Physiological and clinical outcomes associated with fluid bolus therapy administered at rapid response calls for hypotension; A retrospective observational study

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Declaration

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except due reference is made in the text.

Contents

Abstract

Physiological and clinical outcomes associated with fluid bolus therapy administered at rapid response calls for hypotension; A retrospective observational study

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Introduction: Administration of intravenous (IV) fluid bolus (FB) to hospitalised patients with hypotension is accepted as standard care. However, there is limited evidence that IV FB benefits patients, and it may cause harm.

Study Objectives: To evaluate current practice, physiological response and clinical outcomes associated with administration of IV FB to hypotensive patients during Rapid Response Team (RRT) review.

Methods: An exploratory, single centre, retrospective cohort study conducted over one year and including all patients triggering RRT review for systolic blood pressure (SBP) <90mmHg. Accordingly, to preexisting literature physiological 'response' to IV FB was determined as a SBP increment ≥20%. Clinical outcomes of interest were recurrent RRT for hypotension and ICU admission within 24h. Variables significant on univariate analysis (P<0.05) were incorporated into logistic regression model.

Results: Of 992 RRT reviews for hypotension IV FB was administered to 785(79%) patients (mean age 70(55-83)y; baseline SBP 84(78-90)mmHg; heart rate 80(68-93)bpm). 'Response' to FB occurred in 301(42%) patients. Responders to FB were older (OR of response for every 10-year increase in age: 1.15; 95%CI1.04-1.26) and had lower SBP (OR of response for every 10mmHg increase in SBP: 0.33; 95%CI0.27-0.41). Regarding clinical outcomes 56/804 (7%) patients were admitted to ICU and 104/804(13%) had subsequent RRT call(s) for hypotension. The FB volume was predictive for ICU admission such that for every additional 500mls the odds of admission to ICU increased by 30% risk (OR1.30; 95%CI1.06-1.60).

Conclusion(s): From this sample of RRT review for hypotension IV FB is frequently administered but physiological response occurs in less than half of patients. Furthermore, the greater FB volume administered increased the risk for ICU admission. Accordingly, the effectiveness of IV FB during RRT review requires further investigation.

Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
AKI	Acute kidney injury
AUC	Area under the receiver operating curve
CSL	Compound Sodium Lactate
CVP	Central venous pressure
DBP	Diastolic blood pressure
FB	Fluid bolus
FiO2	Fraction of inspired oxygen
HES	Hydroxyethyl starch
HR	Heart rate
ICU	Intensive care unit
IV	Intravenous
LOS	Length of stay
MAP	Mean arterial pressure
MCAR	Missing completely at random
MET	Medical emergency team
NHMRC	National Health and Medical Research Council
PLR	Passive leg raising
PP	Pulse pressure
PPV	Pulse pressure variation
RCT	Randomised controlled trial
RRT	Rapid response team
SBP	Systolic blood pressure
ScVO2	Central venous oxygen saturation
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
SpO2	Percutaneous oxygen saturation
TPTD	Trans pulmonary thermo-dilution

Chapter 1

Introduction/ Background

1.2 Introduction

Rapid response team (RRT) reviews are frequently called for hospitalised ward patients because of hypotension (Jones 2014). The administration of fluid bolus therapy is a mainstay treatment for these patients, despite a paucity of evidence describing positive physiological and clinical outcomes associated with this intervention (Topple et al. 2016). Recent findings relating to fluid bolus therapy in other settings, including its limited positive physiological effects, association with adverse outcomes and limited benefit in sepsis and septic shock; question the therapeutic application in a rapid response call setting (Bihari, Prakash & Bersten 2013; Glassford, Eastwood & Bellomo 2014; Khalid et al. 2014; Lipcsey et al. 2015; Lira & Pinsky 2014).

1.3 Background and Significance

Fluid bolus therapy is a ubiquitous intervention in critical care environments, and describes the rapid administration of discrete volume boluses of intravenous fluid (Glassford, Eastwood & Bellomo 2014; Lira & Pinsky 2014). Recommended by goal driven emergency care guidelines and in campaigns targeting resuscitation of the deteriorating patient, fluid bolus therapy is utilised as a cornerstone therapy in the treatment of the hypotensive, tachycardic, oliguric and/or septic patient. While the intervention is viewed as an essential and life-saving treatment in critically ill patients, recommendation is supported primarily by expert opinion and with minimal experimental or controlled human evidence (Glassford, Eastwood & Bellomo 2014; Hilton & Bellomo 2012).

