GLYCAEMIA AND UPPER GASTROINTESTINAL FUNCTION IN HEALTH AND CRITICAL ILLNESS

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

in the Discipline of Acute Care Medicine, School of Medicine,
Faculty of Health Sciences
University of Adelaide

by

Mark Philip Plummer
02 February 2016
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abstract</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>Declaration</strong></td>
<td>7</td>
</tr>
<tr>
<td><strong>Acknowledgements</strong></td>
<td>8</td>
</tr>
<tr>
<td><strong>Format of thesis</strong></td>
<td>11</td>
</tr>
<tr>
<td><strong>Chapter 1</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Dysglycaemia in the critically ill</strong></td>
<td>13</td>
</tr>
<tr>
<td>1.1 Introduction</td>
<td></td>
</tr>
<tr>
<td>1.2 <em>Literature review</em>: Dysglycaemia and glucose control during sepsis</td>
<td>15</td>
</tr>
<tr>
<td>1.3 <em>Manuscript</em>: Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality</td>
<td>39</td>
</tr>
<tr>
<td>1.4 <em>Manuscript</em>: Stress induced hyperglycaemia and the subsequent risk of type 2 diabetes in survivors of critical illness</td>
<td>62</td>
</tr>
<tr>
<td>1.5 Conclusions</td>
<td>84</td>
</tr>
<tr>
<td>1.5.1 Introduction</td>
<td></td>
</tr>
<tr>
<td>1.5.2 Contribution of the work described in this thesis to the understanding of the prevalence of stress induced hyperglycaemia and unrecognised diabetes</td>
<td></td>
</tr>
<tr>
<td>1.5.3 Contribution of the work described in this thesis to the understanding of the influence of chronic hyperglycaemia on the association between acute hyperglycaemia and mortality</td>
<td></td>
</tr>
<tr>
<td>1.5.4 Contribution of the work described in this thesis to the understanding of the relationship between stress hyperglycaemia and subsequent type 2 diabetes</td>
<td></td>
</tr>
<tr>
<td>1.6 Future directions</td>
<td>85</td>
</tr>
<tr>
<td>1.6.1 Variable blood glucose targets during critical illness based on premorbid glycaemic control</td>
<td></td>
</tr>
<tr>
<td>1.6.2 Mechanisms influencing the interaction between acute hyperglycaemia and outcome in critically ill patients with chronic premorbid hyperglycaemia</td>
<td></td>
</tr>
<tr>
<td>1.6.3 Role for type 2 diabetes screening programs for survivors of stress induced hyperglycaemia</td>
<td></td>
</tr>
<tr>
<td><strong>Chapter 2</strong></td>
<td></td>
</tr>
<tr>
<td><strong>The effect of critical illness on nutrient stimulated gallbladder motility</strong></td>
<td>89</td>
</tr>
</tbody>
</table>
2.1 Introduction

2.2 Literature review: Enterohormones and the response to critical illness

2.3 Manuscript: Critical illness is associated with impaired gallbladder emptying as assessed by 3D ultrasound

2.4 Conclusions

2.4.1 Introduction

2.4.2 Contribution of the work described in this thesis to the understanding of gallbladder motility in the critically ill

2.4.3 Contribution of the work described in this thesis to validating the novel technique of 3D ultrasound assessment of gallbladder volumes during critical illness

2.5 Future directions

2.5.1 The effect of gallbladder motility on lipid absorption and outcome in critical illness

Chapter 3

The effects of exogenous Glucagon-Like Peptide 1 on gastric emptying during extremes of glycaemia and appraisal of a novel intravenous delivery regimen

3.1 Introduction

3.2 Literature review: Incretins and the intensivist: what are they and what does an intensivist need to know about them

3.3 Manuscript: Glucagon-Like Peptide 1 attenuates the acceleration of gastric emptying induced by hypoglycaemia in healthy subjects

3.4 Manuscript: Hyperglycaemia potentiates the slowing of gastric emptying induced by exogenous GLP-1

3.5 Manuscript: The insulinotropic effect of pulsatile compared with continuous intravenous delivery of GLP-1

3.6 Conclusions

3.6.1 Introduction

3.6.2 Contribution of the work described in this thesis to the understanding of the effects of exogenous GLP-1 on gastric emptying

3.6.3 Contribution of the work described in this thesis to the understanding of optimal delivery regimens for exogenous GLP-1

3.7 Future directions
3.7.1 The effect of glycaemic extremes on the gastromotor effects of the commercially available GLP-1 agonists in patients with type 2 diabetes
3.7.2 Determine the utility of GLP-1 as a novel glucose lowering agent in the critically ill

Chapter 4
Stress ulcer prophylaxis in the critically ill

4.1 Introduction

4.2 Literature review: Stress ulceration: prevalence, pathology and association with adverse outcomes

4.3 Manuscript: Pantoprazole or Placebo for stress Ulcer Prophylaxis (POPUP): Randomized double blind exploratory study

4.4 Conclusions

4.4.1 Introduction

4.4.2 Contribution of the work described in this thesis to the understanding of the role for prophylactic proton pump inhibitor administration in the critically ill

