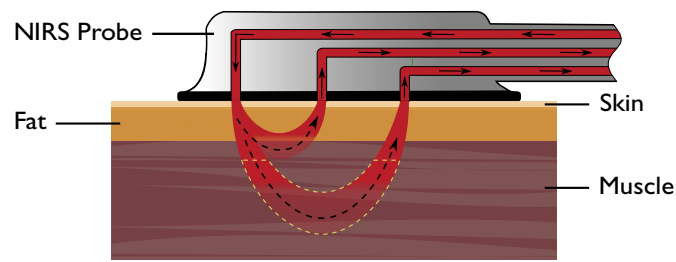


Figure 3.5: A diagrammatic representation of dual beam reflectance NIRS. Two beams of light are shone through the tissue, one superficial and one deep. The signal from the superficial beam is extracted from that of deep beam theoretically removing the contributions of the skin and superficial tissues, e.g. fat, and isolating a measurement from a deep block tissue, approximating to the region illustrated by the dashed yellow line.

ate the StO_2 recording from the deeper target tissue (see Figure 3.5). Although this technique has theoretical advantages there is currently no evidence demonstrating its superiority in clinical situations.

3.3 MEASURING HAEMOGLOBIN CONCENTRATIONS IN MAMMALIAN TISSUES

Every chromophore has its own absorption spectrum which describes its absorption at different wavelengths of light. Water is the most abundant chromophore in the human body, and its spectrum determines the wavelength range of light that can be utilised to interrogate tissues. The absorptivity of water is relatively low between 200–900nm. It gradually increases to an initial peak at 970nm, with subsequent higher peaks occurring at 1500nm and above 1800nm (Delpy and Cope, 1997), see Figure 3.6. Hence water is often described as having a ‘window’ of transparency between 200–900nm through which spectroscopic measurements can be made. While it is possible to use visible light (450–700nm) to interrogate tissues, it has a very little tissue penetration. NIR light (700–1200nm), by contrast, can penetrate tissue to a depth of several centimetres, even through bone such as the skull. More importantly, within the NIR wavelength oxygen dependant transitions of the metalloproteins of three important compounds in mammalian tissue can be detected:

1. haemoglobin
2. myoglobin (which has an identical absorption spectra to haemoglobin)

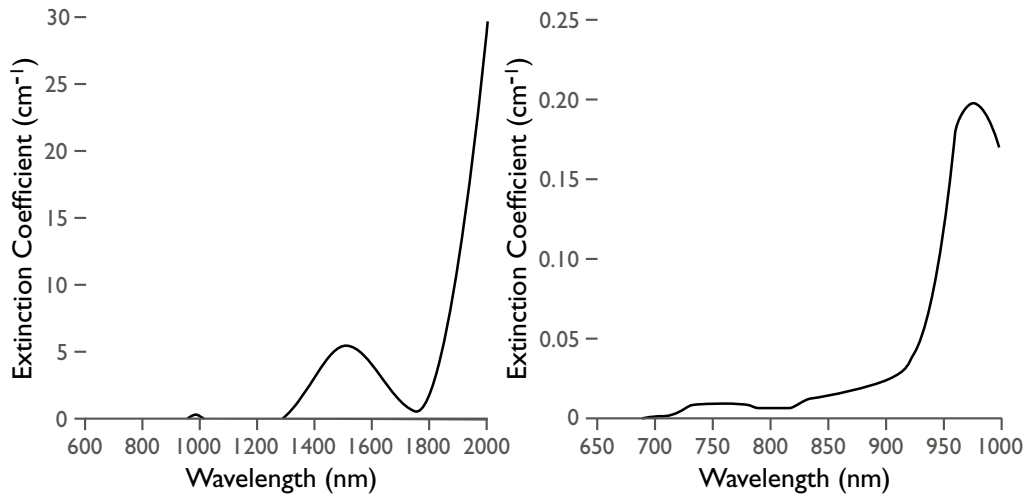


Figure 3.6: The absorption spectra of pure water. Note the absorption peak at 970nm, shown in detail in the right-hand figure, below which the ‘window’ for NIRS measurements of tissue oxygenation occurs.

3. cytochrome oxidase (cytochrome aa₃ — the terminal enzyme in the respiratory chain)

The extinction coefficients at different NIR wavelengths for deoxyhaemoglobin (HHb), oxyhaemoglobin HbO₂ and cytochrome oxidase (CtOx) are shown in Figure 3.7, as can be seen HHb demonstrates a weak absorbance peak at 760nm whereas HbO₂ does not (Jöbsis, 1977; Kuenstner and Norris, 1994). Figure 3.7 also illustrates that HHb strongly absorbs light in the 650 nm wavelength range, although, as has been mentioned, this light has very little tissue penetration, and therefore this phenomenon is of limited clinical use. The differential absorption of HHb and HbO₂ provides the basis for calculating the StO₂ which is taken as the ratio of HbO₂ to total haemoglobin expressed as a percentage:

$$\frac{HbO_2}{HbO_2 + HHb} \times 100$$

This is referred to as the functional haemoglobin saturation, because it ignores the contributions of the two haemoglobin species which do not contribute to functional oxygen carriage: methemoglobin and carboxyhaemoglobin (Tremper, 1989).

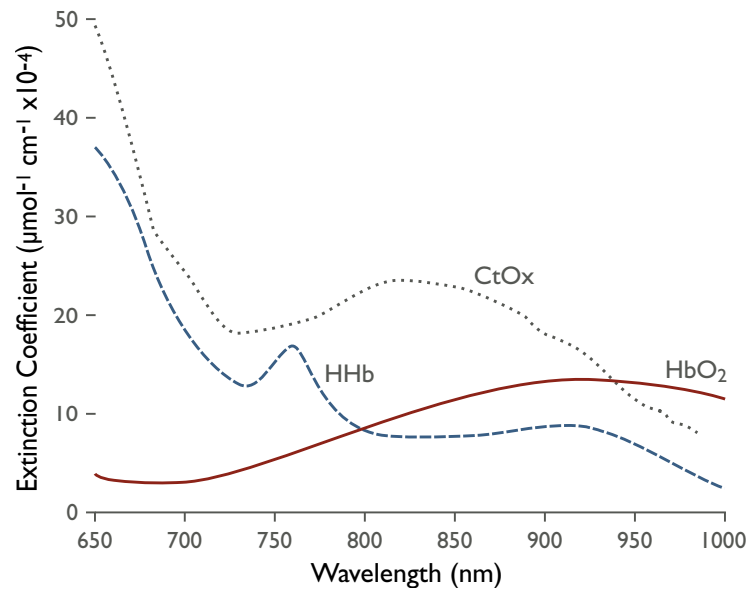


Figure 3.7: The absorption spectra of HbO₂, HHb and CtOx.

It is believed that in most tissues the blood volume is distributed between the arteriolar, capillary and venular compartments in a ratio of 10:20:70 (Wiedeman, 1963), and that as large vessels (>1 mm) absorb NIR light completely they can be excluded from the StO₂ measurement. Therefore the NIRS signal predominantly reflects oxygenation in the venous compartment in a similar fashion to a mixed venous blood gas. Since there is an inverse linear relationship between venous saturation and oxygen extraction, StO₂ values recorded by NIRS are a reflection of both oxygen delivery ($\dot{D}O_2$) and oxygen consumption ($\dot{V}O_2$) in the tissue sample.

3.3.1 The Problems of Other Chromophores

Several other compounds in human tissues have spectra similar to haemoglobin and can interfere with the measurement of StO₂. The most important of these compounds are considered below.

3.3.1.1 MYOGLOBIN As has been mentioned previously, the absorption spectra of haemoglobin and myoglobin are practically identical. While this is not an issue when monitoring tissues with little or no myoglobin, such as the brain, when monitoring skeletal muscle this creates the problem of identifying the exact con-

tribution of myoglobin to the overall NIRS reading, and thus the extent to which the StO₂ reflects intracellular (i.e. myoglobin) or intravascular (i.e. haemoglobin) oxygenation. Although some researchers/manufacturers claim to be able to distinguish between the contributions of myoglobin and haemoglobin to the NIRS signal, the algorithms for doing this have not been widely published and technically these claims are very difficult to validate. In reality the exact contribution of myoglobin to the NIRS signal remains unresolved and probably varies under differing conditions of regional oxygen supply. Most NIRS algorithms circumvent the problem of distinguishing between haemoglobin and myoglobin by considering the two species together, so that StO₂ is effectively calculated as:

$$\frac{HbO_2 + MbO_2}{HbO_2 + MbO_2 + HHb + Mb} \times 100$$

The concentration of myoglobin in muscle is relatively stable and does not change significantly following injury. Since the P₅₀* of myoglobin is very low (5 mmHg), it should remain fully saturated under most clinical conditions. The practical result of this is that changes in StO₂ values predominantly reflect changes in the HHb/HbO₂ ratio, and the contribution of myoglobin can effectively be ignored (Ward et al., 2006).

3.3.1.2 CYTOCHROME OXIDASE CtOx is a large transmembrane protein complex found in mitochondria. It is the terminal enzyme in the respiratory electron transport chain, receiving an electron from each of the four cytochrome c molecules which it transfers to an oxygen molecule, this then binds 4 protons to produce one molecule of water. The translocation of protons across the mitochondrial membrane contributes to the electrochemical potential used by ATP synthase to produce ATP. When oxygen is abundant electrons flow from CtOx and it is oxidised, when oxygen is limiting electrons cannot move away and the enzyme exists in its reduced form, the balance between these two conditions is referred to as the redox state (Michel et al., 1998).

CtOx has a low K_m (Michaelis constant) and is sensitive to mitochondrial, (not tissue or cytosolic) PO₂, requiring relatively low oxygen tensions before entering its reduced state, by contrast haemoglobin deoxygenates much more readily. CtOx

*P₅₀ is the PO₂ at which a compound is 50% saturated with oxygen

is therefore less likely to be of value as an early indicator of hypoxia, however measuring its redox state may have value as a true indicator of tissue hypoxia at a cellular level — haemoglobin desaturations that do not result in a reduction of CtOx are unlikely to be clinically significant (Cooper and Springett, 1997). Since the concentration of CtOx in tissues does not change, at least not in the short term, it is only necessary to know the difference between the absorption spectra of the oxidised and reduced form of the enzyme, i.e. the redox state.

Unfortunately the monitoring of CtOx presents several problems. The oxidised spectrum of CtOx is characterised by a broad peak centred at 830nm, which is absent in the reduced form of the enzyme. The magnitude of the extinction coefficient for CtOx is similar to that of haemoglobin or myoglobin, however since it exists in concentrations many times smaller than that of haemoglobin or myoglobin (Sato et al., 1976), the measurement of CtOx spectra is no simple feat being subject to interference from these other chromophores.

3.3.1.3 MELANIN Melanin contained within the skin is a highly effective absorber of light. Although this absorption can be considered constant and oxygen independent for measurements taken from the same location in the same individual, melanin in the skin will reflect and scatter light affecting its transmission into the tissues below. On this basis it has been suggested that NIRS signal quality may be impaired by darker skin pigmentation. This has been demonstrated in at least one human study where NIRS devices failed to register tissue saturations in nine out of 17 deeply pigmented volunteers undergoing simulated lower limb ischaemia, with failure occurring more commonly in the darker skinned individuals. The authors concluded that ‘NIRS StO₂ measurements should be interpreted with caution, as melanin clearly interferes with the quality of the reflected NIRS signal’ (Wassenaar and den Brand, 2005). Similar problems have been commented on incidentally by other authors (Shuler et al., 2009), but to date there have been no clinical studies specifically addressing this issue.

3.4 COMPARISON TO PULSE OXIMETRY

It is important that StO₂, as measured by NIRS, is distinguished from SpO₂ as recorded by pulse oximetry. Pulse oximetry also uses infrared light, but differs

in that it separates the pulsatile arterial waveform from the non-pulsatile signal, which is assumed to be background artefact and excluded from the calculation of oxygen saturation (Tremper, 1989). Thus SpO_2 is a quantification of arterial haemoglobin saturation — a systemic measurement which should be consistent between monitoring sites. StO_2 by contrast is a local measure reflecting only the oxygenation of the illuminated block of tissue. StO_2 therefore varies from site to site depending upon local tissue conditions, however StO_2 will also be influenced by the global haemodynamic state of the subject, which is the basis upon which NIRS is used to detect hypovolaemia in trauma.

In addition to the clinical differences in the oxygenation index measured by the two techniques, there are several technical differences between how pulse oximetry and NIRS are implemented. Pulse oximetry uses two wavelengths of light: red light in the visible spectrum (660 nm) and infrared light (940nm). By contrast, NIRS uses several wavelengths over the visible red and NIR range to separate the overlapping signals of oxy/deoxyhaemoglobin and other chromophores. Pulse oximetry requires a pulsatile signal to obtain a reading, and in clinical practice is used with a transmission technique. NIRS has the advantage of not requiring a pulse, but instead has the problem of separating the spectrum of haemoglobin from that of other oxygen carrying compounds since it does not use the pulsatile arterial signal to separate them. While transmission spectroscopy with NIRS is possible, it is predominantly used with a reflectance technique in clinical practice.

4. CURRENT STATE OF NIRS AS APPLIED TO TRAUMA RESUSCITATION

The central premise of NIRS when applied to trauma resuscitation is that in the hypovolaemia patient StO_2 will fall as a result of inadequate tissue perfusion. In peripheral tissues StO_2 may also fall as a result of sympathetic mediated vasoconstriction to preserve blood flow to vital organs. As the patient is resuscitated, and adequate tissue perfusion restored, StO_2 values rise again towards normal levels. Since StO_2 can be measured continuously in real time, it should be theoretically possible to accurately monitor the patient's response and titrate resuscitation accordingly.

This chapter discusses current developments in the field of NIRS, as applied to trauma resuscitation, and examines areas for further work.

4.1 THE RANGE OF StO_2 MEASUREMENTS IN NORMAL SUBJECTS

Before StO_2 measurements in trauma subjects can be fully interpreted the range of StO_2 values in normal subjects should be first evaluated. At present there is only one published study describing data for StO_2 values in a normal population at rest.

Crookes et al. (2005) measured StO_2 from the thenar eminences of 707 ambulatory volunteers using an InSpectra™ Tissue Spectrometer (Hutchinson Technology). Subjects were drawn from a population of individuals encountered walking the grounds of the University of Miami Hospital and were predominately composed of university and hospital staff, hospital visitors (including outpatients) and patrons of local businesses. Hospital inpatients were excluded from the study. The ambient conditions on the study days were described as warm and sunny.

The mean thenar StO_2 in the study population was $87 \pm 6\%$ with a skew left distribution as illustrated in the published histogram of results (reproduced in Figure 4.1.) Unfortunately, the study description does not make clear how they established StO_2 values for each subject, e.g. was the first recorded value used, the mean or median of a range of measurements, etc.

Significant differences were found between male (mean StO_2 $88.38 \pm 5.51\%$) and female subjects (mean StO_2 $85.4 \pm 6.69\%$), $p < 0.001$; and between smokers (mean StO_2 $89.59 \pm 4.57\%$) and non-smokers (mean StO_2 $86.03 \pm 6.54\%$), $p < 0.001$.

4.1. THE RANGE OF StO₂ MEASUREMENTS IN NORMAL SUBJECTS

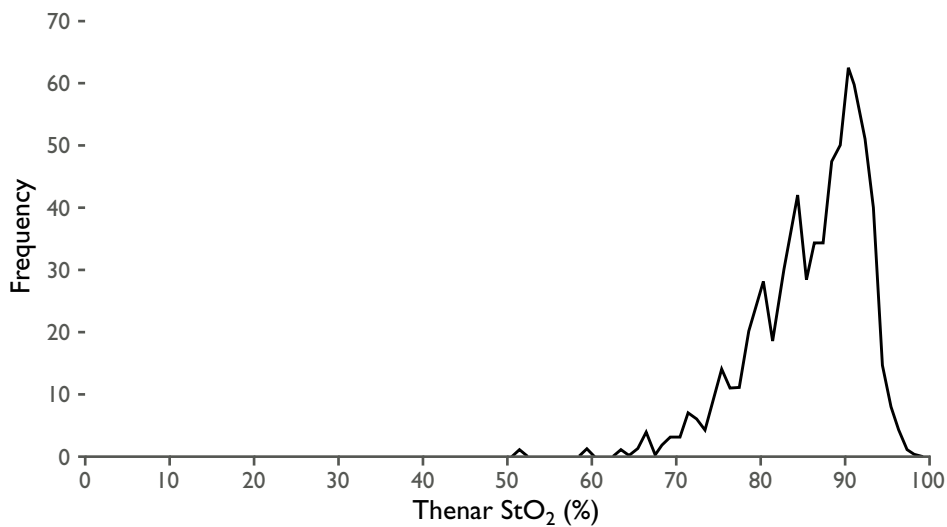


Figure 4.1: Histogram of thenar StO₂ values in normal human volunteers, adapted from Crookes et al. (2005).

Significant differences in thenar StO₂ was also evident between ethnic groups, classified for the purposes of the study as: black; white; Indian; and Hispanic. Although statistically significant differences in StO₂ values were demonstrated between several different sub-populations, all sub-population means fell within one standard deviation of the overall population mean StO₂ and, as the authors recognised, the differences demonstrated were probably a product of the statistical power provided by the large sample and unlikely to be of any clinical significance.

It should be appreciated that the results of this study relate to recordings made with an InSpectra™ Tissue Spectrometer (a single beam NIRS monitor, although the exact model is not specified) and will not necessarily correlate with dual beam algorithms or other manufacturers' devices. Also the results are only relevant to measurements taken from the thenar eminence. Several researchers have used this data as the basis of normal values for studies involving other anatomical sites, despite there being no evidence that such an extrapolation is valid. In fact Crookes et al. (2005) report their own previous animal work as evidence that baseline StO₂ values vary between different muscle groups. Exactly how StO₂ varies between muscle groups/anatomical sites in humans is not currently known.

4.2 NON-TRAUMA HUMAN HYPOVOLAEMIA STUDIES

Studying hypovolaemia in human subjects experimentally is challenging as it is rarely ethical to subject individuals to controlled haemorrhage. However, one area where it does take place is during blood donation, and a few groups have taken advantage of this to study StO₂ changes during this process.

Torella et al. (2002) monitored calf and cerebral (frontal lobe) StO₂ in 40 volunteers undergoing a 470 ml blood donation (roughly equivalent to class I haemorrhage) with a Somanetics INVOS® 4100 System (a dual beam monitor). In a group of 27 males and 13 females the mean estimated blood loss was 10% (range 9–12%) of the total circulating volume, as calculated from height and weight nomograms. There was a statistically significant fall in StO₂ at both sites following blood donation: 3% ($p < 0.001$) in the calf; and 2% ($p < 0.001$) in the frontal lobe. Drops in StO₂ were also recorded during the blood donation, the authors reporting that a statistically significant fall of 1.4% in the calf after 2% blood loss by volume. The frontal lobe appeared less sensitive to change, with a statistically significant fall in StO₂ of 0.9% only becoming observable at 6% total blood volume loss. The authors hypothesise, that the differing sensitivities between the calf and the frontal lobe of the brain are probably related to the brains vascular auto-regulatory functions in the face of hypovolaemia.

These results suggest that NIRS is sensitive to the minimum blood loss volumes usually considered clinically significant, and indeed is able to detect much smaller blood losses. However the changes in StO₂ are quite small, the largest mean difference being 3%, as recorded in the calf. Somanetics reports the sensitivity of their later generation NIRS monitors as being $\pm 1\%$. Assuming a similar sensitivity for the 4100 model used in this study, it is questionable how clinically useful a 3% fall in StO₂ would be. Falls in StO₂ of the magnitude 0.9%, which are less than the tolerances of the machine, are almost certainly clinically meaningless.

Jeger et al. (2010) performed a similar experiment using a Hutchinson InSpec-tra™ Model 650 (a single beam monitor) recording StO₂ values from the thenar eminence before and after 500 ml blood donation. In their study of 20 young women there was no significant change in StO₂ following donation, the median StO₂ dropping only 0.5% ($p = 0.34$) from 79.0% to 78.5% between measurements. This is a surprising finding in light of Torella et al. (2002) results and those of

other studies, which have shown NIRS able to detect volume losses in the range of 500 ml (Soller et al., 2008b) — especially as the decision to include women in this study was on the basis that their lower body mass renders them more susceptible to absolute volume losses. It is not possible to separate the factors that may account for these differing findings, although the differences in the NIRS monitoring protocol are notable. The two studies demonstrating NIRS sensitivity to detect 500 ml blood loss both use dual beam monitors on large muscle groups, the calf (Torella et al., 2002) and the forearm (Soller et al., 2008b), while Jeger et al. (2010) used a single beam machine recording from the thenar eminence. This raises the question as to which of these factors is more important: anatomical location or monitoring algorithm. To date there have been only a few reported attempts to answer this question by comparing NIRS recordings at different sites.

In a simple experiment Bezemer et al. (2009) monitored StO_2 from the thenar eminence and forearm (over the brachioradialis muscle) in the supine and standing positions. Measurements were taken with a Hutchinson InSpectra™ Monitor, the exact model is not specified, but it must have been a 325 or pre-production model as these were the only Hutchinson machines with the multi-depth recording probes available at the time. StO_2 measurements were taken with probes with an interoptode distance of 15 and 25 mm, the larger interoptode distance equating to a greater depth at which the recording was taken. Upon standing there was a significant increase in heart rate, the only other haemodynamic parameter measured. StO_2 in the forearm fell by 7.1% (s.d. 4) for the 15 mm probe separation, $p < 0.05$, and 8.6% (s.d. 4.5) for the 25 mm probe separation, $p < 0.01$. There was no significant change in StO_2 values recorded from the thenar eminence. These results would suggest that the forearm is a more sensitive site for measurement, however the hypovolaemic stress in this experiment was small, and in the absence of any haemodynamic data other than pulse rate difficult to quantify. Soller et al. (2008a) examined StO_2 values from the thenar eminence and the forearm in eight volunteers subject to a simulated hypovolaemia by means of exposure to progressive increments of lower body negative pressure (LBNP). They found that StO_2 values in the forearm decreased by 75% at maximal LBNP, while the thenar values remained statistically unchanged throughout the whole protocol. Unfortunately each element of the study was performed on different (albeit case

matched) subjects, and the authors used a single beam InSpectra™ device on the thenar eminence and their own design of dual beam monitor on the forearm. This makes a practical interpretation of their findings difficult, however given that there is very little fat overlying the thenar eminence, the principle reason for choosing this a monitoring site, signal attenuation from subcutaneous tissues should be minimal giving weight to the authors' argument that 'oxygen saturation determined from deep muscle, not thenar tissue, is an early indicator of central hypovolaemia in humans'. Bartels et al. (2011) performed a similar experiment but recorded StO₂ from the thenar eminence and forearm using a Hutchinson InSpectra™ StO₂ Tissue Oxygenation Monitor. StO₂ measurements were taken using probes with an interoptode distance of 15 and 25 mm. They found that forearm StO₂ was more sensitive to LBNP induced hypovolaemia than the thenar eminence but, in contrast to the other two studies, sensitivity was unrelated to depth of measurement.

Torella and McCollum (2004) examined the differences between cerebral (frontal lobe of the brain) and calf StO₂ in response to haemorrhage during surgery, with an INVOS® 4100 System monitor. Surgical procedures were selected on the basis of a large predicated blood loss. Although the exact nature of individual procedures was not specified, they appear to have been mostly spinal operations. Median blood loss during procedures was 650 ml. Mean calf StO₂ fell by a 3.3%, but this was not statistically significant ($p=0.16$), mean cerebral StO₂ fell by 8.4% which was statically significant ($p=0.016$). These results are interesting, firstly for the calf findings which conflict with the group's previous study (Torella et al., 2002), and secondly for demonstrating a significant fall in cerebral StO₂. Falls in cerebral StO₂ are often perceived as counterintuitive in the light of what is known about cerebral autoregulation, however it is unknown exactly how StO₂ relates to the autoregulatory process or what level of relative tissue hypoperfusion is tolerated in different parts of the brain. One of the flaws of the study is that the general anaesthetic was not controlled for between cases which, given the known effects of anaesthetic agents on cerebral blood flow, is a major confounding factor.

Drawing conclusions from the conflicting results of these studies is difficult. While it seems NIRS has the potential to detect relatively minor degrees of haemorrhage, the absolute change in StO₂ in all studies was small, and mean pre and

post haemorrhage StO_2 values frequently overlap. The reason significant changes were detectable in these studies is that baseline StO_2 values for each subject were known prior to haemorrhage. While establishing baseline StO_2 values is possible in the elective surgical patient, it is a luxury not available in the trauma setting, and this fact may significantly limit the clinical applications of NIRS for detecting blood loss in this patient group.

4.2.1 Lower Body Negative Pressure as Model for Simulating Hypovolaemia

Lower body negative pressure (LBNP) is a standard experimental technique for modelling controlled haemorrhage in human subjects.

In LBNP studies volunteers are placed supine with their lower body, from the waist down, sealed in an airtight chamber. Negative pressure is then applied to the chamber in graduated increments (usually in the range of -10 to -100 mmHg). This leads to a redistribution of blood from the upper body and peripheries to the lower body, in particular the large capacitance veins of the pelvis, inducing central hypovolaemia. Higher negative pressures correspond with increasing degrees of simulated hypovolaemia, and the technique has the advantage that not only can different increments of pressure be used, but also the time period over which each increment is maintained. This allows comparisons of the haemodynamic responses to sudden simulated central hypovolaemia and slowly progressive blood loss, although to date no such study has been performed. The down side of such flexibility is that there is no standardised protocol for the pressure increments used and the time between steps, which means that many studies cannot be easily compared. One of the limitations of LBNP is that it must be performed in the supine position, however since virtually all trauma patients are ultimately monitored and managed in this position, this serves to reflect the practicalities of trauma care.

LBNP can be combined with a head-up tilt. Such a combination was originally designed as a more aggressive means of testing orthostatic tolerance than simple tilt testing (el Bedawi and Hainsworth, 1994). However the effect of tilting is very similar to a LBNP increment, and a head-up tilt has been used in hypovolaemia studies as a further stressor to push individuals to presyncope. A limitation of LBNP for the purposes of modelling hypovolaemia in trauma is that it induces a

<i>Pressure (mmHg)</i>	<i>Approximate Blood Loss (ml)</i>
10–20	400–550 ($\approx 10\%$ of total blood volume)
20–40	550–1000 ($\approx 10\text{--}20\%$ of total blood volume)
≥ 40	> 1000 ($> 20\%$ of total blood volume)

Table 4.1: LBNP pressures and their estimated blood loss equivalent, adapted from Cooke et al. (2004).

pure hypovolaemia without the neurohumoral responses associated with tissue trauma which occur in real patients. Although injuries may be simulated by such means as the application of tourniquets to the limbs, at present there are no published studies using this approach.

The individual response to LBNP is influenced by numerous personal factors including: age, sex, build, physical conditioning and hydration (Cooke et al., 2004). For this reason approximations between pressure increments and the degree of hypovolaemia, as shown in Table 4.1, are difficult and typically demonstrate a wide range. However the response of the same individual to LBNP appears to be very consistent. In one study exposing individuals to the same LBNP pressure on two separate occasions the difference in times to syncope was only 1.1 ± 0.6 mins (el Bedawi and Hainsworth, 1994).

The physiological responses to simulated hypovolaemia have been demonstrated to accurately mimic those observed during real haemorrhage. A summary of the response of common physiological parameters to LBNP and a comparison to known responses during haemorrhage is shown in Table 4.2. There is a good correlation between all parameters, although the heart rate response can vary between subjects depending upon the degree of hypovolaemia (as discussed in Section 1.3.2). In true haemorrhage, advanced stages of hypovolaemia may be associated with tachycardia or bradycardia, the tachycardic response being associated with poor outcome. In the LBNP bradycardia typically occurs immediately before syncope, at which point the experiment is stopped.

4.2.2 Lower Body Negative Pressure Hypovolaemia Studies

In human volunteers exposed to simulated haemorrhage with LBNP, peripheral StO_2 values recorded from the forearm (flexor digitorum profundus) and stroke

<i>Parameter</i>	GRADE OF SHOCK			
	<i>Grade I</i>	<i>Grade II</i>	<i>Grade III</i>	<i>Grade IV</i>
Heart Rate	↑ ↔	↑ ↑	↑ ↑	↑ ↓ ↑
Mean Arterial Pressure	↔ ↔	↑ ↔	↑ ↑	↓ ↓
Stroke Volume	↓ ↓	↓ ↓	↓ ↓	↓ ↓
Cardiac Output	↓ ↓	↓ ↓	↓ ↓	↓ ↓
Central Venous Pressure	↓ ↓	↓ ↓	↓ ↓	↓ ↔ ↓ ↔
Sympathetic Nerve Activity	↑ ↑	↑ ↑	↑ ↑	↓ ↓
Norepinephrine	↑ ↑	↑ ↑	↑ ↑ ↔	↓ ↓
Peripheral Vascular Resistance	↑ ↑	↑ ↑	↑ ↑	↓ ↓
Arginine Vasopressin	↔ ↔	↔ ↔	↔ ↑ ↔	na ↑
Plasma Renin	↔ ↔	↔ ↔	↔ ↑ ↔	na ↑
Angiotensin II	na ↔	na ↔	na ↑	na ↑
Pancreatic Polypeptide Hormone	↔ ↔	↔ ↔	↑ ↑	↑ ↑

Table 4.2: Comparison of systemic physiological responses to LBNP and haemorrhage. Responses to haemorrhage are shown in red and responses observed during LBNP in black. ↑ indicates an increase in the monitored parameter, ↓ a decrease, and ↔ an equivocal response, some parameters may show more than one response, adapted from Cooke et al. (2004).

volume (SV) were shown to be the most sensitive early indicators of simulated haemorrhage from a range of physiological measurements that also included pulse rate, blood pressure and SpO₂. Changes in StO₂ and SV were observed during the first LBNP increment (-15 mmHg), by comparison there was no significant change in heart rate until the third pressure increment (-45 mmHg), and in mean arterial pressure until the forth pressure increment (-60 mmHg). StO₂ was found to correlate well with stroke volume, and was inversely correlated with total peripheral resistance (Soller et al., 2008b). This suggests that early changes in StO₂ occur as a result of vasoconstriction mediated reductions in oxygen delivery. The study used an experimental NIRS device, jointly developed by the University of Massachusetts Medical School (UMMS) and Luxtec Corporation (Massachusetts), to measure StO₂, which means absolute StO₂ values cannot be compared directly with commercial devices. As discussed in Section 4.2 the group also compared StO₂ measurements from the thenar eminence, recorded using a Hutchinson In-Spectra™ machine, to forearm measurement using the UMMS machine (Soller et al., 2008a). Leaving aside the previously discussed limitations of this study, the

only definitive conclusion that could be drawn was that StO₂ measurements from the forearm recorded with the UMMS machine (a dual beam machine) were more sensitive to simulated haemorrhage than those recorded from the thenar eminence with InSpectra™ machine (a single beam machine). However a subsequent study by Bartels et al. (2011) using an InSpectra™ machine to monitor both sites did confirm what Soller et al. (2008a) study suggests: that the forearm is a more sensitive site than the thenar eminence, although the depth at which the measurement was taken appeared unimportant in this study.

In a larger review of their LBNP work involving 30 subjects Soller et al. (2012) have confirmed the finding of their earlier studies, principally that StO₂ and SV decrease proportionally with increments of LBNP, and inversely to total peripheral resistance. Of the physiological parameters recorded StO₂ and SV are the most sensitive to haemodynamic changes induced by LBNP. Similar changes in haemodynamic parameters during LBNP induced hypovolaemia have also been reported in a number of other studies (van Hoeyweghen et al., 2001; Convertino et al., 2004; Bartels et al., 2011).

Although these studies appear to demonstrate the superiority of NIRS over conventional haemodynamic parameters, the changes observed in StO₂ are all relatively small. The fact that any change can be detected at all in the lower increments of LBNP is by virtue of the subjects baseline measurements being available for comparison. As has been mentioned previously, this is a luxury not available in the acutely injured patient, and as a result of this, the promise of these studies may not translate well to the emergency trauma scenario.

4.3 ANIMAL HYPOVOLAEMIA MODELS

NIRS responses to more profound degrees of hypovolaemia than are possible to test in human models, have been examined in a number of animal studies. In resuscitation models where animals have been exposed to controlled haemorrhage and resuscitated to end points determined by conventional haemodynamic parameters, it has been shown in both porcine and rabbit models that peripheral muscle StO₂ correlates strongly with oxygen delivery. StO₂ recorded from visceral organs (e.g. liver) do not demonstrate such a strong correlation, instead showing a blunted response to haemorrhage (Beilman et al., 1999; Rhee et al., 1997). This is presumably

a result of mechanisms preserving the blood supply to central organs in the face of hypovolaemia. As part of the same phenomenon, peripheral vasoconstriction probably accounts for some of the reduction in StO_2 in distal monitoring sites during the early stages of haemorrhage.

Experimental work examining the role of NIRS as a triage tool in hypovolaemia has demonstrated that StO_2 values recorded from the hind limbs of 20 pigs below 40% distinguished resuscitatable animals from non-resuscitatable animals with a sensitivity of 80% and specificity of 100%, but only after the first bolus of resuscitation fluids (Taylor et al., 2005). StO_2 measurements taken from the stomach wall using a modified nasogastric tube demonstrated a similar pattern, although the results after the first fluid bolus were not statistically significant. StO_2 measurements taken from the liver were able to distinguish between resuscitatable and non-resuscitatable animals but only following the second bolus of fluid resuscitation, which again suggests an element of preservation of blood flow to the central organs in keeping with the findings of Beilman et al. (1999). In this model while CO , $\dot{\text{VO}}_2$ and lactate all deteriorated during the shock phase of the experiment, only mixed venous oxygen saturation (SvO_2) differed significantly between survivors and non-survivors.

Motivated by work indicating the StO_2 debt might be predictive of multi-organ dysfunction syndrome (MODS) in human trauma patients (Cohn et al., 2007), Zenker et al. (2007) examined whether the same phenomenon may be predictive of non-survivors before fluid resuscitation is commenced. To estimate the StO_2 debt the authors used a mathematical model they referred to as the threshold area over the curve (TAOC). The model requires integration of the area of the StO_2 curve below a predetermined threshold before a given time-point — in this case the onset of resuscitation (shown schematically in Figure 4.2). The greater the area over the curve, the larger the presumed StO_2 deficit, which it was hypothesised would be inversely correlated with survival. To test this hypothesis 14 piglets were subject to a controlled haemorrhage for 90 minutes before receiving colloid resuscitation. StO_2 , pulse rate and invasive measures of blood pressure were recorded. MAP was found to be the best discriminator of survival at the point of resuscitation, but was unable to distinguish survivors from non-survivors for time-points prior to two minutes before resuscitation. StO_2 and TAOC (using

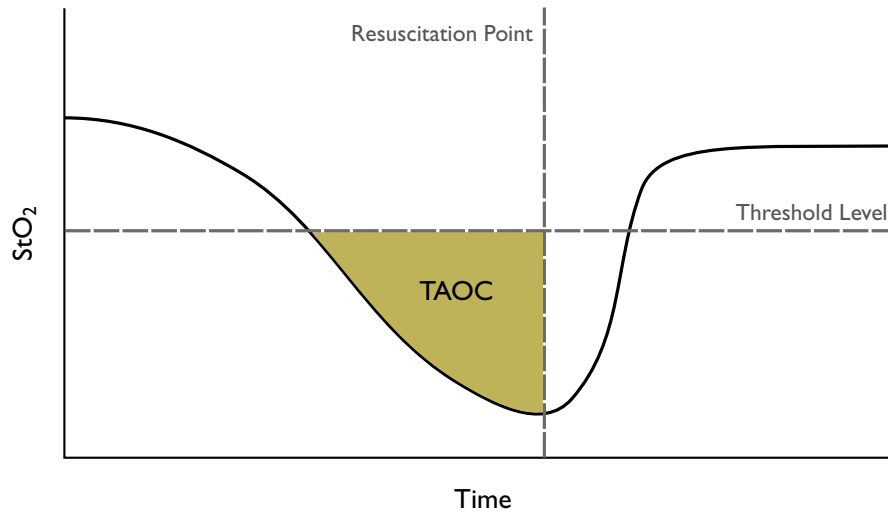


Figure 4.2: A diagrammatic representation of the threshold area over the curve (TAOC) calculation. The area of interest falls below a specified threshold StO_2 and the StO_2 curve before the time-point of interest. TAOC is hypothesised to provide an estimate of StO_2 debt, adapted from Zenker et al. (2007).

a threshold value of 75%) measurements performed similarly at resuscitation, however TAOC demonstrated a greater predictive capability prior to resuscitation, outperforming all other indices at time points greater than 10 minutes before the onset of resuscitation. One limitation of this study is that the authors repeatedly performed the TAOC analysis for all StO_2 thresholds between 40–100% before analysing them for significance and finding that StO_2 thresholds between 67–75% yielded positive results. While the TAOC concept demonstrates promise it has yet to be validated, and there appears to be no further published work developing this concept.

In an experiment to determine if NIRS could be used to guide the resuscitation of hypovolaemic subjects, Chaisson et al. (2003) created a computer controlled closed-loop resuscitation system with infusion volumes and rates being automatically titrated to physiological endpoints. The study was unique in using conscious sheep as subjects, rather than anaesthetised animals used in most other studies, thereby preventing the problems associated with anaesthetic agents modifying the response to shock. Twelve sheep were exposed to an uncontrolled haemorrhage using a 4 mm aortotomy and after 20 minutes were resuscitated with crystalloid

to either 100% of baseline CO or a peripheral StO₂ of 49% as an endpoint. The authors do not explain how these endpoints were determined, other than they were based on preliminary work. However, in choosing a lower than normal StO₂ they make the interesting point that their earlier experiments demonstrated: baseline StO₂ levels are not achieved following resuscitation for haemorrhage (presumably using crystalloid only resuscitation) despite achieving baseline or supranormal CO. All but one of the animals survived to the end of the study, the one death occurring early in the StO₂ endpoint group apparently as a result of heart failure. Unsurprisingly mean fluid resuscitation volumes were lower in the StO₂ endpoint group (100% of haemorrhage volume) compared to the CO group (180% of haemorrhage volume). Skeletal muscle and brain StO₂ were similar between the two groups despite the MAP and CO being greater in the CO endpoint group. Base excess fell during the haemorrhage and recovered during resuscitation. Despite showing a greater fall during haemorrhage in the StO₂ group, base excess recovered more fully in this group at the end of resuscitation ($p < 0.05$). This work demonstrates that StO₂ can be used to guide resuscitation, and confirmed what is only more recently becoming accepted: that limited resuscitation to lower than normal physiological parameters may be associated with equivalent or better outcomes than conventional resuscitation.