Hypotension is a primary cause for deterioration in a ward patient population requiring RRT review with fluid bolus therapy a ubiquitous treatment strategy (Calzavacca et al. 2010; Flabouris et al. 2010; Herod et al. 2014; Jones et al. 2006; Khalid et al. 2014; Weingarten et al. 2012). Rapid response systems form a method for the early identification and monitoring of patients at risk of deterioration, in an aim to reduce adverse outcome and mortality (Herod et al. 2014). While the composition of the RRT varies between institutions, the RRT are called to review ward patients with vital signs outside predetermined parameters (Herod et al. 2014). Calls for hypotension, defined as a systolic blood pressure less than 90mmHg represent the most frequent trigger for rapid response team activation and highlight a significant patient population where the outcome of fluid bolus therapy is poorly

evidenced (Calzavacca et al. 2010; Flabouris et al. 2010; Herod et al. 2014; Jones et al. 2006; Weingarten et al. 2012).

Fluid bolus therapy aims to replenish intra-vascular volume, correcting haemodynamic instability and end-organ hypoperfusion (Glassford, Eastwood & Bellomo 2014; Lira & Pinsky 2014; Vincent & Weil 2006). Despite consensus on the importance of fluid bolus therapy, the intervention has been the topic of ongoing debate and controversy relating to its constituents and expected outcomes (Glassford, Eastwood & Bellomo 2014; Lira & Pinsky 2014). A recent survey of acute care physicians across Australia and New Zealand found heterogeneity in the volume and fluid type defining the term as well as a disparity in expected physiological outcome (Glassford et al. 2015). The ideal fluid for administration varied between specialties with ICU specialists favouring balanced solutions such as Compound Sodium Lactate and Plasmalyte, and ED physicians utilising 0.9% Saline (Glassford et al. 2015). ICU specialists were also more likely to bolus colloid solutions, with the majority of ICU specialists identifying 4% Albumin is suitable for fluid bolus therapy (Glassford et al. 2015). Similarly a study of fluid bolus practice among ICU nurses found that while the majority of respondents felt that a fluid bolus constituted the administration of 250mls 'as quickly as possible', volumes and administration speeds varied from 100-1000mls given over 30-60 minutes (Eastwood et al. 2015). Administration of IV fluid is a frequent intervention performed at rapid response calls, however is minimally described in the literature (Flabouris et al. 2010, Topple et al. 2016). In a setting of varied practice among clinical specialties it is not clear what constitutes the current practice of fluid administration by the RRT.

Patients receiving RRT review represent a patient population at risk of adverse outcome, with increased mortality and hospital length of stay (LOS) independently associated with a delay in RRT activation, repeat RRT reviews and delay in necessary ICU transfer (Calzavacca et al. 2010; Khalid et al. 2014; Quach et al. 2008; Stelfox, Bagshaw & Gao 2014). In a retrospective observational study Khalid et al (2014) found that hypotensive ward patients who were initially stabilised by the RRT only to re-deteriorate eventually requiring ICU transfer faced increased mortality, illness severity and prolonged ICU LOS. Given the questionable magnitude and duration of effect provided fluid bolus therapy, it is intuitively plausible that its use at rapid response calls may be associated with repeat rapid response calls and a delay in ICU transfer among those who are not likely to exhibit a lasting response (Glassford, Eastwood & Bellomo 2014).

While an established body of evidence exists surrounding various resuscitation solutions, there is limited evidence detailing the degree and duration of physiological benefit of fluid bolus therapy, leading to an emerging evidence base questioning the efficacy of the intervention across a number of settings (Glassford, Eastwood & Bellomo 2014; Lira & Pinsky 2014). In a pivotal randomised clinical trial Maitland et al (2011) investigated the widely endorsed and recommended practice of rapid early fluid resuscitation in shock; and observed that for children in Africa resuscitated with boluses of normal saline or 5% human albumin had a 3.3% increased risk of absolute death by 48 hours, when compared to the no bolus controls. While generalisability to adult critically ill patients in first world countries should be circumspect, this landmark observation questions decades of practice in resource-rich countries and the current understanding of the pathophysiology of shock (Maitland, K., Babiker, A, Kiguli, S, Molyneux, E 2012; 2011). Data in adult patients in first world countries is however limited. In a prospective observational study of patients presenting with acute sepsis, Bihari et al (2013) reported an association between fluid bolus therapy and adverse outcome, with reduced paO2/FiO2 ratios and greater Sequential Organ Failure Assessment (SOFA) scores post fluid bolus. There was also limited physiological benefit associated with the fluid bolus therapy with lack of sustained elevation in mean arterial pressure in the 94% of subjects who were administered further fluid boluses (Bihari, Prakash & Bersten 2013). Similarly, Lipcsey et al (2015) performed a retrospective observational study of patients with infection associated hypotension receiving fluid bolus therapy in the emergency department, and reported that fluid bolus therapy had negligible effect on systolic or mean arterial blood pressure.