4.5 Future directions

4.5.1 Large multi-centre trials to determine the safety and efficacy of routine stress ulcer prophylaxis in the critically ill

APPENDIX A
Presentations at national and international meetings

APPENDIX B
Prizes awarded during candidature

APPENDIX C
Grants awarded during candidature
NOTE: Statements of authorship appear in the print copy of the thesis held in the University of Adelaide Library.
Abstract

This thesis comprises four distinct but complementary chapters with a broad focus of glycaemia and upper gastrointestinal function in health and critical illness, encompassing four literature reviews, two epidemiological-observational and two interventional studies in the critically ill and three proof-of-principle studies in healthy volunteers.

Hyperglycaemia occurs frequently in the critically ill, both in patients with diabetes, and in those with previously normal glucose tolerance. The literature is reviewed on the impact of dysglycaemia in the patient with sepsis, emphasising the interaction between acute dysglycaemia, chronic hyperglycaemia and outcomes (chapter 1.2). Observational studies were performed to estimate the prevalence of stress induced hyperglycaemia in the critically ill and to evaluate the subsequent risk of diabetes. I established that: (i) stress induced hyperglycaemia occurs in ~50% of patients, and (ii) peak blood glucose concentrations are associated with greater mortality in patients with adequate premorbid glycaemic control but not in those with chronic hyperglycaemia (chapter 1.3). In a large, state-wide retrospective observational study I established that stress induced hyperglycaemia doubles the risk for subsequent type 2 diabetes (chapter 1.4).

Dysregulated enterohormone secretion is thought to mediate critical illness induced abnormalities of glycaemia and upper gastrointestinal function. A review of the literature is presented on the clinically relevant enterohormone disturbances (chapter 2.2). In a prospective comparative study of critically ill patients and healthy volunteers, I quantified gallbladder dysmotility in critical illness, a phenomenon that was independent of plasma concentrations of the enterohormone cholecystokinin (chapter 2.3).

The therapeutic potential for the incretin enterohormones in the management of stress induced hyperglycaemia is reviewed in detail with a focus on glucagon-like peptide 1 (GLP-1) (chapter 3.2). Upper gastrointestinal function and glycaemia are inextricably linked and in healthy volunteer studies I examined the effect of GLP-1 on gastric emptying during extremes of glycaemia. I demonstrated that GLP-1 attenuated the acceleration of gastric emptying engendered by hypoglycaemia (chapter 3.3) and that
the slowing of gastric emptying induced by hyperglycaemia is potentiated by GLP-1 (chapter 3.4). In a study investigating the islet cell effects of GLP-1 I demonstrated that intravenous pulsatile delivery of GLP-1 has an equivalent insulinotropic effect to continuous delivery in healthy volunteers (chapter 3.5).

Prophylactic administration of proton pump inhibitors for the prevention of gastric stress related mucosal injury is widely prescribed yet has the potential to cause harm and has been inadequately evaluated in the critically ill. A review of the literature highlighting this paradox is presented in chapter 4.2. In a prospective, double-blind randomised, placebo-controlled trial I demonstrated that prophylactic administration of a proton pump inhibitor was neither superior nor inferior to placebo in preventing clinically significant upper gastrointestinal bleeding during critical illness (chapter 4.3).

In summary, these studies have yielded a number of important insights including; the incidence of stress induced hyperglycaemia and the subsequent risk of diabetes, quantification of gallbladder motility in critical illness, the gastrokinetic effects of GLP-1 during extremes of glycaemia, the insulinotropic effects of pulsatile GLP-1 delivery, and an evaluation of stress ulcer prophylaxis in the critically ill.
Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. I acknowledge that copyright of published works contained within this thesis (as listed below) resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University’s digital research repository, the Library Search, the Australasian Digital Theses Program (ADTP) and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Mark Philip Plummer

08 January 2016
Acknowledgements

I entered into this doctoral programme completely naïve to the challenges of clinical research and have been grateful for the mentoring and encouragement that I have received from my collaborators. The publications that make up this thesis represent only a fraction of my overall experience and none of the successes, or the enjoyment I have had achieving them, would have been possible without a number of key individuals.

First and foremost, I am indebted to Associate Professor Adam Deane (Deano), my primary supervisor and close friend, who took me under his wing as a very green junior registrar and has now shaped my career path in critical care and research. He has been the driving force behind every ethics application, grant, manuscript, abstract presentation and award, and has mentored me through each process with humour, patience and enormous generosity of his time. I greatly admire his integrity, commitment to family and skills as a clinician-scientist and I look forward to our ongoing collaborations in the future.