4.4 HUMAN CLINICAL STUDIES OF NIRS IN TRAUMA RESUSCITATION

Despite the good body of work validating NIRS as a tool for detecting blood loss from a known baseline, there have been relatively few published clinical studies examining NIRS in human trauma subjects. In one of the earliest of these studies McKinley et al. (2000) examined subcutaneous tissue and skeletal muscle StO₂ and compared them to systemic oxygen delivery index (DO₂I) in a small group ($n=8$) of severely injured patients. Other indicators of physiological status recorded during the study, included base deficit, lactate and mixed venous saturations (SvO₂). They found that over a 24 hour period of resuscitation skeletal muscle StO₂ (as recorded from the deltoid), but not subcutaneous StO₂, was highly correlated with improvements in DO₂I ($r=0.95$), the only other parameter changing significantly being lactate. Although this seems to validate muscle recordings of StO₂ from the deltoid as a legitimate indicator of systemic oxygen delivery, there are several

concerning elements in their results. The finding of an initial muscle StO_2 of $15 \pm 2\%$ appears inconsistent with the recorded SvO_2 levels greater than 70%. If StO_2 is a measure of arterial and venous oxygenation at a capillary level, SvO_2 would be expected to be much lower. The reported subcutaneous StO_2 (average 78–87%) were close to the expected normal range and did not change significantly during resuscitation, a finding inconsistent with other reports which have demonstrated significant falls in subcutaneous pO_2 following haemorrhage (Ward et al., 2006).

Crookes et al. (2005) examined the ability of thenar eminence muscle StO_2 to identify degrees of shock in trauma patients. They first established normal ranges in 707 health subjects, demonstrating a mean StO_2 of $87 \pm 6\%$, and also finding statistically significant differences between males and females ($p < 0.001$), smokers and non-smokers ($p < 0.001$) and between different ethnic groups. They then examined 145 trauma patients who were categorised on the basis of haemodynamic data into one of four groups: no shock; mild shock; moderate shock; and severe shock. It was found that while NIRS could identify the severely shocked patients (for the purposes of this study defined as a systolic blood pressure less than 80 mmHg), it could not differentiate between the no, mild and moderate shock groups. The reasons for this are unclear. It may be a consequence of classification bias occurring as a result of the author's dependence upon haemodynamic parameters (which in themselves are poor indicators of the degree of hypoperfusion for the reasons discussed in Section 1.3.2) to classify the degree of shock. It may be due to inherent problems with NIRS, a lack of suitability of the thenar eminence as monitoring site, differences in ethnically related skin pigmentation or the confounding influence of myoglobin's contribution to the NIRS signal. Although the thenar eminence is often accepted as a site for recording peripheral StO_2 in trauma, there is evidence suggesting it may be less sensitive in detecting changes compared to other sites, and its use is largely one of practicality: it is readily accessible; has little pigmentation (anecdotally reported to interfere with StO_2 measurements) (Wassenaar and den Brand, 2005; Shuler et al., 2009)); and has limited overlying fat.

Cohn et al. (2007) evaluated how well StO_2 predicted MODS in patient presenting with major torso trauma. They monitored thenar eminence StO_2 for the first 24 hours in 383 trauma patients meeting any of the following inclusion criteria: blood transfusion requirement within 6 hours of admission; a base deficit ≥ 6 mEq/L; at

least one of pelvic fracture, two or more long bone fractures, multiple rib fractures or pulmonary contusion, or major blunt or penetrating torso trauma. Additional clinical data collected included: heart rate; systolic blood pressure; pH; base deficit; INR; and temperature. Fifty patients in the study developed MODS. It was found that minimum StO_2 values recorded within the first hour of admission could identify patients likely to go on to develop MODS with a sensitivity of 78% and specificity of 39%. The negative predictive value of StO_2 was 91%, but the positive predictive value was only 18% (i.e. StO_2 had a high false positive rate of predicting MODS). StO_2 had the same power predicting MODS as blood pressure and arterial base deficit, with a greater sensitivity but lower specificity. The conclusion was that NIRS performs similarly to conventional measurement of perfusion status in predicting MODS, but has the advantage of being continuous and non-invasive.

The same group reported what is presumably the same dataset (identical time period, inclusion criteria and number of patients), reporting the results for the subgroup analysis of those patients undergoing massive transfusion (defined by the study as more than 3000 ml or 10 units of packed red cells administered in the first 24 hours) (Moore et al., 2008). Of the original 383 patients, 30% (114) required massive transfusion. All parameters recorded, with the exception of temperature, demonstrated a significant difference between the massive transfusion and no massive transfusion groups, although there was a large degree of overlap in all measurements between groups. Using a multivariate logistic regression process the authors built models using data at 30 and 60 minutes to predict the need for massive transfusion. Five significant independent predictors of massive transfusion were found: systolic blood pressure; ISS; transfer from other hospital; INR (only in the 30 minute model); and pH (only in the 60 minute model). Obviously these models are of little practical use as ISS is not available in the early stages of resuscitation, and transfer from another hospital can only be a useful parameter within their trauma system. StO_2 was not found to be useful as a predictor of massive transfusion in their model, despite demonstrating significant differences between groups. The outcomes of patient undergoing massive transfusion were categorised as either poor (MODS and/or death) or good (survival without MODS). StO_2 , age and pH were shown to be significant predictors of poor outcome, however StO_2 was the only measurement demonstrating this consistently at one, two and three hours.

Ultimately the results appear to show that although it is possible to predict the need for massive transfusion, a model involving several measurements is required to achieve this accurately. StO₂ appears to be a useful predictor of poor outcome in these patients, but it is probably best interpreted in context of other measurements.

Although most attempts at clinical assessment of NIRS have been made in the civilian environment, there are now two reports of its use in a deployed military setting. In a small (n=8) case series report, casualties suffering from battlefield injuries were monitored with StO₂ recordings taken from the thenar eminence. StO₂ levels below 70% were found to be effective in tracking the response to resuscitation, although the nature of the study design and the small number of subjects meant the value of StO₂ in guiding resuscitation prospectively could not be assessed (Beilman and Blondet, 2009). In a larger study, 147 combat casualties managed at a single US Army combat support hospital had their thenar eminence StO₂ measured to determine if NIRS could predict the need for 'life-saving interventions' or transfusion. The severity of injuries in the study was mixed with only 49% of patients requiring life-saving intervention and 29% requiring a blood transfusion. StO₂ was not found to be a useful predictor of the need for life-saving intervention, transfusion or massive transfusion. But in the cohort of patients with a systolic blood pressure greater than 90 mmHg, it did identify patients who subsequently required a blood transfusion, suggesting that NIRS may have a triage role, particularly in those patients who appear initially haemodynamically stable (Beekley et al., 2010).

4.5 EFFECT OF EXERCISE ON NIRS MEASUREMENTS

Major trauma frequently occurs following a period of prolonged or intense exertion. In civilian practice this may take the form of the runner or cyclist injured on the roads during training or while engaged in other recreational pursuits. In the military environment contemporary conflicts have been characterised by injuries occurring following prolonged periods of patrolling or while being engaged in a fire-fight.

Exercise is known to modulate the physiological response to haemorrhage. In models of haemorrhage using lower body negative pressure, prior exercise has been shown to attenuate the reduction in blood pressure associated with

the redistribution of blood. These effects appear to persist for at least 24 hour following completion of exercise (Convertino and Adams, 1991; Convertino, 2003). Various mechanisms have been proposed to account for these protective effects, including an increase in α -1 adrenoreceptor responsiveness (Convertino, 2003) or baroreceptor sensitivity (Engelke et al., 1995) induced by exhaustive exercise.

Wade (2010) examined the cardiovascular response to a controlled haemorrhage of 37% blood volume in swine subject to a one hour run at a workload of 70% maximum heart rate. He reported a lower reduction in mean arterial pressure in the exercised animals (26 ± 9 mmHg) compared to rested controls (49 ± 2 mmHg) despite a similar reduction in CO in both groups. The increase in plasma adrenaline was also lower in the exercised animal, suggesting that the differences in blood pressure between the groups were due to increased peripheral vasoconstriction occurring as a result of enhanced receptor sensitivity in the exercised animals.

NIRS has been extensively studied in exercising muscles across a range of athletic disciplines although mostly focusing on highly controlled endurance exercises such as cycling, rowing and arm cranking. The StO_2 response to exercise has been described in four stages (Özyener, 2002). In phase I there is an immediate increase in StO_2 from baseline values at the onset of zero load exercise. During phase II there is a gradual decline in StO_2 in working muscles. Similar changes have also been seen in the inactive biceps brachii muscle during cycling (Ogata et al., 2007). The fall in StO_2 levels out at phase III despite increases in work load unless $\dot{V}\text{O}_{2\max}$ is achieved. Phase IV describes recovery and is associated with a rise in StO_2 values to above baseline values (presumably as a result of a hyperaemic response) which return to baseline levels within 2–3 minutes (Chance et al., 1992).

Understanding the StO_2 changes during recovery, particularly in non-exercising muscle, are important for interpreting StO_2 values recorded in trauma patients who have been exercising, yet this is the least understood phase of the exercise response. Nagasawa (2008a) examined the effects of 20 minutes of cycling at 30, 50 and 70% of $\dot{V}\text{O}_{2\max}$ on post-exercise StO_2 in the non-exercising forearm flexor muscles. The results showed that StO_2 was increased over baseline values following exercise and furthermore that higher intensity exercise produced greater increases in StO_2 , although the actual magnitude of these changes was relatively

small (between $1.3 \pm 0.1\%$ and $2.2 \pm 0.3\%$). Recovery times for StO_2 to return to baseline levels were relatively short: within three minutes for exercise performed at 30 and 50% of $\dot{V}\text{O}_{2\max}$; and five minutes for exercise performed at 70% of $\dot{V}\text{O}_{2\max}$. A similar study performed using unilateral leg raises, performed at 40, 60 and 80% of the one repetition maximum (1RM) demonstrated similar findings except that the relative rise in StO_2 in the non-exercising forearm muscles was inversely related to the intensity of exercise performed. Again, increases in StO_2 were relatively small: $1.8 \pm 0.2\%$ at 40% 1RM; $1.7 \pm 0.2\%$ at 60% 1RM; and $1.4 \pm 0.3\%$ at 80% 1RM. All values returned to baseline within 5 minutes of finishing exercise Nagasawa (2008b).

At present there is no work examining StO_2 changes during exercise in a military population, although physiologically they are likely to be similar to those studies that have used athletes as subjects. Nearly all the exercise studies have used isolation strength work or highly specific cardiovascular endurance protocols. There are no studies examining the effects of a mixed exercise protocol, of the type simulating the demands of military field work, on muscle oxygenation at sites likely to be of interest to the clinician monitoring a trauma patient.

Part II

EXPERIMENTAL STUDIES

5. GENERAL METHODS

5.1 SELECTION OF NIRS DEVICE

At the time of investigation there were three commercially available NIRS devices on the UK market.

1. *InSpectra™ StO₂ Tissue Oxygenation Monitor 325* manufactured by Hutchinson Technology. The InSpectra™ 325 was a single channel, single beam NIRS monitor, marketed as suitable for monitoring from any external somatic site. The device was unique in accepting probes with different interoptode spacing, enabling it to monitor at different tissue depths, however to achieve this the machine required a 10–15 minute calibration/warm-up time with each change of probe. Probes were reusable, although they were used with a disposable light shield. Commercial support for this device was withdrawn in July 2009, and largely for this reason and the practical limitations of the calibration time, this device was not considered suitable for further investigation.
2. *InSpectra™ StO₂ Tissue Oxygenation Monitor 650* manufactured by Hutchinson Technology. This device was the successor to the InSpectra™ 325, retaining the same single channel and beam capacity, but no longer being compatible with probes with different interoptode distances, and thus limited to a single depth measurement of approximately 25 mm. The device was marketed for recording StO₂ from the thenar eminence and was supplied with disposable probes shaped specifically for this purpose, although it was CE marked and FDA licenced to record from any external body surface. The probes and cables were supplied as a single disposable unit. This had advantages for sterility but resulted in a high per unit cost. The InSpectra™ 625 had a maximum measurement frequency of 5 seconds.
3. *INVOS® 5100C System* manufactured by Somanetics (shown in Figure 5.1). This device was marketed for cerebral and somatic monitoring and had CE marking and FDA licensing for both. The probes were of a single generic design, with smaller probes available for paediatric monitoring. The probes were single use, but unlike the InSpectra™ cables and pre-amps were not

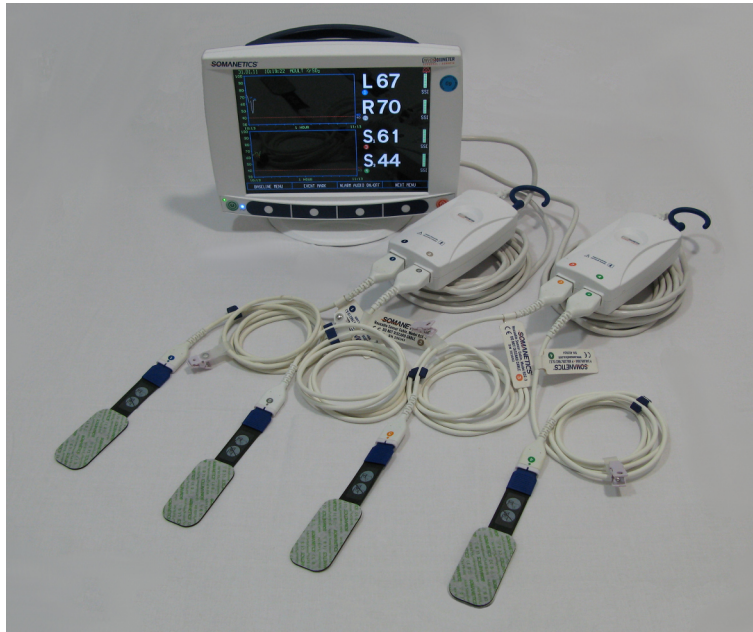


Figure 5.1: The INVOS® 5100C System monitor shown in a four channel configuration.

disposable. The INVOS® System was a dual beam machine taking two readings using a separation of 30 mm and 40 mm, subtracting the superficial reading from the deep one to ensure measurement of deep tissue. The monitor was capable of recording up to four channels simultaneously, with a maximum frequency of six seconds. Full details of the INVOS® System's technical operating specifications are given in Appendix A.

The INVOS® System monitor was selected as the model most suited to studying StO_2 in military trauma subjects based upon the theoretical advantage of isolated deep tissue measurements, the capacity to simultaneously monitor up to four channels compared to a single channel for the InSpectra™ model and a smaller generically designed probe with a lower per unit cost than the InSpectra™ 650.

5.2 DATA EXPORT FROM THE INVOS® SYSTEM

The INVOS® System records data in real time and outputs it in an ASCII plain text format with a fixed column width and CRLF line terminators. The machine has an internal memory capable of storing up to 24 hours worth of data which can subsequently be exported to a USB stick. If the USB stick is detected by the

machine while monitoring data is dumped directly to that. A 2 GB stick would typically provide in excess of 15,000 hours continuous recording.

StO₂ data is recorded against a time and date stamp. The time stamp intervals correspond to the recording frequency set by the user, the minimum setting (and default value) is every six seconds. When the monitoring period straddles midnight, the active data file is closed and a new one created. This feature is not documented by the manufacturer but presumably exists to limit the maximum size of the data files. When analysing data crossing midnight, it requires the corresponding files to be correctly identified and concatenated manually.

In addition to StO₂ data the machine also records several other fields including signal strength and the sensor ID for each channel in use. Users may also manually insert one of 160 pre-defined event marks corresponding to a clinical event, against the time stamp. This is useful experimentally for synchronising recordings with other devices. A sample dataset illustrating a four channel output is shown in Figure 5.2, a list of column descriptors is given in Table 5.1.

5.3 WORK FLOW FOR INVOS[®] SYSTEM DATA MANAGEMENT

The INVOS[®] System has the potential to produce relatively large data files, especially when continuously monitoring patients using multiple channels, which presents practical problems for data management. The manufacturer recommends that data files be imported directly into a spreadsheet application using merged space delimiters as the field separator, where they can subsequently be viewed and manipulated. This method was used on occasion when working with individual files, but was found to be impractical when managing large numbers of files or files of a large size. For the purposes of this work the following schema was used to clean files to produce input suitable for analysis:

1. Data was exported from USB stick to a host computer running a POSIX compliant operating system.
2. If the data recording crossed midnight, the contents of matching files was confirmed by viewing the file in a text editor and the files concatenated using the GNU core utilities *cat* command.
3. Data files were cleaned, stripping out duplicate space delimiters and removing all fields except the date/time stamp and StO₂ fields, using a

5.3. WORK FLOW FOR INVOS® SYSTEM DATA MANAGEMENT

08.11.10 14:35:03 82 0 4 -3.7033 -4.2846 0 0 95 0 4 -2.1054 -1.6574 0 0 70 0 4 -3.8234 -3.1443 0 0 88 0 4 -5.1134 -4.3684 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:35:09 84 0 4 -3.7323 -4.363 0 0 95 0 4 -2.3488 -1.7755 0 0 68 0 4 -3.8043 -3.1123 0 0 87 0 4 -4.9776 -4.2378 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:35:16 81 0 4 -3.7911 -4.378 0 0 95 0 4 -2.3475 -1.782 0 0 70 0 4 -3.822 -3.1101 0 0 86 0 4 -4.986 -4.2133 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:35:22 81 0 4 -3.7911 -4.3796 0 0 95 0 4 -2.3317 -1.7894 0 0 71 0 4 -3.8102 -3.1117 0 0 87 0 4 -4.9626 -4.2161 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:35:28 82 0 4 -3.7901 -4.3807 0 0 95 0 4 -2.3619 -1.8239 0 0 72 0 4 -3.8174 -3.1128 0 0 88 0 4 -4.9778 -4.2282 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:35:35 82 0 4 -3.7901 -4.3827 0 0 95 0 4 -2.3425 -1.8054 0 0 70 0 4 -3.8285 -3.1165 0 0 87 0 4 -4.9787 -4.1774 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:35:41 81 0 4 -3.7965 -4.3887 0 0 95 0 4 -2.3484 -1.8261 0 0 72 0 4 -3.8253 -3.1165 0 0 87 0 4 -4.9544 -4.2099 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:35:47 81 0 4 -3.7978 -4.389 0 0 95 0 4 -2.3538 -1.8266 0 0 73 0 4 -3.8253 -3.1159 0 0 87 0 4 -4.969 -4.2211 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:35:54 82 0 4 -3.8007 -4.3889 0 0 95 0 4 -2.353 -1.8265 0 0 70 0 4 -3.8441 -3.1179 0 0 86 0 4 -4.9447 -4.1603 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:36:00 83 0 4 -3.8066 -4.393 0 0 95 0 4 -2.3551 -1.8477 0 0 75 0 4 -3.8441 -3.1179 0 0 86 0 4 -4.9447 -4.1603 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:36:07 80 4 -3.812 -4.3968 0 0 95 0 4 -2.3625 -1.8529 0 0 75 0 4 -3.8608 -3.1126 0 0 87 0 4 -4.9442 -4.2092 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:36:13 82 0 4 -3.8158 -4.3998 0 0 95 0 4 -2.3859 -1.8499 0 0 75 0 4 -3.8505 -3.1147 0 0 87 0 4 -4.9596 -4.1947 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:36:19 81 0 4 -3.8189 -4.4037 0 0 95 0 4 -2.3661 -1.8651 0 0 75 0 4 -3.8415 -3.1158 0 0 86 0 4 -4.8972 -4.1654 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:36:26 81 0 4 -3.8218 -4.408 0 0 95 0 4 -2.3807 -1.8719 0 0 76 0 4 -3.8541 -3.1193 0 0 86 0 4 -4.8962 -4.1591 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:36:32 81 0 4 -3.8183 -4.4069 0 0 95 0 4 -2.3641 -1.8641 0 0 74 0 4 -3.8364 -3.1146 0 0 87 0 4 -4.8624 -4.1754 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:36:38 81 0 4 -3.8215 -4.4093 0 0 95 0 4 -2.34 -1.8635 0 0 73 0 4 -3.8278 -3.1143 0 0 86 0 4 -4.8793 -4.1623 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:36:45 82 0 4 -3.825 -4.413 0 0 95 0 4 -2.3598 -1.8674 0 0 74 0 4 -3.8399 -3.1193 0 0 87 0 4 -4.852 -4.1134 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:36:51 81 0 4 -3.8291 -4.4152 0 0 95 0 4 -2.3795 -1.8798 0 0 74 0 4 -3.823 -3.1195 0 0 87 0 4 -4.8346 -4.1268 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:36:57 81 0 4 -3.8222 -4.4086 0 0 95 0 4 -2.3777 -1.8786 0 0 70 0 4 -3.8162 -3.1135 0 0 86 0 4 -4.8686 -4.1533 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:37:04 81 0 4 -3.8231 -4.4105 0 0 95 0 4 -2.3747 -1.8774 0 0 71 0 4 -3.8361 -3.1151 0 0 87 0 4 -4.8431 -4.1277 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:37:10 80 4 -3.8197 -4.4095 0 0 95 0 4 -2.3707 -1.8761 0 0 71 0 4 -3.8243 -3.1138 0 0 85 0 4 -4.8626 -4.1153 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:37:17 80 4 -3.8229 -4.4103 0 0 95 0 4 -2.3807 -1.8848 0 0 72 0 4 -3.8234 -3.1148 0 0 86 0 4 -4.8408 -4.1128 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:37:23 80 4 -3.8192 -4.4081 0 0 95 0 4 -2.384 -1.8849 0 0 70 0 4 -3.8255 -3.1139 0 0 86 0 4 -4.8654 -4.1448 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:37:29 79 0 4 -3.8173 -4.4054 0 0 95 0 4 -2.3755 -1.8789 0 0 71 0 4 -3.8235 -3.1135 0 0 86 0 4 -4.8408 -4.1244 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:37:36 81 0 4 -3.8171 -4.3976 0 0 95 0 4 -2.3659 -1.8796 0 0 70 0 4 -3.8263 -3.1139 0 0 85 0 4 -4.8754 -4.1234 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:37:42 80 4 -3.8315 -4.5124 0 0 95 0 4 -2.3524 -1.8544 0 0 95 0 4 -2.3678 -1.8796 0 0 74 0 4 -3.8264 -3.1139 0 0 86 0 4 -4.7835 -4.1063 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:37:48 81 0 4 -3.876 -4.5524 0 0 95 0 4 -2.3405 -1.8493 0 0 69 0 4 -3.8048 -3.1102 0 0 86 0 4 -4.7483 -4.0493 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:37:55 80 4 -3.8814 -4.5544 0 0 95 0 4 -2.3308 -1.8635 0 0 70 0 4 -3.8244 -3.1134 0 0 85 0 4 -4.7647 -4.0576 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:38:01 81 0 4 -3.8743 -4.5487 0 0 95 0 4 -2.3145 -1.844 0 0 71 0 4 -3.8182 -3.1127 0 0 85 0 4 -4.7435 -4.077 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:38:07 81 0 4 -3.8718 -4.5464 0 0 95 0 4 -2.3138 -1.8457 0 0 70 0 4 -3.8343 -3.1105 0 0 85 0 4 -4.8127 -4.0975 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:38:14 81 0 4 -3.8699 -4.5447 0 0 95 0 4 -2.3092 -1.8351 0 0 70 0 4 -3.8189 -3.1128 0 0 86 0 4 -4.7713 -4.0633 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:38:20 81 0 4 -3.8573 -4.5342 0 0 95 0 4 -2.3068 -1.8354 0 0 70 0 4 -3.8243 -3.1137 0 0 85 0 4 -4.7529 -4.0369 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:38:26 80 4 -3.8573 -4.5342 0 0 94 0 4 -2.3068 -1.8354 0 0 70 0 4 -3.8243 -3.1137 0 0 85 0 4 -4.7529 -4.0369 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:38:33 80 4 -3.8563 -4.5314 0 0 94 0 4 -2.3 -1.8316 0 0 71 0 4 -3.841 -3.1148 0 0 84 0 4 -4.7529 -4.0369 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:38:39 80 4 -3.8532 -4.5273 0 0 94 0 4 -2.2712 -1.8083 0 0 72 0 4 -3.8172 -3.1151 0 0 86 0 4 -4.7522 -4.0384 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:38:45 81 0 4 -3.8711 -4.5433 0 0 95 0 4 -2.2999 -1.8297 0 0 74 0 4 -3.835 -3.1127 0 0 85 0 4 -4.7327 -4.0254 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:38:52 80 4 -3.8689 -4.5392 0 0 95 0 4 -2.3042 -1.8294 0 0 74 0 4 -3.8279 -3.1118 0 0 85 0 4 -4.7269 -4.0201 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:38:58 80 4 -3.8644 -4.5328 0 0 95 0 4 -2.2743 -1.81 0 0 73 0 4 -3.8072 -3.1 0 0 86 0 4 -4.7503 -4.0363 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:39:04 80 4 -3.8547 -4.5243 0 0 94 0 4 -2.256 -1.8002 0 0 73 0 4 -3.8186 -3.1063 0 0 86 0 4 -4.7317 -4.0159 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:39:11 80 4 -3.8557 -4.5239 0 0 94 0 4 -2.2445 -1.7938 0 0 72 0 4 -3.8147 -3.0995 0 0 84 0 4 -4.6796 -3.9749 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:39:17 81 0 4 -3.8136 -4.5093 0 0 94 0 4 -2.1654 -1.7474 0 0 74 0 4 -3.8049 -3.0904 0 0 85 0 4 -4.6796 -3.9749 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:39:23 82 0 4 -3.905 -4.6236 0 0 94 0 4 -2.2877 -1.8387 0 0 73 0 4 -3.8074 -3.0911 0 0 86 0 4 -4.837 -4.0561 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:39:30 83 0 4 -3.8986 -4.6177 0 0 95 0 4 -2.27 -1.832 0 0 73 0 4 -3.7644 -3.0556 0 0 87 0 4 -4.9662 -4.1571 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:39:36 83 0 4 -3.9069 -4.6281 0 0 95 0 4 -2.3304 -1.8745 0 0 70 0 4 -3.7737 -3.0542 0 0 85 0 4 -5.0919 -4.276 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:39:42 82 0 4 -3.9161 -4.6383 0 0 95 0 4 -2.3683 -1.9011 0 0 69 0 4 -3.7735 -3.0746 0 0 89 0 4 -5.188 -4.3653 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:39:49 82 0 4 -3.9182 -4.6414 0 0 95 0 4 -2.3958 -1.9243 0 0 68 0 4 -3.7942 -3.0946 0 0 85 0 4 -5.1298 -4.3653 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:39:55 81 0 4 -3.9012 -4.6273 0 0 95 0 4 -2.3851 -1.9138 0 0 68 0 4 -3.8038 -3.1095 0 0 87 0 4 -5.1535 -4.3691 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:40:01 81 0 4 -3.9015 -4.6264 0 0 95 0 4 -2.3839 -1.915 0 0 68 0 4 -3.8006 -3.1122 0 0 87 0 4 -5.1798 -4.3889 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:40:08 81 0 4 -3.8985 -4.6312 0 0 95 0 4 -2.3956 -1.925 0 0 70 0 4 -3.8268 -3.1135 0 0 88 0 4 -5.1759 -4.373 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:40:14 81 0 4 -3.8994 -4.6223 0 0 94 0 4 -2.373 -1.9045 0 0 68 0 4 -3.8135 -3.1134 0 0 88 0 4 -5.1612 -4.3585 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:40:20 81 0 4 -3.8959 -4.6166 0 0 94 0 4 -2.3677 -1.9018 0 0 69 0 4 -3.8232 -3.1134 0 0 86 0 4 -5.1871 -4.3784 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:40:27 81 0 4 -3.8915 -4.6162 0 0 94 0 4 -2.3552 -1.8928 0 0 69 0 4 -3.8285 -3.1146 0 0 86 0 4 -5.1524 -4.343 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:40:33 81 0 4 -3.8887 -4.6136 0 0 94 0 4 -2.3447 -1.8854 0 0 68 0 4 -3.8202 -3.1143 0 0 88 0 4 -5.1689 -4.3567 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:40:39 81 0 4 -3.8856 -4.6114 0 0 94 0 4 -2.331 -1.8666 0 0 70 0 4 -3.834 -3.1128 0 0 87 0 4 -5.1817 -4.3502 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:40:45 82 0 4 -3.8825 -4.6075 0 0 95 0 4 -2.2972 -1.8503 0 0 69 0 4 -3.837 -3.1152 0 0 86 0 4 -5.1121 -4.2956 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:40:52 82 0 4 -3.8847 -4.6108 0 0 94 0 4 -2.2777 -1.8301 0 0 70 0 4 -3.8376 -3.1152 0 0 88 0 4 -5.1121 -4.2956 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:41:05 82 0 4 -3.8763 -4.605 0 0 94 0 4 -2.2716 -1.8231 0 0 71 0 4 -3.8363 -3.1141 0 0 85 0 4 -5.0941 -4.2973 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:41:11 81 0 4 -3.8717 -4.61 0 0 94 0 4 -2.0962 -1.7284 0 0 70 0 4 -3.815 -3.1134 0 0 86 0 4 -5.1448 -4.3207 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:41:17 82 0 4 -3.8512 -4.5954 0 0 95 0 4 -2.1994 -1.7757 0 0 70 0 4 -3.8184 -3.1126 0 0 84 0 4 -5.1244 -4.3065 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:41:24 81 0 4 -3.8563 -4.595 0 0 95 0 4 -2.2311 -1.7984 0 0 68 0 4 -3.7818 -3.0924 0 0 82 0 4 -5.1996 -4.3441 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:41:30 81 0 4 -3.8432 -4.5857 0 0 95 0 4 -2.2015 -1.78 0 0 68 0 4 -3.7749 -3.0937 0 0 87 0 4 -5.1766 -4.3002 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:41:36 81 0 4 -3.8577 -4.5962 0 0 95 0 4 -2.2307 -1.8126 0 0 68 0 4 -3.8172 -3.1161 0 0 87 0 4 -5.2033 -4.3263 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:41:43 81 0 4 -3.8596 -4.5981 0 0 95 0 4 -2.2429 -1.8226 0 0 68 0 4 -3.8186 -3.1192 0 0 79 0 4 -5.17 -4.3004 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0
08.11.10 14:41:43 81 0 4 -3.8654 -4.6021 0 0 94 0 4 -2.2223 -1.8012 0 0 69 0 4 -3.8089 -3.1194 0 0 95 0 4 -5.2452 -4.3976 0 0 AB0912040628-0 AB0912040757-0 AB0912040628-0 AB0912040780-0

Figure 5.2: An example of data output from the INVOS® System in a four channel configuration. For clarity extra spaces have been removed and the column spacing has been aligned. A list of the column descriptors is provided in Table 5.1.

<i>Column</i>	<i>Descriptor</i>	<i>Column</i>	<i>Descriptor</i>
A	Date	R	Event Mark
B	Time	S	Status
C	StO ₂ (Channel 1)	T	Baseline
D	Event Mark	U	Area Under Curve
E	Status	V	Upper Alarm Limit
F	Baseline	W	Lower Alarm Limit
G	Area Under Curve	X	StO ₂ (Channel 4)
H	Upper Alarm Limit	Y	Event Mark
I	Lower Alarm Limit	Z	Status
J	StO ₂ (Channel 2)	AA	Baseline
K	Event Mark	AB	Area Under Curve
L	Status	AC	Upper Alarm Limit
M	Baseline	AD	Lower Alarm Limit
N	Area Under Curve	AE	Channel 1 Sensor ID
O	Upper Alarm Limit	AF	Channel 2 Sensor ID
P	Lower Alarm Limit	AG	Channel 3 Sensor ID
Q	StO ₂ (Channel 3)	AH	Channel 4 Sensor ID

Table 5.1: Column descriptors from the INVOS® System ASCII file data output. Columns specifiers are listed alphabetically as they would appear if imported into a spreadsheet application.

custom BASH script. The script was able to batch process files and accept arguments to change the field delimitator and the number of channels in the output file. A modified version of this BASH script with instructions for use is reproduced in Appendix B.

4. Custom post-processing of data files, e.g. insertion of additional data fields, was performed either in a text editor or a spreadsheet application.
5. Visual confirmation of the integrity of the resulting data file was performed by iterative plotting of the data using gnuplot. For large data sets this process was automated using an Emacs keyboard macro or BASH script.

5.4 MONITORING SITES

The INVOS® System is capable of measuring the StO₂ of almost any site in the body. However, for the human studies described in this manuscript only a limited number of sites were used to allow comparison of StO₂ measurements between experiments.

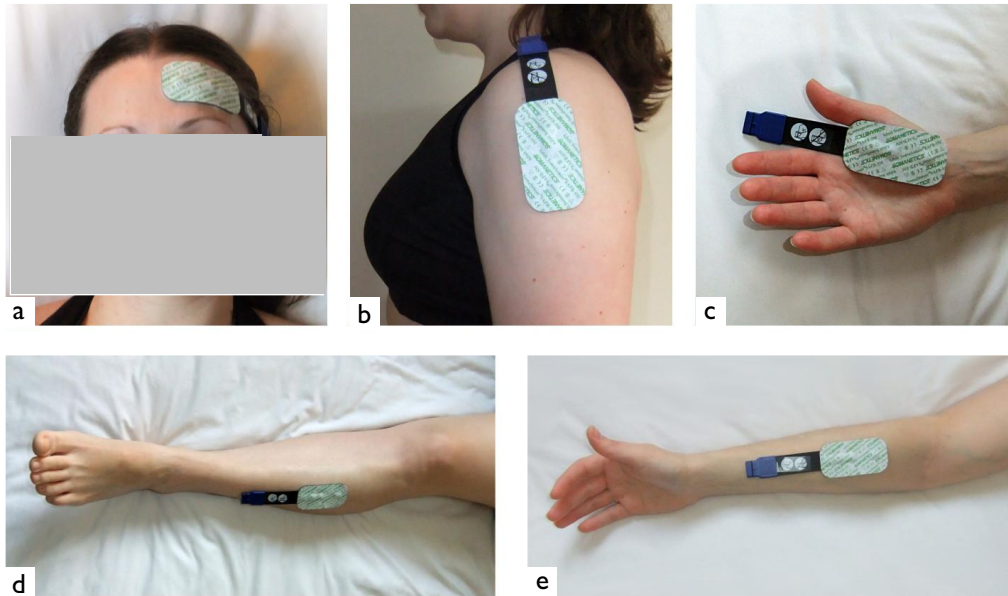


Figure 5.3: Positions of NIRS probes used in the human studies: a) frontal lobe of the brain; b) deltoid; c) thenar eminence; d) anterior compartment of the leg; e) forearm.

The siting of probes used in the human studies was as follows (see Figure 5.3):

- *the frontal lobe of the brain* — with the probe positioned one finger breadth above the orbital ridge, with the probe/cable connection directed laterally and the distal end of the probe located in the mid-line.
- *the deltoid* — with the probe positioned two finger breadths above the deltoid insertion, with the probe/cable connection directed cranially.
- *thenar eminence* — with the probe positioned with its distal end abutting the distal palmar crease, and its long axis directed towards the first web-space.
- *the anterior compartment of the leg* — with the probe positioned one finger breadth lateral to the anterior margin of the tibia at the midpoint between the knee and the ankle. The probe cable/connection was directed distally.
- *the forearm* — with the probe positioned with its long axis parallel to the axis of the arm, over the midpoint of flexor digitorum profundus muscle. The probe cable/connection was directed distally.

6. NIRS HUMAN VOLUNTEER SIMULATED HAEMORRHAGE STUDY

The material presented in this chapter was part of a collaborative work performed in conjunction with James Cook University Hospital, South Tees Hospitals NHS Foundation Trust and the Defence Science and Technology Laboratory (DSTL). Haemodynamic data used in this chapter is presented courtesy of Lt Col Jeremy Henning.

My contribution to this work was developing and writing the NIRS elements of the study protocol, training other researchers in the NIRS elements of the protocol, data collection and data analysis.

6.1 INTRODUCTION

Most clinical studies examining the application of NIRS in trauma have utilised the thenar eminence as a site for recording skeletal muscle StO_2 . Preference for this site may in part be due to one of the most widely used commercial NIRS monitors (the Hutchinson InSpectra™ StO_2 Tissue Oxygenation Monitor 650) being marketed almost exclusively for recording from the thenar eminence and having a probe specifically designed for this. As a monitoring site the thenar eminence has several attractions: it is easily accessible; has only a thin overlying layer of fat — which can cause problems with signal attenuation particularly in single beam monitors; and has low levels of pigmentation minimising the problems of melanin associated absorption/scattering of the infrared beam. Despite these practical merits, there is no convincing evidence that thenar eminence StO_2 provides a more accurate indicator of the patient physiology than that recorded from other anatomical sites. In fact the few studies that have attempted to compare NIRS measurements from different sites suggest that StO_2 recorded from the thenar eminence may be inferior to other skeletal muscle sites.