Sepsis has been identified as a major contributor to hypotension among a deteriorating patient population requiring RRT review. Both Bihari et al (2013) and Lipscey et al (2015) identify sepsis as a factor predictive of fluid non-responsiveness, as evidenced by the boluses administered in the studies producing minimal positive physiological outcome. As such the high prevalence of sepsis among hypotensive ward patients may translate to a limited response to fluid bolus therapy across the population. The response to fluid bolus therapy in a hypotensive ward patient population has not been described in the literature and therefore there is minimal evidence describing patient characteristics which may predict fluid responsiveness.

1.4 Statement of the Clinical Problem

Limited data exists relating to the physiological outcome and current practice of fluid bolus therapy in a hypotensive ward patient population requiring RRT activation. What is evident is that hypotension is a leading cause for RRT activation and fluid bolus therapy is a likely treatment approach (Calzavacca et al. 2010; Flabouris et al. 2010; Herod et al. 2014; Jones et al. 2006; Khalid et al. 2014; Weingarten et al. 2012). Additionally, that re-deterioration and delay in necessary ICU transfer among this population significantly increases mortality (Calzavacca et al. 2010; Khalid et al. 2014; Quach et al. 2008; Stelfox, Bagshaw & Gao 2014). It is reasonable to predict that given the poorly documented responsiveness to fluid in this cohort, potentially futile persistence with the intervention may result in a delay to ICU for those who are likely to be unresponsive. Alternatively, this therapy may be effective in reducing the number of admissions to ICU, thereby, reducing costs and improving healthcare efficiencies. Identifying the physiological characteristics and clinical outcomes of patients responsive to fluid bolus therapy administered at rapid response calls for hypotension will therefore contribute to otherwise sparse literature on the topic and could potentially highlight patients likely to require earlier ICU admission.

1.5 Purpose of the Study

The purpose of this single centre, retrospective, observational study was to explore the current practice of, as well as the physiological and clinical outcomes associated with fluid bolus therapy administered at RRT calls for hypotension. This study aimed to determine the clinical outcomes associated with the treatment, including repeat RRT calls and admission to ICU, as well as to establish the baseline physiological characteristics of ‘responders’ and ‘non-responders’ to fluid bolus therapy administered at rapid response calls for hypotension.

1.6 Research Questions

1. What is the current practice at this institution related to the administration of fluid bolus therapy at RRT calls for hypotension?
2. What are the physiological characteristics of patients responsive and non-responsive to fluid bolus administered at rapid response calls for hypotension?
3. What is the outcome of administering fluid bolus therapy on repeat RRT calls for hypotension, ICU admission and in-hospital mortality?
4. What are the demographic and baseline characteristics of hypotensive ward patients who receive fluid bolus therapy at a RRT call and are admitted to ICU within 24 hours?
5. What are the demographic and baseline characteristics of hypotensive ward patients who receive fluid bolus therapy at a RRT call and are not admitted to ICU within 24 hours?

1.7 Research Design

This was a retrospective observational cohort study of rapid response call data conducted at a 680 bed teaching hospital, with a 42 bed tertiary intensive care unit. Initially designed to also include data from an additional similarly described hospital, site governance complications meant the exclusion of this secondary site. The study site records all rapid response call and Code Blue (Respiratory or cardiac arrest and airway compromise) episodes which occur within the hospital. The data is recoded prospectively during the rapid response call, then later entered into a designated rapid response call database. This dataset includes patient demographic data, reason for rapid response team activation, interventions performed pre and during the rapid response call, physiological observational data and outcome of the rapid response call.

1.7.1 Participants

Cases were identified from the study site's rapid response call database, with participants comprising all patients and episodes from the rapid response call database who had a call triggered for systolic blood pressure less than 90mmHg, within the 12 month study period commencing 1/7/13 to 30/6/14.

Patients have been excluded from the study if they are <18 years old; have incomplete data relating to fluid bolus therapy or limited documentation of observation.

1.7.2 Research Outcomes

This study aimed primarily to explore the use of fluid bolus therapy at RRT calls for hypotension and the associated physiological response and clinical outcomes. It is hypothesised that fluid responders and non-responders will be different in terms of their baseline characteristics and physiological parameters. Furthermore, the study aimed to evaluate clinical outcomes, including ICU admission within 24 hours of the call, repeat RRT review and in hospital mortality, which may be associated with the type and volume of fluid bolus administered at rapid response calls.