I am also grateful for the supervisory support from Professors Michael Horowitz and Marianne Chapman. After supervising Adam’s PhD, Michael was kind enough to take on another enthusiastic but ‘culturally inept’ intensive care physician. I am particularly grateful for his advice on study design, his thorough and considered reviews of manuscript drafts and the good times shared at diabetes meetings in Barcelona and Boston. As the director of the Royal Adelaide Hospital Intensive Care Research Unit, Marianne Chapman has fostered an enjoyable environment of productivity and success. Her leadership, incisive intellect and tolerance were invaluable.

The interventional studies would have been impossible without the assistance of a number of exceptional research scientists. For the first two years I had the pleasure of working with Ms Caroline Cousins whose diligence and tireless work ethic drove the studies forward. Towards the end of my doctoral programme, Mr Matthew Summers and Ms Emma Giersch became collaborators and I am similarly grateful for their friendship and assistance. The scintigraphic studies relied upon the technical expertise
of Mr Lawrence Trahair who, for a vegetarian, cooks an excellent radioactive beef patty. Ms Jenny Ong provided enthusiastic support in her administrative role through the University of Adelaide, Discipline of Acute Care Medicine. I was fortunate to undertake my studies within the established Intensive Care Research Unit at the Royal Adelaide Hospital and am thankful for the support of the unit managers Ms Stephanie O’Connor and Mr Alexis Poole. Within this unit, the camaraderie that developed among my fellow higher degree students, Dr Palash Kar, Ms Lee-anne Chapple and Mr Shane Selvanderan was a highlight. I am particularly grateful to Shane for his contribution to chapter 4.3.

Professor Karen Jones performed an honorary supervisory role and her assistance with analysing the scintigraphic images, sourcing sulphur colloid, reviewing manuscripts and editing presentations was greatly appreciated. Statistical guidance was provided by Ms Kylie Lange and I am grateful for her patience as I cut my teeth on SPSS. Dr Mark Finnis was a fantastic ally and chapters 1.4 and 4.3 owe much to his tenacity, enthusiasm and data management skills.

The clinical research relied on the support of the Royal Adelaide Hospital Intensive Care Unit Nursing and Medical Staff and their unwavering assistance made these technically difficult studies achievable. It is also important to acknowledge the assistance of Mr Stephen Duong and Ms Tran Nguyen from the Department of Pharmacy at the Royal Adelaide Hospital and the assistance of the Royal Adelaide Hospital Research Ethics Committee. Many of the studies relied on the participation and trust of a cohort of healthy volunteers who tolerated multiple cannulations, fasting, post-pyloric tubes and episodes of hypoglycaemia with good humour and stoicism. I am especially grateful to the families who gave consent for their loved ones to be involved in this research. The nature of research during critical illness necessitates consenting a third-party, often during times of extreme stress and despair, and I was humbled by the willingness of families to allow me into their lives at these difficult times.

I was fortunate to receive financial assistance during the doctoral programme that allowed me to pursue full-time research and ensured that the studies could be undertaken. These included a co-funded University of Adelaide/Royal Adelaide Hospital Dawes Scholarship, a National Health and Medical Research Council of Australia Postgraduate Scholarship and research grants from the Royal Adelaide
Hospital Research Foundation, Intensive Care Foundation, Maurice Sando Foundation and Diabetes Australia Research Trust.

The ongoing and unwavering support of my family should be highlighted. To my wife Jess, who became my family halfway through this PhD, thank you for your love, friendship, boundless support and for tolerating my oddities. As Phil constantly reminds me, I am extremely lucky to have you. To my brothers, Stephen and Chris thank you for your friendship and for feigning interest when I talked about obscure gut hormones. Finally, to my parents, Rosie and Phil, thank you for providing me with every opportunity to pursue my goals. I know Mum would be proud of me and I wish she could be here to see this come to fruition.
Format of Thesis

This thesis is by publication, supplemented by narrative, as per University of Adelaide Guidelines. The thesis comprises four distinct chapters each with a brief narrative introduction followed by a published literature review and clinical trials. In total the thesis comprises eleven manuscripts; 4 reviews of the literature and 7 clinical trials. At the time of submission of this body of work, ten of the manuscripts have been published or accepted for publication. The manuscript that comprises chapter 1.4 is currently under review with *Intensive Care Medicine*. None of the manuscripts were solicited. Each of the four chapters are followed by a narrative conclusion of the major findings and future directions.

The eleven manuscripts are presented in the style of the publication to which they were submitted, accounting for the heterogeneity in American and UK English, and the variance in referencing style and manuscript structure. The references for the 11 publications are included in each respective manuscript and, for consistency, references for the introductions, conclusions and future directions of each chapter follow each section.

The publications are as follows.

**Plummer MP**, Deane AM. Dysglycemia and glucose control during sepsis. *Clinics in Chest Medicine* [accepted for publication] (IF 2.1). Relevant section in this thesis; Chapter 1.2.