Soller et al. (2008a) recorded StO_2 from the thenar eminence using a Hutchinson InSpectra™ monitor, and from the forearm using their own experimental dual beam NIRS monitor, in human volunteers exposed to a simulated haemorrhage using lower body negative pressure (LBNP). They found that forearm StO_2 decreased by 75% at maximal LBNP, while thenar eminence StO_2 showed no significant

change throughout the whole protocol. The study was limited somewhat by the forearm and thenar eminence measurements being recorded on different (albeit case matched) subjects, and using different machines with different algorithms. While these limitations make a practical interpretation of the results difficult, they do suggest that there may be better sites than the thenar eminence for detecting hypovolaemia associated changes in skeletal muscle StO_2 . In a similar experiment Bartels et al. (2011) measured thenar eminence and forearm StO_2 at two different depths in volunteers subjected to LBNP. They found that forearm NIRS measurements were more sensitive to hypovolaemia than thenar measurements, but that depth of measurement had no impact on the sensitivity of the NIRS readings.

Aside from the potentially poor sensitivity in detecting hypovolaemia, the thenar eminence also has significant practical limitations as monitoring site. The injury mechanisms seen in the military environment produce upper limb injuries/amputation with a much higher frequency than that seen in civilian trauma. In such cases monitoring at more a proximal site is the only option.

Although not as widely studied, deltoid StO_2 has been shown to correlate well with systemic oxygen delivery in severely injured patients (McKinley et al., 2000). Exactly how the deltoid compares to the thenar eminence or forearm for NIRS monitoring is unknown, as the sites have never been compared. From a practical standpoint the deltoid holds significant appeal as a monitoring site since it is easily accessible, and at least one site should be available for monitoring in most patients — significant bilateral injuries/amputation of the deltoid being unlikely to be associated with a survivable injury pattern.

Many trauma patients require analgesia. Morphine is probably the most commonly used analgesic agent in major trauma in both military and civilian practice. Morphine is carried by ambulance crews and front line military personnel are issued with auto-injectors for prehospital use. There is evidence that morphine affects the response to haemorrhage, however the nature of this response varies between the models used. In anaesthetised rats administration of morphine prior to haemorrhage has been shown to delay the vagally mediated bradycardia associated with the biphasic response to hypovolaemia (Ohnishi et al., 1998). When administered in established shock, morphine appears to attenuate the response to resuscitation (Molina et al., 2004) and is associated with increased mortality

(Feuerstein and Siren, 1986; Marshall et al., 1998). In a conscious sheep haemorrhage model, activation of central opioid receptors is associated with the onset of the decompensatory phase of haemorrhage, blocking of these opioid receptors delays the decompensatory phase (Frithiof and Rundgren, 2006). Morphine use in the presence of hypovolaemia is often cautioned against (Joint Formulary Committee, 2012), although the nature of its effects on the human haemorrhagic response are still largely unknown.

6.2 AIM

This study aimed to compare the relative sensitivities of StO_2 recorded from the deltoid, forearm, thenar eminence and frontal lobe of the brain, in detecting degrees of hypovolaemia in human subjects. A secondary objective was to compare the effects of morphine administration on the haemodynamic response to LBNP and determine if these would be reflected in StO_2 measurements.

6.3 MATERIALS AND METHODS

The study design was that of a prospective randomised double-blinded cross-over trial in conscious human volunteers. Subjects were randomised to receive either morphine or placebo before being exposed to a simulated hypovolaemia with LBNP. After a minimum interval of seven days, the protocol was repeated with subjects crossing over to the other arm of the study and receiving either morphine or placebo, depending upon what was administered in the first trial. Both subjects and investigators were blinded as to the contents of the infusion during each subject visit. Ethical approval was obtained from the Northern and Yorkshire Research Ethics Committee. Regulatory approval for the use of morphine in the protocol was obtained from Medicine and Healthcare Products Regulatory Agency.

The study was conducted in the operating theatre department at The James Cook University Hospital, Middlesbrough between 1 Dec 2012 – 27 April 2013. All experimental procedures were performed under the supervision of a physiologist, the investigating clinician, and a research nurse trained in echocardiography to measure the stroke distance. In addition to the research team there was a separate welfare team consisting of consultant anaesthetist with nursing/operating department practitioner (ODP) support. The welfare team were independently responsible for subject safety and had the right to end a subject's study at any time.

6.3.1 *Study Population*

The study sample was drawn from medical students attending Newcastle University. Eligible for inclusion was any individual in good health, for the purposes of this study considered to be ASA (American Society of Anesthesiologists) Grade I, between the ages of 18–30 years. The health status of volunteers was assessed by a pre-study clinical interview and examination performed by a qualified medical practitioner. This included:

- measuring of vital signs e.g. blood pressure and heart rate
- blood sampling for standard haematology and biochemistry
- urine analysis for recreational drugs and dipstick testing
- in female subjects a urine β hCG test (pregnancy test)

This assessment was repeated, minus the blood tests, prior to each arm of the study. The following exclusion criteria were applied:

1. an ASA Grade II or above
2. a history of lower limb or pelvic trauma within the last three months
3. a family history of thromboembolic disease
4. history of recreational drug use (the use of prescribed drugs was already excluded by the ASA requirement)
5. known allergies to latex or simple adhesives of the type used by ECG electrode and dressings
6. participation in another trial within the previous three months
7. in female subjects: a positive pregnancy test

Subjects were asked to refrain from consuming alcohol or tobacco products for a minimum of 24 hours prior to the study, and from caffeine from midnight the day before the study. Following an explanation of the study protocol by the Principle Investigator, or a medically qualified designated member of the study team, written consent was obtained from all subjects.

6.3.2 *Monitoring and Protocol*

Subjects were asked to empty their bladder immediately before the study to prevent reflexes arising from having a distended bladder. Subjects were placed supine in

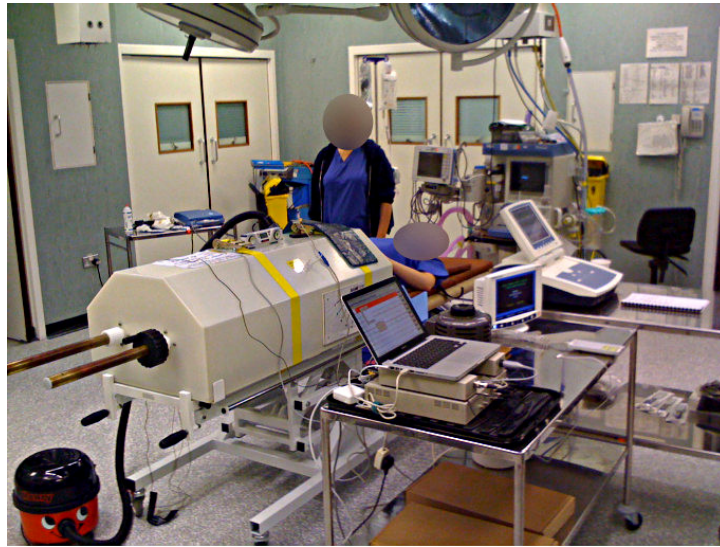


Figure 6.1: A subject undergoing experimentation in the lower body negative pressure chamber.

the LBNP chamber, this was a custom built box — the same one used by van Hoeyweghen et al. (2001), see Figure 6.1. A neoprene skirt with a polyethylene liner was used to form an air-tight seal between the subjects' lower body and the pressure chamber.

A 16F gauge cannula was placed in the antecubital fossa under 1% lidocaine local anaesthetic to be used for the infusion and to estimate the CVP using the technique described by van Hoeyweghen et al. (2001). Zero pressure for CVP measurements was set at the phlebostatic axis, defined as a horizontal line passing through the fourth intercostal space. Where intravenous access in the antecubital fossa was not possible, a 20F gauge cannula was placed in the back of the hand, although it was not then possible to estimate the CVP in these subjects. Patency of the cannula was maintained by intermittent flushes with 0.9% saline boluses.

Heart rate was recorded continuously using a three lead electrocardiogram (ECG). Beat-to-beat systolic and diastolic blood pressures were recorded non-invasively using a Finometer® MIDI continuous blood pressure monitor (Finapres Medical Systems) positioned on the middle finger of the left hand raised to the same level as the heart. The Finometer® also provided a derived measure of stroke volume. A sphygmomanometer was placed on the upper arm not containing the

cannula to take a manual reading of blood pressure to validate the Finometer® at the start of the study, and used as a backup in case of Finometer® failure.

StO₂ values were recorded using an INVOS® System monitor in a four channel set up. Four sites were monitored simultaneously, the side of the site being determined by the positioning of the other monitoring (see Figure 5.3 on page 64 for an illustration of the probe positions):

1. *the deltoid* — with the probe positioned two finger breadths above the deltoid insertion, with the probe/cable connection directed cranially.
2. *the forearm* — with the probe was position with its long axis parallel to the axis of the arm, with the cable directed distally, over the midpoint of flexor digitorum profundus muscle.
3. *the thenar eminence* — with the probe positioned with its distal end abutting the distal palmar crease, and its long axis directed towards the first web-space.
4. *the frontal lobe of the brain* — with the probe positioned one finger breadth above the orbital ridge, with the probe/cable connection directed laterally, and the distal end of the probe located in the midline.

Stroke distance was assessed by echocardiography, all measurements being taken by the same researcher to avoid inter-observer variability. Stroke distance was measured twice during the baseline monitoring phase, five minutes after the induction of each LBNP increment and five minutes after finishing the suction protocol. At each interval three separate measurements were taken and the mean of these used to calculate the stroke distance. Using the recorded physiological measurements derived values for cardiac output (stroke volume x heart rate) were calculated.

Following attachment of the monitoring, subjects were then rested for 30 minutes, after which baseline physiological measurements were made. Morphine (0.2 mg/kg) made up to a 10 ml volume in 0.9% saline, or the equivalent volume of placebo (water) made up to 10 ml with 0.9% saline was administered via the intravenous cannula. Five minutes after the infusion a further set of baseline measurements were made. Ten minutes after the administration of the infusion

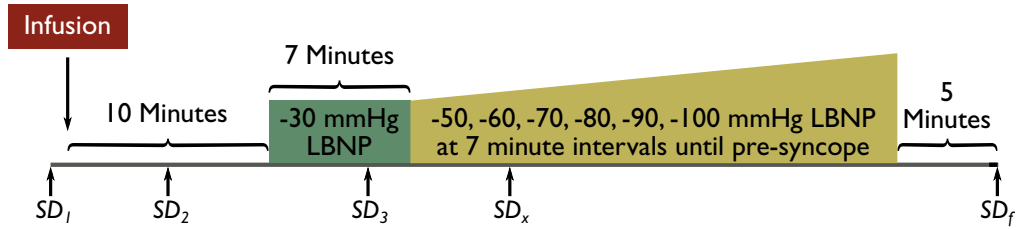


Figure 6.2: LBNP study timeline. SD denote stroke distance measurement. Stroke distances were measured five minutes after the start of each LBNP increment (SD_3 and SD_x). A final stroke distance measurement SD_f was taken five minutes after the point of presyncope and the release of the LBNP.

the simulated hypovolaemia protocol was started. A summary of the study protocol timeline is shown in Figure 6.2.

6.3.3 Lower Body Negative Pressure Protocol

Subjects were exposed to progressive increments of LBNP, each lasting seven minutes, to the point of presyncope. For the purposes of this study, presyncope was defined as a drop in systolic blood pressure greater than 20 mmHg, sustained for at least 10 heart beats associated with other autonomic features such as nausea, sweating, or pallor, with or without a bradycardia.

The first pressure increment was -30 mmHg followed by -50 mmHg, the pressure was then increased in -10 mmHg steps at 7 minute intervals, to a maximum of -100 mmHg. At the point of presyncope the pressure was immediately reduced to half the current pressure for one minute and then gradually released to atmospheric pressure (i.e. 0 mmHg) over the following minute.

Five minutes after completion of the LBNP protocol a final stroke distance measurement was made before the monitoring was detached and the subject released from pressure chamber. Subjects were then transferred to the recovery area and given something to eat and drink. Once the welfare team were satisfied with the subjects' recovery they were discharged.

6.3.4 Data Analysis

Representative values for the continuously monitored physiological parameters were derived from the median values recorded between the fifth and sixth minute of that pressure step or after the release of the negative pressure in the case of the

recovery measurement. For the baseline measurements the median of the values lying 30 seconds either side of the baseline measurement point were used. These points corresponded to the recording of the stroke distance measurements (SD_1 and SD_2) allowing direct comparison of these parameters.

Testing of the data distribution for normality was performed by examination of Q-Q plots and performance of a Shapiro-Wilks test. Non-parametric comparison of means was performed using a Wilcoxon signed-rank and Kruskal-Wallis test. Correlation analysis was performed by calculating a Spearman's rank correlation coefficient. All statistical tests were undertaken using the R programming language and environment for statistical computing (R Development Core Team, 2009), with a significance threshold of $p \leq 0.05$.

6.4 RESULTS

6.4.1 *Demographics of Study Population*

A total of 12 individuals were screened for the study, two of which were excluded: one who developed an unrelated medical condition between the two arms of the study necessitating exclusion; and the other who withdrew after sustained a lower limb injury between screening and the study starting. Of the 10 subjects enrolled into the study, there were six males and four females. The mean age of subjects was 22.5 years (range 20–26, s.d. 1.9). All 10 subjects completed both arms of the protocol, although in two subjects the study protocol was ended early. In one subject the protocol was terminated when the subject started vomiting during the late stages of the morphine arm. In another subject the study was stopped when there was loss of the Finometer® reading at a point where the subject was judged clinically to be close to presyncope.

In one subject there was a technical failure with the time synchronisation stamp on the NIRS trace during the morphine arm the study, meaning StO_2 data could not be matched to the experimental phase or other physiological parameters. StO_2 data was therefore excluded in this morphine arm of this subject during analysis.

PLACEBO GROUP StO ₂ (%)						
	Site	Mean	Median	Range	Q1-Q3	s.d.
<i>Pre-infusion</i>	Deltoid	87.8	88	78-95	86-93	6.5
	Forearm	80.2	78	69-95	70-88	10.3
	Thenar	62.6	59	49-83	54-72	12.5
	Head	77.3	77	66-87	75-83	6.5
<i>Post-infusion</i>	Deltoid	88.4	89	74-95	85-94	6.6
	Forearm	75.8	78	60-87	70-82	9.1
	Thenar	60.2	60	43-82	53-66	12.7
	Head	75.9	77	67-87	71-79	7.1
MORPHINE GROUP StO ₂ (%)						
	Site	Mean	Median	Range	Q1-Q3	s.d.
<i>Pre-infusion</i>	Deltoid	89.0	93	77-95	84-95	6.6
	Forearm	77.9	77	68-92	70-83	8.6
	Thenar	67.8	67	49-92	57-73	13.8
	Head	75.9	77	62-85	69-84	9.0
<i>Post-infusion</i>	Deltoid	89.0	93	73-95	86-95	7.9
	Forearm	76.6	75	66-89	69-84	8.4
	Thenar	72.8	71	54-95	63-79	13.5
	Head	82.9	84	69-94	76-88	8.4

Table 6.1: Summary statistics for the baseline StO₂ values in the placebo and morphine groups.

6.4.2 Baseline Physiological Measurements and Effect of Morphine

Summary statistics for baseline StO₂ values are given in Table 6.1. There was no significant difference in pre-infusion StO₂ measurements between the placebo and morphine groups. There were significant differences in mean StO₂ when comparing anatomical sites, $p < 0.01$ for all comparisons (using the combined data from the placebo and morphine groups), with the exception of the comparison between the frontal lobe of the brain and forearm, $p = 0.27$. A summary of the pre-infusion StO₂ values at each site is presented in Figure 6.3. It can be seen that StO₂ in skeletal muscle groups decreased the more distal the monitoring site. Cerebral StO₂ values were similar those of the forearm but fell within a tighter range.

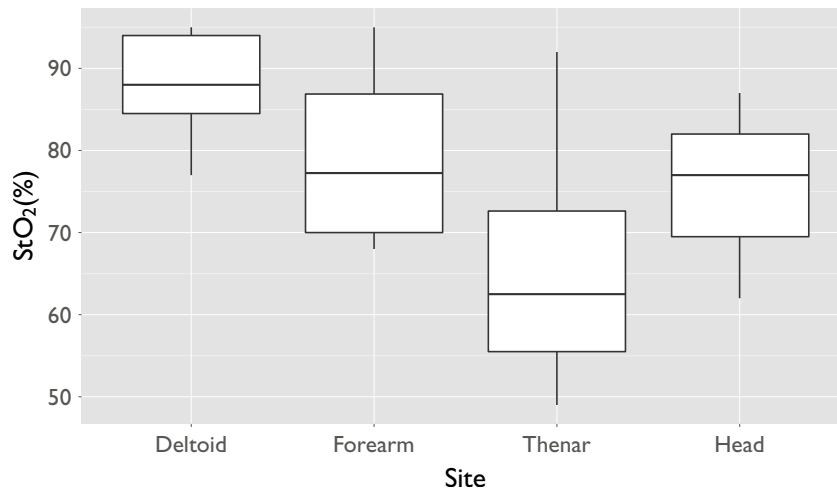


Figure 6.3: Box plot of pre-infusion StO_2 values at each site based on the combined values of the placebo and morphine groups. Plot whiskers denote maximum and minimum data points.

The infusion of placebo had no significant effect on the baseline StO_2 values recorded from the deltoid ($p=0.73$), thenar eminence ($p=0.25$), or head ($p=0.37$). In the forearm there was a $4.4 \pm 3.67\%$ fall in StO_2 following infusion ($p=0.02$). Morphine administration was not associated with any change in StO_2 in the deltoid ($p=0.97$) or forearm ($p=0.17$). However it was associated with a significant increase in the StO_2 values recorded in thenar eminence, by $5.02 \pm 3.38\%$ ($p<0.01$), and the head, by $7 \pm 1.93\%$ ($p<0.01$).

Summary statistics for the baseline values of the other physiological parameters are shown in Table 6.2. There were no significant difference in baseline measurements between the placebo and morphine groups for any of the physiological parameters listed in Table 6.2. In the placebo group heart rate fell by 5.7 ± 3.15 bpm, $p=0.004$ and CO fell by 569 ± 259 ml/min, $p=0.001$ following infusion. Morphine administration was associated with a 4.0 ± 3.6 mmHg increase in DBP, $p=0.04$. There were no other significant differences in the pre and post infusion values for any of the other physiological parameters in either the placebo or the morphine groups.

PLACEBO GROUP						
	<i>Parameter</i>	<i>Mean</i>	<i>Median</i>	<i>Range</i>	<i>Q1-Q3</i>	<i>s.d.</i>
<i>Pre-infusion</i>	HR	68	70	55–80	60–76	9.6
	SBP	120	124	99–134	115–127	11.1
	DBP	68	68	48–82	62–77	10.6
	MAP	89	91	75–100	80–95	9.1
	CVP	–	–	–	–	–
	CO	6078	6262	2820–7911	5160–7194	1561.5
<i>Post-infusion</i>	HR	63	63	52–73	56–69	7.7
	SBP	120	122	88–139	114–129	14.4
	DBP	70	67	56–84	64–79	9.7
	MAP	89	90	71–104	83–96	10.1
	CVP	–0.20	–0.10	–2.30–1.20	–0.65–0.45	1.09
	CO	5509	5827	2490–7171	4743–6779	1536.1
MORPHINE GROUP						
	<i>Parameter</i>	<i>Mean</i>	<i>Median</i>	<i>Range</i>	<i>Q1-Q3</i>	<i>s.d.</i>
<i>Pre-infusion</i>	HR	70	72	57–86	61–76	10.6
	SBP	124	124	108–137	120–131	9.8
	DBP	68	66	51–85	61–75	10.5
	MAP	89	86	74–107	81–100	11.9
	CVP	–	–	–	–	–
	CO	6598	6393	4496–9341	5998–7162	1329.7
<i>Post-infusion</i>	HR	71	69	53–101	57–77	16.1
	SBP	127	127	102–158	120–134	16.6
	DBP	72	70	60–90	64–79	10.5
	MAP	94	91	77–114	88–103	12.6
	CVP	–1.17	–0.50	–5.30–0.70	–1.39–0.88	2.18
	CO	6781	6766	4380–9599	5773–7426	1584.8

Table 6.2: Summary statistics for the baseline physiological measurements in the placebo and morphine groups, n.b. CVP is expressed as the difference from the initial baseline value to correct to calibration errors.

HR = heart rate (bpm); SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); MAP = mean arterial pressure (mmHg); CVP = central venous pressure (mmHg); CO = cardiac output (mL/min).

6.4.3 *Effect of the Simulated Hypovolaemia Protocol*

The mean values for physiological data at each stage of the experimental protocol are presented in Table 6.3. The table also shows the results of a Kruskal-Wallis test for each parameter by experimental phase. For the purposes of this analysis, experimental phases were treated as ordinal data rather than continuous variables, since the volume of simulated hypovolaemia is not necessarily proportional to the absolute negative pressure applied to the LBNP chamber. Note that the placebo group only includes pressure increments down to -80 mmHg, since no subject completed a -90 mmHg increment in that arm of the study.

In the placebo group there was a general trend of decreasing StO_2 values in deltoid and forearm with progressive increments of LBNP. The forearm values showed a greater change, both absolutely and relatively, when compared to the deltoid. Both sites demonstrated a rapid recovery to just below baseline values within five minutes of the pressure being released. Thenar eminence and head StO_2 values demonstrated a highly inconsistent relationship with LBNP: the thenar measurements initially falling then rising, while the head demonstrated very little change in StO_2 values over the course of the protocol. These changes are summarised graphically in Figure 6.4. Of all the NIRS sites only the forearm demonstrated a statistically significant difference in values between all phases of the protocol ($p=0.047$), the correlation between box pressure and StO_2 being $r_s=.52$.

Stroke distance demonstrated the strongest correlation with increments of LBNP falling consistently with progressive increments of LBNP ($r_s=.82$, $p>0.0001$). Stroke volume also demonstrated a significant strong correlation with box pressure ($r_s=.70$, $p=0.001$). Of the traditional physiological parameters only heart rate had a significant correlation with box pressure, $r_s=-.81$, $p<0.001$. CO fell consistently with increasing increments of LBNP, although the relationship was not significant ($p=0.145$). Of the other physiological parameters none demonstrated a statistically significant relationship with LBNP, although SBP and to a lesser extent MAP showed a general decreasing trend with LBNP increments. DBP demonstrated no obvious relationship with LBNP.

The administration of morphine appeared to blunt many of the physiological responses to simulated hypovolaemia. StO_2 changes in the morphine group are

PLACEBO GROUP											
Phase	Deltoid	Forearm	Thenar	Head	HR	SBP	DBP	MAP	CVP	SD	SV
<i>Pre-infusion</i>	88	80	63	76	68	120	68	89	NA	21	91
<i>Post-infusion</i>	88	76	60	77	63	120	70	89	(-0.20)	21	88
<i>-30 mmHg</i>	85	70	58	77	70	117	71	90	(-1.8)	17	69
<i>-50 mmHg</i>	83	66	62	77	86	108	70	85	(-2.40)	12	55
<i>-60 mmHg</i>	83	66	64	76	105	103	69	82	(-2.30)	10	46
<i>-70 mmHg</i>	81	65	67	78	122	107	73	86	(-3.7)	7	43
<i>-80 mmHg</i>	82	64	71	74	132	105	65	83	(-3.67)	4	35
<i>Recovery</i>	87	74	60	78	60	121	75	95	(0.62)	19	88
<i>p-value</i>	0.062	0.047	0.868	0.982	<0.001	0.060	0.973	0.758	NA	<0.001	0.001
MORPHINE GROUP											
<i>Pre-infusion</i>	89	78	68	76	70	124	68	89	NA	NA	94
<i>Post-infusion</i>	89	77	73	83	71	127	72	94	(-1.17)	21	97
<i>-30 mmHg</i>	85	72	70	82	74	122	71	90	(-3.2)	17	84
<i>-50 mmHg</i>	85	71	72	81	89	116	70	88	(-3.2)	15	69
<i>-60 mmHg</i>	86	71	68	81	102	112	73	88	(-4.3)	14	57
<i>-70 mmHg</i>	89	70	67	78	113	106	70	84	(-3.9)	9	49
<i>-80 mmHg</i>	87	69	69	79	123	98	65	79	(-4.4)	9	45
<i>-90 mmHg</i>	84	60	65	74	167	99	68	82	(-2.8)	5	28
<i>Recovery</i>	90	77	71	84	64	120	71	93	(0.9)	19	98
<i>p-value</i>	0.849	0.288	0.988	0.794	0.001	0.047	0.910	0.896	NA	0.001	<0.001
											0.726

Table 6.3: Mean values for physiological parameters during the LBNP protocol. n.b. CVP is expressed as the difference from the pre-infusion baseline value to correct to calibration errors, and is show in parenthesis. StO₂ (%); HR = heart rate (bpm); SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); MAP = mean arterial pressure (mmHg); CVP = central venous pressure (mmHg); SD = stroke distance (cm); SV = stroke volume (mL); CO = cardiac output (mL/min); MD = Minute distance (cm/min).

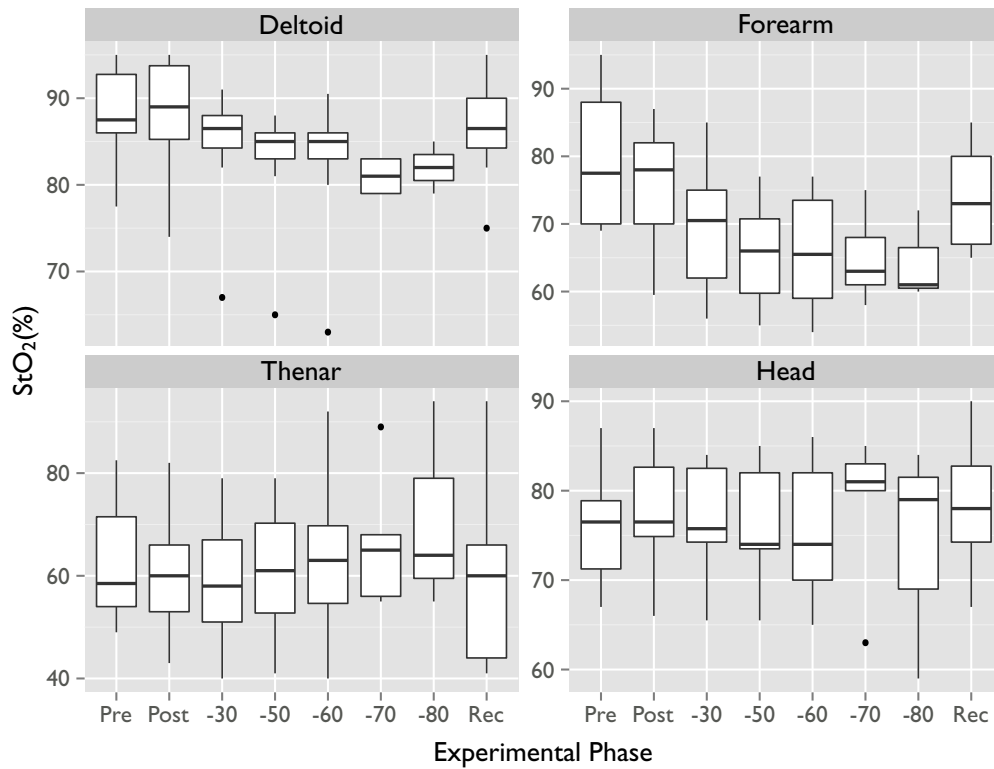


Figure 6.4: Box plots of StO_2 data over the course of the LBNP protocol for the placebo group. Sampling points: Pre=Pre-infusion baseline; Post=Post-infusion baseline; Rec=Recovery; integers denote increments of LBNP in mmHg. Plot whiskers denote maximum and minimum data points, excluding outliers which are shown separately.

summarised in the box plot in Figure 6.5. There were smaller changes, in forearm StO_2 , stroke distance, stroke volume, heart rate and CO values in response to LBNP than in the placebo group. Forearm StO_2 correlation with box pressure was weaker ($r_s=.43$), and its relationship with LBNP increments no longer significant, $p=0.288$. Of the other NIRS monitoring sites, deltoid, thenar and head StO_2 appeared largely discordant with LBNP (thenar eminence StO_2 actually increased from baseline over the course of the protocol), and none of the sites demonstrated a statistically significant relationship with LBNP. SBP showed a much stronger relationship with LBNP than in the placebo arm, consistently falling across all increments of LBNP ($p=0.047$), and better correlation with box pressure $r_s=.47$. Stroke distance ($r_s=.75$, $p=0.001$), stroke volume ($r_s=.77$, $p<0.001$), and heart rate ($r_s=-.64$, $p=0.001$) all demonstrated a significant relationship with LBNP, as they also did in the placebo

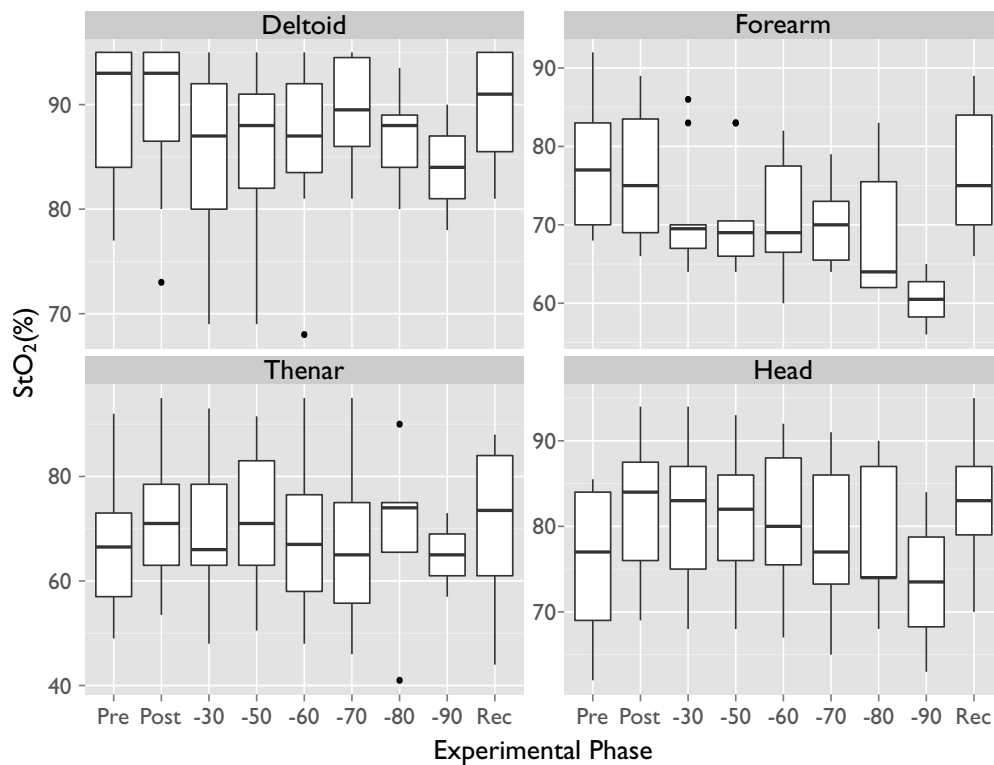


Figure 6.5: Box plots StO₂ data over the course of the LBNP protocol in the morphine group. Sampling points: Pre=Pre-infusion baseline; Post=Post-infusion baseline; Rec=Recovery; integers denote increments of LBNP in mmHg. Plot whiskers denote maximum and minimum data points, excluding outliers which are shown separately.

arm of the study, although the correlation was weaker in the morphine arm. None of the other physiological parameters demonstrated a statistically significant trend over the course of the protocol.

6.4.4 Effect of Morphine on LBNP Tolerance

In the placebo group none of the subjects completed a LBNP increment greater than -80 mmHg, while in the morphine arm two subjects completed a -90 mmHg increment. The LBNP increments completed by each subject in the two study arms are shown in Table 6.4. Morphine administration was associated with an increased LBNP tolerance in five subjects, and a lower tolerance in two subjects. In three subject there was no change in LBNP tolerance between the morphine and placebo arms. Although the morphine arm demonstrated an overall greater

<i>Subject</i>	<i>Placebo Increment (mmHg)</i>	<i>Morphine Increment (mmHg)</i>	<i>Placebo Time (mins)</i>	<i>Morphine Time (mins)</i>
2	60	60	1170	1398
3	80	90	1998	2550
4	60	80	1055	1884
5	70	80	1626	1962
6	60	50	1152	720
9	60	60	1164	1476
10	70	50	1758	1050
11	80	80	1926	2310
12	30	70	822	1518
13	80	90	2328	2622

Table 6.4: Increments of LBNP completed and duration of the protocol from induction of LBNP by subject in each arm of the study. Subjects who achieve a greater LBNP increment in the morphine arm are shown in red, those who achieved a lower increment are shown in blue.

tolerance to LBNP, this difference was not statistically significant when examined either by increment of LBNP achieved ($p=0.34$) or duration of the LBNP tolerated before pre-syncope ($p=0.23$).

6.5 DISCUSSION

The design of this study provided not only an opportunity to examine the effects of LBNP and morphine administration on StO_2 , but also to address some broader questions about StO_2 values and trends. The two arms of the study allowed direct comparison of NIRS measurements at identical sites in the same subject. It is notable that there was no difference in the pre-infusion StO_2 values of subjects between the two arms of the study. This suggests that despite the relative large range of StO_2 values recorded at each site, StO_2 is consistent within individual subjects under similar conditions. It also provides some validation of the NIRS technique and the specifically the INVOS® System's algorithm. There were however significant differences in StO_2 values recorded between different sites. In the skeletal muscle sites StO_2 was consistently lower the more distal the monitoring site. This drop would appear intuitive as blood flows further away from the core, and there is less muscle mass to supply and hence lower oxygen demands. This is an important finding, as it indicates that StO_2 values cannot be extrapolated

between different sites and used as reference ranges, as has been done in at least one study (see Arató et al. (2009) for an example of this). Instead reference StO_2 ranges must be established separately for each site of interest. The differences in StO_2 between different monitoring sites are examined in more detail in Chapter 7; but in summary, the findings presented there confirm the variation in StO_2 between sites observed in this study.

The administration of placebo was associated with a significant fall in forearm StO_2 from 80.2% to 75.8%. This a surprising finding, since there should be no difference, and this probably represents a type I error rather than a real finding. The administration of morphine was associated with a significant rise in thenar eminence and cerebral StO_2 . This effect is probably due to the vasodilatory effects of morphine (Afshari et al., 2009), increasing the ratio of arterial blood in the NIRS monitoring window and thus raising the StO_2 . But this raises the question as to why the deltoid and forearm do not show a similar effect? Cerebral blood flow is recognised to be sensitive to a number of pharmacological and chemical agents, so the findings in the brain are possibility a consequence of this. In the thenar eminence, the lower resting StO_2 values compared to other skeletal muscle sites, means that the effects of vasodilation are more likely to be reflected in StO_2 measurements here due to a greater change in the ratio of arterial to venous blood in the NIRS monitoring window. It should be noted that despite the statistical significance of some the StO_2 changes following infusion, all post-infusion StO_2 measurement fell within one standard deviation of the pre-infusion values, i.e. within the sample control range. Thus it would not be possible to identify the effects of morphine administration on StO_2 in an subject or group unless the individuals' baseline StO_2 values were known beforehand.

The main aim of this study was to examine the sensitivities of different NIRS monitoring sites in detecting simulated hypovolaemia. Of the sites studied only the deltoid and forearm demonstrated discernible changes with progressive increments of the LBNP. The thenar eminence and brain showed no clear pattern of response to simulated hypovolaemia. The findings in relation to the brain are not surprising. In the face of relatively modest degrees of hypovolaemia, such as those used in this experiment, cerebral autoregulation would be expected to maintain blood flow to the brain. The relationship of thenar eminence StO_2 to LBNP is consistent with

the findings of Soller et al. (2008a) and Bartels et al. (2011), who have previously shown negligible changes in thenar StO₂ in response to LBNP. However it should be appreciated that those studies used different NIRS monitors/algorithms to this study, and the results presented here confirm these findings with the INVOS® System.

Forearm StO₂ was the most sensitive to simulated hypovolaemia, being the only site to demonstrate a statistically significant change in response to incremental changes in LBNP. Again this finding is consistent with previous studies, although this is the first time a direct comparison between the deltoid and forearm has been performed. Deltoid StO₂ has been shown to correlate strongly with systemic oxygen delivery in clinic studies (McKinley et al., 2009) (see Section 4.4 for a more detailed discussion), and examining Figure 6.4 the trend in deltoid StO₂ is clearly discernible. It is therefore likely that deltoid StO₂ could be used to detect clinically significant changes in patients with greater degrees of blood loss. This is fortunate for military patients who are much more likely than their civilian counterparts to sustain injuries that make monitoring at distal sites, such as forearm for thenar eminence, difficult or impossible. Despite demonstrating a statistically significant change in StO₂ in the placebo arm of the study the absolute change in forearm StO₂ over the course of the experiment was relative small (from 80–64%). The mean StO₂ during the -80 mmHg pressure increment (64%) lay just outside the pre-infusion reference range (69–95%) and actually inside the post-infusion range (60–87%). This is a problem also mirrored in the results of Soller et al. (2008a) and McKinley et al. (2009) and illustrates the point, that in the mild to moderate hypovolaemia, isolated StO₂ measurements are difficult to interpret without a knowledge of the resting values for that patient. Obviously this is a luxury not available in the clinical environment, and unless grossly deranged, it is likely that monitoring the trend in StO₂ during the course of resuscitation would be more useful than knowing the absolute values.