1.8 Practice Implications

Historically fluid bolus therapy is administered to replete intravascular volume in response to a perceived hypovolaemia, however the physiological effect of fluid bolus therapy in hypotensive patients requiring rapid response team review has not been studied. Further research into fluid bolus therapy at rapid response calls for hypotension will provide a description of current practice and evaluate the intervention against clinical outcomes, including ICU admission and in-hospital mortality. Determining the prevalence of fluid responsiveness and characterising responders and non-responders may help to guide treatment at rapid response calls and potentially avoid delays in appropriate ICU transfer.

1.9 Strengths and Limitations

1.9.1 Strengths

This study contributes to a sparse existing literature base which describes the physiological effects of fluid bolus therapy administered to hypotensive patients requiring rapid response team review (Khalid et al. 2014). A strength of this study is the pragmatic setting in which the data has been collected, where the intervention performed represents current practice trends. Data gathered from the site's database is collected by Critical Care Registered Nurses prospectively as interventions are performed. The use of an existing database has allowed for the inclusion of a large volume of patients, which would not have been otherwise possible given the time and funding constraints associated with a nursing masters project.

1.9.2 Limitations

While there are strengths associated with the use of this existing dataset, limitations have arisen due to the retrospective nature of the data. Missing data has proved a significant issue and reduced the degree of analysis which could be conducted.

The exclusion of the second study site means that as a single centre study, the results lack external validity and generalisability. This limits the contribution of the results to a literature source which is already made up of primarily single centre studies (Jones 2014).

1.10 Definition of Terms

1.10.1 Fluid Bolus

The working definition of a fluid bolus as a volume ≥250mls administered over ≤ 1 hour was limited in a setting of poor data availability. Missing data and poor documentation of the fluid administered at

RRT calls has resulted in the use of clinician opinion as a means of identifying fluid bolus administration.

In half of cases the only documentation that a fluid bolus was administered by the RRT was through a tick box system on the observation form. Of the 992 cases analysed only 54.3% documented the volume of fluid administered throughout the call, and even fewer (36.4%) included detail relating to the type of fluid administered. Upon encountering this issue the definition was expanded to include clinician opinion, as indicated by using the form's treatment tick box system.

Currently there is no consensus or published definition of a fluid bolus used for hypotension, either in volume or type of fluid, as such using a clinician lead definition may increase the variability in fluid bolus classification in this study.

1.10.2 Responder

A positive responder to fluid bolus therapy describes a participant with a ≥20% rise in systolic blood pressure at conclusion of the rapid response call, attributed to the administration of fluid bolus therapy.

The lack of consensus regarding what constitutes a positive response to fluid bolus therapy is described further within the literature review. This definition of 20% increase in SBP is based upon two studies which measure blood pressure response to fluid bolus therapy against cardiac output. Monnet et al (2011), in an observational study aimed to evaluate the extent systemic arterial pressure could be used as a surrogate for cardiac output, Monnet et al demonstrated that pulse pressure and systolic arterial pressure could be used to detect changes to cardiac output following fluid administration. The study found that fluid induced changes in cardiac output correlated with changes in pulse pressure and systolic pressure (r=.55, p<0.0001). Monnet et al (2011) reported that the best cut off value for changes in systolic pressure was 8%, with an area under the receiver operating curve (AUC) of 0.757 (p0.0001), sensitivity of 74 (66-81) and specificity of 67(57-77). Lakhal et al (2013) reported similar results with the use of invasive systolic arterial pressure as a surrogate for measuring response to fluid bolus therapy (AUC 0.79 (0.71-0.86). In this prospective study, Lakhal et al (2013) aimed to assess the reliability of invasive *and* non-invasive blood pressures to identify patients whose cardiac output increases after fluid bolus therapy. Unlike Monnet el at (2011), Lakhal et al examined non-invasive blood pressure measurements which mean the results are more generalisable to a ward environment where invasive measurements are not available. This study highlighted the limitations associated with non-invasive measurement, with the method producing a large "grey zone" of 3-22%.

From this it is determined that a SBP rise >22% detected using measured using an osscillometric blood pressure device is a reliable indication that a patient has responded. With the results of the two studies taken into account the definition of 20% rise in SBP was reached to minimise false positive cases and for clinician ease of calculation.

1.10.3 Non-Responder

A non-responder describes a participant not responsive to the administration of fluid bolus therapy, as indicated by a change to systolic blood pressure <20%.