Of all the physiological parameters stroke distance and heart rate demonstrated the strongest correlation with LBNP increments, $r_s=.82$ and $r_s=-.81$ respectively, and were superior to forearm StO₂ measurement. However these parameters are not necessarily the best means of monitoring the physiological status of the trauma patient since they are not without practical limitation. Stroke distance

requires manual measurement by echocardiography; it is time consuming and technically demanding to perform. Although the recording are made in real time, they are intermittent, and thus provide only a snap shot of the patients' physiology. The measurement of stroke distance requires special training, and even then there is significant inter-observer variability (this was avoided in this study by using the same technician for all measurements). For these reasons the measurement of stroke distance remains confined to the cardiology clinic and the research environment. Heart rate has a biphasic response to hypovolaemia, initially increasing but then demonstrating a 'paradoxical' drop as the reduction in central blood volume approaches 30%. Only with further blood loss is there an increase in heart rate signalling the progression towards irreversible shock (see Section 1.3.2 for a more detailed discussion of this phenomenon). This biphasic response was not seen in this study, either because none of the subjects approached a 30% reduction in central blood volume (the study being terminated at the point of presyncope), or the response was absent in this young fit group who compensated well for the hypovolaemia. For this reason heart rate probably performed better in this study than it does in clinical practice.

Finometer® measurements of stroke volume also correlated well with box pressure ($r_s=.70$), which is consistent with the findings of Soller et al. (2012). The Finometer® provides an interesting technique for assessing volume state in the hypovolaemic patient: being non-invasive and providing real time, continuous output. However the device does have significant practical limitations: it requires calibration with an arm calibration module; monitoring is performed via the fingers which may be damaged in trauma patients; and the hand has to be kept in the same relative position to heart while monitoring. These limitations make the Finometer® impractical for use in real trauma patients, and largely limit its use to the research environment.

None of the other physiological parameters demonstrated a significant correlation with LBNP. In particular CO, despite being the product of two significantly correlated variables (heart rate and stroke volume) did not show a significant relationship with box pressure, although it did demonstrate a modest correlation $r_s=.40$. The reasons for this are unclear, but it could represent a non-linear relationship between independent and response variables.

Morphine administration attenuated the response of most physiological measurements in response to simulated hypovolaemia when compared to the placebo group. The pharmacology of morphine's effects in human trauma patients is still poorly understood, but vasodilation and effects on the central nervous system may account for the results seen in this study. Vasodilation would explain the blunting of the NIRS signals and the fact that StO_2 was significantly higher in the thenar eminence and head following morphine infusion, and generally higher at all sites throughout the LBNP protocol. Because of the skew left distribution of StO_2 values* anything that causes a shift to the right in the StO_2 curve will compress the range of values at their upper end leading to an apparent reduction in sensitivity. A combination of these reasons probably account for the fact that non of the NIRS monitoring sites showed a statistically significant relation with box pressure in the morphine group. However the general trend of decreasing StO_2 values could still be discerned in the forearm (see Figure 6.5), although it was largely lost in the deltoid. It is probable that the trends would become more obvious in patients with higher degrees of blood loss, and therefore NIRS may still be of value in the severely injured trauma patient even after morphine administration.

Stroke volume, stroke distance and heart rate all correlated well with box pressure in both the placebo and morphine groups. Although for the reasons discussed above only heart rate provides a practical tool for clinical use, providing the caveat regarding its biphasic response to hypovolaemia is understood. None of the blood pressure parameters provided a reliable indicator of the degree of hypovolaemia. Diastolic blood pressure in particular had no discernible relationship with box pressure, as would be expected in cases of mild to moderate hypovolaemia where a narrowing of the pulse pressure is part of the compensatory mechanisms to maintain blood flow, only subsequently falling as the hypovolaemia progresses.

6.6 CONCLUSION

The main finding of this study is that there were significant differences between StO_2 values recorded at different anatomical sites, both in terms of their resting

*This occurs probably as a result of a combination of physiological factors and algorithmic compression of StO_2 values in the upper range by the NIRS monitor. The distribution of StO_2 measurement is discussed more fully in Section 4.1 and assessed experimentally for the INVOS® System monitor in the NIRS normal values and response to exercise study described in Chapter 7.

values and their sensitivity to LBNP simulated hypovolaemia.

Of the NIRS monitoring sites studied here, the forearm was the most sensitive to changes induced by a mild to moderate simulated hypovolaemia. In cases where the forearm cannot be used, the deltoid is a possible alternative. Although deltoid StO_2 did not vary significantly with LBNP in this study it did demonstrate discernible changes which would probably be more obvious in the severely hypovolaemic patient. The thenar eminence and frontal lobe of the brain appear to be unreliable monitoring sites, demonstrating no useful trend changes in this study. The administration of morphine attenuated the StO_2 response (and that of conventional haemodynamic parameters) to hypovolaemia, but did not completely eliminate it.

7. NORMAL NIRS VALUES AND RESPONSE TO EXERCISE STUDY

7.1 INTRODUCTION

To interpret the results of NIRS measurements from experimental studies and in clinical practice, it is necessary to have a working knowledge of the normal range of StO₂. Unfortunately, despite a large body of ongoing work in the field, to date there has only been one published description of the range of normal StO₂ values.

Crookes et al. (2005) recorded StO₂ values from the thenar eminences of 707 ambulatory volunteers, using an InSpectra™ Tissue Spectrometer (Hutchinson Technology). A detailed discussion of their findings is presented in Section 4.1, however in summary their work found that there was a wide range of normal StO₂ values with a skew left distribution (see Figure 4.1 on page 42). Mean StO₂ for all subjects was $87 \pm 6\%$, however significant differences were found between males (mean StO₂ $88.38 \pm 5.51\%$) and females (mean StO₂ $85.4 \pm 6.69\%$), $p < 0.001$; between smokers (mean StO₂ $89.59 \pm 4.57\%$) and non-smokers (mean StO₂ $86.03 \pm 6.54\%$), $p < 0.001$; and between different ethnic groups (although these differences were small enough to probably be of limited clinical significance).

It should be appreciated that Crookes et al. (2005) findings apply only to StO₂ recordings made with the same model InSpectra™ Tissue Spectrometer. Machines using different algorithms or different physical designs, such as dual beam monitors, would be likely to record different absolute values, although the distribution of the population values would be expected to be similar. Furthermore it cannot be assumed that StO₂ values at other anatomical sites would record the same values, or even necessarily the same distribution pattern. How StO₂ values vary between anatomical sites is currently unknown, although Crookes et al. (2005) report observing differences in resting StO₂ values at different anatomical sites in their previous animal work. It is therefore important that when establishing normal StO₂ values as a basis for further work that it should be performed using similar apparatus, and for each anatomical site that is intended to be studied. Given the, albeit small, differences observed between sexes and ethnic groups, the normal range of StO₂ values should ideally be established in a population group similar to

the one of interest.

In military and civilian environments, trauma often occurs following a period of exertion, for example the soldier injured during combat, the cyclist involved in a road traffic collision, or the patient with chronic exertional compartment syndrome. Exercise is known to have an effect on StO₂ values in both working and non-working muscle groups, and has been well studied (see Section 4.5 for a more detailed discussion). However, the NIRS changes during recovery following exercise, particularly in non-working muscle groups, are still not well understood. It has been shown that StO₂ increases in non-working muscle groups following exercise, the increase being proportional to the work performed, and that values typically return to normal within five minutes of cessation of exercise (Nagasawa, 2008a,b). Unfortunately, these studies used isolation exercises (leg raises) or highly specific exercise protocols (cycling), and it is unclear how these findings may relate to ‘uncontrolled’ mixed exercise of the type that commonly precede trauma.

7.2 AIM

The primary aim of this study was to establish descriptive data for StO₂ values at rest from a number of anatomical sites of use to clinical practice, in the most clinically relevant population for the military — young infantry males. A secondary aim was to determine if a mixed exercise protocol caused significant changes in StO₂, that would need to be considered when interpreting StO₂ values in post-exercise subjects.

7.3 MATERIALS AND METHODS

The experimental design was that of a prospective cross-sectional study in human volunteers. Full ethical approval for the study protocol was obtained from the Ministry of Defence Research Ethics Committee (MoDREC) and written consent obtained from all participants. The study was conducted at 42 Royal Marine Commando Regiment (Cdo Reg), Plymouth and Commando Training Centre (CTC) Royal Marines, Lympstone between the dates of 8–16 th November 2011.

7.3.1 *Study Population*

The study sample was selected to be representative of the injured military population seen in recent conflicts from Iraq and Afghanistan. The study group was

drawn from 42 Cdo Reg, Plymouth, an infantry regiment and Hunter Troops 2 and 3 CTC, Lympstone, an infantry training regiment. Hunter Troops 2 and 3 are advanced rehabilitation groups within CTC and similar in composition to a standard infantry regiment.

Eligible for inclusion in the study were all male military personnel in the participating Commando units between the ages of 18–35 years, subject to the following exclusion criteria:

1. any medically downgraded individual below Joint Medical Employment Standard (JMES)*: MFD (Fully Deployable) A4 (fit to be flown in a passenger aircraft) L2 (Fit for unrestricted duties but with a medical risk marker) M1 (fit for unrestricted duties) or M6 (maritime assessment not currently required) E1 (fit for worldwide service in all environments).
2. any individual currently in receipt of light duties, excluding them from physical training.
3. any confirmed or suspected bony injury, i.e. fracture or stress fracture, to either the arms or legs within the previous 8 weeks.

Eligible subjects were identified from unit personnel tables; downgraded and medically unfit individuals were identified by unit company commanders and excluded. Eligible subjects received a written and verbal brief at least 48 hours in advance of the study day, individuals wishing to volunteer for the study were then allocated a study day and time, and asked to refrain from exercise for 24 hours prior to participation, and from smoking or alcohol consumption from midnight the day before.

On the study day subjects were asked to read the subject information leaflet, before undergoing a brief screening interview to confirm they had no medical conditions meeting the exclusion criteria.

*JMES is standardised record of an individuals' employability based on their physical and mental condition. An equivalent standard was taken for members of Hunter Troop 2 and 3 who, having not completed basic training, are not eligible for deployment. A summary of JMES codes is given in Appendix D.

7.3.2 NIRS Monitoring Protocol

The study was conducted indoors in the gymnasium halls of 42 Cdo Reg and CTC to minimise the variations in ambient temperature. Subjects were requested to attend in standard physical training clothing, t-shirt and shorts, with appropriate running shoes. The study protocol was performed in pairs to encourage competition during the exercise phase.

Subjects were rested supine on an exercise mat for 10 minutes after which they moved across to the designated monitoring mats to allow attachment of the NIRS monitoring. Two INVOS® System NIRS monitors were used in a four channel setting. The internal clocks of the two machines were synchronised with the investigators' watches to ensure consistency between the time stamped data and the time of exercise completion. StO₂ readings were taken from the following sites (see Figure 5.3 on page 64 for an illustration of the probe positions):

1. *the left deltoid* — with the probe positioned two finger breadths above the deltoid insertion, with the probe/cable connection directed cranially.
2. *the right deltoid* — with the probe positioned two finger breadths above the deltoid insertion, with the probe/cable connection directed cranially.
3. *the left leg* — with the probe positioned one finger breadth lateral to the anterior margin of the tibial, midway between the knee and the ankle so as to monitor the anterior compartment of the leg. The probe cable/connection was directed distally.
4. *the left frontal lobe of the brain* — with the probe positioned one finger breadth above the orbital ridge, with the probe/cable connection directed laterally and the distal end of the probe located in the midline.

To ensure accurate readings, the hair over the monitoring site on the leg was clipped with an electric razor prior to probe attachment. In one individual it was also necessary to clip the hair over the deltoid regions. Probes were reused between subjects. To ensure adequate adhesion and exclude extraneous light, probes were secured at each site with medical tape. NIRS readings from the four anatomical sites were recorded every six seconds for 10 minutes in the rested (pre-exercise) state, after which the probes were removed and the subject allowed to get up and prepare for the exercise protocol.

7.3.3 Exercise Protocol

To simulate the physical demands of a soldier working in the field, the US Marine Corps (USMC) Fitness Test was chosen as a widely used standard protocol testing range of physical attributes. All exercises were performed under the supervision of a qualified unit physical training instructor (PTI). A complete description of the requirements of the USMC Fitness Test are given in Appendix C, in summary the test consists of:

1. *Overarm pull-ups* — maximum number possible in a single set.
2. *Sit-ups* — maximum number possible in two minutes. A weighted barbell was provided for secure the feet for those individuals who chose to use it.
3. *Three mile run* — completed at individual best effort. For the purpose of standardisation, this test was performed on a Technogym Run 700 model treadmill set to a 1% incline to simulate outdoor running.

Each exercise was separated by a two minute rest and the performance in each element recorded by the PTI. At the end of the run it was expected that most individuals would be working at their VO_2max , thus standardising the effort between subjects. Upon completion of the run, subjects were returned to the monitoring mat. The monitoring sites were towel dried and a further 10 minutes of StO_2 monitoring performed using the same protocol as that used for the pre-exercise monitoring. Owing to the practicalities of performing the monitoring and run in separate rooms, there were differences in the length of time subjects took to return to the monitoring mat. This, coupled with differences in the time required to reattach the probes and ensure a good reading led to variations in the time interval between subject finishing the exercise protocol and starting the post-exercise monitoring. To correct for this time discrepancy each individual had the exact time at which they finished their run recorded, which was then used to adjust the time stamp on the NIRS data to ensure all comparisons of data in the post-exercise phase were performed at the same time period with respect to completing the exercise protocol.

<i>No</i>	<i>Field</i>	<i>Comments</i>
1	Study specific number	Generated by study
2	Regimental Number	
3	Date of Birth	
4	Age	Calculated from date of birth
5	Smoker	Binary field (yes/no)
6	Estimated current tobacco consumption	Packs per day
7	Estimated tobacco pack year history	Packs per day per year
8	StO ₂ values in left leg pre-exercise	
9	StO ₂ values in left deltoid pre-exercise	
10	StO ₂ values in right deltoid pre-exercise	
11	StO ₂ values in left frontal lobe pre-exercise	
12	StO ₂ values in left leg post-exercise	
13	StO ₂ values in left deltoid post-exercise	
14	StO ₂ values in right deltoid post-exercise	
15	StO ₂ values in left frontal lobe post-exercise	
16	Number of pull-ups performed	
17	Number of sit-ups performed	
18	Run time	
19	Time of finishing run	GMT
20	Time of starting post-exercise monitoring	GMT
21	Lag time between run and starting post-exercise monitoring	Calculated from fields 19 & 20

Table 7.1: Data fields used in the NIRS exercise study. N.B. one packet of cigarettes is taken to be 20 cigarettes; a pack year is the equivalent of smoking one packet of cigarettes every day for a year.

7.3.4 Data Collection

In addition to the NIRS data and exercise performance results, additional basic demographic data and details of subjects' smoking history were collected. A summary of the separate data fields for which information was collected is given in Table 7.1.

7.3.5 Data Analysis

Testing the data distribution for normality was undertaken by examining Q-Q plots and confirmed with a Anderson-Darling test. Comparisons of parametric data was performed using a paired t-test. Comparison of non-parametric data was performed using Wilcoxon rank-sum and Kruskal-Wallis tests. All statistical tests

were undertaken using the R programming language and environment for statistical computing (R Development Core Team, 2009) with a significance threshold of $p \leq 0.05$.

7.4 RESULTS

7.4.1 *Demographics of Study Population*

A total of 107 (88 at 42 RM Cdo and 19 at CTC) male subjects were screened for the study, two subjects, both at CTC, were excluded on the grounds of sustaining a lower limb injury within the previous eight weeks. All of the 105 eligible volunteers completed the whole of the study protocol. The mean age of subjects was 22.7 years (s.d. 4.0, range of 18–36 years). All subjects were Caucasian with the exception of one black (African ethnicity) subject.

There were 33 current smokers in the cohort, accounting for 31% of the subjects. There were no ex-smokers, i.e. everyone who had previously smoked was still a current smoker. Within the smoking group the mean number of cigarettes smoked per day was 9.5 (s.d. 5.1, range 0.25–20). The mean pack year history was 2.9 (s.d. 3.3), but there was a wide range of 0–15 pack years due to one outlier at the upper end. The breakdown of current tobacco consumption and pack year history is give in Table 7.2. There was no significant correlation between smoking and StO_2 values in the resting or post-exercise state.

7.4.2 *Exercise Performance*

All 105 subjects completed the exercise protocol. Summary statistics for the exercise performance data are presented in Table 7.3 as an indicator of the physical conditioning of the study population.

7.4.3 *NIRS Values at Rest*

Histograms for the raw pre-exercise data are shown in Figure 7.1. Sample data for both deltoids showed a skew left distribution, data for the brain and leg appeared normally distributed, but did not conform to normality when assessed with a Q-Q plot or Anderson-Darling test. Transformation of the data to conform with normality was not possible. Assessment of the median StO_2 values for each subject did conform to normality, thereby allowing statistical analysis with parametric tests.

<i>Subject</i>	<i>Current Tobacco Consumption</i>	<i>Pack year History</i>	<i>Subject</i>	<i>Current Tobacco Consumption</i>	<i>Pack year History</i>
1	10	1	18	1	0
2	10	0.25	19	4	1
3	5	0.5	20	12	1
4	10	0.5	21	10	2.5
5	20	10	22	2	8
6	10	1	23	10	4
7	10	2.5	24	6	0.5
8	5	3	25	5	0.5
9	5	4	26	10	4
10	20	4	27	7	6
11	1	0	28	15	2
12	10	1	29	4	1
13	10	1	30	20	6
14	10	1.5	31	20	15
15	10	0.5	32	10	3
16	10	0.5	33	10	3
17	10	2			

Table 7.2: Data for tobacco consumption in smokers.

<i>Exercise</i>	<i>Mean</i>	<i>Median</i>	<i>Standard Deviation</i>	<i>Range</i>
Sit-ups	79	80	11	55–114
Pull-ups	16	15	5	6–37
Run time (mins)	20:47	20:43	1:17	17:00–23:11

Table 7.3: Exercise performance data for each of the elements of the USMC fitness test.

Descriptive statistics for median StO₂ values at rest are presented in Table 7.4. Comparison of StO₂ values between the left and right deltoid with a two sample t-test showed no significant difference NIRS values recorded at the two sites (p-value 0.302). There were significant differences in StO₂ measurement between the deltoids and the leg, deltoid and brain and leg and brain (all p-values <0.001).

The effect of time, as an independent variable during the recording period, on StO₂ measurements was assessed with Kruskal-Wallis test. The respective p-values: left deltoid 0.996; right deltoid 0.988; leg 1.00; and brain 1.00, suggest that the time of measurement has no influence upon StO₂. However, plots of StO₂ against time,

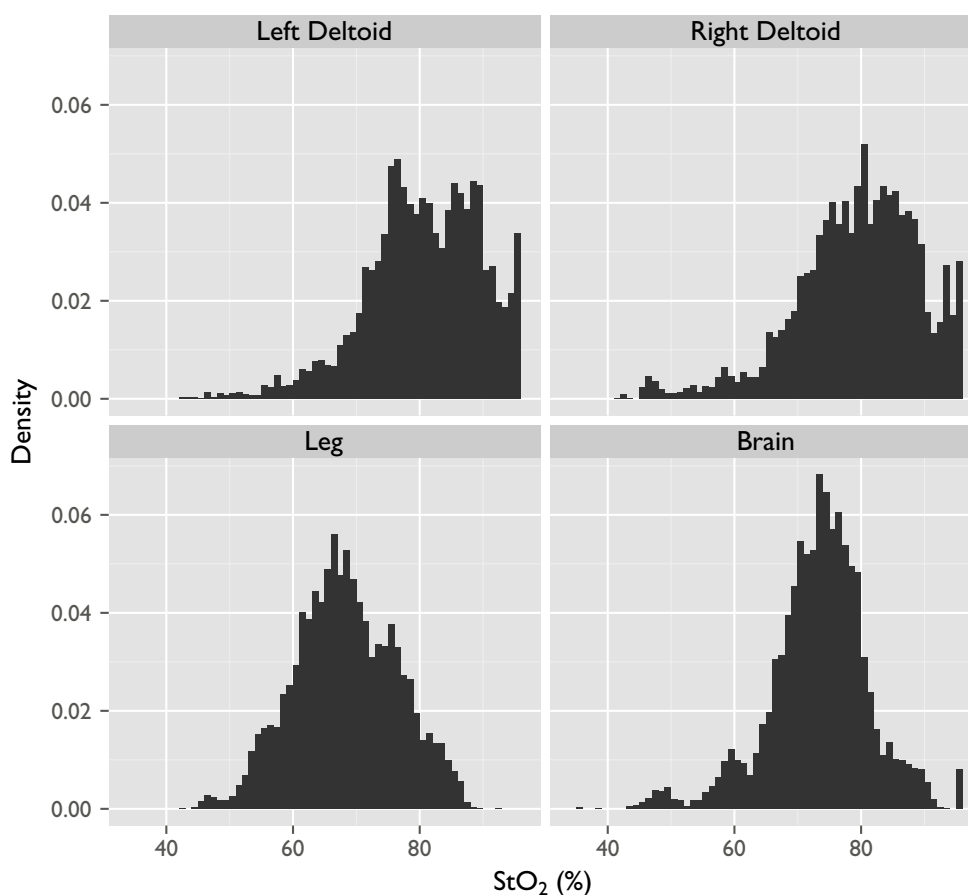


Figure 7.1: Histograms of the raw pre-exercise StO_2 data at each monitoring site. Note the skew left distribution of StO_2 measurement in the deltoids. StO_2 values in the brain and leg appear to be normally distributed but did not conform to normality when analysed with the Anderson-Darling test.

appeared to demonstrate a ‘warm-up’ period of rising StO_2 values during the first 1–2 minutes of recordings, which then plateaued to stable values (Figure 7.2). To examine this phenomenon further median StO_2 values of each of ten successive observations corresponding to the first and fifth minutes of measurement were compared. The fifth minute was selected as an arbitrary point at which steady state recordings appeared to have been achieved as assessed by visual inspection of the traces shown in Figure 7.2. StO_2 values from the first and fifth minute for each anatomical site were compared with a Wilcoxon rank-sum test. The respective p-values were: left deltoid 0.03; right deltoid 0.044; brain 0.156; leg 0.15. This

		<i>Mean</i>	<i>95% CI for Mean</i>	<i>Range</i>	<i>Q₁–Q₃</i>	<i>s.d.</i>
<i>Raw data</i>	Left Deltoid	80.0	79.8–80.2	42–95	75–87	9.1
	Right Deltoid	78.8	78.6–79.0	41–95	73–86	9.7
	Leg	67.7	67.7–68.0	42–92	62–74	8.1
	Brain	72.9	72.8–73.1	43–95*	69–78	7.9
<i>Median</i>	Left Deltoid	80.1	78.4–81.8	49–95	75–87	8.9
	Right Deltoid	78.8	77.0–80.4	46–95	74–85	9.5
	Leg	67.7	66.2–69.2	47–85	63–74	7.8
	Brain	73.0	71.6–74.5	47–95	69–78	7.6

* There was a single outlying lower reading of 35% recorded in the brain.

Table 7.4: Descriptive statistics for pre-exercise raw and median StO₂ data.

confirms significant differences between the one and five minute points for both deltoids, but not for the brain or leg. To confirm the validity of using the five minute data as representative sample of steady state recording, i.e. the five minute is not part of the warm of ‘warm-up’ period, a significance test was performed between the five minute dataset and the subsequent recordings (the 6–10 minute period). A further comparison of the one minute dataset against the 6–10 minute period was also performed to see if differences could be detected between these datasets. The results of the Wilcoxon rank-sum test for these analyses are shown in Table 7.5. These results show significant differences in the StO₂ values at one minute compared to those recorded after six minutes at all sites except for the brain. The five minute values did not show a significant difference when compared to the post six minute data, for any site. There was no evidence to suggest that five minute data and subsequent measurements are from different populations, implying that the ‘warm-up’ period is complete at the five minute point.

7.4.4 Response of NIRS Values to Exercise

As discussed in Section 7.3.2, for practical reasons there were differences in the length of time between subjects finishing the exercise protocol and starting the post-exercise monitoring. Examining this time difference, it was found that all subjects had a common monitoring period ten minutes after completion of the exercise protocol. To avoid the confounding effect of subjects being at different

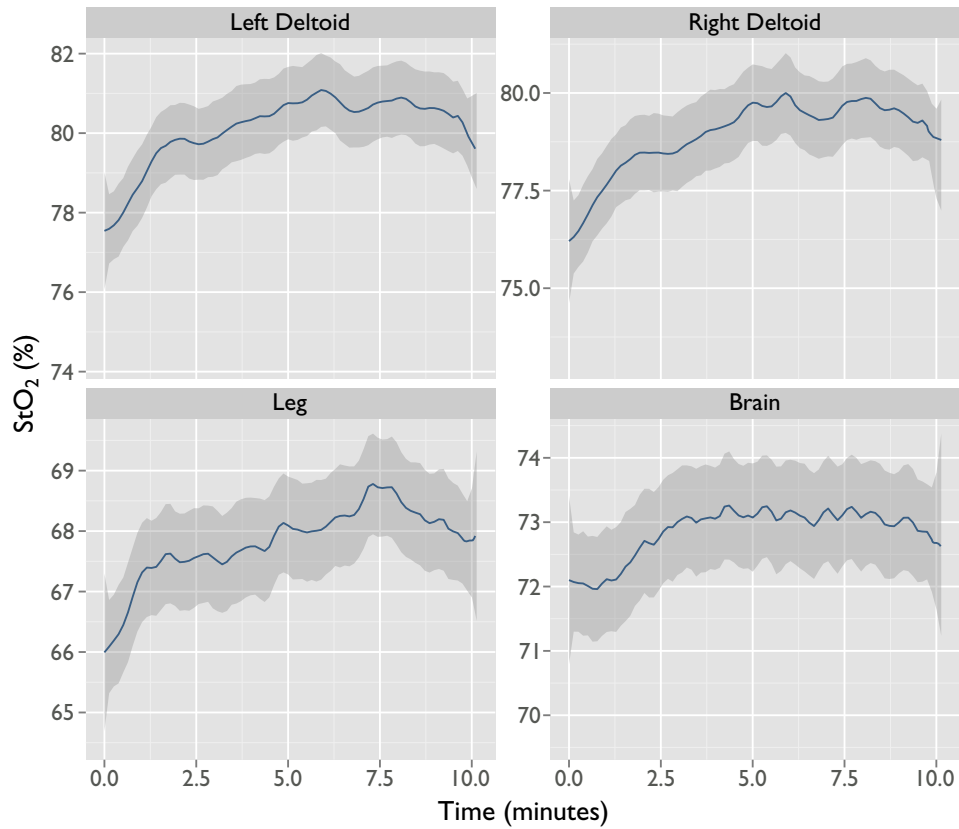


Figure 7.2: StO_2 measurements over time for each monitoring site in the pre-exercise phase. The 95% confidence interval for the data is shown in grey. Note the gradual rise in StO_2 , most obvious in the deltoid traces, during the first minute of recording.

	<i>p-value</i>	
	<i>One Minute</i>	<i>Five Minute</i>
Left Deltoid	0.005	0.924
Right Deltoid	0.008	0.856
Brain	0.059	0.999
Leg	0.029	0.794

Table 7.5: Results for Wilcoxon rank-sum tests comparing the pre-exercise data recorded from the first and fifth minutes to that from the 6–10 time period.

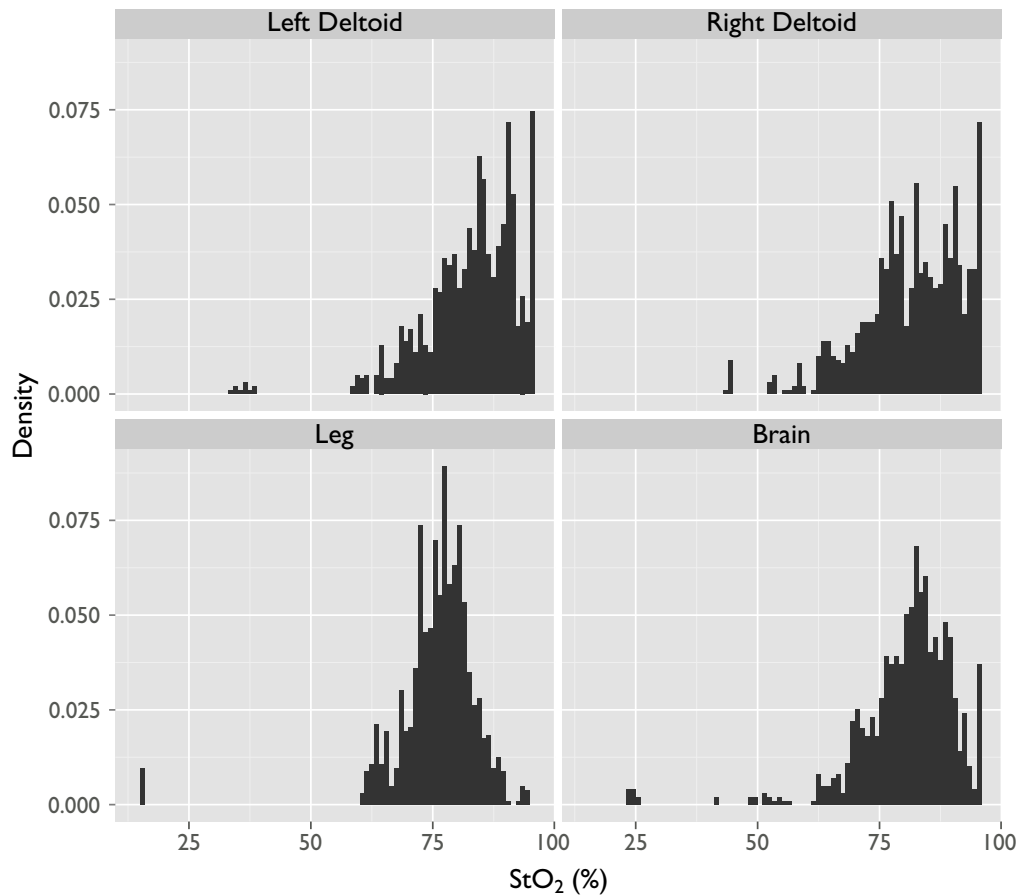


Figure 7.3: Histograms of the raw post-exercise StO₂ data at each monitoring site. Note the peak at 95% corresponding to maximum recording limit of the INVOS® System. This peak is more obvious than in the pre-exercise data due to the right shift in StO₂ following exercise.

stages of post-exercise recovery, StO₂ data from the 10-min to 11-min period following completion of the run were used for the post-exercise data analysis.

Histograms of the raw post-exercise NIRS data at all time points are shown in Figure 7.3. This data need to be interpreted with care as the raw data is taken from individuals at different stages of the post exercise recovery period. Despite this the data patterns are similar to those seen in the pre-exercise data (Figure 7.1), although the curves are slightly shifted to the right — most obvious in the brain and leg data. Again when assessed with Q-Q plots and an Anderson-Darling test, none of the raw datasets conformed with normality and it was not possible to

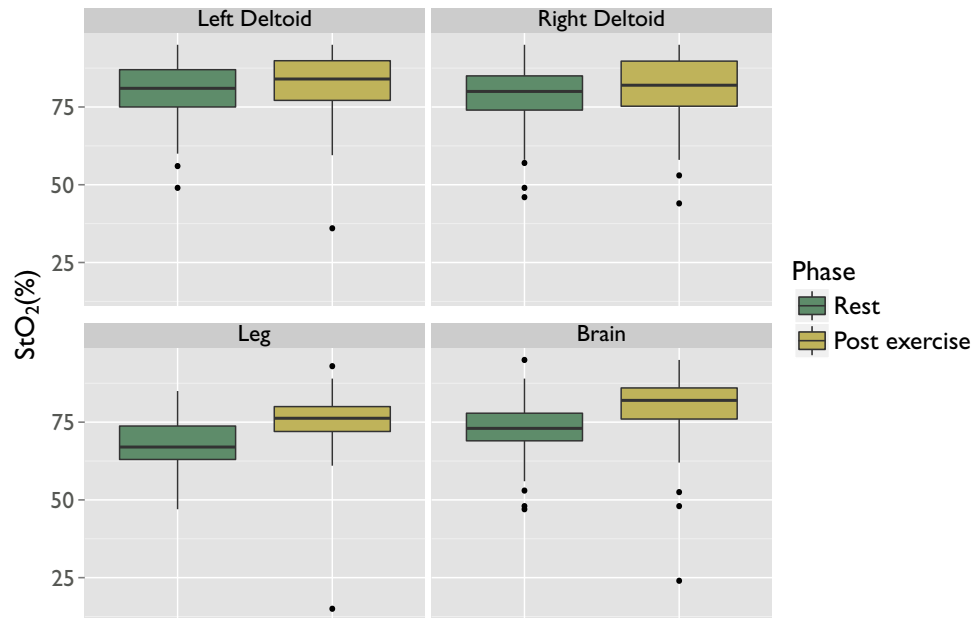
	<i>p-value</i>	
	<i>One Minute</i>	<i>Five Minute</i>
Left Deltoid	0.031	0.849
Right Deltoid	0.112	0.955
Brain	0.373	0.630
Leg	0.830	0.044

Table 7.6: Results for Wilcoxon rank sum tests comparing the post-exercise data from minutes one and five to the data from the 6–10 time period.

transform them.

Descriptive statistics for the post-exercise median StO_2 values are presented with a box plot representation of the same data in Figure 7.4, for reference the pre-exercise data is also shown. StO_2 was significantly higher at all sites in the post-exercise NIRS data compared to the pre-exercise data. The differences at each site for the raw data being: left deltoid by $3.1 \pm 2.0\%$ ($p=0.002$); right deltoid by $2.6 \pm 2.3\%$ ($p=0.003$); leg by $8.0 \pm 2.3\%$ ($p<0.001$); and brain by $8.6 \pm 1.9\%$ ($p<0.001$). Similar differences were seen when comparing the median data: left deltoid by $3.1 \pm 3.0\%$ ($p=0.002$); right deltoid by $1.4 \pm 2.7\%$ ($p=0.025$); leg by $7.3 \pm 2.1\%$ ($p<0.001$); and brain by $4.7 \pm 3.9\%$ ($p<0.001$).

Examination of the raw post-exercise data from each site did not demonstrate any time related phenomenon. A Kruskal-Wallis test applied to this data using the same procedure as that applied to the pre-exercise data returned p -values of 1.00 for all sites, suggesting that there was no relationship between StO_2 and the time at which the measurement was taken. To further examine the possibility of a ‘warm-up’ effect being present in the post-exercise values, the same analysis comparing the NIRS values from the one minute and five minute intervals to the 6–10 minute period was performed. The results of this analysis, presented in Table 7.6, show that the values recorded at one minute in the left deltoid and five minutes in the brain differ from those data recorded between 6–10 minutes at 95% confidence. The other six data subsets show no evidence of this difference.



		Mean	95% CI for mean	Range	Q ₁ –Q ₃	s.d.
<i>Pre-exercise</i>	Left Deltoid	80.1	78.4–81.8	49–95	75–87	8.9
	Right Deltoid	78.8	77.0–80.4	46–95	74–85	9.5
	Leg	67.7	66.2–69.2	47–85	63–74	7.8
	Brain	73.0	71.6–74.5	47–95	69–78	7.6
<i>Post-exercise</i>	Left Deltoid	83.3	81.8–84.9	36–95	77–90	7.9
	Right Deltoid	81.7	80.0–83.4	44–95	75–90	8.8
	Leg	75.8	74.6–77.0	15–95*	72–80	6.2
	Brain	81.6	80.1–82.9	24–95	76–86	6.9

Figure 7.4: Box plot and summary statistics for median StO₂ values from each monitoring site for the pre and post-exercise. Outliers are included in the summary statistics but are shown separated from the main data in the box plots. The data shows a statistically significant increase in StO₂ at all sites following exercise. Plot whiskers denote maximum and minimum data points, excluding outliers which are shown separately.

* In the post-exercise leg group there were two outliers recording a consistently low StO₂ of 15%, which represents the lowest value of the INVOS® System’s recording scale.

7.5 DISCUSSION

The main finding of this study is that there is a wide range of normal StO₂ measurements and descriptive data for values recorded from the deltoid, anterior compartment of the leg, frontal lobe of brain have been presented. Although all sites demonstrated a similar range of StO₂ values (between approximately 46–95%), they had different distributions and mean values. Mean StO₂ values in the head (73%) were significantly lower than those recorded in either deltoid (left deltoid 80%, right deltoid 79%, $p < 0.001$), and the values in the leg lowest of all (68%, $p < 0.001$ for comparisons with the deltoid and cerebrum). This is an important observation, since it means StO₂ reference ranges cannot simply be extrapolated between sites and should be established for each monitoring site of interest. The exception to this is when comparing identical contralateral sites. There was no significant difference between the mean StO₂ values recorded from the left and right deltoids ($p = 0.302$) — the 1% difference observed being within the $\pm 1\%$ accuracy of the INVOS® System quoted by the manufacturer (see Appendix A). This is as would be expected, providing there was no significant difference between contralateral sides, such as injury or vascular compromise, and validates the internal consistency of the technique, demonstrating that when monitoring for systemic physiological changes either side may be used. Although not demonstrated by this study, this finding is likely to be equally applicable to anatomical sites other than the deltoids. At least one clinical study has used StO₂ reference ranges established from one site to interpret values recorded from a different locations. Arató et al. (2009) used thenar eminence reference ranges as baseline for comparing to StO₂ values recorded from the lower limb in compartment syndrome. The finding of such studies should be reevaluated in the light of this understanding of the differences in StO₂ between different sites.

Examining the raw pre-exercise data shown in Figure 7.1, the difference in StO₂ distribution between sites can be appreciated. Deltoid StO₂ demonstrates a skew left distribution which is noticeably different from that of the leg or cerebrum (although the median values do demonstrate a normal distribution). It is unlikely that such a difference should arise as a result of physiological phenomenon as the mechanisms controlling the resting blood supply to the deltoid and the anterior compartment of the leg are fundamentally the same. More probably this difference

arises as a result of compression of the data at the upper end of the monitoring range. Similarly, the isolated peak seen at 95% in the distribution is a result of the arbitrary upper limit in the machine's monitoring scale, rather than a physiological phenomenon. This compression of the monitoring scale at its upper end is probably a deliberate decision on the part of manufacturer to reduce the range of 'normal' StO₂ values and improve granularity at the more clinically useful lower end.

Despite the differences in mean StO₂ between monitoring sites, the absolute range and spread of values were very similar. Standard deviations for the raw data were between 7.9–9.7, meaning 95% of measured normal values would be expected to fall within 20% of the mean for that site. All sites demonstrated a similar absolute minimum of between 41%–43%. This provides a potential clear cut off of 40%, at which the distinction between potentially normal and clearly abnormal StO₂ values can be made. While this may provide a convenient means of identifying gross pathology, the very wide range of normal values are likely to limit the utility of the device in the trauma setting once the initial resuscitation is complete and StO₂ values approach or enter the lower range of normality. It is possible that trend changes in StO₂ values in the normal range would be of more use in monitoring the response to resuscitation than the absolute values themselves.

The 'warm-up' of gradually increasing StO₂ measurements at the start of the pre-exercise recording was an unexpected finding. Since individuals had rested supine for 10 minute prior to monitoring, it is difficult to explain this as a physiological phenomenon. It is more likely that this is a machine or technique related factor. One possible explanation is that the heating effect of the infrared light causes local vasodilation, thereby increasing the ratio of arterial to venous blood in the monitoring window and raising StO₂. If this is the case, then it might be argued that the same effect should be seen in the post-exercise data. There are at least two confounding factors in the post-exercise state that are not present at rest and may explain why this does not occur:

1. in the post exercise state, the tissues (particularly in the leg and deltoid) are already warm and vasodilated and the small amount of heating from NIRS probe has no effect. The only way to exclude this as factor would be

to leave individuals attached to the monitor throughout the exercise and post-exercise monitoring period.

2. in the post exercise period subjects are recovering from the exercising state and experiencing a progressive reduction in cardiac output as they pay off the oxygen debt. We know from the studies of individual muscle groups, that StO_2 progressively falls to baseline during this period*. This would make detecting the small effect of a simultaneously occurring 'warm-up' effect very difficult.

This study is unable to distinguish between these simultaneously occurring events, not least because the time interval before starting the post-exercise monitoring varied between subjects — but this was never one of the study aims. What this study does demonstrate is that 'warm-up' is complete at five minutes. When performing experimental studies this should be considered, but waiting five minutes for a stable reading defeats one of the main advantages of NIRS and is not practical for the trauma scenario. However, to put the results into context, the effect of the 'warm-up' is at most a 3% change in StO_2 . This falls only just outside the quoted $\pm 1\%$ tolerances of the machine and around one third of a standard deviation of the deltoid measurement. As such the effect of this phenomenon in the clinical environment is likely to be negligible.

Comparing the resting and post-exercise StO_2 values, there was a statistically significant increase in StO_2 observed at all sites, which persisted for at least 10 minutes following cessation of exercise. The increase in StO_2 was greater in the brain (+8.6%) and leg (+8.0%) than the deltoids (+3.1%). The reason for this difference in magnitude of changes between different sites is probably multi-factorial. Firstly the deltoids recorded a higher StO_2 at rest and therefore have less room to increase before being subject to the previously discussed compression effects at the top end of the scale. The order and type of exercises used in the protocol are also likely to impact upon the relative increases in StO_2 . The pull-ups were the first exercise to be performed, and although they have an upper body focus, they only

*The studies of Nagasawa (2008a) and Nagasawa (2008b) suggested that StO_2 in exercised muscles should return to base line within five minutes of completing exercise, but this is not consistent with the results presented here where a statistically significant increase in StO_2 was seen to persist for at least 10 minutes following exercise.

really involve the posterior deltoid. On average there was a 35 minute time lag between completion of the pull-ups and the 10 minute point of the post-exercise monitoring. This may be sufficient to allow recovery from the deltoid specific pull-ups, although it would still be expected that they would show a rise in StO₂ as result of the run. This would be consistent with findings of previous studies which have demonstrated a rise in StO₂ in non-working muscles following exercise (Ogata et al., 2007; Nagasawa, 2008b,a), but what is interesting here, is that effect persists for considerably longer than the other studies report. This may be a result of some deltoid work during the pull-up phase interacting with the rise that would be expected globally from the other two exercise, and it is not possible to separate these two effects with this study design. It may also be a consequence of this study targeting a higher workload, i.e./ the subjects' $\dot{V}O_{2max}$, or the much greater size of this study (105 subjects vs the 7–8 subjects used in most other exercise studies) providing greater power in detecting much smaller changes in StO₂. Similarly the large change in leg StO₂ measurement, compared to the deltoids, is probably at least partly due to this being the last exercise preformed before post-exercise monitoring, and that the anterior compartment of the leg is intensely worked by running.

Two subjects recorded leg StO₂ values of 15% post-exercise, which represents the lower limit of the INVOS® System's range. Both individuals denied any lower limb symptoms and had no history of chronic exertional compartment syndrome, both the monitors and probes used on these subjects recorded as expected in subsequent subjects, and there was no effect of repositioning the leg probes in these individuals. It is therefore unclear if this data reflects a subclinical condition or an unexplained technical failure with the monitoring, however as the readings for these individuals flatlined at the lower limit of the monitor's range, it is likely to be the latter.

The relatively large change in cerebral StO₂ is interesting, as it initially appears counterintuitive to many clinicians, who expect cerebral auto-regulation to minimise the changes in oxygen supply to the brain and may attribute this finding to changes in scalp perfusion. While this may have an effect, the dual-beam algorithm of the INVOS® System should minimise the contributions of the scalp signal to the overall reading. Cerebral auto-regulation functions to protect the

brain from reductions in cerebral perfusion, not reduce blood flow in the face of increased cardiac output. Although exercise does not significantly increase the brain's global oxygen demands, it has been shown to increase regional cerebral blood flow, believed to be a consequence of increased systemic arterial blood pressure and cardiac output, and regional metabolic changes (Herholz et al., 1987; Ide et al., 1999; Ide and Secher, 2000). The increase in StO_2 seen here is likely a reflection of this.

Due to the variable period of the post-exercise monitoring, it is not possible to comment on how StO_2 changes during the post-exercise period; nor, due to the duration of the post-exercise monitoring, is it possible to determine when StO_2 returns to baseline. However, this is probably not important in the trauma scenario for the reason that despite the fact there was a statistically significant increase in StO_2 value following exercise, nearly all post-exercise StO_2 measurements fell within the resting value range, and the actual increase in StO_2 after exercise was less than one standard deviation of the resting measurement. It is thus unlikely that this increase in StO_2 following exercise is clinically significant, at least in the uninjured normovolaemic patient, however falls in StO_2 recorded immediately following exercise may represent clinical pathology. In the injured patient the exact effect of interaction between the effects of exercise and the physiological consequences of varying degrees of hypovolaemia on StO_2 are still unknown.

Age was not associated with any differences in either the resting or post exercise StO_2 measurements. This is at odds with the findings of Crookes et al. (2005), but not necessarily surprising, as the study population here was deliberately drawn from a narrow range.

While performing the study no problems recording StO_2 values were encountered that could be attributed to skin pigmentation, although only one Black subject (Fitzpatrick Skin type V) was included in the study, all other subjects were various shades of Caucasian (Fitzpatrick Skin type I–III)*. Problems were

*The Fitzpatrick Scale is a numerical grading scale of skin colour based on genetic background and reaction to sun exposure. There are six grades: Type I — white, very fair/albino skin (always burn and never tans); Type II — white, fair (usually burns, tans with difficulty); Type III — Beige (sometimes burns mildly, tans to light brown); Type IV — Beige with brown tint, Mediterranean type (rarely burns, tans with ease to moderate brown); Type V — Dark Brown (very rarely burns, tans easily); and Type VI — Black (never burns, tans easily)



Figure 7.5: Examples of tattoos over the deltoid region that caused difficulty obtaining StO_2 readings during the study. Note the dark pigmentation and dense patterning of the tattoos (reproduced with permission of the subjects).

encountered obtaining deltoid StO_2 reading in several subjects with tattoos over the monitoring site, requiring slight adjustments of the probe position to obtain a signal. Tattoos causing problems were typically dense and darkly coloured, see Figure 7.5 for examples. This is the first time this problem has been described, although issues of recording StO_2 in dark skinned individuals, due to the light absorbing and scattering properties of melanin, have been previously reported (Wassenaar and den Brand, 2005; Shuler et al., 2009). It is likely that dark tattoo pigments behave in a similar fashion. Given the present popularity for such tattoos amongst infantry soldiers, this is an issue military physicians using NIRS, particularly in the acute setting, should be aware of.

7.6 CONCLUSION

This work has established reference ranges for resting StO_2 in an infantry population at three sites likely to be of interest to military clinical practice. It has shown that typical StO_2 values differ depending upon the site of monitoring, and that normal ranges established at one site can not simply be extrapolated to another, unless it is an identical site on the contralateral side. Despite the differences observed in mean StO_2 , the actual range of values were very similar for all sites. Importantly an StO_2 of 40% appears to represent the absolute lower limit of normality, values recorded below this in the deltoid, anterior compartment of the leg, or frontal lobe of the brain are highly suggestively of abnormal physiology. Above 40% the normal range of StO_2 values is wide, which makes interpreting them in the clinical environment very difficult, and it is likely that trend changes, rather than absolute values, will be more useful in this situation.

Exercise was associated with a statistically significant increase in StO_2 at all sites that persisted for at least 10 minutes into the recovery period. However this change was relatively small, and all post-exercise StO_2 measurements fell within the reference range of the resting values. As such this phenomenon in isolation is unlikely to cause problems with the interpretation of StO_2 values in clinical practice.

8. NIRS ANIMAL TRAUMA AND HAEMORRHAGE MODEL

The material presented in this chapter formed part of a collaborative work performed in conjunction with the Defence Science and Technology Laboratory (DSTL), Porton Down. Physiological data used in this chapter is presented courtesy of [REDACTED] and by permission of DSTL.

My contribution to this work was developing and writing the NIRS elements of the study protocol, training other researchers in the NIRS elements of the protocol, data collection, and all data analysis.

8.1 INTRODUCTION

Conventionally hypoperfusion in the trauma patient is assessed (at least during the early stage of resuscitation) against a range of simple clinical signs and basic physiological measurements. These include assessments of cerebation, capillary refill, looking for signs of increased sympathetic activity such as pallor and sweating, and measuring heart rate and blood pressure. While such features have value when evaluated in the context of the clinical picture, taken alone they lack specificity or sensitivity.

Blood pressure and heart rate are the simplest objective clinical signs of cardiovascular status and are relied upon by most clinicians assessing volume status in the trauma patient. Unfortunately the relationship between heart rate and blood pressure and blood loss is not linear, and is widely misunderstood (Secher and Bie, 1985). Both heart rate and blood pressure demonstrate a biphasic response to haemorrhage. Small reductions in central blood volume are associated with a modest rise in heart rate and a narrowing of the pulse pressure, with or without a fall in systolic pressure. As the reduction in the central volume approaches 30%, there is often a 'paradoxical' drop in heart rate, mediated by a Bezold-Jarish-like vagal reflex associated with a loss of peripheral sympathetic activity (Campagna and Carter, 2003). Further reductions in blood volume are associated with an increase in heart rate as the patient progresses towards uncompensated shock. Unfortunately this pattern is not consistent: young or athletic individuals will often maintain their blood pressure in the face of significant hypovolaemia, only to rapidly fall at the point of decompensation; in the elderly β -blocker may inhibit

the tachycardia; in the trauma patient sympathetic stimulation as a result of tissue injury and pain may ‘override’ the baroreflex induced relative bradycardia and lead to an elevation in blood pressure and heart rate. The end result is that the assessing clinician has little idea where on the biphasic phase response curve the patient is, or if it will occur at all.

To mitigate the limitations of heart rate and blood pressure a number of other measurements of volume status are commonly used. Central venous pressure (CVP) and pulmonary artery catheters provide an accurate means of assessing volume state. The problem with CVP monitoring is that it provides no indication of cardiac output (CO), and a low CVP may be a reflection of low central volume or reduced myocardial contractility — of which trauma is associated with both (Abou-Khalil et al., 1994; Yang et al., 2004). For this reason it is sometimes suggested that a pulmonary artery catheter is required to provide the distinction, although it has been demonstrated that CVP alone can be used to successfully guide trauma resuscitation (McKinley et al., 2009). Unfortunately the measurement of CVP and pulmonary artery pressures are invasive, require specialist skills, equipment calibration and take time to insert, which largely limits their use to the intensive care or theatre environments.

The principle problem with hypovolaemic shock is organ hypoperfusion, and the goal of resuscitation is to restore adequate tissue perfusion. Therefore measures of end organ perfusion should provide a good indicator of the patient’s true resuscitation state. Of all the assessment techniques in common clinical use it is arterial blood gas (ABG), and in particular lactate and base excess, that have been shown to correlate most closely with oxygen delivery and utilisation in trauma patients (Davis et al., 1991; Kincaid et al., 1998). Both parameters have certain caveats regarding their interpretation in the trauma subject (see Section 1.3.2 for a detailed discussion), however the main limitation remains a practical one. ABG measurements are invasive, difficult to draw repeatedly without an arterial line, and intermittent — providing only a ‘snap-shot’ of the patient’s physiological state which typically lag behind the true clinical condition. Some of these problems can be partially ameliorated by using venous samples; and the base excess and lactate of venous samples have been shown to correlate well with those of arterial specimens (Davis, 1994). However the need for carefully calibrated equipment to

process blood gas samples, largely limits their use to the hospital environment.

The idealised tool for assessment of the trauma patient should provide an accurate measure of end organ perfusion. Parameter values should be recorded continuously and read off in real time. Ideally the tool would be non-invasive, robust, compact and easy to use. NIRS meets these practical requirements. It has been shown to correlate well with volume of blood loss in human and animal hypovolaemia models. However the number of conflicting studies and the different NIRS algorithms used make interpreting the accuracy of StO₂ compared to conventional physiological parameters difficult. In particular the relationship between StO₂ and ABG parameters has not been studied in a controlled haemorrhage model.

Fluid resuscitation protocols have undergone significant changes in the last 30 years. The early aggressive blind fluid resuscitation protocol, best epitomised by the old ATLS® guidelines (American College of Surgeons, 1997) have fallen out of favour. This approach being associated with higher mortality rates than early hypotensive resuscitation (Bickell et al., 1991; Stern et al., 1993; Solomonov et al., 2000), or even no fluid resuscitation during the prehospital period (Martin et al., 1992; Bickell et al., 1994). However once in hospital, where definitive means of haemorrhage control are available, there appears to be no survival benefit to continuing hypotensive resuscitation (Dutton et al., 2002). In fact animal evidence suggests that prolonged periods of hypotensive resuscitation are associated with an increase in mortality compared to normotensive resuscitation (Garner et al., 2010). For this reason British Military practice has adopted ‘novel-hybrid resuscitation’: one hour of hypotensive resuscitation after which normotensive resuscitation is attempted regardless of the patient location or estimated evacuation timelines; and it is this approach to resuscitation that is modelled in this study.

8.2 AIM

The aim of this study was to evaluate NIRS as a tool for assessing global perfusion and resuscitation in an animal model designed to simulate military trauma and contemporary resuscitation practices, principally ‘novel-hybrid resuscitation’. The primary objective was to compare StO₂ to ABG measurements and examine the phase relationship, if any, between these parameters. Secondary objective included



Figure 8.1: A Large White Sow.

comparing StO₂ to conventional physiological assessments; and assessing the effect of recording StO₂ in hypovolaemic subjects from an injured limb.

8.3 MATERIALS AND METHODS

The experimental design was that of a prospective animal model study. The study was performed on terminally anaesthetised Large White pigs (see Figure 8.1), and conducted in accordance with the Animals (Scientific Procedures) Act 1986. All experiments took place [REDACTED], between the period June 2012–July 2013. The chosen model was one of muscle injury and haemorrhage followed by one hour of hypotensive resuscitation with crystalloid (simulating the prehospital casualty management) followed by 2½ hours of normotensive resuscitation with blood products. The protocol was based on previous studies and model development work described by Garner et al. (2009, 2010).

8.3.1 *Preparation of the Animal Model*

Seven Large White pigs ([REDACTED]) weighing between 48–56 kg were studied. The animals were housed at a indoor facility [REDACTED] for one week before each study where they were fed a wheat-soya based ration at

1.5–1.7 kg/day and allowed free access to water. Prior to the study the animals were fasted for 18 hours, but still allowed water freely.

The pigs were sedated with intramuscular midazolam hydrochloride (0.1 mg/kg) before gaseous induction with 5% isoflurane via a ‘snout-mask’. The animals were intubated and anaesthesia maintained with isoflurane in nitrous oxide and oxygen with the FiO_2 maintained at 0.33. The left carotid artery and vein were cannulated with an 8F gauge intravenous line, after which anaesthesia was maintained using a total intravenous anaesthesia (TIVA) technique with alfaxalone (Alfaxan®, Ventoquinol UK Ltd, UK), at a rate of 50–200 µg/kg/min. The animals were weaned off isoflurane and allowed to breath spontaneously for the remainder of the experiment. The right internal jugular vein and left femoral artery and vein were cannulated. A flow directed balloon tipped catheter (Swan-Ganz catheter) was passed via the right internal jugular vein, and the pressure changes at the catheter tip were monitored to confirm positioning in the pulmonary artery.

Following preparation with povidone-iodine solution a midline laparotomy was performed. The spleen was pre-contracted by topical application of adrenaline soaked gauze prior to splenectomy*. A 14F gauge suprapubic catheter was placed in the bladder and used to drain the bladder at hourly intervals to prevent autonomic responses associated with bladder distension. The abdomen was then closed with a mass closure technique. Temperature was monitored throughout the experiment and maintained at approximately 38°C through the use of warming blankets or the application of external cooling.

8.3.2 *Experimental Protocol*

The framework for experimental timeline is shown in Figure 8.2. Approximately one hour following laparotomy baseline physiological measurements were taken. The animals were then subject to a controlled muscle trauma by the application of four shots with a penetrating captive bolt pistol to the right hind leg, the location of the shots is shown in Figure 8.3. The shots were angled so as to cause only soft tissue trauma and avoid bony injury. Immediately after the shots the animals were subject to a controlled haemorrhage of approximately 35% of total blood volume at

*Splenectomy is necessary in the porcine model to prevent autotransfusion by splenic contraction, which is a prominent response to hypotension (as part of the broader contraction in the splanchnic circulation) in pigs but less important in humans.

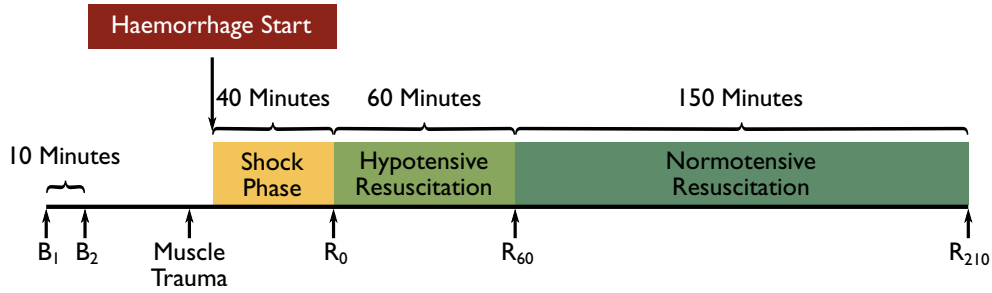


Figure 8.2: Animal haemorrhage and trauma model experimental timeline and key time points. B₁ and B₂ denote baseline ABG sampling points. R_x denotes time after start of resuscitation protocol.

an exponentially decreasing rate designed to simulate major arterial haemorrhage. The rate of blood loss was in accordance with the following formula:

$$V = B_o \times (1 - e^{-0.04t})$$

where V equals the total blood loss (in mL/kg) at time t , and B_o is the estimated total blood volume of the animal described by the formula:

$$B_o = 161.4751 \times W^{-0.2197}$$

where W is the body weight of the animal in kg (Garner et al., 2010).

The total duration of haemorrhage was approximately 10 minutes after which the animal was subject to a 30 minute shock phase, with a target systolic blood pressure of 60 mmHg maintained by saline infusion at a rate of 3 mL/kg/min to a maximum total volume of 500 mL. After this the animal received a 60 minute period of hypotensive resuscitation with a target systolic blood pressure of 80 mmHg maintained by resuscitation with saline. This period was designed to simulate the resuscitation strategy and timelines of the prehospital military environment. After 60 minutes the animal entered the ‘hospital resuscitation phase’, and was resuscitated to a ‘normotensive’ target blood pressure of 110 mmHg with crossmatched packed red cells and plasma in a 1:1 ratio, drawn from DSTL’s animal blood bank. Normotensive resuscitation was performed for 2 ½ hours, after which the animal was killed with an intravenous overdose of sodium pentobarbitone.

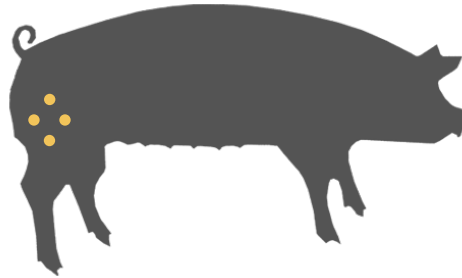


Figure 8.3: Site of application of shots (shown in yellow) with the penetrating captive bolt pistol to produce a controlled muscle injury.

8.3.3 *Physiological Measurements and NIRS Monitoring*

Heart rate was monitored by electrocardiogram electrodes placed on the ventral surface of the animal, and non-invasive SpO_2 by a pulse oximeter probe attached to the tail. Arterial blood pressure was monitored invasively via the carotid artery cannula using a strain gauge manometer (Sensoror 840, SensoNor, Norway), and central venous pressure (CVP) monitored via the right internal jugular vein with the pressure transducer zeroed at the level of the heart. The Swan-Ganz catheter was used to record pulmonary artery pressure and estimate the cardiac output (CO), recorded as six minute rolling average. Arterial and venous blood gas samples were drawn off in heparinised syringes from the femoral lines at fixed intervals according to the schedule in Table 8.1, and analysed using a Gem Premier 3000 Blood Gas Analyser (Instrumentation Laboratories, Warrington, UK).

StO_2 measurements were taken at six second intervals from both the injured and uninjured hind legs using an INVOS® System NIRS monitor in a two channel configuration. The probes were positioned over the mid-portion of the lateral aspect of the upper leg with the probe/cable connection directed distally. To ensure accurate reading the hair over the probe site was shaved prior to probe attachment, and further secured with medical tape to achieve firm adhesion and exclude extraneous light.

8.3.4 *Data Acquisition and Collection*

Cardiovascular data was recorded continuously using a computerised data acquisition system (Maclab 8/s, ADInstruments, Oxford UK); and associated software

<i>Time (mins)</i>	<i>Sample</i>	<i>Comments and Timing</i>
5	B ₁	Baseline measurement
15	B ₂	Second baseline taken 10 minutes after B ₁
30	PREINJ	Taken 15 minutes after B ₂ and 5 minutes before delivery of leg shots
65	H ₁	Taken approximately 25 minutes after start of haemorrhage
80	H ₂	Taken approximately 40 minutes after start of haemorrhage (Immediately before start of resuscitation protocol)
95	R ₁₅	Taken 15 minutes after start of resuscitation protocol
110	R ₃₀	Taken 30 minutes after start of resuscitation protocol
125	R ₄₅	Taken 45 minutes after start of resuscitation protocol
140	R ₆₀	Taken 60 minutes after start of resuscitation protocol (end of hypotensive resuscitation phase)
155	R ₇₅	Taken 75 minutes after start of resuscitation protocol
170	R ₉₀	Taken 90 minutes after start of resuscitation protocol
200	R ₁₂₀	Taken 120 minutes after start of resuscitation protocol
230	R ₁₅₀	Taken 150 minutes after start of resuscitation protocol
260	R ₁₈₀	Taken 180 minutes after start of resuscitation protocol
290	R ₂₁₀	Taken 210 minutes after start of resuscitation protocol

Table 8.1: Timing of ABG samples.

(Chart v4.2.3, ADInstruments) used for data extraction and analysis. Cardiovascular data was read off at 12 second intervals during the shock and hypotensive resuscitation periods, and at one minute intervals during all other parts of the experiment. ABG data was read directly from the blood gas analyser, the machine's clock having previously been synchronised with the main data acquisition system.

To ensure synchronisation between cardiovascular data and StO₂ measurements a synchronised event stamp was inserted into the output of both systems. The StO₂ data was then exported using the schema described in Sections 5.2 and 5.3 and the NIRS timestamps adjusted in a spreadsheet application to correct for the time difference between the two data acquisition systems.

8.3.5 Data Analysis

Cardiovascular and ABG data were matched to the nearest corresponding timestamp in the NIRS dataset using a custom AWK script. The six second sampling frequency of the NIRS data meant that the time discrepancy between the different

datasets would never be more than three seconds. Tests of normality were performed using Q-Q plots and a Shapiro-Wilks test. Non-parametric comparisons of means between two groups was performed using a Wilcoxon signed-rank test. Non-parametric comparisons between multiple groups was performed using Friedman's ANOVA.

To perform the time lag analysis between ABG measurements and other physiological variables the data was first standardised. Spline interpolation was performed on the ABG data to produce a continuous curve which was compared by cross-correlation to other physiological parameters. The time difference between parameters at the point of maximal correlation, i.e. the time lag, and the correlation coefficient at that point, were recorded for each analysis.

All statistical tests were undertaken using R (R Development Core Team, 2009) with a significance threshold of $p \leq 0.05$.

8.4 RESULTS

Seven animals weighing between 48–56 kg (mean 51.7 kg) were studied. All animals completed the whole of the study protocol.

8.4.1 *Baseline Measurements*

Summary data for baseline values from B₁ and B₂ for key physiological measurements are presented in Table 8.2. Baseline StO₂ values were not normally distributed when analysed with a Q-Q plot or Shapiro-Wilks test, and therefore a comparison of means was performed with a Wilcoxon signed-rank test. The mean StO₂ was 5.7% greater in left (control) limb compared to the right (injured), however this difference was not significant in either the B₁ ($p=0.057$) or B₂ ($p=0.106$) data.

8.4.2 *Effect of the Hypovolaemia Protocol*

The effect of the hypovolaemic protocol on StO₂ is shown on a per animal basis in Figure 8.4, and for all combined measurements in Figure 8.5. In all cases StO₂ fell sharply in both limbs at the start of the shock phase. Hypotensive resuscitation was associated with a modest rise in StO₂ in most animals improving throughout the duration of the phase. In the majority of animals the start of normotensive

		<i>Mean</i>	<i>Median</i>	<i>Range</i>	<i>s.d.</i>
<i>NIRS</i>	StO ₂ Left (%)	67.3	65.5	59.0–81.0	7.4
	StO ₂ Right (%)	61.6	62.5	52.0–69.0	5.6
<i>Haemodynamic Measurements</i>	HR (bpm)	154	159	134–168	12
	SBP (mmHg)	164	161	151–184	9
	DBP (mmHg)	128	126	120–139	7
	MAP (mmHg)	143	142	134–159	8
	CVP (mmHg)	3.38	3.17	2.44–5.35	0.78
	CO (l/min)	7.70	7.59	7.08–8.89	0.56
<i>ABG Parameters</i>	Hb (g/dl)	12.2	12.3	11.6–13.0	0.4
	pH	7.43	7.44	7.37–7.45	0.02
	HCO ₃ (mM)	32.52	32.80	29.20–35.00	1.60
	BE (mEq/l)	7.78	8.10	4.50–10.10	1.68
	Lactate (mM)	1.16	0.90	0.70–3.10	0.75

Table 8.2: Descriptive statistics for baseline values of the main physiological parameters. Data has been calculated from the combined values of the B₁ and B₂ sampling points (HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; CVP = central venous pressure; CO = cardiac output; BE = base excess).

resuscitation coincided with a rapid increase in StO₂. Two animals demonstrated significant deviation from this pattern. The trace in animal 1 shows a rise in StO₂ in the left limb during the shock phase with little response during normotensive resuscitation. In contrast the right limb in this animal appeared to flat-line for most of the shock and hypotensive resuscitation phases but otherwise followed a similar pattern to other animals. Examination of individual data points from the right limb during this stable period demonstrated a static StO₂ of 37%, which would suggest a technical error in NIRS recordings since even ‘stable’ recordings usually demonstrate some noise. Animal 2 demonstrated a swift StO₂ drop in both limbs at the start of the shock phase but little response to either hypotensive or normotensive resuscitation. The StO₂ during these periods continued to demonstrate variability and noise, suggesting that these are true values.

Examining Figure 8.5 it can be seen that StO₂ recorded from the left limb was greater than the right limb for the duration of the experimental protocol. Comparison of raw StO₂ data from the left and right limbs for the whole of the

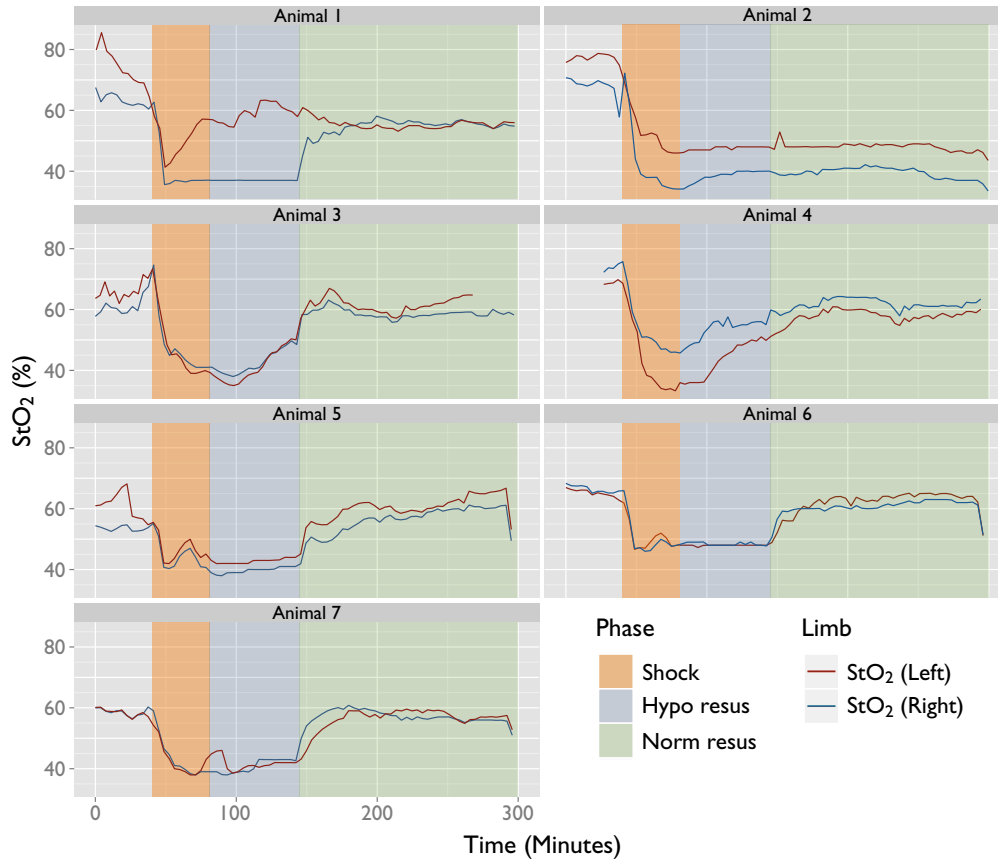


Figure 8.4: StO₂ in each limb by animal. The experimental phase is denoted by the background colour: shock phase; hypotensive resuscitation (with saline); and normotensive resuscitation (with whole blood). Note to remove noise in the dataset and improve readability, data has been plotted as a LOESS curve.

experimental protocol confirmed a significant difference of approximately 3.6% between the limbs ($p < 0.0001$).

Mean values for the key physiological parameters at the ABG sampling points are shown in Table 8.3, and selected parameters are graphed in Figures 8.6 and 8.7. All physiological and ABG parameters demonstrated significant differences between the four phases of the experiment (baseline, haemorrhage/shock, hypotensive resuscitation and normotensive resuscitation) compared using measurements from the representative time points B₁, H₂, R₄₅ and R₁₅₀ respectively), $p < 0.01$ for all comparisons (Friedman's ANOVA).

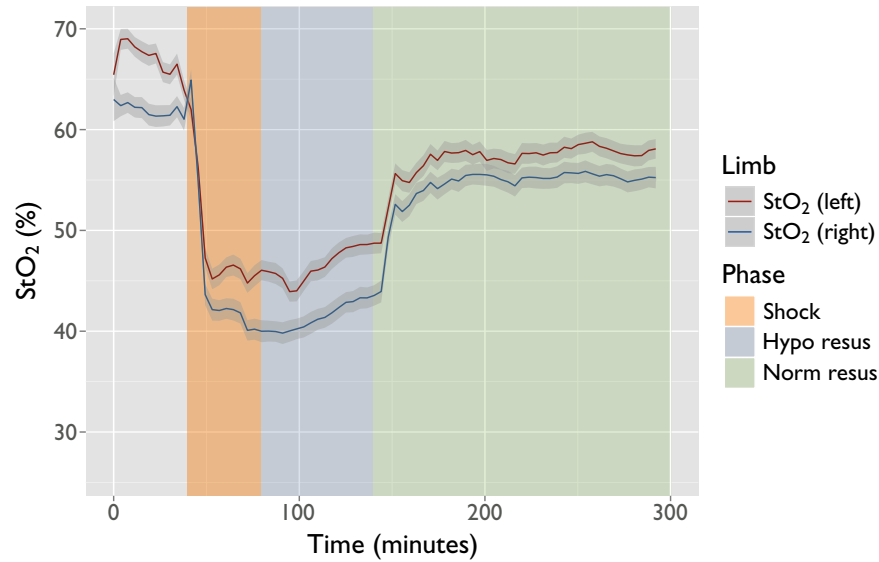


Figure 8.5: Mean StO₂ for all animals during the course of the protocol. The 95% confidence interval for the data is shown in grey.

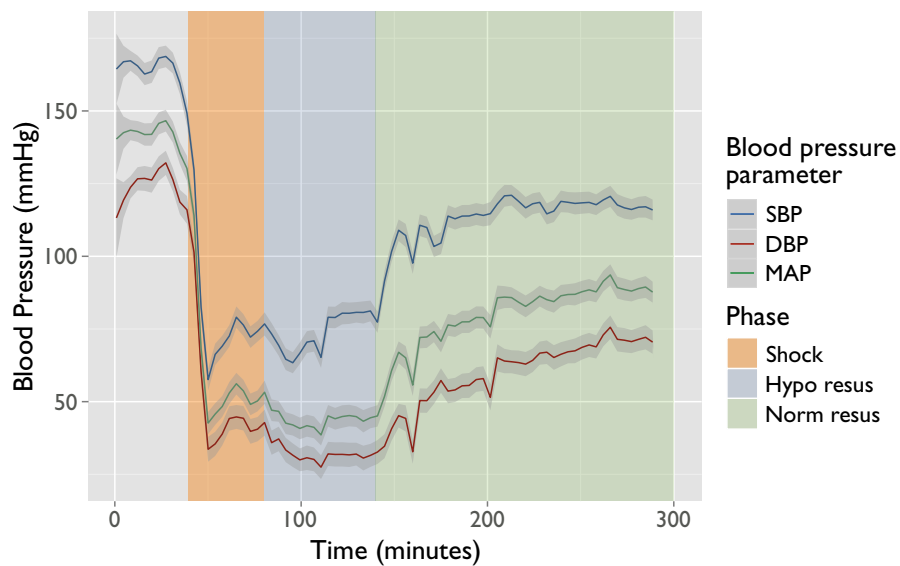


Figure 8.6: Mean values for blood pressure measurements during the course of the protocol. The 95% confidence interval for the data is shown in grey.

Sample	PARAMETER												
	StO ₂ left (%)	StO ₂ right (%)	HR (bpm)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	CVP (mmHg)	CO (l/min)	Hb (g/dl)	pH	HCO ₃ (mM)	BE (mEq/l)	Lactate (mM)
B ₁	68.8	62.7	157	163	125	141	3.20	7.63	12.3	7.44	32.40	7.73	1.25
B ₂	65.7	60.5	151	166	129	144	3.55	7.77	12.1	7.43	32.63	7.82	1.07
PREINJ	66.4	63.4	144	164	127	142	3.67	7.61	12.2	7.45	33.01	8.49	0.89
H ₁	45.3	43.0	238	78	46	56	2.13	2.40	10.6	7.40	24.47	0.44	4.77
H ₂	44.9	40.7	252	72	40	49	2.07	2.43	10.6	7.39	19.96	-3.41	7.41
R ₁₅	43.0	41.1	248	61	32	41	2.06	1.90	10.1	7.34	14.81	-8.99	10.19
R ₃₀	45.9	42.9	224	70	31	42	2.37	1.71	9.1	7.25	12.74	-12.50	12.34
R ₄₅	48.3	44.3	219	81	34	47	2.70	1.90	8.4	7.19	12.39	-13.96	13.63
R ₆₀	49.1	45.0	213	80	33	46	2.82	2.71	8.3	7.19	11.87	-14.51	13.96
R ₇₅	55.5	53.0	199	110	48	69	4.15	4.41	8.6	7.15	13.72	-13.72	13.73
R ₉₀	57.6	55.3	198	111	53	75	4.58	7.48	8.4	7.16	13.81	-13.44	14.13
R ₁₂₀	57.6	56.6	201	117	61	82	4.31	7.40	8.8	7.21	16.03	-10.71	13.21
R ₁₅₀	57.9	56.1	200	120	66	87	5.35	6.75	8.9	7.26	18.01	-7.90	11.20
R ₁₈₀	58.7	56.4	204	118	70	89	6.09	6.19	9.2	7.29	20.21	-5.39	8.84
R ₂₁₀	58.3	56.4	203	117	73	90	6.08	5.91	8.9	7.33	22.33	-2.84	6.79

Table 8.3: Mean values for the key physiological parameters at the ABG sampling points (HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; CVP = central venous pressure; CO = cardiac output; BE = base excess; HCO₃ = bicarbonate).