Chapter 2

Integrative Literature Review

2.1 Introduction

Fluid bolus therapy is a ubiquitous intervention in critical care settings, viewed as an essential and life-saving intervention in the primary treatment of hypotensive and critically ill patients. Recommendation for its use is supported primarily by expert opinion and with minimal experimental or controlled human evidence (Glassford, Eastwood & Bellomo 2014; Hilton & Bellomo 2012). Despite a paucity of evidence describing positive physiological and clinical outcomes associated with the intervention, fluid bolus therapy remains the cornerstone treatment for the management of the hypotensive patient (Glassford, Eastwood & Bellomo 2014). Furthermore, recent findings relating to fluid bolus therapy in other settings, such as its association with adverse outcomes, and its negligible benefit in sepsis and septic shock, question the therapeutic application in a rapid response call setting (Bihari, Prakash & Bersten 2013; Glassford, Eastwood & Bellomo 2014; Khalid et al. 2014; Lipcsey et al. 2015; Lira & Pinsky 2014).

2.1.2 Integrative Review Framework

Utilising an integrative literature review model, analysing the results of original studies and systematic reviews which contribute to evidence regarding fluid bolus therapy in a hypotensive ward patient population, this chapter aims to define concepts, review evidence and synthesise the current literature on the topic. This review will detail the search strategies utilised to identify the included sources, evaluate the findings in the literature, synthesise the results of the review and identify the strengths and limitations of the existing literature.

2.2 Article search and selection strategy

A number of databases, including PubMed, Medline, Science Direct and Ovid, were searched and reviewed existing literature, from the last 10 years, relating to fluid bolus therapy, rapid response systems and fluid responsiveness. Using the MeSH search terms:

- ‘hypotension’ OR ‘hypotensive’ OR ‘shock’
- ‘fluid bolus’ OR ‘fluid challenge’ OR ‘fluid resuscitation’
- ‘responder’ OR ‘responsive’
- AND ‘rapid response team’ OR ‘medical emergency team’ OR ‘MET call’

The search was then expanded to linked citations as appropriate. Articles were initially assessed by the title and abstract, were selected for review, and then included for appropriateness based on the following inclusionary and exclusionary criteria:

Inclusion Criteria

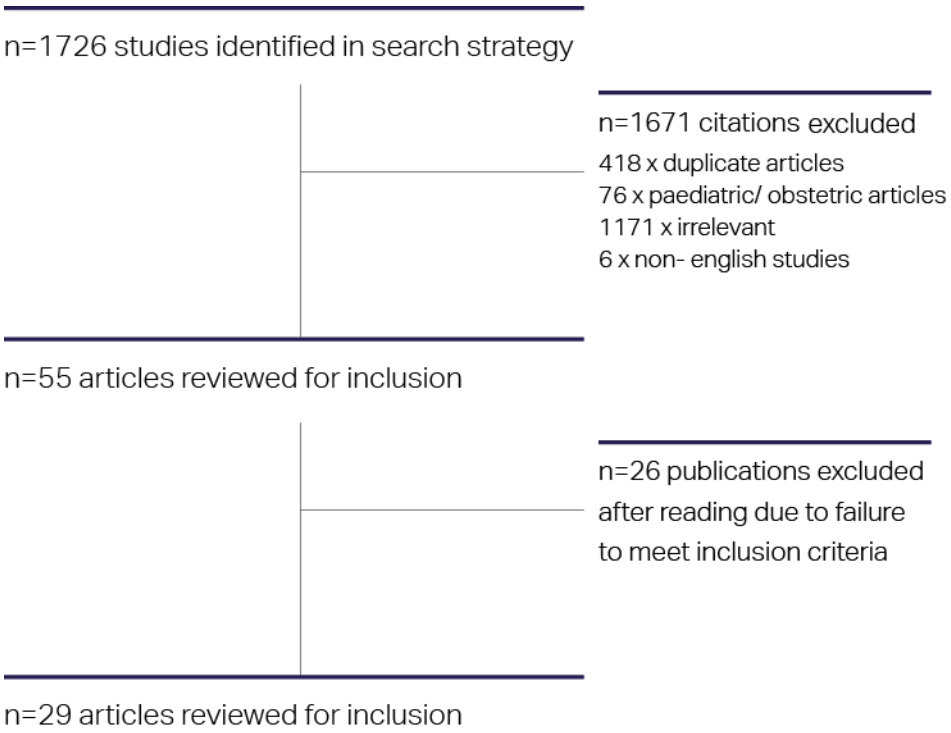
- English language publications
- Studies involving hypotensive ward, emergency department or intensive care patient populations
- Studies utilising non-invasive haemodynamic monitoring and clinical assessment methods utilised to assess fluid responsiveness which are representative of those available to rapid response teams.
- Studies investigating the primary intervention of fluid bolus administration
- Studies contributing evidence to current fluid bolus and rapid response team practice