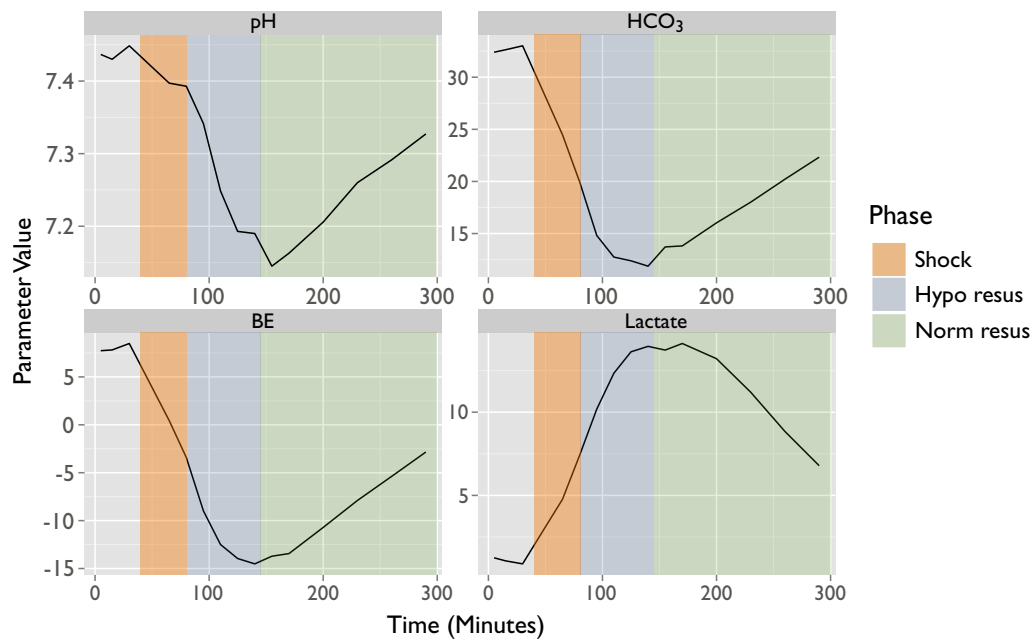


Figure 8.7: Mean values for the main ABG parameters over the course of the protocol. Parameter values are expressed in the respective unit for that parameter: Bicarbonate (HCO₃) mM; Base Excess (BE) mEq/l; lactate (mM). Note at ABG parameters appear to change prior to the shock phase, this is an artefact of ABG recording intervals rather than a physiological phenomena.

8.4.3 Correlation Between Physiological Parameters

A correlation matrix for the main physiological parameters is shown in Table 8.4, demonstrating strong correlations between most measurements. The correlation between the StO₂ data recorded from the left and right limbs was $r_s = .75$ ($p < 0.0001$) for the raw (noisy) data, rising to $r_s = .94$ ($p < 0.0001$) when comparing smoothed data with the noise removed (effectively a comparison of the curves presented in Figure 8.5). NIRS measurements correlated well with most other parameters although recordings from the left limb tended to demonstrate a stronger correlation than those from the right. Both StO₂ monitoring sites had similar correlations with all blood pressure recordings ($r_s = .70-.79$, $p < 0.0001$) and also strongly correlated with CO ($r_s = .73-.78$, $p < 0.0001$). Left limb StO₂ demonstrated a modest correlation with all ABG parameters (all $p < 0.05$), except for pH for which there was only a weak correlation ($r_s = 0.29$). Similar, but slightly weaker, correlations were seen in the right limb StO₂ values. The relationship between blood pressure and ABG

	StO ₂ (left)	StO ₂ (right)	HR	SBP	DBP	MAP	CVP	CO	Hb	pH	HCO ₃	BE	Lactate
StO ₂ (left)	—	0.75	-0.71	0.77	0.70	0.77	0.25	0.78	0.13	0.29	0.54	0.47	-0.42
StO ₂ (right)	0.75	—	-0.65	0.76	0.73	0.79	0.35	0.73	0.05	0.22	0.43	0.36	-0.29
HR	-0.71	-0.65	—	-0.65	-0.56	-0.63	-0.20	-0.64	-0.12	-0.24	-0.50	-0.42	0.35
SBP	0.77	0.76	-0.65	—	0.87	0.93	0.48	0.82	0.23	0.25	0.50	0.43	-0.40
DBP	0.70	0.73	-0.56	0.87	—	0.98	0.27	0.78	0.46	0.49	0.73	0.67	-0.62
MAP	0.77	0.79	-0.63	0.93	0.98	—	0.36	0.83	0.37	0.40	0.66	0.59	-0.54
CVP	0.25	0.35	-0.20	0.48	0.27	0.36	—	0.41	-0.23	-0.37	-0.11	-0.19	0.16
CO	0.78	0.73	-0.64	0.82	0.78	0.83	0.41	—	0.14	0.22	0.50	0.42	-0.29
Hb	0.13	0.05	-0.12	0.23	0.46	0.37	-0.23	0.14	—	0.80	0.69	0.74	-0.78
pH	0.29	0.22	-0.24	0.25	0.49	0.40	-0.37	0.22	0.80	—	0.87	0.93	-0.91
HCO ₃	0.54	0.43	-0.50	0.50	0.73	0.66	-0.11	0.50	0.69	0.87	—	0.98	-0.93
BE	0.47	0.36	-0.42	0.43	0.67	0.59	-0.19	0.42	0.74	0.93	0.98	—	-0.95
Lactate	-0.42	-0.29	0.35	-0.40	-0.62	-0.54	0.16	-0.29	-0.78	-0.91	-0.93	-0.95	—

Table 8.4: Correlation matrix of main physiological parameters (HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; CVP = central venous pressure; CO = cardiac output; Hb = haemoglobin concentration; BE = base excess; HCO₃ = bicarbonate).

parameters was similar to that of StO_2 , but the correlation slightly stronger (all $p < 0.05$). Of the blood pressure measurements DBP demonstrated the strongest correlation with ABG parameters and SBP the weakest.

All ABG parameters were very strongly correlated with each other ($r_s = .87-.98$, all $p < 0.0001$). ABG measurements were the only variables to show a strong correlation with Hb. There was no significant relationship between Hb and either left ($r_s = .13$, $p = 0.19$) or right limb StO_2 ($r_s = .05$, $p = 0.59$). Of the standard haemodynamic measurements DBP and to a lesser extent MAP were the only parameters to demonstrate a significant correlation with Hb ($r_s = .46$, $p < 0.0001$ and $r_s = 0.37$, $p = 0.0002$ respectively), although these correlations were quite modest.

8.4.4 *Effect of Limb Injury on StO_2*

Table 8.5 presents summary statistics for StO_2 values during the three periods most relevant for interpreting the effects of limb injury on StO_2 :

1. prior to limb injury (using values from one minute either side of the PREINJ sampling point)
2. after limb injury but before haemorrhage (using those values in the two minute interval immediate before haemorrhage)
3. for the duration of the hypovolaemia (including the haemorrhage phase) and resuscitation protocol

StO_2 measurements from the left limb (control) were approximately 5.5% greater than the right limb (injured) prior to injury. This is a similar relationship to that seen at the baseline sampling points, however unlike the B_1 and B_2 points this difference was statistically significant, $p < 0.0001$. This difference was reversed during the period following limb trauma in the period prior to haemorrhage with the right limb StO_2 being approximately 1.7% greater than the left limb, $p < 0.0001$. This difference reversed again during the rest of the protocol with left limb StO_2 being on average 3.3% greater than the right limb, $p < 0.0001$.

The differences between the limbs during the pre-injury phase meant that the left limb could not reliably be used as a control to assess the effect of limb injury on StO_2 values recorded from the right limb, and the only comparison that could be made was between the right limb StO_2 values before and after injury, but before

	<i>Mean</i>	<i>Median</i>	<i>Range</i>	<i>s.d.</i>
PRIOR TO LIMB INJURY				
<i>StO₂ Left (%)</i>	67.5	66.0	55.0–89.0	7.3
<i>StO₂ Right (%)</i>	62.0	62.0	51.0–74.00	5.4
POST LIMB INJURY				
<i>StO₂ Left (%)</i>	63.2	62.0	53.0–71.0	7.1
<i>StO₂ Right (%)</i>	64.9	65.0	54.0–76.00	6.6
DURING HYPOVOLAEMIA PROTOCOL				
<i>StO₂ Left (%)</i>	53.0	54.0	33.0–73.0	7.9
<i>StO₂ Right (%)</i>	49.7	51.0	33.0–75.0	9.2

Table 8.5: Summary statistics for all StO_2 values from the periods prior to limb injury, after limb injury but before haemorrhage, and for the duration of the hypovolaemia and resuscitation protocol.

haemorrhage. Injury was associated with a significant increase in StO_2 in the right limb, by $2.9 \pm 1.2\%$, $p < 0.001$. This change occurred during a period when the StO_2 in the left (control) limb fell significantly by $4.2 \pm 1.3\%$, $p < 0.0001$.

8.4.5 Phase Relationship Between Physiological Parameters

Comparing Figures 8.5, 8.6 and 8.7 it can be seen that all parameters followed a similar pattern in their response to the hypovolaemia protocol, however the ABG curves lagged behind the StO_2 and blood pressure curves. This is most obvious comparing the initial descent curves during the haemorrhage phase and the location where the curves ‘bottom out’ — shortly after the 100–110 minute point in the StO_2 and blood pressure curves but around the 140 minute in the HCO_3 and BE curves.

To formally assess the time lag a cross-correlation analysis was performed comparing StO_2 and haemodynamic parameters to the principal ABG measurements. The results of the cross-correlation, showing the time lag at which maximal correlation occurred and the correlations coefficient at that point, are shown in Table 8.6. It can be seen that ABG measurements phase lagged all other physiological parameters. This lag was greatest for pH (between 37–52 minutes, mean 47 minutes), lag times were similar for base excess (between 18–32 minutes, mean 26.7 minutes) and lactate (between 23–37 minutes, mean 29.7 minutes). Diastolic blood

	<i>Physiological Variable</i>	<i>Correlation Coefficient</i>	<i>Lag (minutes)</i>
<i>pH</i>	Left StO ₂	0.69	52
	Right StO ₂	0.69	52
	Heart rate	-0.60	46
	Systolic Blood Pressure	0.67	52
	Diastolic Blood Pressure	0.73	37
	Mean Arterial Pressure	0.71	43
<i>Base Excess</i>	Left StO ₂	0.69	31
	Right StO ₂	0.67	32
	Heart rate	-0.63	24
	Systolic Blood Pressure	0.66	32
	Diastolic Blood Pressure	0.78	18
	Mean Arterial Pressure	0.74	23
<i>Lactate</i>	Left StO ₂	-0.65	36
	Right StO ₂	-0.63	37
	Heart rate	0.59	27
	Systolic Blood Pressure	-0.65	37
	Diastolic Blood Pressure	-0.75	23
	Mean Arterial Pressure	-0.72	28

Table 8.6: Results of a cross-correlation analysis comparing haemodynamic and StO₂ data to the principle ABG measurements (pH, base excess and lactate). The maximum correlation and the point at which this occurred for each comparison are presented.

pressure demonstrated the greatest maximum correlation with ABG parameters, followed by mean arterial pressure and then StO₂. Heart rate demonstrated the lowest correlation with the principle ABG measurements of all the parameters assessed.

8.5 DISCUSSION

Examining the StO₂ response to the study protocol, most obviously demonstrated in Figure 8.4, it can be seen that StO₂ values responded quickly and appropriately to each phase of resuscitation protocol. In all cases there was an immediate fall in StO₂ in both limbs in response to haemorrhage. The response to hypotensive resuscitation was muted but overall there was a modest increase in StO₂ which rose sharply in most animals at the start of the normotensive resuscitation phase, but quickly plateaued thereafter. This clearly demonstrates the utility of NIRS in

tracking the patient's response to major haemorrhage and immediate resuscitation, however once the patient is adequately resuscitated it is unclear how NIRS may be used to guide further management other than in detecting significant deteriorations.

Although most animals followed the same general trend of NIRS recordings, two animals demonstrated a noticeable deviation from this. In Animal 2 there was a large drop in StO_2 during the haemorrhage/shock phase, and a small increase with hypotensive resuscitation after which the StO_2 plateaued at low levels. The response of the other physiological parameters to the experimental protocol for this animal also demonstrated a similar pattern, suggesting that this animal appears to have had a poor response to resuscitation rather than there being an isolated problem with NIRS monitoring. Animal 1 showed a rise in the left limb StO_2 part way through the haemorrhage phase. This change was also seen in the pulse rate (which decreased) but was not reflected in the blood pressure traces. The right limb StO_2 measurements demonstrated almost no response after the initial haemorrhage to either shock or hypotensive resuscitation. Examining the raw data from this period it was observed that the StO_2 flatlined at 37% for this period. This would strongly suggest there was a technical problem with the NIRS recording since, as can be appreciated from examining other traces, even when StO_2 values are stable there is always some noise in the signal. This illustrates one of the problems with the current generation of NIRS devices — that they give little indication of when they are not recording correctly. Although a flat line trace is obvious in retrospect, it may not be appreciated for some time in a real life clinical scenario. This presents a strong argument for monitoring two sites simultaneously; if the traces start to diverge and one site is recording seemingly stable values this may be an early indicator of technical problem with that probe or monitoring site.

The novel finding of this study is a formal demonstration of the lag time between haemodynamic and NIRS measurements, and ABG recordings. Whilst it is well known that it takes time for physiological disturbance to be reflected in the ABG measurements, the size of the lag between haemodynamic and ABG recordings has been largely unstudied. The ABG parameters of primary interest were base excess and lactate, since these are the ones which have been previously shown to most closely correlate with anaerobic metabolism in trauma patients (Davis

et al., 1991; Kincaid et al., 1998). For completeness pH was also analysed, which demonstrated significantly greater lag times than base excess or lactate, and lower correlations with other physiological parameters. This occurs probably as a result of compensation in the spontaneously breathing porcine model. Base excess and lactate demonstrated broadly similar lag times for all comparisons with haemodynamic parameters and StO_2 . Diastolic blood pressure had the shortest lag time and the greatest maximal correlation for comparisons with both base excess ($r=.78$, with a lag of 23 minutes) and lactate ($r=-.72$, with a lag of 28 minutes). Mean arterial pressure demonstrated the next highest maximum correlation, which is not necessarily surprising since it is derived from the diastolic blood pressure. Both StO_2 monitoring sites had a similar lag time and correlation for base excess ($r=.67-.69$, with a lag time of 31–32 minutes) and lactate ($r=-.63-.65$, with a lag time of 36–37 minutes). Heart rate demonstrated the lowest maximal correlation.

Although diastolic blood pressure demonstrated the highest time lagged correlation, as has been discussed blood pressure monitoring has significant practical limitations when applied in the acute trauma setting — principally the difficulty of obtaining frequent readings without an arterial line. NIRS does not suffer from this problem, providing a non-invasive, continuous, real time means of monitoring resuscitation. The same argument can be made for heart rate monitoring, although as discussed previously heart rate response in trauma is subject to multiple confounding factors, and it had the weakest (but still reasonable) time lagged correlation of all the parameters in this study.

Tissue injury is known to cause an increase in StO_2 in the affected muscle due to a presumed hyperaemic effect. The rise in StO_2 values seen immediately after the controlled muscle injury (but before the start of haemorrhage) in the injured limb suggests that this effect occurs within a matter of minutes. Despite the effect of injury, the right limb accurately tracked the physiological changes during the protocol in a similar fashion to the uninjured left limb, the correlation between the two limbs being $r_s=.75$. This correlation may not be as high as expected for identical sites, but much of the discrepancy is probably accounted for by the degree of noise in the raw StO_2 measurements (illustrated in Figure 8.8). When the analysis was repeated with the noise removed (in effect a comparison between the curves presented in Figure 8.5) the correlation rose to $r_s=.94$. These

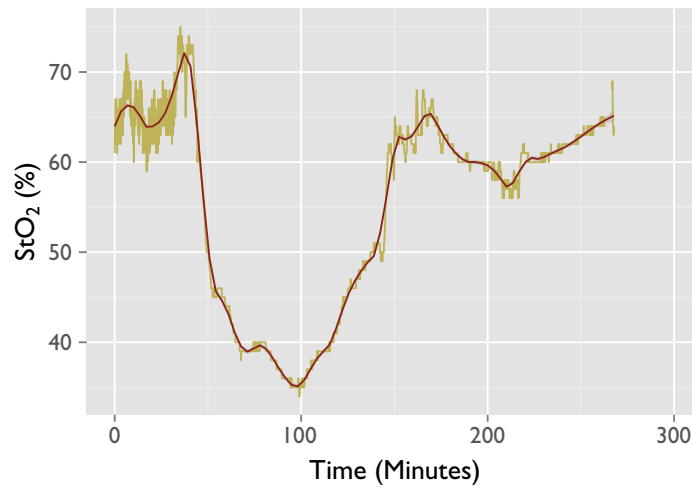


Figure 8.8: An example of raw StO₂ data (yellow) recording from the left leg of animal 3, with the same data smoothed as LOESS curve (red), demonstrating the high signal noise of the NIRS trace when recorded with a six second frequency.

results demonstrate that an injured limb can be used to accurately monitor StO₂ changes in the hypovolaemia patient, and that the hyperaemic response to injury is apparently ‘overridden’ by the effects of hypovolaemia. Unfortunately it is difficult to fully assess the effects of limb injury on StO₂ during hypovolaemia as there were significant differences in StO₂ between the injured and control limbs at the PREINJ point. The uninjured limbs on average recording an StO₂ 5% higher than the control limbs, which is much larger than the 1% difference demonstrated between identical contralateral sites in the normal NIRS values and response to exercise study (see Chapter 7). Differences in StO₂ values between the left and right limb were also observed at the baseline measuring points (B₁ and B₂), although unlike those at the PREINJ point these were not significant. It is therefore possible that the differences seen at the PREINJ point represent a type I error. Another explanation is that it is a consequence of the insertion of a femoral line on the left side, which may account for why the uninjured limb StO₂ measurements were paradoxically higher than those of the injured limb. Unfortunately the use of a femoral line was an unavoidable part of the experimental protocol. To avoid committing any errors in interpretation, the left limb was therefore not treated as control for assessing the effect of injury on StO₂ values during the protocol.

Haemoglobin concentration had no meaningful correlation with StO_2 values, $r=.13$ for the left limb and $r=.05$ for the right, and at best only a weak correlation with other non blood gas measurements. This is not surprising since haemoglobin concentration is not an indicator of resuscitation, but the particularly poor correlation with StO_2 serves to illustrate a commonly misunderstood point: StO_2 is a measure of the ratio of oxygenated to deoxygenated haemoglobin, and is not dependant on the haemoglobin concentration per se.

8.6 CONCLUSION

This work has demonstrated that NIRS can be used to detect significant degrees of blood loss and monitor the response of hypovolaemic subjects to initial resuscitation. StO_2 values recorded from injured limbs are able to adequately track the response to haemorrhage and resuscitation, despite the hyperaemic effect of limb injury reported in normovolaemic subjects.

StO_2 measurements phase led changes in base excess and lactate by 31–37 minutes. Although diastolic and mean arterial blood pressure correlated most strongly with ABG measurements, StO_2 also performed well (and better than heart rate), and has significant practical advantages over conventional haemodynamic parameters used in the assessment of hypovolaemic patients.

9. NIRS TRAUMA RESUSCITATION STUDY

9.1 INTRODUCTION

Despite the good body of work examining NIRS as a tool for assessing blood loss in hypovolaemia models there have been relatively few clinical studies in trauma patients. In an early small study (n=8), McKinley et al. (2000) demonstrated that deltoid muscle StO₂, but not subcutaneous StO₂, was highly correlated to systemic oxygen delivery index (DO₂I), and outperformed conventional haemodynamic parameters. Subsequent studies almost exclusively used thenar eminence StO₂ in their assessment of the trauma patient. Crookes et al. (2005) attempted to use thenar eminence StO₂ to identify degrees of shock in 145 trauma patients — the degree of shock being determined by conventional haemodynamic parameters. They found that although NIRS could identify patients in the most severely shocked group it was unable to distinguish between lesser degrees of shock. In two subsequent studies by the same group thenar StO₂ was recorded for 24 hours in 383 major trauma patients. It was found that the lowest recorded StO₂ values within the first hour of admission could identify patients likely to develop MODS with a sensitivity of 78% and specificity of 39%. The negative predictive value of StO₂ was 91%, but the positive predictive value was only 18% and NIRS was not found to perform any better than conventional measures of perfusion status (Cohn et al., 2007). In a subgroup analysis of the patients who underwent massive transfusion, StO₂ was the only factor shown to predict MODS or death consistently at one, two and three hours after admission. Although NIRS was unable predict the need for massive transfusion in this group (Moore et al., 2008).

There have been two studies of NIRS in the deployed military environment, both in Iraq. The first of these was a report of a small case series (n=8) which demonstrated that NIRS could be used in the deployed setting and suggested that StO₂ measurements below 70% accurately tracked the patients' response to resuscitation (Beilman and Blondet, 2009). In a study of 147 combat casualties, thenar StO₂ measurements were recording during initial resuscitation in ED to determine if NIRS might have a triage role. Thenar StO₂ values were not found to be a useful predictor of the need for 'life-saving intervention' or transfusion. But in the cohort of patients with a systolic blood pressure greater than 90 mmHg it

did predict the need for transfusion, leading the authors to conclude that NIRS may have a triage role in those patients who initially appear haemodynamically stable (Beekley et al., 2010).

One of the principle problems with these studies is that they have all, with one exception, used StO_2 values recorded from the thenar eminence. As has been demonstrated by the experimental evidence presented in Chapter 6 the thenar eminence is not the most sensitive site for detecting hypovolaemia. Furthermore the IED related blasted injuries that have characterised military deployments in Afghanistan in the early part of the 21st century often result in injuries to the thenar eminence rendering it an unsuitable monitoring site in these cases. Soller et al. (2008a), Bezemer et al. (2009) and the evidence presented in Chapter 6 demonstrated the forearm to be the most sensitive site for detecting hypovolaemia. Unfortunately the forearm suffers from the same practical limitation as the thenar eminence of being frequently injured by IEDs. Therefore in this study the deltoid was selected as the primary monitoring site. Although not as sensitive as the forearm, it has been shown to be able to detect relatively small changes in volume state, and it is unlikely that significant bilateral injuries/amputations of the deltoid would occur in the presence of a survival injury pattern.

9.2 AIM

The aim of this study was to test NIRS monitoring in a deployed military setting on patient cohort with a high injury burden and identify any practical constraints to its use in the military environment. Secondary aims included comparing deltoid StO_2 to ABG parameters with a view to assessing if the phase relationship between StO_2 and BE and lactate reported in Chapter 8 could be demonstrated in seriously injured human trauma patients. Cerebral StO_2 was also monitored to determine how this responded in severe trauma and evaluate its relationship to deltoid StO_2 .

9.3 MATERIALS AND METHODS

The experimental design was that of a single centre, prospective, observational, cohort study. Ethical approval was obtained out of committee from the Chairman of the Ministry of Defence Research Ethics Committee (MoDREC). The study was conducted at the Role 3 facility, Camp Bastion, Afghanistan between the period 21 October 2010 to 15 October 2011.

Role 3, Camp Bastion was originally tented, but during the time of this investigation it was established as a hard standing facility serving allied forces in the Helmand province and extended areas of Southern Afghanistan. The hospital was a tri-service, multinational facility with consultant level specialists in general surgery, orthopaedic surgery, plastic surgery, emergency medicine, general medicine and radiology. Despite the multinational nature of the facility all care was delivered withing a UK clinical governance framework. During the period of study, the hospital had four major trauma bays in the ED, a four table theatre capacity, eight bedded ITU and two general wards with additional isolation and overflow capacity.

9.3.1 *Study Population*

Eligible for inclusion in the study were all patients admitted to Bastion Role 3 facility, as a trauma alert, who were managed either in Trauma Bay One (the primary trauma bay) or by ‘right turn*’ directly into theatre. The following exclusion criteria were applied:

1. patients with significant injuries to both deltoids or those with bilateral humeral fractures — due to the potential for inference of such injuries with the StO₂ recording.
2. patients judged by the duty surgeon or anaesthetist to be obviously not T1[†] upon arrival in the Emergency Department (ED). If there was any ambiguity about the patients’ treatment priority upon arrival there were enrolled in the study.
3. patients aged 16 years or under.

9.3.2 *Materials*

StO₂ measurements were recorded with an INVOS® System NIRS monitor in a two channel setting. During the study it was found necessary to use the INVOS®

*‘Right turn’ was the term adopted for critically unstable patients who bypassed ED and went straight to theatre for simultaneous resuscitation and surgery. It was named after the layout of the department with theatres being accessed through a door on the right upon entering the ED.

[†]T1 is one of the five patient treatment priority categories defined by NATO and British Military doctrine. The T1 category describes patients requiring immediate, life saving treatment. A detailed description of treatment categories is given in Appendix E

System monitor with a bespoke power cable encompassing a surge protector to protect the machine from the unstable power supply in Camp Bastion. Blood gas measurements were taken using an i-STAT® System hand-held blood gas analysis unit (Abbott Point of Care, Princeton, USA). Pulse rate, blood pressure and SpO₂ (measured as a routine part of patient care) were also recorded.

To ensure data integrity, prior to any monitoring a clock synchronisation between all monitoring apparatus and other sources of time-stamped data was performed. This included:

- INVOS® System Monitor
- wall clocks in ED and theatres
- i-STAT® System hand-held blood gas analysis units in ED, theatres, ITU and the laboratory

9.3.3 *Monitoring Protocol*

Monitoring was initiated upon patient arrival in trauma bay one in ED, or in theatre for 'right turn' patients. It was continued for 12 hours after arrival in the Intensive Therapy Unit (ITU) or ward, or up until the point of casualty evacuation from the facility, whichever was sooner. If during the ITU monitoring phase the patient returned to theatre, this was considered a further significant physiological insult and the monitoring period extended for an additional 12 hours after returning to the ITU or ward.

All patients underwent continuous StO₂ monitoring from one deltoid site with or without monitoring of cerebral StO₂ — which was not performed in cases of head/scalp injuries over the cerebral monitoring site. Deltoid measurements were recorded on channel one of the NIRS machine and cerebral StO₂ on channel two. By default StO₂ recordings were taken from the left hand side unless there was an injury to that side precluding monitoring. Where the skin overlying the monitoring site was contaminated with blood or dirt the site was cleaned with chlorhexadine before siting the probe. The positions of the NIRS probes at each anatomical site were identical to those used in the previous studies (see Figure 5.3, page 64):

1. *the deltoid muscle* — recorded with the probe positioned two finger breadths

<i>Management Period</i>	<i>ABG Frequency</i>
Initial resuscitation in ED	Every 15 minutes
Operating theatre management	Every 15 minutes
ITU management	Every 15 minutes for the first hour Hourly after the first hour

Table 9.1: The proposed ideal protocol for frequency of ABG measurements.

above the deltoid insertion with the probe/cable connection directed cranially. If the left deltoid was injured then the right deltoid was monitored. If both deltoids were injured then the patient was excluded from the trial.

2. *the frontal lobe of the brain* — recorded with the probe positioned one finger breadth above the orbital ridge with the probe/cable connection directed laterally and the distal end of the probe positioned approximately in the midline. If the left side of the forehead or frontal lobe of the brain was injured then right side was monitored. If both sides were injured the brain was not monitored but the patient remained in the study with just deltoid monitoring.

At times when patients were moved, i.e. between ED to theatres, theatres to ITU, or to the CT scanning room, it was necessary in some circumstances to detach the INVOS® System monitor to facilitate transport. Monitoring was recommenced as soon as possible after completing the transfer.

Regular ABG measurements were taken targeted to the idealised protocol outlined in Table 9.1. In practice, clinical and environmental constraints (in particular limited personnel, and cartridges for the i-STAT®) limited the frequency with which ABG measurements could be taken.

All other standard physiological parameters (i.e. pulse rate and blood pressure) were recorded as a routine part of patient care, which were extracted retrospectively from the patient records.

9.3.4 Data Collection

Patient demographic information was collected contemporaneously along with basic clinical details, and recorded on a study specific template along with ABG

<i>Field</i>	<i>Comment</i>
Hospital number	
Sex	Male Female
Date of Birth	
Age	Calculated from date of birth
Nationality	
Date and time of injury	Local time
Date and time of arrival in ED	Local time
Date and time of arrival in theatre	Local time
Date and time of arrival in ITU	Local time
Mechanism of injury	IED GSW RTA Assault Accident
Injuries sustained	By region
Haemoglobin	Recorded against time sampled
ABG Data	Recorded against time sampled
Haemodynamic parameters	Pulse rate Blood pressure

Table 9.2: Data fields used in the study.

data. NIRS data was recorded on the machine's USB stick and subsequently transferred to CD-R. Photocopies of the ED charts, intra-operative anaesthetic charts and ITU documentation along with the CD containing the NIRS data were mailed back through a secure military system to the Royal Centre for Defence Medicine (RCDM) where physiological data was manually extracted to a spreadsheet. A summary of the data fields for which information was collected is shown in Table 9.2.

9.3.5 Data Analysis

Comparison of non-parametric distributions was performed using a Wilcoxon signed-rank test. Comparison of multiple non-parametric distributions was performed using as Kruskal-Wallis test.

All statistical tests were undertaken using R (R Development Core Team, 2009) with a significance threshold of $p \leq 0.05$.

9.4 RESULTS

A total of 71 patients were enrolled in the study. Due to the practical constraints of collecting data in a deployed multinational operational clinical environment many datasets were found to be of poor quality, lacking either sufficient ABG or

standard physiological measurements to allow meaningful interpretation. After examining the datasets, 20 subjects were found to have sufficient data for analysis.

9.4.1 *Demographics of Study Population and Injury Burden*

Of the subgroup of 20 subjects all were male with a mix of nationalities: six British; five Americans; and nine local nationals. Ages were not recorded for 5 subjects (for the Afghans age is often not known and usually estimated), but of the age data available the mean age was 25.4 years with a range of 16*–54 years.

The injury mechanism was by IED in 18 cases and gunshot wound in two cases. A summary of the principle injuries in each patient by anatomical location are shown in Tables 9.3 and 9.4. Twelve patients suffered major traumatic lower limb amputation or required completion amputation, nine of which were bilateral. Ten patients underwent laparotomy either for primary injury or to obtain vascular control for a high amputation. Two patients required thoracotomy.

The overall injury burden was extremely high. ISS (injury Severity Score) and TRISS (Trauma Injury Severity Score) predicted mortality values for subjects are shown in Table 9.5. For subjects with an unknown age the mean age for the group was used. The median ISS score for all subjects was 20. There was one death during the monitoring period — subject 1 who died in ITU 10 hours 21 minutes after admission.

Time of injury was recorded for 10 subjects. In those subjects the mean time to arrival in ED was 66 minutes (range 30–175 minutes, s.d. 40 minutes). The mean time spent in ED (including time in CT if performed before theatre) was 28 minutes (range 5–69 minutes, s.d. 18 minutes), and the mean time in theatre (including CT if performed before arrival in ITU) was 227 minutes (range 97–510 minutes, s.d. 120 minutes).

9.4.2 *StO₂ and Physiological Parameter Response to Resuscitation*

The general trend among patients was one of significantly deranged physiological measurements responding rapidly to resuscitation in ED with this improvement extending into the theatre phase. Patients often demonstrated some instability in theatre but usually stabilised before transfer to the ITU. In ITU patients generally

*Estimated age.

<i>Patient</i>	<i>Head and neck</i>	<i>Torso</i>	<i>Upper limb</i>	<i>Lower limb</i>
1 [†]	GSW neck	Resuscitative thoracotomy	Brachial artery injury	—
2 [*]	Fracture to base of skull and maxilla	Traumatic pneumothorax	—	Traumatic AKA, contralateral mal- leolar fracture
3	—	Perineal injuries, laparotomy for vascular control	Frag wounds to hand	Traumatic bilateral amputations (AKA & BKA)
4	—	Shoulder and chest burns	Elbow laceration	Traumatic BKA, contralateral frag wound to foot
5 ^{**†}	—	x2 lung resections for frag wounds, bowel perforation, scrotal injuries	Axillary artery and vein injuries	Fibular and right calcaneous fracture, multiple frag wounds
6 [*]	—	Bowel (serosal) and kidney injuries. Splenic laceration. Perineal injuries	Traumatic bilateral lower limb ampu- tations, pelvic fracture	—
7 [*]	Fragment in orbit	PEA arrest, perineal injuries	—	Bilateral AKAs
8	—	—	—	Traumatic bilateral BKAs
9 [*]	—	—	Hand and forearm wounds	Traumatic BKA, contralateral femoral fracture and sciatic nerve injury
10	—	—	Frag injuries to arm	Traumatic BKA, completion BKA on contralateral side

^{*} patient underwent laparotomy

[†] patient underwent thoracotomy

Table 9.3: Summary of the major injuries in patients 1–10 by anatomical location.

<i>Patient</i>	<i>Head and neck</i>	<i>Torso</i>	<i>Upper limb</i>	<i>Lower limb</i>
11*	—	Extensive pelvic frag injuries, symphysis pubis fracture	—	Traumatic bilateral amputations (TKA & BKA)
12*	Mandibular fracture dislocation	Extensive abdominal, perineal and scrotal injuries	Ulnar fracture and extensive soft tissue injuries	Traumatic Bilateral BKA
13*	—	GSW to pelvis with intra-abdominal bleeding, sacral	—	Femur fracture
14	—	Frag wounds to back	Frag wounds to forearm	Traumatic BKA, completion BKA on contralateral side
15	Frag perforation injury to trachea	Frag injury to axilla and chest	—	Extensive soft tissue frag injuries
16	—	—	Frag wounds both arms	Traumatic BKA, contralateral tibial fracture
17	Frag wounds to scalp and left eye	Frag wounds chest, buttocks and scrotum	Frag wounds to left hand	Bilateral traumatic BKAs
18*	—	Frag wound to left flank, intra-abdominal bleeding	Frag wound to shoulder	Popliteal artery injury
19	—	—	Frag wounds to forearm	Fibular fracture, extensive frag injuries
20*	—	Small pneumothorax. Large abdominal/retroperitoneal frag injuries	—	Traumatic bilateral amputations (AKA & TKA)

* patient underwent laparotomy

Table 9.4: Summary of the major injuries in patients 11–20 by anatomical location.

<i>Patient</i>	<i>ISS</i>	<i>TRISS Predicted Mortality (%)</i>	<i>Patient</i>	<i>ISS</i>	<i>TRISS Predicted Mortality (%)</i>
1	29	98.8 (P)	11	20	89.3
2	29	94.6	12	9	76.9
3	26	93.2	13	20	97.9 (P)
4	17	86.6	14	17	86.6
5	22	98.1 (P)	15	21	98.0 (P)
6	29	94.6	16	16	85.6
7	26	93.2	17	27	93.7
8	16	85.6	18	19	97.8 (P)
9	9	76.9	19	5	70.4
10	16	85.6	20	54	99.3

Table 9.5: Injury Severity Scores (ISS) and Trauma Injury Severity Score (TRISS) predicted mortality values for patients. For gunshot wounds and blast injuries where the principle injuries were due to fragmentation the penetrating TRISS predicted mortality, denoted by (P), was been used.

recorded physiological and StO_2 values within normal limits*, or demonstrated a steady improvement. For this reason most of the following analysis focuses on the ED and early theatre phases of the patient journey where the greatest physiological change occurred and hence the relationships between different physiological parameters can be best observed.

Figure 9.1 shows the deltoid and head StO_2 data for the ED and theatre phases of the study from all subjects fitted to a LOESS model, illustrating the StO_2 response to resuscitation. Deltoid and head StO_2 follow a broadly similar pattern — starting at low levels upon arrival rising rapidly as resuscitation commences, before plateauing around the 60 minute point after completion of the initial resuscitation, although there is still significant variability in StO_2 in many subjects in the recording period after this. Three subjects (subjects 14, 15 and 16) demonstrated a marked fall in StO_2 values upon arrival prior to responding to resuscitation.

A box plot of StO_2 values during each phase of the study is shown in Figure 9.2. There were significant differences in StO_2 during each phase (ED, theatre and ITU) of the study for both the deltoid ($p < 0.0001$) and cerebral ($p < 0.0001$) sites (Kruskal-Wallis test). In the deltoid, mean StO_2 rose during each phase of the

*The normal range of StO_2 values is described in the experimental data presented in Chapter 7.