Exclusion Criteria

- Studies taking place in a peri-operative setting
- Paediatric and obstetric studies
- Studies utilising monitoring techniques to determine fluid responsiveness which are not available in a ward setting, such as invasive cardiac output monitoring, trans-thoracic ultrasound or assessments that are dependent on patients being mechanically ventilated

Despite the exclusion of paediatric studies from this review, one such article has been included. The results of the Fluid Expansion as Supportive Therapy (FEAST) trial conducted by Maitland et al (2011) have been included in the summary as this study represents the only randomised controlled trial comparing fluid bolus therapy to an alternate treatment and therefore forms an important contribution to the literature.

2.2.1 Study selection flow chart



2.2.2 Critical appraisal tool

The articles selected for inclusion in this integrative review were critically appraised using the checklists developed by the Critical Appraisal Skills Program (CASP). Each checklist is tailored to a specific study design and allows for the systematic appraisal of the article to determine the rigour and validity of the study methodology, and identify clinical importance and statistical significance of results (CASP 2014). The outcome of the literature appraisal which was undertaken can be found in appendix 1 (page 118), where the information is presented in table format.

2.3 Findings

A number of emergent themes have become evident in the contemporary literature relating to the use of fluid bolus therapy, including:

- its association with adverse outcomes (Bihari, Prakash & Bersten 2013; Glassford, Eastwood & Bellomo 2014; Lipcsey et al. 2015; Lira & Pinsky 2014; Maitland, K. et al. 2011)
- limited positive physiological effect (Bihari, Prakash & Bersten 2013; Khalid et al. 2014; Lipcsey et al. 2015)
- heterogeneity in its classification (Finfer et al. 2004; Flabouris et al. 2010; Glassford, Eastwood & Bellomo 2014; Khalid et al. 2014; Lira & Pinsky 2014; Myburgh et al. 2012; Raghunathan et al. 2014).
- ambiguity in predicting fluid responsiveness
- heterogeneity in defining a positive response to fluid bolus therapy

Limited data exists relating to the physiologic outcome of fluid bolus therapy in a hypotensive ward patient population requiring rapid response activation, however what is evident is:

- the epidemiology of this patient population (Calzavacca et al. 2010; Cross et al. 2015; Flabouris et al. 2010; Herod et al. 2014; Jones 2014; Khalid et al. 2014; Weingarten et al. 2012)
- and factors associated with their increased mortality (Bagshaw et al. 2010; Calzavacca et al. 2010; Khalid et al. 2014; Quach et al. 2008; Stelfox, Bagshaw & Gao 2014).

2.3.1 Adverse outcome associated with fluid bolus therapy

Recent evidence indicating adverse outcome from the administration of fluid bolus therapy includes incidence of increased mortality, worsening pulmonary functions and factors associated with resuscitative fluid type including acute kidney injury and acidosis (Bihari, Prakash & Bersten 2013; Lipcsey et al. 2015; Maitland, K. et al. 2011).

In a pivotal randomised controlled trial Maitland et al (Maitland, K. et al. 2011) investigated the widely endorsed and recommended, practice of rapid early fluid resuscitation in shock across six hospitals in Kenya, Tanzania, and Uganda. There was no access to critical care facilities available at the sites. The trial included provider training in triage and emergency paediatric life support to optimise case recognition, supportive management, as well as adherence to the protocol. The primary end point

investigated was mortality at 48 hours post randomisation, finding that children with febrile medical illness and impaired perfusion resuscitated with boluses of normal saline or 5% human albumin had a 3.3% increased risk of absolute death by 48 hours when compared to the no bolus controls (Maitland, K. et al. 2011). While limited by its poor generalisability to adult critical care in a first world country and method limitations relating to the study utilising broad inclusion criteria and a failure to include final diagnosis, this research does present as a landmark study which questions decades of practice in resource-rich countries, and the current understanding of the pathophysiology of shock. (Maitland, K. et al. 2011)

Negative outcome was similarly seen in a single-centre, prospective observational study of 102 patients presenting with acute sepsis, where Bihari et al (2013) reported an association between fluid bolus therapy and adverse associations. This single-centre study set in the ICU of an Australian tertiary hospital investigated the prevalence, efficacy and outcome of fluid bolus therapy administered after the initial six hour resuscitative period recommended in sepsis (Dellinger et al. 2013). One hour following the administration of fluid bolus therapy deleterious effects in patients became evident, despite a limited increase in MAP, and no change to central venous gas saturation or serum lactate (Bihari, Prakash & Bersten 2013). The results of the study demonstrated the deleterious effect fluid bolus therapy had on PaO2/FiO2 ratio and acute lung injury scores, patient temperature and haemoglobin levels (Bihari, Prakash & Bersten 2013).

The reduced haemoglobin level reported one hour following fluid bolus was further analysed, finding greater significance when boluses of red blood cells were omitted from total resuscitation (Bihari, Prakash & Bersten 2013). This highlights potential exacerbation of the impaired oxygen delivery associated with sepsis, which may precipitate the need for transfusion. Furthermore, the results of Bihari et al (2013) highlight fluid bolus therapy as a major contributor to the daily fluid balance, with 30.8-52.4% of the cumulative fluid balance seen during the study period received as fluid boluses. Although emerging evidence demonstrates an independent association with positive fluid balance adverse outcome, the relationship between fluid bolus therapy and positive fluid balance remains poorly understood (Glassford, Eastwood & Bellomo 2014).

Studies comparing various fluid types have indicated that the type of resuscitation fluid used may have adverse outcomes in specific clinical conditions (Glassford, Eastwood & Bellomo 2014; Lira & Pinsky 2014; Raghunathan et al. 2014). In a systematic review of new literature regarding fluid type and volume for resuscitation Lira and Pinsky (2014) summarise the increased harm associated with the use of hydroxyethyl starch (HES) solutions. Lira and Pinsky (2014) advocate that the use of HES should be avoided based on evidence of increased incidence of acute kidney injury and requirement

for renal replacement therapy. Similarly the use of the widely utilised 0.9% Saline is also associated with adverse outcome, with Lira and Pinsky (2014) attributing its use in resuscitation to hyperchloraemic acidosis and increased risk of developing acute kidney injury in susceptible individuals, including those with compromised renal function and existing metabolic acidosis.

In light of a growing evidence base highlighting adverse outcome associated with fluid bolus therapy, a greater understanding fluid responsiveness in a ward patient population requiring rapid response calls could allow for a more targeted approach to treatment, thereby limiting the negative effects associated with the intervention.

2.3.2 Limited physiological effect of fluid Bolus therapy, primarily in sepsis

While widely endorsed, the use of fluid bolus therapy in sepsis is supported with minimal evidence and has been met with limited success in recent studies by both Bihari et al (2013) and Lipcsey et al (2015). Similar results have been reported by Khalid et al (2014) in a hypotensive ward patient population who re-deteriorated following rapid response team review where fluid bolus therapy was administered.

In a prospective observational study investigating the prevalence and physiological outcome of fluid bolus therapy in a septic ICU population Bihari et al (2013) were unable to demonstrate positive outcome from the treatment. Fluid bolus administration in the period following initial resuscitation was common, with 97% of the septic population studied ordered the therapy. The primary indication for administration of fluid bolus in this population was low blood pressure, followed by increasing vasopressor dose, and despite a clinician perceived success rate of up to 70.9% there was a minimal physiological response. While the data demonstrates a statistically significant rise in MAP one hour following fluid bolus administration, there was also a concomitant rise in vasopressor infusion rate. When adjusted for the confounding effect of inotropic infusion, the rise in MAP was no longer significant, therefore fluid bolus had no positive outcome to the patient (Bihari, Prakash & Bersten 2013).

This finding was further demonstrated by Lipcsey et al (2015) in a retrospective observational study of patients with infection associated hypotension receiving primary resuscitative fluid bolus therapy in the emergency department. This study, which focuses on fluid resuscitation during the first six hours of admission, found that the administration of fluid bolus therapy was associated with weak, heterogeneous and unpredictable blood pressure changes, with the results unable to demonstrate that the intervention could provide a sustained and reliable increase in MAP.

In a retrospective observational study of hypotensive patients who re-deteriorated following stabilisation by the Medical Emergency Team, Khalid et al (2014) reported no variation in fluid bolus volumes administered to patients requiring immediate ICU transfer, who re-deteriorated requiring ICU transfer, or who responded to fluid resuscitation. When examining these results it can be extrapolated that more than 50% of patients were not responsive fluid bolus therapy alone, requiring commencement of an inotropic infusion and eventually ICU transfer (Khalid et al. 2014). Patients who were deemed not initially responsive to fluid were commenced on a low dose dopamine infusion on the ward to reduce the deleterious effects of persistent hypotension, a practice not generalisable to an Australian hospital setting. (Khalid et al. 2014)

While the results of Bihari et al (2013) and Lipcsey et al (2015) were based on exclusively septic populations, Khalid et al found similar results across a hypotensive ward patient population requiring rapid response team review. This evidence demonstrates sepsis as a factory likely predictive of fluid non-responsiveness and can be used to hypothesis the response rate of rapid response patients receiving fluid bolus therapy for hypotension.