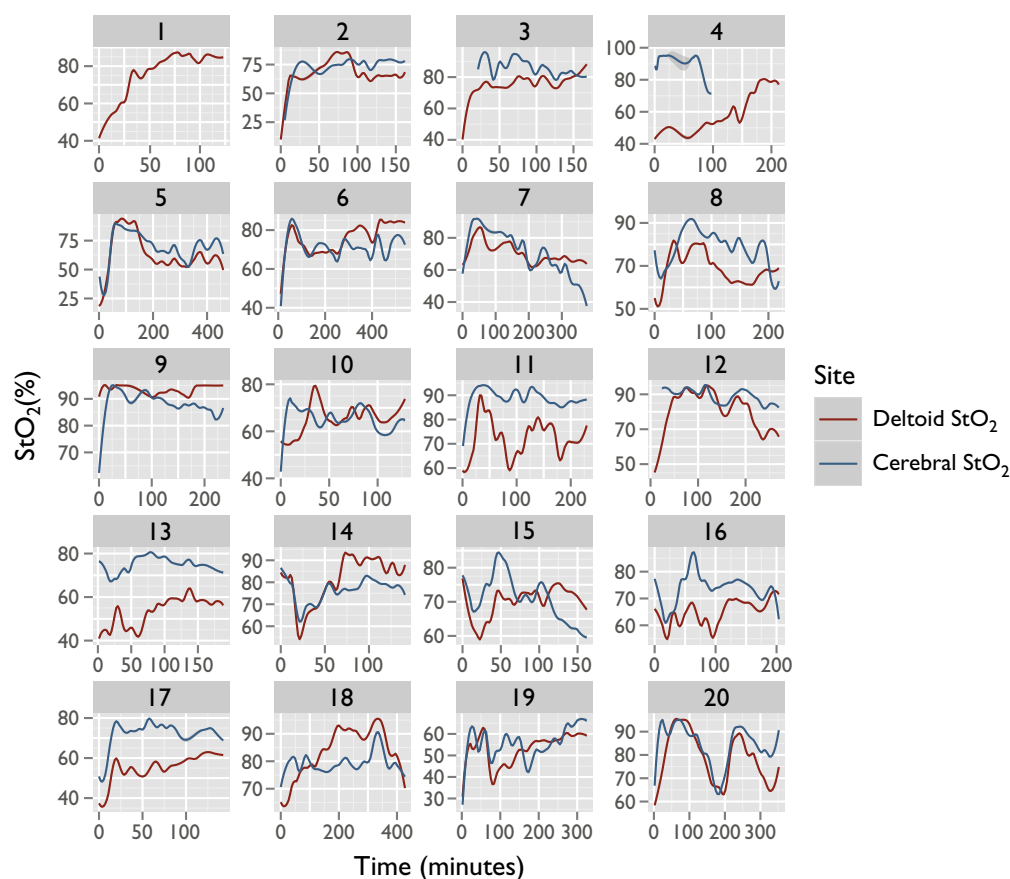


Figure 9.1: Deltoid and cerebral StO₂ data by patient from the ED and theatre phase of the study.

study: from 59.4% during the ED phase, 72.5% in theatre, to 73.8% in the ITU phase. The differences between the theatre and ITU phases were relatively small and were separately tested with a Wilcoxon rank-sum test which confirmed significance ($p < 0.0001$). Cerebral StO₂ did not follow the same pattern of progressive rises recording mean values of: 68.8% in ED; 76.2% in theatre; and 72.8% in ITU.

There were significant differences between deltoid and cerebral StO₂ values during the study ($p < 0.0001$). Although the actual difference in the mean StO₂ between the deltoid (73.1%) and cerebral (73.5%) for the whole study duration was relatively small, there were larger differences during each study phase. During the ED phase cerebral StO₂ was $7.5 \pm 0.5\%$ higher than deltoid StO₂ ($p < 0.0001$). During the theatre phase this difference was reduced to $4.0 \pm 0.5\%$ ($p < 0.0001$). In the ITU

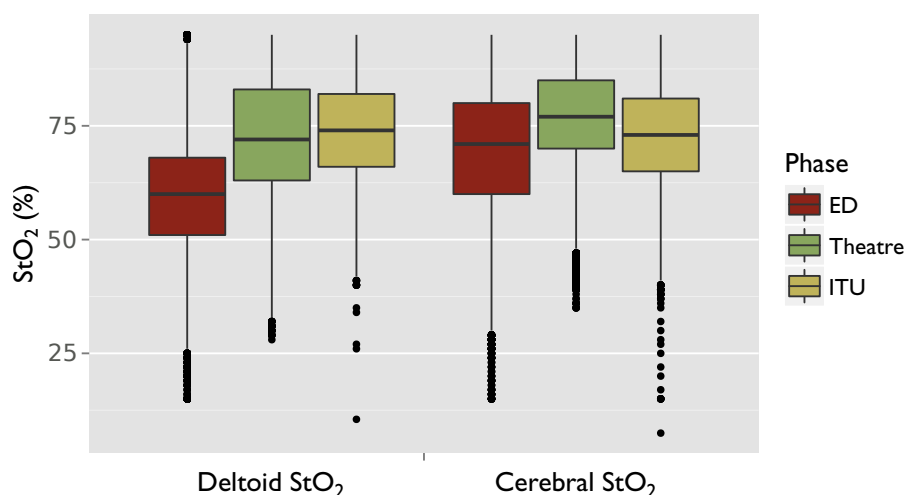


Figure 9.2: Box plot of StO₂ values during each phase of the study. Plot whiskers denote maximum and minimum data points, excluding outliers which are shown separately.

phase this relationship reversed and deltoid StO₂ was 1.0% ($p < 0.0001$) higher than cerebral StO₂ ($p < 0.0001$). The relationship between deltoid and cerebral StO₂ also appeared to vary across their range of values. Figure 9.3 shows a scatterplot of deltoid StO₂ against cerebral StO₂, with linear and LOESS models fitted to the data. It can be seen that for deltoid StO₂ values greater than 50% the linear and LOESS models closely match. Linear regression analysis for deltoid StO₂ values $\geq 50\%$ demonstrated the relationship between cerebral and deltoid StO₂ could be predicted by:

$$\text{cerebral StO}_2 = 0.53 \times \text{deltoid StO}_2 + 34.7, R^2=0.31 (p < 0.0001)$$

Below deltoid values of 50% the curves diverge and there is a separate linear component in LOESS curve, most obvious for deltoid values between 25%–40%. Linear regression analysis on values in this range demonstrated the relationship between cerebral and deltoid StO₂ could be predicted by:

$$\text{cerebral StO}_2 = 2.02 \times \text{deltoid StO}_2 - 27.5, R^2=0.40 (p < 0.0001).$$

Mean values for the other principle physiological and ABG parameters are summarised in Table 9.6. Patients were generally tachycardic for the duration of the study, although heart rate did fall during each stage of the hospital admission.

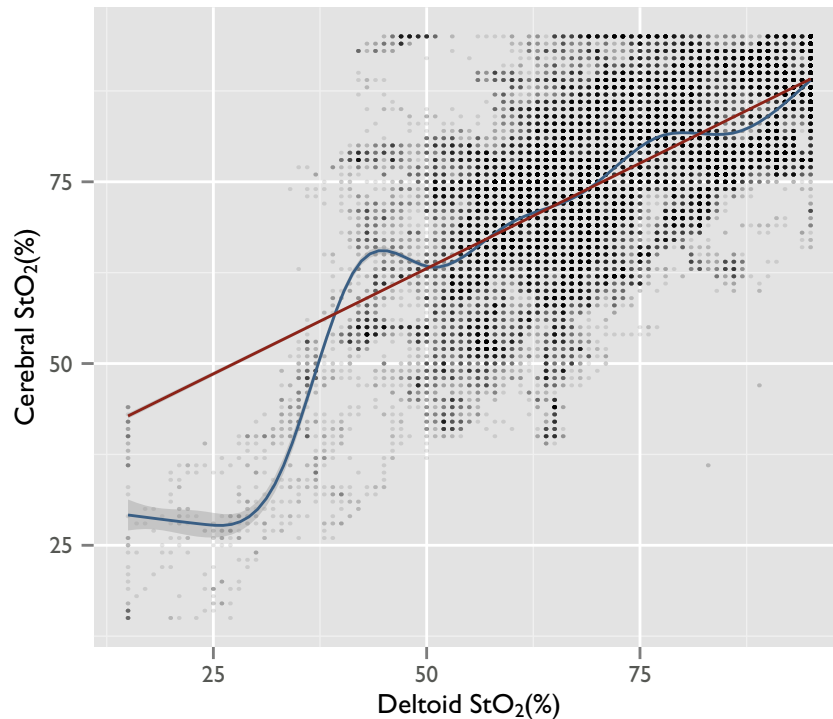


Figure 9.3: A scatterplot of deltoid against cerebral StO₂. The alpha transparency of the data points has been reduced to demonstrate the data distribution. The linear regression line is shown in red and a LOESS model fitted to the data drawn in blue. Note that for deltoid StO₂ values above 50% the LOESS and regression curves are closely related, but below 50% they become discordant, suggesting a different relationship between cerebral and deltoid StO₂ in the lower range.

Mean blood pressures during each stage were not markedly deranged, being within normal limits for the majority of the ED phase, although they did fall slightly during the theatre phase. All blood pressure measurements subsequently rose again during the ITU phase, but the average values were still below those recorded in ED. The ABG parameters (pH, BE and lactate) behaved in a more predictable way, although lactate measurements were only available in theatre and ITU since the i-STAT® cartridges used in ED did not have the lactate module. The pattern was one of significant acidosis in ED which gradual improved during the time in theatre and ITU.

<i>Physiological Parameter</i>	<i>Phase</i>		
	<i>ED</i>	<i>Theatre</i>	<i>ITU</i>
HR (bpm)	113	108	102
SBP (mmHg)	123	109	116
DBP (mmHg)	77	62	65
MAP (mmHg)	92	78	82
pH	7.15	7.30	7.38
HCO ₃ (mmol/L)	19.7	22.3	27.0
BE (mmol/L)	-10.29	-4.15	2.34
Lactate (mmol/L)	—	6.51	2.78

Table 9.6: Mean values for physiological parameters during each of the study phases. Note that is no lactate value during the ED phase since the i-STAT® cartridges used in ED did not have the lactate module.

9.4.3 Correlation Between Physiological Parameters

A correlation matrix for the main physiological variables during the combined ED and theatre phases is shown in Table 9.7. There was a moderate correlation between deltoid and cerebral StO₂ throughout the study, $r_s=.55$ and during each phase of the study: in ED $r_s=.56$; in theatre $r_s=.64$; and in ITU $r_s=.55$.

StO₂ and standard physiological measurements generally correlated poorly with ABG parameters. Of the variables examined only heart rate demonstrated a modest correlation with any of the ABG measurements (specifically with lactate, $r_s=.49$). There were poor correlations for all comparisons of StO₂ recorded from the deltoid or cerebrum with heart rate or blood pressure measurements.

9.4.4 Phase Relationship Between StO₂ and ABG Parameters

The variability in the frequency of ABG data collection provided a limited number of time-points with which a phase comparison with StO₂ could be made. This coupled with the differences in patients' degree of injury, resuscitation state on arrival in ED, and response to resuscitation at different time-points meant it was not possible to build a robust model examining the phase relationship between StO₂ and ABG parameters.

	<i>Deltoid StO₂</i>	<i>Cerebral StO₂</i>	<i>HR</i>	<i>SBP</i>	<i>DBP</i>	<i>MAP</i>	<i>pH</i>	<i>HCO₃</i>	<i>BE</i>	<i>Lactate</i>
<i>Deltoid StO₂</i>	—	0.64	-0.12	0.18	0.10	0.07	0.32	0.04	0.17	0.20
<i>Cerebral StO₂</i>	0.64	—	-0.18	0.19	0.20	0.14	0.24	0.15	0.19	0.25
<i>HR</i>	-0.12	-0.18	—	-0.19	-0.16	-0.07	-0.35	-0.13	-0.18	0.49
<i>SBP</i>	0.18	0.19	-0.19	—	0.75	0.91	0.23	0.21	0.22	-0.04
<i>DBP</i>	0.10	0.20	-0.16	0.75	—	0.95	0.25	0.32	0.32	-0.00
<i>MAP</i>	0.07	0.14	-0.07	0.91	0.95	—	0.34	0.35	0.36	-0.01
<i>pH</i>	0.32	0.24	-0.35	0.23	0.25	0.34	—	0.73	0.87	-0.43
<i>HCO₃</i>	0.05	0.15	-0.13	0.22	0.32	0.35	0.73	—	0.93	-0.43
<i>BE</i>	0.17	0.19	-0.18	0.22	0.32	0.36	0.87	0.94	—	-0.46
<i>Lactate</i>	0.20	0.26	0.49	-0.04	-0.00	-0.01	-0.43	-0.43	-0.46	—

Table 9.7: A correlation matrix for the main physiological variables during the combined ED and theatre phases (HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; BE = base excess; HCO₃ = bicarbonate).

9.5 DISCUSSION

This study set out to assess the practical constraints of using current generation NIRS devices in the deployed military environment. With respect to that goal it was clearly demonstrated that StO₂ can be successfully measured in the role 3 environment. It proved easy to train end-users how to use the INVOS® System monitor, and the technique was universally reported as being simple to use and understand. It is a testament to the ease of recording StO₂ data that the limiting factor in addressing the other study aims was the difficulty in collecting conventional physiological data rather than StO₂ data which was of high quality in nearly all of the patients studied. Although not documented by the manufacturer the INVOS® probes are largely radiolucent to x-rays and it was found that they did not impact CT image quality when left in place during head or body scans.

Along with pulse rate and SpO₂ monitoring (assessed with pulse oximetry), StO₂ was the only objective physiological measurement that could be initiated immediately upon patient arrival and that provided a continuous, real time assessment of the patients' response to the initial resuscitation. In this respect NIRS has significant advantages over blood pressure monitoring which cannot be recorded continuously without an arterial line, while non-invasive measures of blood pressure have several practical problems and questions about their true accuracy.

A few practical limitations of NIRS use in the deployed clinical environment were identified during the study. One of the early problems was the sensitivity of the INVOS® System monitor to the unstable electricity supply (particularly from the backup generator) in Camp Bastion. There was a regular requirement to replace blown fuses until a custom inline surge protector was built into the device's power supply cable. Obviously this is a device specific issue rather than a generic problem with NIRS per se. A more insidious problem was the tendency of the device to record seemingly valid StO₂ measurements when not attached to a patient or when the probe became partially detached. This is a problem that has been noted in previous studies, but it is a particular issue in the clinical environment where patients are frequently dirty, wet, bleeding or sweating, and ensuring adequate probe adhesion can be difficult. Outside the controlled experimental environment constant vigilance was required to ensure the probe stayed in place; for this reason the deltoid probe was frequently secured with an additional layer of adhesive tape.

Hopefully this problem will be fixed in the next generation of devices which should either warn or stop recording once the probe becomes detached.

Assessing the StO_2 response to resuscitation (shown in Figure 9.1) it can be seen that in most patients StO_2 responded rapidly to the initial resuscitation rising from initially low values to reach a peak/plateau within 30 minutes of arriving in the ED. Once patients had been resuscitated to within the normal range of StO_2 values the role of NIRS in guiding further resuscitation was less clear and this is reflected in the small difference between the mean StO_2 in the theatre and ITU phases. It is likely at this point that trend changes in StO_2 are more useful than the absolute values, particularly for identifying acute deteriorations in a patient's condition. This was demonstrated in part by the StO_2 traces of several subjects where, after initial resuscitation, there were significant fluctuations in StO_2 values corresponding to resuscitative or intraoperative events. Cerebral StO_2 , in particular, appeared to be sensitive to the induction of anaesthesia, usually occurring in the late ED phase. Given the known effects of several anaesthetic agents on cerebral blood flow this is not necessarily surprising. Unfortunately the effect was too inconsistent between subjects to demonstrate any definitive relationship between induction of anaesthesia and StO_2 .

There were significant differences between the cerebral and deltoid StO_2 during all phases of the monitoring protocol. This point is not surprising, given the differences in their resting values (demonstrated in Chapter 7). Both sites appear to track the resuscitation process in most patients, a finding which seemingly contradicts those presented in the human volunteer simulated haemorrhage study (Chapter 6) where cerebral StO_2 was shown to correlate poor with degrees of hypovolaemia, presumably as a consequence of cerebral autoregulation. The reason cerebral StO_2 provides a reliable indicator of resuscitation in this study is probably due to the much greater hypovolaemic insult experienced by this group of patients overwhelming the cerebral autoregulatory process. It is noticeable however that cerebral StO_2 values were preserved in several subjects (subjects 3, 4, 12 and 13) in the face of very low deltoid StO_2 . It is not clear why cerebral autoregulation should have been preserved in some subjects but lost in others, although anaesthetic agents and other drugs may have played a part.

Cerebral StO_2 was significantly greater than deltoid StO_2 during the ED and

theatre phases, by between approximately 4–8%. This is the reverse of the normal relationship at rest, where cerebral StO_2 are typically around 7% less than that of the deltoids. This would appear to support the idea that there is an element of cerebral autoregulation preserving StO_2 in the presence of hypovolaemia. Further evidence for cerebral autoregulation can be seen in Figure 9.3 where two distinctly different linear relationships between cerebral and deltoid StO_2 can be seen in the upper and lower ranges. In the higher range (for these purposes considered to be deltoid StO_2 values greater than 50%) cerebral StO_2 values increased by 0.53% for every 1% increase in deltoid StO_2 . In the lower range (analysed for deltoid values between 25–40%) cerebral StO_2 values increase by 2.02% for every 1% rise in deltoid StO_2 strongly suggesting that in this range cerebral StO_2 is preserved relative to deltoid StO_2 .

Although cerebral StO_2 tracked the resuscitation process in most patients, several of the findings in this study indicate it is likely to have a lower sensitivity for detecting hypovolaemia compared to the deltoid. Firstly, cerebral autoregulation will blunt the response to hypovolaemia. Secondly, the fact that cerebral StO_2 recorded higher values than the deltoid during the key resuscitative phases means that cerebral StO_2 values will be subject to greater degrees of compression of their upper values potentially reducing the granularity of measurement scale (see Section 7.5 for a discussion of this phenomenon). These findings are consistent with those presented in the human volunteer simulated haemorrhage study (Chapter 6) which suggested that deltoid StO_2 was a more sensitive indicator of hypovolaemia than cerebral StO_2 . How deltoid StO_2 compares to values recorded from the forearm, reported to be the most sensitive site in experimental studies, in real trauma patients remains unknown.

Unfortunately it was not possible to examine the phase relationship between physiological parameters and ABG measurements. Although an attempt at building a model using the methodology described in Chapter 8 was performed, it was found that the limited frequency of haemodynamic data, in particular ABG data, coupled with the heterogenicity of the injuries and resuscitation pathway meant that a phase relationship between the resuscitation curves of the different parameters could not be identified. However a lag between StO_2 and the ABG response could be observed examining the data for individual subjects (see Fig-

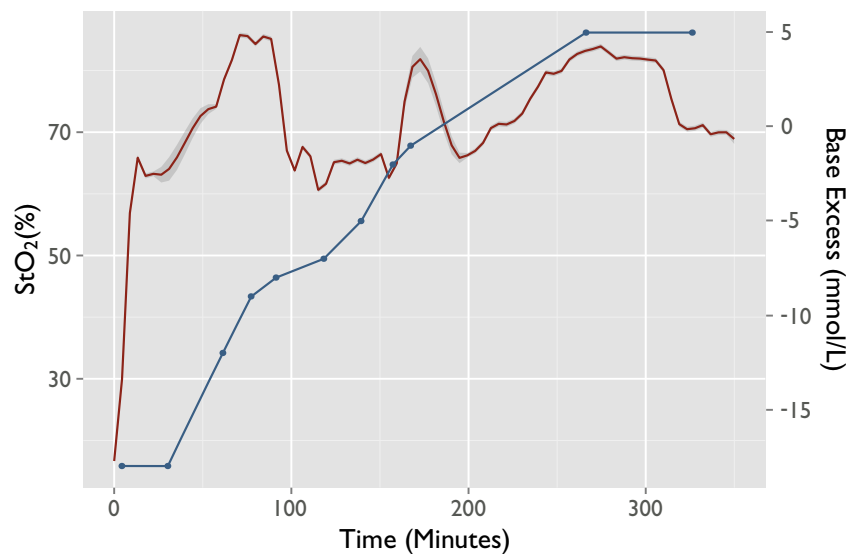


Figure 9.4: StO₂ (shown in red) and base excess (shown in blue) data from patient 2, demonstrating the delayed response in the base excess curve compared to the StO₂ curve.

ure 9.4), even it if could not be mathematically demonstrated. StO₂ and ABG parameters correlated poorly (see Table 9.7). This is not surprising given that the values are being compared effectively out of phase*; and equally the correlation between haemodynamic and ABG parameters was also poor, with the exception of heart rate which had a moderate correlation with lactate. The overall impression is that NIRS along with the other conventional physiological measurements all assess slightly different elements of the patients physiology. NIRS has significant advantages over other means of assessing physiology, principally its ease of use and non-invasive nature. However NIRS is not a panacea for the problem of assessing the trauma patient, and the experience of this study suggests it is best used in conjunction with other means of assessment to provide additional information on the physiological status of patient and their response to the early stages of resuscitation.

*ABG measurements were demonstrated to lag changes in StO₂ by approximately 35 minutes in the animal trauma data presented in Chapter 8.

9.6 CONCLUSION

This study has demonstrated that NIRS can be successfully and usefully used in the deployed military environment. StO_2 values accurately track patients' response to initial resuscitation however once the values are in the normal range then changes in StO_2 are of more clinical use than the absolute values themselves.

Cerebral StO_2 demonstrates a degree of autoregulation in many patients and as such is likely to be a less sensitive indicator of global physiological state than most skeletal muscle sites. Although NIRS has significant practical advantages over conventional means of patient assessment it has not been demonstrated to be superior to them. As such, NIRS at present can only be recommended as an adjunct, albeit a very useful one, to the assessment of the trauma patient.

10. CONCLUSION

The introductory chapters to this work attempted to illustrate that significant improvements in the early and late mortality associated with major trauma can be achieved by goal directed correction of hypovolaemia. The problem in delivering this care lies with the current means of assessing the degree hypovolaemia and response to resuscitation. Conventional assessments of physiology all have significant shortcomings either in their sensitivity, specificity or practicality. Crookes et al. (2005) identified five properties of the ‘ideal tool’ for assessing end organ consequences of hypovolaemia associated with trauma:

1. it should be non-invasive
2. provide continuous reading of the measured parameter
3. provide an objective parameter of tissue perfusion, ideally at a cellular level in end organs
4. be robust and portable
5. should influence management leading to an improved patient outcome

As a tool for assessing the trauma patient NIRS certainly meets the first two of these criteria; this work aimed to examine how it performed in the last three.

In laying the groundwork for subsequent field testing of the NIRS device several important considerations for the clinical application of StO₂ in trauma patients have been addressed. Firstly the normal range of NIRS values was established from a number of anatomical sites relevant to trauma management. It was found that StO₂ varies significantly between sites, except for anatomically identical contralateral sites (confirmed for the deltoids but the finding is likely to be equally applicable to other sites). This means that reference ranges for StO₂ values cannot simply be extrapolated between sites but must be established for each site of interest, a point that has not always been appreciated in the published literature. In the upper limb StO₂ values appear to decrease progressively with more distal monitoring sites, unfortunately the lower limb was not studied in sufficient detail to determine if a similar relationship exists there. The distribution of NIRS values was also observed to vary, with some sites demonstrating a skew left distribution, while others appeared to be more normally distributed. This would

appear counterintuitive for a physiological measurement that would be expected to demonstrate a normal distribution. It seems this finding is a function of the monitoring algorithm used by the INVOS® System, which compresses values at the upper end of its monitoring scale, rather than a true physiological phenomenon. Thus sites with a high StO₂, such as the deltoid, have their upper ranges compressed and appear to have a skew left distribution, while sites with a lower StO₂, such as the frontal lobe of the brain, experience less compression in their upper values and demonstrate a distribution more closely approximating to normal.

In establishing the normal range of StO₂ values one of the major limitations of NIRS has been demonstrated: the large range over which normal values lie. Interestingly despite the different distribution of StO₂ values, all the sites studied in this work had a similar lower end cutoff in their resting values of around 40%. It would seem then that StO₂ values below this point can be confidently interpreted as abnormal — in the context of trauma this is likely to mean significant blood loss (assuming there are not local phenomena which may account for a low StO₂, e.g. disruption of regional blood supply). For StO₂ measurements above 40%, and certainly above the lower quartiles of the resting values for that site, the interpretation of the StO₂ becomes more difficult and the experience of the NIRS trauma resuscitation study was that in this range trend changes become more important than absolute values.

Exercise was found to significantly increase StO₂ at all of the sites investigated (deltoid, anterior compartment of leg and frontal lobe of the brain) — an effect that persisted for at least 10 minutes. However the size of the increase at 10 minutes after cessation of exercise was relatively small, between 3–7%, and fell well within the interquartile ranges of the resting StO₂ values. As such it is unlikely this phenomenon in isolation would cause problems with the interpretation of StO₂ values in clinical practice. However exercise is known to modulate the physiological response to hypovolaemia and the effect of this on StO₂ in the hypovolaemic patient remains unknown.

Most human trauma studies investigating NIRS have recorded StO₂ from thenar eminence. The preference for this site appears to be driven at least in part by the fact that one of the most widely used commercial NIRS monitors (the In-Spectra™ Tissue Spectrometer) is marketed almost exclusively for recording from

the thenar eminence. The thenar eminence certainly has several attractions as monitoring site: it is easily accessible; has only a thin layer of overlying fat; and has low levels of melanin pigmentation which can absorb or scatter infrared light distorting the StO₂ measurement. However there is no convincing evidence that thenar eminence StO₂ provides a more accurate assessment of patient physiology than that recorded from other sites. The data presented in the human volunteer simulated haemorrhage study (described in Chapter 6) suggests that the thenar eminence is not sensitive to small degrees of hypovolaemia. Of the sites studied only the forearm (over flexor digitorum profundus) demonstrated a statistically significant change in response to lower body negative pressure (LBNP) induced hypovolaemia, although discernible but non-significant changes were also observed in the deltoid. Cerebral StO₂ did not respond significantly to increments of LBNP which was presumed to be a consequence of cerebral blood flow autoregulation. This phenomenon was demonstrated more convincingly in the trauma resuscitation study (Chapter 9) where regression analysis demonstrated that cerebral StO₂ was preserved relative to deltoid StO₂ in the lower ranges.

The administration of morphine attenuated the StO₂ response to hypovolaemia across all sites, an effect also observed in most of the other physiological measurements. However, as the evidence of the trauma resuscitation study demonstrates, where morphine administration was near universal, morphine cannot mask the StO₂ changes associated with significant hypovolaemia.

Examination of NIRS in major trauma/haemorrhage subjects was performed in an animal haemorrhage model and in human trauma patients in the deployed military environment. In the animal model the relationship between StO₂ and ABG parameters was examined, where it was found that StO₂ phase led changes in base excess and lactate by 31–37 minutes. A similar relationship was also observed in human patients, although it could not be robustly demonstrated due to a lack of ABG data points and the variability between subjects. Limb injury, known to affect StO₂ in resting subjects, does not appear to influence StO₂ trend changes in hypovolaemic subjects (although the absolute values may change) which suggests that injured monitoring sites can still be used to track patients' response to resuscitation. Both the animal and human studies demonstrated that NIRS could be used to accurately assess the response of subjects to resuscitation in real time.

However the greatest utility appears to be during the initial triage and resuscitation of the patient when StO₂ values are outside the normal range. As discussed above once the patient is resuscitated to within the normal range, absolute StO₂ numbers become hard to interpret, however significant trend changes, i.e. sudden drops in StO₂ suggesting ongoing blood loss, continue to be useful. The human trauma resuscitation study proved that NIRS can be successfully used in the deployed military environment at role 3 as a useful adjunct to patient assessment. It is a testament to the ease of use of the technique that continuous high quality StO₂ data was recorded from nearly every subject enrolled in the study, while the frequency of routinely collected physiological data was to prove the major limiting factor in interpreting the study outcomes.

In the course of performing the experiments described in this work considerable experience with the INVOS® System monitor has been accrued, and several previously undescribed practical problems encountered. The difficulties described by other researchers obtaining StO₂ measurements from deeply pigmented individuals were not encountered. However problems obtaining readings from sites with darkly coloured tattoos were experienced and this represents the first description of this issue. Although the INVOS® System has a measure of signal quality this was not always found to be reliable, and technical failings of monitoring were often only obvious in retrospect, such as the flat line recording in the right limb of the animal 1 in the animal trauma and haemorrhage model (see Figure 8.4, page 117). A more insidious problem was the tendency of the device to record seemingly valid StO₂ measurements when not attached to the patient or when the probe became partially detached. A clear example of this is demonstrated in the photograph of the INVOS® System monitor shown in Figure 5.1, page 60, where the machine appears to be recording valid StO₂ values despite the probes being stuck to a cotton sheet overlying a wooden table. Hopefully problems such as these will be addressed in the next generation of devices.

In assessing the role of NIRS in the management of trauma patients, it has been demonstrated that it reasonably meets the first four criteria of Crookes et al. (2005) 'ideal tool' described at the start of this chapter. The technique provides a continuous real time measure of an objective assessment of tissue perfusion. Current devices are portable and robust enough to withstand use in the deployed

military environment with potential for pre-hospital roles. The superiority of NIRS over conventional physiological assessments of resuscitation status has not been demonstrated. However NIRS has significant practical advantages over measuring blood pressure or ABGs and provides useful information complimenting that of conventional means of assessment. It has yet to be shown that NIRS meets the last of Crookes et al. (2005) criteria — that it can positively influence the clinical outcomes of real trauma patients, and it is here that future research efforts should be directed. The computer controlled closed-loop NIRS resuscitation model described by Chaisson et al. (2003) presents one potential approach for examining this issue. Unfortunately StO₂ resuscitation endpoints have not yet been determined (and are likely to vary between devices), without which the interpretation of such studies would be difficult. Even if an StO₂ resuscitation endpoint could be defined, a closed-loop protocol is unlikely to find application in current models of real-life resuscitation, which perhaps explains why this study design has not seen further development in the literature.

One way to examine the effects of NIRS monitoring in a clinical setting would be to monitor StO₂ in trauma patients randomised into two groups: one where the StO₂ measurements are available to clinicians to facilitate their decision making process; and the other where clinicians are blinded to the StO₂ values. Patients could then be case matched or grouped according to injuries, and management and outcomes between the groups compared. This has the advantage of assessing NIRS as it would be used in the clinical environment, i.e. as an adjunct to clinical assessment and decision making, rather than as an absolute endpoint in itself. However determining differences between the groups would be likely to require a large study population, probably necessitating a multi-centred design. The experience of the NIRS Trauma Resuscitation Study (Chapter 9) found that familiarising clinicians with StO₂ monitoring to the extent that they are comfortable to use it to guide their decision making process takes one to two months even in a high volume trauma centre. While undertaking such a training and familiarisation exercise on a multi-centre basis, in civilian trauma centres, is certainly feasible the effort involved should not be underestimated.

In addition to the issue as to whether StO₂ monitoring can positively affect the outcomes of trauma patients, several other unresolved questions remain from

this work. The range of normal StO_2 values has at present only been established for the deltoid, anterior compartment of the leg and frontal lobe of the brain. Determining the range of values from other sites, particularly the forearm, should be a priority if these sites are to be investigated in future studies. Although it was established that StO_2 remains elevated up to 10 minutes after completion of exercise, the pattern of StO_2 during recovery and time taken to return to baseline are unknown. However, how clinically useful an understanding of these effects would be is questionable given the very small increases in StO_2 seen shortly after exercise. A more interesting problem is the effect of prior exercise on the StO_2 (and other physiological parameters) response to haemorrhage. Animal studies examining this issue have given conflicting results, and the response in humans remains unstudied. This problem could be addressed with a cross-over study similar to that presented in the NIRS Human Volunteer Simulated Haemorrhage Study (Chapter 6), but with the two arms of the study being exercise or no exercise prior to the lower body negative pressure simulated hypovolaemia. The interaction of other relevant factors, such as the administration of morphine or the effect of (simulated) limb injury, could then also be easily examined by the addition of extra arms to the study.

Given the aforementioned difficulties demonstrating a positive impact of StO_2 monitoring on trauma resuscitation outcomes it seems plausible that widespread adoption of NIRS will occur first in other clinical areas where assessments of local tissue perfusion are required. Of the possible applications relevant to trauma, monitoring for compartment syndrome and free flap failure have shown the most promise (Barker et al., 2011; Chen et al., 2015). In both these conditions NIRS directly measures the outcome of interest (oxygenation of the target tissue), rather than using peripheral tissue oxygenation as a proxy measure of global resuscitation; and both, rightly or wrongly, are usually treated as binary conditions, i.e. patients either have compartment syndrome or they do not, providing a clear endpoint against which StO_2 can be assessed. The fact that NIRS has not seen more widespread use in these areas is probably a consequence of the relatively high cost of the equipment and a lack of familiarity with the technique. However as the cost of the technology falls, NIRS will probably see more frequent use for these or similar applications leading to an increased awareness and uptake of the

technique in other areas.

With regards to the future role of NIRS in the military, development in this field is likely to parallel or follow that of the civilian experience — both in the pre-hospital and secondary care environments. This work has demonstrated the difficulties of performing robust research in the deployed military environment, manifest not least by the fact that 51 of the 71 patients enrolled in the NIRS Trauma Resuscitation Study (Chapter 9) were excluded from analysis due to difficulties collecting ‘routine’ haemodynamic and ABG data. Compared to the civilian setting, deployed military research faces several additional challenges including: reduced numbers of staff; potentially unreliable logistical support; unstable power supplies; and security concerns. Even tasks as simple as recording and transmitting study data securely can become major challenges and a variety of different approaches were required during the course of this work in response to changes in the security environment and local policy in Afghanistan. The end of British operations in Helmand and the closure of the Role 3 facility in Camp Bastion with the return to contingency operations will further limit the opportunities for NIRS research in the deployed environment. Future operations are likely to be smaller and even more resource constrained, with no single static site providing a focal point for the study of a large volume of military trauma. As a consequence it is probable that future military applications of NIRS will first be developed at Role 4/civilian major trauma centres before being translated to the deployed environment.

APPENDICES

A. INVOS® 5100C SYSTEM SPECIFICATIONS

The INVOS® System complies with the international regulatory standards: IEC 60601 – 1, UL 60601 – 1, CSA 22.2.601 – 1, CE 0197. Physical specification and operation ranges, as defined by manufacturers' literature (Somanetics Corporation, 2008), are as follows:

PHYSICAL DIMENSIONS:	<i>Height</i>	24cm
	<i>Width</i>	29cm
	<i>Depth</i>	19cm
	<i>Weight</i>	4.95kg
	<i>Preamplifier Cable Length</i>	4.5m
	<i>Sensor Cable Length</i>	1.5m
OPERATIONAL LIMITS:	<i>StO₂ Measurement Range</i>	15–95%
	<i>Repeatability</i>	Within 1 StO ₂ index point from unit to unit (in vitro)
	<i>Alarm Limit Range</i>	High 20–95% Low 15–90
	<i>Trend Memory</i>	24 hours (2 samples/min)
	<i>Safety Class</i>	Continuous Operation Type BF Class I
ENVIRONMENTAL OPERATING RANGE:	<i>Operating Temperature</i>	16°C– 32°C
	<i>Storage Temperature</i>	–20°C– +45°C
	<i>Humidity</i>	20%–80%, non-condensing
	<i>Altitude</i>	Max 3048 m
ELECTRICAL SPECIFICATIONS:	<i>Power</i>	AC mains or backup battery
	<i>Input Voltage</i>	100–240 V AC
	<i>Frequency</i>	50/60 Hz
	<i>Current</i>	1.0 A (100 V) – 0.5 A (240 V)
	<i>Fuse</i>	2.5 A 250 V
	<i>Backup Battery</i>	12 V DC (approx 20 mins)
	<i>Digital Output</i> <i>Data Export</i>	RS-232 communications USB 2.0 Flash Memory

B. BASH SCRIPT FOR CLEANING INVOS® SYSTEM DATA FILES

This script was used clean files produced by the INVOS® System Monitor, undergoing several additions and modifications throughout its use. It strips out duplicate space delimiters and removes all fields except the date/time stamp and the specified StO₂ fields.

The script can process either individual files or batch process all files in the current directory. It accepts arguments to change the field delimiter and the number of channels retained in the output file, default values are space and one channel. The script has been tested on a system running Linux kernel 3+ with GNU Core Utilities and BASH version 4+, although it should be easily portable to other shells with only minor modifications. Instructions for use are given in the script help output.

```
#!/bin/bash
```

```
function help-output() {  
    cat <<EOF  
nirs-clean-file
```

NAME

```
nirs-clean-file - cleans data files produced by Inspectra INVOS  
System monitor
```

SYNOPSIS

```
nirs-clean-file [-f filename] [-c 1|2|3|4] [s space|comma|semi] [-h]
```

DESCRIPTION

```
Cleans the data files produced by the InSpectra INVOS System monitor  
removing all columns except the date, time stamp and the selected  
number of channels outputs between 1-4. Field delimiters can be  
selected as space, comma or semicolon. Default options are 1  
channel output with comma delimiters. NIRS values recording "0"  
are replaced with "NA". When call called on individual files those  
files will be processed and outputted to the current directory with  
a .csv post-fix. If a file with that name already exists in the  
current directory it will be overwritten without warning. If  
called without any options or no file specified the program will  
run in batch mode processing every file in the current directory  
with the output placed in nirs_output_file directory. If the  
nirs_output_files directory already exists the
```

nirs_output_directory is created with the current time stamp.

EXAMPLES

Clean file "file_name" leaving data from channels 1-2 and use comma separators.

```
$ nirs-clean-file -f file_name -c 2 -s comma
```

Clean all files in the current directory using default values (1 channel and space separators).

```
$ nirs-clean-file
```

Clean all files in current directory using channels 1-4 and comma separators.

```
$ nirs-clean-file -c 4 -s comma
```

EOF

}

```
# Sets the fields to be removed in the cut command
```

```
CHANNEL_1="1-3"
```

```
CHANNEL_2="1-3,10"
```

```
CHANNEL_3="1-3,10,17"
```

```
CHANNEL_4="1-3,10,17,24"
```

```
CVS_SEPARATOR=","
```

```
SPACE_SEPARATOR=" "
```

```
SEMI_SEPARATOR=";"
```

```
# Default values
```

```
type_of_file="$CVS_SEPARATOR"
```

```
type_of_file_descriptor="comma"
```

```
no_of_channels="$CHANNEL_1"
```

```
no_of_channels_descriptor="1"
```

```
nirs_output_dir="."
```

```
target_file=""
```

```
# Parse script options
```

```
while getopts f:c:s:h opt
```

```
do
```

```
    case $opt in
```

```
        f) if [ -f $OPTARG ]; then
```

```
            target_file="$OPTARG"
```

```
        else
```

```
            echo "$OPTARG is not a valid file in the current directory."
```

```
            exit 1
```

```
        fi
```

```
    ;;
```

```

c) if [ $OPTARG -eq 1 ]; then
    no_of_channels="$CHANNEL_1"
    no_of_channels_descriptor="1"
    elif [ $OPTARG -eq 2 ]; then
    no_of_channels="$CHANNEL_2"
    no_of_channels_descriptor="2"
    elif [ $OPTARG -eq 3 ]; then
    no_of_channels="$CHANNEL_3"
    no_of_channels_descriptor="3"
    elif [ $OPTARG -eq 4 ]; then
    no_of_channels="$CHANNEL_4"
    no_of_channels_descriptor="4"
    else
    echo "$OPTARG is an invalid number of channels, select a
        number between 1-4"
    exit 1
    fi
;;

s) if [ $OPTARG = space ]; then
    type_of_file="$SPACE_SEPARATOR"
    type_of_file_descriptor="space"
    elif [ $OPTARG = comma ]; then
    type_of_file="$CVS_SEPARATOR"
    type_of_file_descriptor="comma"
    elif [ $OPTARG = semi ]; then
    type_of_file="$SEMI_SEPARATOR"
    type_of_file_descriptor="semicolon"
    else
    echo "$OPTARG is an invalid separator"
    exit 1
    fi
;;

h) help-output
    exit
;;

*) echo "Invalid option. Use the -h option to see help.";
    exit 1
;;

esac
done

function clean-command() {
    output_file=${target_file%.*}${target_file#*.}
    tr -s ' ' "$type_of_file" < "$target_file" | cut -d "$type_of_file" \
-f "$no_of_channels" | sed "s/\b0\b/NA/g" > \
"${nirs_output_dir%}/}/${output_file}.csv"

```

```

        echo "$target_file cleaned with $type_of_file_descriptor separators \
and $no_of_channels_descriptor channels"
    }

function directory-processing() {
# check output directory does not exist and if so create it, otherwise
# make a directory with a timestamp
    if [ ! -d nirs_output_files ]; then
        nirs_output_dir="nirs_output_files"
        mkdir $nirs_output_dir
    else
        nirs_output_dir="nirs_output_files_$(date +%F-%T)"
        mkdir "$nirs_output_dir"
    fi
# process all files in target directory and place in output directory
    for target_file in *
    do
        if [ -f "$target_file" ]; then
            clean-command
        else
            echo "$target_file is not a valid file, therefore ignored"
        fi
    done
}

# if script is invoked with a target file then process that file with the
# given or default options.
if [ -n "$target_file" ]; then
    clean-command
    exit
fi

# if script is invoked without a target file then batch process all files
# in that directory with the given or default options.
if [ -z "$target_file" ]; then
    directory-processing
    exit
fi

```

C. US MARINE CORPS PHYSICAL FITNESS TEST PROTOCOL

The US Marine Corps (USMC) Physical Fitness Test is a widely used and standardised fitness protocol. The protocol consists of three exercise performed in order, with two minutes rest between each exercise:

1. *Pull-ups*

Pull-ups begin in the 'dead-hang' position with the palms facing forward on the bar, the arms locked out and the body motionless. A successful pull-up is completed by raising the body until the chin is above the bar, and then lowering to the locked out position. The legs may be held in any position as long as they are kept below waist level. Excess movement, swinging of the trunk or legs is not allowed and pull-ups completed in that style are not counted. A change in grip position is allowed but only the hands may touch bar; if the feet touch the ground at any time the exercise is over.

Standard: Maximum number of pull-ups that can be achieved before coming off the bar. There is no time limit.

2. *Sit-ups*

Must be completed on a flat surface. In the starting position, individuals lie on their backs with knees bent to 45° and both feet flat on the floor. Arms must be folded across the chest and should remain in contact with the chest for the repetition to be counted. A single repetition consists of raising the upper body from the starting position until the body is vertical and then returning to the starting position.

Standard: As many repetitions as possible in two minutes.

3. *3 Mile (4.8 km) run*

Performed over a reasonably flat course, this is a timed event.

Standard: Individual best effort.

D. JOINT MEDICAL EMPLOYMENT STANDARD

The Joint Medical Employment Standard (JMES) was introduced on 23 November 2009, with the aim of simplifying unifying the medical employment standard codes across the three services (Army, Navy and Air Force). A JMES description consists of elements describing its date of award and next review, whether it is temporary or permanent, a Medical Deployment Standard, a Medical Employment Standard — composed of four elements, and a descriptor of any medical limitations. Defence Instructions and Notices (DIN) 2009DIN01–183 — The Joint Medical Employment Standard (Surgeon General’s Department, 2009) is the primary reference in this area.

D.1 MEDICAL DEPLOYMENT STANDARD

The Medical Deployment Standard (MDS) describes the medical capacity to deploy, it has three categories:

1. MFD — Medically Fully Deployable
2. MLD — Medically Limited Deployability
3. MND — Medically Not Deployable

D.2 MEDICAL EMPLOYMENT STANDARD

The Medical Employment Standard (MES) ascribes a numerical value to four functional areas, describing the individual’s standard in relation to their branch/trade. The four functional areas are: Air, Land, or Maritime environments, and any requirement for Environmental and Medical Support denoted by the four prefixes A, L, M and E respectively. All four functional elements are always described for each individual, a typical description for a medically fully deployable soldier being A4 L1 M1 E1. Details of MES codes are summarised in Table D.1.

D.2. MEDICAL EMPLOYMENT STANDARD

MES code	Description	Comments
AIR		
A1	Fit for flying duties without restriction	Aircrew only
A2	Fit for flying duties but has sub-optimal hearing or eye sight	Aircrew only
A3	Fit for limited flying duties	Aircrew only
A4	Fit to be flown in a passenger aircraft	
A5	Unfit to be taken into the air	
A6	Air assessment not currently required	Not normally used
LAND		
L1	Fit for unrestricted duties	
L2	Fit for unrestricted duties but with a medical risk marker	e.g. early noise induced hearing loss
L3	Fit for limited duties but with some restriction subject to medical risk assessment	
L4	Fit for specific limited duties within branch/trade	
L5	Unfit for service in the Land environment	
L6	Land assessment not currently required	Not normally used
MARITIME		
M1	Fit for unrestricted duties	
M2	Fit for unrestricted duties with caveats to be stated	
M3	Fit for limited duties in harbour or ashore with caveats to be stated	
M4	Fit for limited duties ashore only, may not be in own trade or skill with caveats stated	
M5	Unfit for service in the maritime environment	
M6	Maritime assessment not currently required	Not normally used
ENVIRONMENT AND MEDICAL SUPPORT		
E1	Fit for worldwide service in all environments	
E2	Restricted employment outside UK	e.g. unfit for hot or cold environments
E3	Employment in UK only	
E4	Employment subject to single Service manning restriction	
E5	Medically unfit for duty and under medical care	Holding category
E6	Pregnant	

Table D.1: JMES codes

E. NATO TRIAGE TREATMENT CATEGORIES

NATO and British Military Doctrine describe five priority treatment categories, these are defined with prefix T (for treatment). Although mainly intended for triaging patients in mass causality situations, categories are often assigned to individual patients as a simple, albeit limited, means of communicating injury severity and urgency of treatment. The five categories are as follows:

T1 (P1) — individuals requiring immediate, life saving, treatment. In the mass casualty situation this treatment should be simple, non-time consuming procedures in an individual likely to survive, e.g. airway manoeuvre, application of tourniquet or emergency amputation. This category may be given the suffix A, B, or C denoting if the primary problem is with the airway, breathing, or circulation.

T2 (P2) — individuals who will tolerate a delay in major surgery or medical treatment, without significantly impairing their chance of survival. Patients may enter this category from T1 following simple treatment measures. Examples include the management of open long bone fractures and large joint dislocations.

T3 (P3) — individuals requiring minimal treatment (*'the walking wounded'*) who can take care of themselves or be helped by medically untrained individuals, and whose outcome will not be prejudiced by a delay in the provision formal medical care. Examples include lacerations and simple fractures.

Dead — as determined by the person performing the categorisation. This is only a category class and not a formal declaration of death as under UK law death can only be declared by a licenced medical practitioner.

In the mass casualty situation one further category may be invoked:

T4 (P1 Hold) — expectant treatment. These are individuals whose injuries are so severe they have a poor chance of survival regardless of the treatment instigated. These individuals can receive supportive measures, such as adequate

analgesia, but would not get definitive treatment in preference to less severely injured individuals. Once the backlog of T1 and appropriate T2 cases has been cleared, T4 casualties become eligible for medical intervention — if they have survived. This category is not applied to single casualties, or multiple casualties in a compensated situation.

BIBLIOGRAPHY

BIBLIOGRAPHY

- Abney, W. and Festing, E.R. (1881) On the influence of the atomic grouping in the molecules of organic bodies on their absorption in the infra-red region of the spectrum. **Philosophical Transactions of the Royal Society of London**, 172: 887–918.
- Abou-Khalil, B., Scalea, T.M., Trooskin, S.Z., Henry, S.M. and Hitchcock, R. (1994) Hemodynamic responses to shock in young trauma patients: need for invasive monitoring. **Critical Care Medicine**, 22 (4): 633–639
- Afshari, R., Maxwell, S.R.J., Webb, D.J. and Bateman, D.N. (2009) Morphine is an arteriolar vasodilator in man. **Br J Clin Pharmacol**, 67 (4): 386–393
- American College of Surgeons (1997) **Advanced Trauma Life Support (ATLS®)**. 7th ed., American College of Surgeons
- Anderson, I.D., Woodford, M., de Dombal, F.T. and Irving, M. (1988) Retrospective study of 1000 deaths from injury in England and Wales. **British Medical Journal (Clinical Research Edition)**, 296 (6632): 1305–1308
- Arató, E., Kürthy, M., Sínay, L., Kasza, G., Menyhei, G., Masoud, S., Bertalan, A., Verzár, Z., Kollár, L., Roth, E. and Jancsó, G. (2009) Pathology and diagnostic options of lower limb compartment syndrome. **Clinical Hemorheology and Microcirculation**, 41: 1–8
- Aviado, D.M. and Aviado, D.G. (2001) The Bezold-Jarisch reflex. a historical perspective of cardiopulmonary reflexes. **Annals of the New York Academy of Sciences**, 940: 48–58
- Bacter, C.R., Canizaro, P.C., Carrico, C.J. and Shires, G.T. (1970) Fluid resuscitation of hemorrhagic shock. **Postgraduate Medicine**, 48 (3): 95–99
- Barker, T., Midwinter, M. and Porter, K. (2011) The diagnosis of acute lower limb compartment syndrome: Applications of near infrared spectroscopy. **Trauma**, 13 (2): 125–136
- Bartels, S.A., Bezemer, R., de Vries, F.J.W., Milstein, D.M.J., Lima, A., Cherpanath, T.G.V., van den Meiracker, A.H., van Bommel, J., Heger, M., Karemaker, J.M. and Ince, C. (2011) Multi-site and multi-depth near-infrared spectroscopy in a model of simulated (central) hypovolemia: lower body negative pressure. **Intensive Care Med**, 37 (4): 671–677

- Beekley, A.C., Martin, M.J., Nelson, T., Grathwohl, K.W., Griffith, M., Beilman, G. and Holcomb, J.B. (2010) Continuous noninvasive tissue oximetry in the early evaluation of the combat casualty: a prospective study. **J Trauma**, 69 Suppl 1: S14–S25
- Beilman, G.J. and Blondet, J.J. (2009) Near-infrared spectroscopy-derived tissue oxygen saturation in battlefield injuries: a case series report. **World Journal of Emergency Surgery**, 4: 25
- Beilman, G.J., Groehler, K.E., Lazon, V. and Ortner, J.P. (1999) Near-infrared spectroscopy measurement of regional tissue oxyhemoglobin saturation during hemorrhagic shock. **Shock**, 12 (3): 196–200
- Bersten, A.D. and Soni, N. (eds.) (2009) **Oh's Intensive Care Manual**, chap. 24 Oxygen Therapy. 6th ed., Elsevier, pp. 315–326
- Bezemer, R., Karemaker, J.M., Klijn, E., Martin, D., Mitchell, K., Grocott, M., Heger, M. and Ince, C. (2009) Simultaneous multi-depth assessment of tissue oxygen saturation in thenar and forearm using near-infrared spectroscopy during a simple cardiovascular challenge. **Critical Care**, 13 Suppl 5: S5
- Bickell, W.H., Bruttig, S.P., Millnamow, G.A., O'Benar, J. and Wade, C.E. (1991) The detrimental effects of intravenous crystalloid after aortotomy in swine. **Surgery**, 110 (3): 529–536
- Bickell, W.H., Wall, M.J., Pepe, P.E., Martin, R.R., Ginger, V.F., Allen, M.K. and Mattox, K.L. (1994) Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. **New England Journal of Medicine**, 331 (17): 1105–1109
- Brohi, K., Cohen, M.J., Ganter, M.T., Matthay, M.A., Mackersie, R.C. and Pittet, J.F. (2007) Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? **Annals of Surgery**, 245 (5): 812–818
- Brohi, K., Cohen, M.J., Ganter, M.T., Schultz, M.J., Levi, M., Mackersie, R.C. and Pittet, J.F. (2008) Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. **Journal of Trauma**, 64 (5): 1211–7
- Campagna, J.A. and Carter, C. (2003) Clinical relevance of the bezold-jarisch reflex. **Anesthesiology**, 98 (5): 1250–1260
- Chaisson, N.F., Kirschner, R.A., Deyo, D.J., Lopez, J.A., Prough, D.S. and Kramer, G.C. (2003) Near-infrared spectroscopy-guided closed-loop resuscitation of hemorrhage. **Journal of Trauma**, 54 (5 Suppl): S183–S192

- Chalkley, D., Cheung, G., Walsh, M. and Tai, N. (2011) Deaths from trauma in London—a single centre experience. **Emergency Medical Journal**, 28 (4): 305–309
- Champion, H.R., Bellamy, R.F., Roberts, C.P. and Leppaniemi, A. (2003) A profile of combat injury. **Journal of Trauma**, 54 (5 Suppl): S13–S19
- Chance, B., Dait, M.T., Zhang, C., Hamaoka, T. and Hagerman, F. (1992) Recovery from exercise-induced desaturation in the quadriceps muscles of elite competitive rowers. **American Journal of Physiology**, 262 (3 Pt 1): C766–C775
- Chawla, L.S., Nader, A., Nelson, T., Govindji, T., Wilson, R., Szlyk, S., Nguyen, A., Junker, C. and Seneff, M.G. (2010) Utilization of base deficit and reliability of base deficit as a surrogate for serum lactate in the peri-operative setting. **BMC Anesthesiology**, 10 (1): 16
- Chen, Y., Shen, Z., Shao, Z., Yu, P. and Wu, J. (2015) Free flap monitoring using near-infrared spectroscopy
- Cohn, S.M. (2007) Near-infrared spectroscopy: potential clinical benefits in surgery. **Journal of the American College of Surgeons**, 205 (2): 322–332
- Cohn, S.M., Nathens, A.B., Moore, F.A., Rhee, P., Puyana, J.C., Moore, E.E., Beilman, G.J. and StO₂ in Trauma Patients Trial Investigators (2007) Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. **Journal of Trauma**, 62 (1): 44–54
- Convertino, V.A. (2003) Evidence for altered alpha-adrenoreceptor responsiveness after a single bout of maximal exercise. **Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology**, 95 (1): 192–198
- Convertino, V.A. and Adams, W.C. (1991) Enhanced vagal baroreflex response during 24 h after acute exercise. **American Journal of Physiology**, 260 (3 Pt 2): R570–R575
- Convertino, V.A., Ludwig, D.A. and Cooke, W.H. (2004) Stroke volume and sympathetic responses to lower-body negative pressure reveal new insight into circulatory shock in humans. **Autonomic Neuroscience**, 111 (2): 127–134
- Cooke, W.H., Ryan, K.L. and Convertino, V.A. (2004) Lower body negative pressure as a model to study progression to acute hemorrhagic shock in humans. **Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology**, 96 (4): 1249–1261

- Cooper, C.E. and Springett, R. (1997) Measurement of cytochrome oxidase and mitochondrial energetics by near-infrared spectroscopy. **Philosophical Transactions of the Royal Society of London Series B, Biological Sciences**, 352 (1354): 669–676
- Cosgriff, N., Moore, E.E., Sauaia, A., Kenny-Moynihan, M., Burch, J.M. and Galloway, B. (1997) Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. **Journal of Trauma**, 42 (5): 857–61
- Crookes, B.A., Cohn, S.M., Bloch, S., Amortegui, J., Manning, R., Li, P., Proctor, M.S., Hallal, A., Blackbourne, L.H., Benjamin, R., Soffer, D., Habib, F., Schulman, C.I., Duncan, R. and Proctor, K.G. (2005) Can near-infrared spectroscopy identify the severity of shock in trauma patients? **Journal of Trauma**, 58 (4): 806–13; discussion 813–6
- Davis, J.W. (1994) The relationship of base deficit to lactate in porcine hemorrhagic shock and resuscitation. **Journal of Trauma**, 36 (2): 168–172
- Davis, J.W., Davis, I.C., Bennink, L.D., Bilello, J.F., Kaups, K.L. and Parks, S.N. (2003) Are automated blood pressure measurements accurate in trauma patients? **Journal of Trauma**, 55 (5): 860–863
- Davis, J.W., Parks, S.N., Kaups, K.L., Gladen, H.E. and O'Donnell-Nicol, S. (1996) Admission base deficit predicts transfusion requirements and risk of complications. **Journal of Trauma**, 41 (5): 769–774
- Davis, J.W., Shackford, S.R. and Holbrook, T.L. (1991) Base deficit as a sensitive indicator of compensated shock and tissue oxygen utilization. **Surgery, Gynecology and Obstetrics**, 173 (6): 473–476
- Delpy, D.T. and Cope, M. (1997) Quantification in tissue near-infrared spectroscopy. **Philosophical Transactions of the Royal Society of London Series B, Biological Sciences**, 352: 649–659
- Dempfle, C.E. and Borggreffe, M. (2007) Acidosis and impaired blood coagulation: what and how to correct before using recombinant human factor viia. **Critical Care Medicine**, 35 (6): 1627–1629
- Duncan, A., Meek, J.H., Clemence, M., Elwell, C.E., Tyszczuk, L., Cope, M. and Delpy, D.T. (1995) Optical pathlength measurements on adult head, calf and forearm and the head of the newborn infant using phase resolved optical spectroscopy. **Physics in Medicine and Biology**, 40 (2): 295–304

- Dutton, R.P., Mackenzie, C.F. and Scalea, T.M. (2002) Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. **Journal of Trauma**, 52 (6): 1141–1146
- el Bedawi, K.M. and Hainsworth, R. (1994) Combined head-up tilt and lower body suction: a test of orthostatic tolerance. **Clinical Autonomic Research**, 4 (1-2): 41–47
- Engelke, K.A., Doerr, D.F. and Convertino, V.A. (1995) A single bout of exhaustive exercise affects integrated baroreflex function after 16 days of head-down tilt. **American Journal of Physiology**, 269 (3 Pt 2): R614–R620
- Feuerstein, G. and Siren, A.L. (1986) Effect of naloxone and morphine on survival of conscious rats after hemorrhage. **Circulatory shock**, 19 (3): 293–300
- Frithiof, R. and Rundgren, M. (2006) Activation of central opioid receptors determines the timing of hypotension during acute hemorrhage-induced hypovolemia in conscious sheep. **The American Journal of Physiology - Regulatory, Integrative and Comparative Physiology**, 291 (4): R987–R996
- Garner, J., Watts, S., Parry, C., Bird, J., Cooper, G. and Kirkman, E. (2010) Prolonged permissive hypotensive resuscitation is associated with poor outcome in primary blast injury with controlled hemorrhage. **Annals of Surgery**, 251 (6): 1131–1139
- Garner, J.P., Watts, S., Parry, C., Bird, J. and Kirkman, E. (2009) Development of a large animal model for investigating resuscitation after blast and hemorrhage. **World J Surg**, 33 (10): 2194–2202
- Great Britain (1986) Great Britain. **Animals (Scientific Procedures) Act 1986**. Chapter 16. London: The Stationery Office
- Heckbert, S.R., Vedder, N.B., Hoffman, W., Winn, R.K., Hudson, L.D., Jurkovich, G.J., Copass, M.K., Harlan, J.M., Rice, C.L. and Maier, R.V. (1998) Outcome after hemorrhagic shock in trauma patients. **Journal of Trauma**, 45 (3): 545–549
- Herholz, K., Buskies, W., Rist, M., Pawlik, G., Hollmann, W. and Heiss, W.D. (1987) Regional cerebral blood flow in man at rest and during exercise. **Journal of Neurology**, 234 (1): 9–13
- Herschel, W. (1800) Experiments on the refrangibility of the invisible rays of the sun. **Philosophical Transactions of the Royal Society**, 90: 284–292
- Hindle, P.H. (2007) **Handbook of Near-Infrared Analysis**, chap. Historical Development. 3rd ed., CRC Press, pp. 3–6

- Hodgetts, T., Davies, S., Midwinter, M., Russell, R., Smith, J., Clasper, J., Tai, N., Lewis, E., Ollerton, J., Massetti, P., Moorhouse, I., Hunt, N. and Hepper, A. (2007) Operational mortality of uk service personnel in Iraq and Afghanistan: a one year analysis 2006-7. **Journal of the Royal Army Medical Corps**, 153 (4): 252-254
- Husain, F.A., Martin, M.J., Mullenix, P.S., Steele, S.R. and Elliott, D.C. (2003) Serum lactate and base deficit as predictors of mortality and morbidity. **American Journal of Surgery**, 185 (5): 485-491
- Ide, K., Horn, A. and Secher, N.H. (1999) Cerebral metabolic response to submaximal exercise. **Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology**, 87 (5): 1604-1608
- Ide, K. and Secher, N.H. (2000) Cerebral blood flow and metabolism during exercise. **Progress in Neurobiology**, 61 (4): 397-414
- Jaicks, R.R., Cohn, S.M. and Moller, B.A. (1997) Early fracture fixation may be deleterious after head injury. **Journal of Trauma**, 42 (1): 1-5; discussion 5-6
- James, J.H., Luchette, F.A., McCarter, F.D. and Fischer, J.E. (1999) Lactate is an unreliable indicator of tissue hypoxia in injury or sepsis. **Lancet**, 354 (9177): 505-508
- Jeger, V., Jakob, S.M., Fontana, S., Wolf, M., Zimmermann, H. and Exadaktylos, A.K. (2010) 500 ml of blood loss does not decrease non-invasive tissue oxygen saturation (sto2) as measured by near infrared spectroscopy - a hypothesis generating pilot study in healthy adult women. **The Journal of Trauma Management & Outcomes**, 4: 5
- Jöbsis, F.F. (1977) Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. **Science**, 198 (4323): 1264-1267
- Jöbsis-vanderVliet, F.F. (1999) Discovery of the near-infrared window into the body and the early development of near-infrared spectroscopy. **Journal of Biomedical Optics**, 4(4): 392-396
- Joint Formulary Committee (2012) **British National Formulary (BNF)**. 64th ed., Pharmaceutical Press
- Kauvar, D.S. and Wade, C.E. (2005) The epidemiology and modern management of traumatic hemorrhage: US and international perspectives. **Critical Care**, 9 Suppl 5: S1-S9

- Kincaid, E.H., Miller, P.R., Meredith, J.W., Rahman, N. and Chang, M.C. (1998) Elevated arterial base deficit in trauma patients: a marker of impaired oxygen utilization. **Journal of the American College of Surgeons**, 187 (4): 384–392
- Kowalenko, T., Stern, S., Dronen, S. and Wang, X. (1992) Improved outcome with hypotensive resuscitation of uncontrolled hemorrhagic shock in a swine model. **Journal of Trauma**, 33 (3): 349–53; discussion 361–2
- Krausz, M.M. (2006) Initial resuscitation of hemorrhagic shock. **World Journal Emergency Surgery**, 1: 14
- Krishna, G., Sleight, J.W. and Rahman, H. (1998) Physiological predictors of death in exsanguinating trauma patients undergoing conventional trauma surgery. **Australian and New Zealand Journal of Surgery**, 68 (12): 826–829
- Kuenstner, J. and Norris, K. (1994) Spectrophotometry of human hemoglobin in the near infrared region from 1000 to 2500 nm. **Journal Of Near Infrared Spectroscopy**, 2 (2): 59–65
- Lier, H., Krep, H., Schroeder, S. and Stuber, F. (2008) Preconditions of hemostasis in trauma: a review. the influence of acidosis, hypocalcemia, anemia, and hypothermia on functional hemostasis in trauma. **Journal of Trauma**, 65 (4): 951–960
- MacFarlane, P.D., Grint, N. and Dugdale, A. (2010) Comparison of invasive and non-invasive blood pressure monitoring during clinical anaesthesia in dogs. **Veterinary Research Communications**, 34 (3): 217–227
- Marshall, H., Prehar, S., Kirkman, E., Little, R. and Ohnishi, M. (1998) Morphine increases mortality after haemorrhage in the rat. **Journal of Accident and Emergency Medicine**, 15: 133
- Martin, D. and Windsor, J. (2008) From mountain to bedside: understanding the clinical relevance of human acclimatisation to high-altitude hypoxia. **Postgraduate Medical Journal**, 84 (998): 622–7
- Martin, R.R., Bickell, W.H., Pepe, P.E., Burch, J.M. and Mattox, K.L. (1992) Prospective evaluation of preoperative fluid resuscitation in hypotensive patients with penetrating truncal injury: a preliminary report. **Journal of Trauma**, 33 (3): 354–61; discussion 361–2
- Matcher, S.J., Elwell, C.E., Cooper, C.E., Cope, M. and Delpy, D.T. (1995) Performance comparison of several published tissue near-infrared spectroscopy algorithms. **Analytical Biochemistry**, 227 (1): 54–68

- McGwin, G., Nunn, A.M., Mann, J.C., Griffin, R., Davis, G.G., MacLennan, P.A., Kerby, J.D., Acker, J.E. and Rue, L.W. (2009) Reassessment of the tri-modal mortality distribution in the presence of a regional trauma system. **Journal of Trauma**, 66 (2): 526–530
- McKinley, B.A., Marvin, R.G., Cocanour, C.S. and Moore, F.A. (2000) Tissue hemoglobin O₂ saturation during resuscitation of traumatic shock monitored using near infrared spectrometry. **Journal of Trauma**, 48 (4): 637–642
- McKinley, B.A., Sucher, J.F., Todd, S.R., Gonzalez, E.A., Kozar, R.A., Sailors, R.M. and Moore, F.A. (2009) Central venous pressure versus pulmonary artery catheter-directed shock resuscitation. **Shock**, 32 (5): 463–470
- Meislin, H., Criss, E.A., Judkins, D., Berger, R., Conroy, C., Parks, B., Spaite, D.W. and Valenzuela, T.D. (1997) Fatal trauma: the modal distribution of time to death is a function of patient demographics and regional resources. **Journal of Trauma**, 43 (3): 433–440
- Michel, H., Behr, J., Harrenga, A. and Kannt, A. (1998) Cytochrome c oxidase: structure and spectroscopy. **Annual Review of Biophysics and Biomolecular Structure**, 27: 329–356
- Mikulaschek, A., Henry, S.M., Donovan, R. and Scalea, T.M. (1996) Serum lactate is not predicted by anion gap or base excess after trauma resuscitation. **Journal of Trauma**, 40 (2): 218–22; discussion 222–4
- Molina, P.E., Zambell, K.L., Zhang, P., Vande Stouwe, C. and Carnal, J. (2004) Hemodynamic and immune consequences of opiate analgesia after trauma/hemorrhage. **Shock**, 21 (6): 526–534
- Moore, F.A., Nelson, T., McKinley, B.A., Moore, E.E., Nathens, A.B., Rhee, P., Puyana, J.C., Beilman, G.J., Cohn, S.M. and Group, S.S. (2008) Massive transfusion in trauma patients: tissue hemoglobin oxygen saturation predicts poor outcome. **J Trauma**, 64 (4): 1010–1023
- Murray, C.J. and Lopez, A.D. (1997) Alternative projections of mortality and disability by cause 1990–2020: Global burden of disease study. **Lancet**, 349 (9064): 1498–1504
- Nagasawa, T. (2008a) Oxygen consumption in nonexercising muscle after exercise. **International Journal of Sports Medicine**, 29 (8): 624–629
- Nagasawa, T. (2008b) Resistance exercise increases postexercise oxygen consumption in nonexercising muscle. **European Journal of Applied Physiology and Occupational Physiology**, 104 (6): 1053–1059

- Ogata, H., Arimitsu, T., Matsuura, R., Yunoki, T., Horiuchi, M. and Yano, T. (2007) Relationship between oxygenation in inactive biceps brachii muscle and hyperventilation during leg cycling. **Physiological Research**, 56 (1): 57–65
- Ohnishi, M., Kirkman, E., Hiraide, A. and Little, R.A. (1998) Bradycardia and hypotension associated with severe hemorrhage are reversed by morphine given centrally or peripherally in anesthetized rats. **J Trauma**, 45 (6): 1024–1030
- Özyener, F. (2002) Evaluation of the intra-muscular oxygenation during exercise in humans. **Journal of Sports Science and Medicine**, 1: 15–19
- Peden, M., McGee, K. and Sharma, G. (2002) **The Injury Chart Book: a Graphical Overview of the Global Burden of Injuries**. World Health Organization
- Pfeifer, R., Tarkin, I.S., Rocos, B. and Pape, H.C. (2009) Patterns of mortality and causes of death in polytrauma patients—has anything changed? **Injury**, 40 (9): 907–911
- Plyler, E.K. (1962) The scientific contributions of William Weber Coblentz. **Applied Spectroscopy**, 16: 73–113
- Polinder, S., Meerdink, W.J., Mulder, S., Petridou, E., van Beeck, E. and E. U. R. O. C. O. S. T. Reference Group (2007) Assessing the burden of injury in six european countries. **Bulletin of the World Health Organization**, 85 (1): 27–34
- R Development Core Team (2009) **R: A Language and Environment for Statistical Computing**. R Foundation for Statistical Computing, Vienna, Austria
- Rhee, P., Langdale, L., Mock, C. and Gentilello, L.M. (1997) Near-infrared spectroscopy: continuous measurement of cytochrome oxidation during hemorrhagic shock. **Critical Care Medicine**, 25 (1): 166–170
- Rixen, D., Raum, M., Bouillon, B., Lefering, R., Neugebauer, E. and Arbeitsgemeinschaft “Polytrauma” of the Deutsche Gesellschaft für Unfallchirurgie (2001) Base deficit development and its prognostic significance in posttrauma critical illness: an analysis by the trauma registry of the deutsche gesellschaft für unfallchirurgie. **Shock**, 15 (2): 83–89
- Ryan, J.M. (2000) **Bailey and Love’s Short Practice of Surgery**, chap. Warfare Injuries. 23rd ed., London: Arnold, pp. 291–290
- Sato, N., Hagihara, B., Kamada, T. and Abe, H. (1976) A sensitive method for the quantitative estimation of cytochromes a and a₃ in tissues. **Analytical Biochemistry**, 74 (1): 105–117

- Secher, N.H. and Bie, P. (1985) Bradycardia during reversible haemorrhagic shock—a forgotten observation? **Clinical Physiology**, 5 (4): 315–323
- Severinghaus, J.W. (2002) This history of clinical oxygen monitoring. **International Congress Series**, 1242: 115–120
- Sherry, E. (2003) **Trauma**, chap. The Trauma Problem. Oxford University Press, pp. 1–9
- Shuler, M.S., Reisman, W.M., Whitesides, T.E., Kinsey, T.L., Hammerberg, E.M., Davila, M.G. and Moore, T.J. (2009) Near-infrared spectroscopy in lower extremity trauma. **Journal of Bone and Joint Surgery American Volume**, 91 (6): 1360–1368
- Smith, J., Caldwell, E., D’Amours, S., Jalaludin, B. and Sugrue, M. (2005) Abdominal trauma: a disease in evolution. **ANZ Journal of Surgery**, 75 (9): 790–794
- Soller, B.R., Ryan, K.L., Rickards, C.A., Cooke, W.H., Yang, Y., Soyemi, O.O., Crookes, B.A., Heard, S.O. and Convertino, V.A. (2008a) Oxygen saturation determined from deep muscle, not thenar tissue, is an early indicator of central hypovolemia in humans. **Critical Care Medicine**, 36 (1): 176–182
- Soller, B.R., Yang, Y., Soyemi, O.O., Ryan, K.L., Rickards, C.A., Walz, J.M., Heard, S.O. and Convertino, V.A. (2008b) Noninvasively determined muscle oxygen saturation is an early indicator of central hypovolemia in humans. **Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology**, 104 (2): 475–481
- Soller, B.R., Zou, F., Ryan, K.L., Rickards, C.A., Ward, K. and Convertino, V.A. (2012) Lightweight noninvasive trauma monitor for early indication of central hypovolemia and tissue acidosis: a review. **Journal of Trauma and Acute Care Surgery**, 73 (2 Suppl 1): S106–S111
- Solomonov, E., Hirsh, M., Yahiya, A. and Krausz, M.M. (2000) The effect of vigorous fluid resuscitation in uncontrolled hemorrhagic shock after massive splenic injury. **Critical Care Medicine**, 28 (3): 749–754
- Somanetics Corporation (2008) INOVS® system specifications. [manufacturers’ Promotional Material]
- Søreide, K. (2009) Epidemiology of major trauma. **British Journal of Surgery**, 96 (7): 697–698

- Søreide, K., Krüger, A.J., Vårdal, A.L., Ellingsen, C.L., Søreide, E. and Lossius, H.M. (2007) Epidemiology and contemporary patterns of trauma deaths: changing place, similar pace, older face. **World Journal of Surgery**, 31 (11): 2092–2103
- Stepanov, B.I. (1977) Gustav Robert Kirchhoff (on the ninetieth anniversary of his death). **Journal of Applied Spectroscopy**, 27 (3): 1099–1104
- Stern, S.A., Dronen, S.C., Birrer, P. and Wang, X. (1993) Effect of blood pressure on hemorrhage volume and survival in a near-fatal hemorrhage model incorporating a vascular injury. **Annals of Emergency Medicine**, 22 (2): 155–163
- Stokes, G.G. (1864) On the reduction and oxidation of the colouring matter of the blood. **Proceedings of the Royal Society**, 13: 355–364
- Surgeon General's Department (2009) 2009DIN01-183 — The joint medical employment standard
- Taylor, J.H., Mulier, K.E., Myers, D.E. and Beilman, G.J. (2005) Use of near-infrared spectroscopy in early determination of irreversible hemorrhagic shock. **Journal of Trauma**, 58 (6): 1119–1125
- Torella, F., Cowley, R.D., Thorniley, M.S. and McCollum, C.N. (2002) Regional tissue oxygenation during hemorrhage: can near infrared spectroscopy be used to monitor blood loss? **Shock**, 18 (5): 440–444
- Torella, F. and McCollum, C.N. (2004) Regional haemoglobin oxygen saturation during surgical haemorrhage. **Minerva Medica**, 95 (5): 461–467
- Tremper, K.K. (1989) Pulse oximetry. **Chest**, 95 (4): 713–715
- Trunkey, D.D. (1983) Trauma. **Scientific American**, 249: 28–35
- van der Zee, P., Cope, M., Arridge, S.R., Essenpreis, M., Potter, L.A., Edwards, A.D., Wyatt, J.S., McCormick, D.C., Roth, S.C. and Reynolds, E.O. (1992) Experimentally measured optical pathlengths for the adult head, calf and forearm and the head of the newborn infant as a function of inter optode spacing. **Advances in Experimental Medicine and Biology**, 316: 143–153
- van Hoeyweghen, R., Hanson, J., Stewart, M.J., Dethune, L., Davies, I., Little, R.A., Horan, M.A. and Kirkman, E. (2001) Cardiovascular response to graded lower body negative pressure in young and elderly man. **Experimental Physiology**, 86 (3): 427–435
- Wade, C.E. (2010) Prior exercise alters responses to hemorrhage. **Shock**, 34 (1): 68–74

- Ward, K.R., Ivatury, R.R., Barbee, R.W., Turner, J., Pittman, R., Filho, I.P.T. and Spiess, B. (2006) Near infrared spectroscopy for evaluation of the trauma patient: a technology review. **Resuscitation**, 68 (1): 27–44
- Wassenaar, E.B. and den Brand, J.G.H.V. (2005) Reliability of near-infrared spectroscopy in people with dark skin pigmentation. **Journal of Clinical Monitoring and Computing**, 19 (3): 195–199
- Weeks, M.E. (1932) The discovery of the elements. xiii. some spectroscopic discoveries. **Journal of Chemical Education**, 9: 1413
- Wiedeman, M.P. (1963) Dimensions of blood vessels from distributing artery to collecting vein. **Circulation Research**, 12: 375–378
- World Health Organization (2008) The global burden of disease: 2004 update. Tech. rep., World Health Organization
- Yang, S., Zheng, R., Hu, S., Ma, Y., Choudhry, M.A., Messina, J.L., Rue, L.W., Bland, K.I. and Chaudry, I.H. (2004) Mechanism of cardiac depression after trauma-hemorrhage: increased cardiomyocyte IL-6 and effect of sex steroids on il-6 regulation and cardiac function. **American Journal of Physiology - Heart and Circulatory Physiology**, 287 (5): H2183–H2191
- Žaja, J. (2007) Venous oximetry. **Signa Vitae**, 2 (1): 6–10
- Zenker, S., Polanco, P.M., Kim, H.K., Torres, A., Vodovotz, Y., Clermont, G., Pinsky, M.R., Severyn, D.A. and Puyana, J.C. (2007) Thresholded area over the curve of spectrometric tissue oxygen saturation as an indicator of volume resuscitability in porcine hemorrhagic shock. **Journal of Trauma**, 63 (3): 573–8; discussion 578–80
- Zhao, H., Tanikawa, Y., Gao, F., Onodera, Y., Sassaroli, A., Tanaka, K. and Yamada, Y. (2002) Maps of optical differential pathlength factor of human adult forehead, somatosensory motor and occipital regions at multi-wavelengths in NIR. **Physics in Medicine and Biology**, 47 (12): 2075–2093