2.3.3 Heterogeneity in classification of fluid bolus therapy (volume/ fluid type)

Heterogeneity exists regarding what constitutes a fluid bolus, a variety of fluids and volumes administered across various studies with little consensus in the literature (Glassford, Eastwood & Bellomo 2014). Lira and Pinsky (2014) highlight the disparity in international and local fluid administration practices in a systematic review of literature regarding current recommendations and recent clinical evidence of various resuscitative solutions.

The type of fluid used for resuscitation has proved a contentious issue, with research into the use of crystalloid vs colloid, starches and more recently balanced vs non-balanced solutions among critically ill and peri-operative patients ongoing and strongly debated (Lira & Pinsky 2014). In a randomised controlled trial comparing albumin and saline for fluid resuscitation in the intensive care unit, Finfer et al (2004) reported no difference in all-cause mortality across the two cohorts during a 28-day study period. Myburgh et al (2012) reported a similar negligible effect to mortality in a RCT comparing hydroxyethyl starch to saline, however the results of the trial highlighted an adverse association between the use of hydroxyethyl starch and an increased incidence of renal replacement therapy. Recent evidence comparing the type of crystalloid fluids used for resuscitation suggests improved outcomes associated with the use of balanced solutions, including reduced mortality and improved renal outcomes (Raghunathan et al. 2014). A large, multicentre retrospective cohort study of septic

patients receiving balanced and non-balanced fluids for resuscitation reported a lower risk of in hospital mortality in patients managed with balanced solutions. Despite association with adverse outcome, in a systematic review of fluid bolus therapy in sepsis, Glassford et al (2014) reported that 0.9% saline was the most commonly used solution used across the studies reviewed.

Only two studies include data relating to the use of fluid bolus therapy during the rapid response call. Utilising data from the MERIT study, Flabouris et al (2010) explore the interventions performed by rapid response teams and simply reported that IV fluids were used in 30% of calls in RRT and control hospitals, with no mention of bolus volume or fluid type. Khalid et al (2014) provided more detail in relation to IV fluid administration in the retrospective observational study of hypotensive ward patients who re-deteriorated following stabilisation by the RRT, reporting mean volumes of 707 – 872ml administered. Khalid et al (2014) did not include data relating to how many boluses were administered or which fluid was used.

With little consensus across literature regarding exactly what defines a fluid bolus there is likely to be high variability in the practice (Glassford, Eastwood & Bellomo 2014). There is minimal data relating to the practice of fluid bolus therapy at RRT calls and as such audit of the volume and type of fluid administered will allow for assessment of the safety and efficacy of the practice, which may improve patient outcomes.

2.3.4 Ambiguity in predicting fluid responsiveness

Fluid bolus therapy represents a first line treatment for acute circulatory failure and organ hypoperfusion (Glassford, Eastwood & Bellomo 2014). Targeting the restoration of intravascular volume and increasing cardiac output, fluid bolus therapy aims to increase ventricular preload and thereby stroke volume (Monnet et al. 2012). Despite being a life-saving intervention, indiscriminate fluid administration is associated with deleterious outcomes including interstitial fluid accumulation, and positive fluid balance (Lira & Pinsky 2014). While accurate prediction of fluid responsiveness in critically ill patients is crucial, the optimal method remains a matter of debate. In critical care and perioperative setting a number of methods exist for the accurate prediction of fluid responsiveness, including transthoracic ultrasound and invasive haemodynamic monitoring, however these measures are not available in the ward setting, therefore further complicating the RRT assessment (Saugel et al. 2013). Strategies for estimating patients' fluid status on the ward include physical examination and the passive leg raising (PLR) test and the fluid challenge test. Two studies were identified which

evaluated ward available methods for predicting fluid responsiveness (Duus et al. 2015; Saugel et al. 2013).

In a prospective study, Saugel et al. (2013) investigated whether physical examination, central venous pressure (CVP), central venous oxygen saturation ($ScvO_2$), and transpulmonary thermodilution (TPTD)-derived parameters can predict fluid responsiveness. Upon evaluation it was reported that physical examination, CVP, ScvO2, the PLR test, and the TPTD-derived volumetric preload parameter global end-diastolic volume index were limited in their prognostic capabilities in predicting fluid responsiveness. In view of the difficulties surrounding prediction of fluid responsiveness, Saugel et al (2013) advocate the use of a fluid challenge test of 7ml of crystalloid fluid per kg of body weight administered over 30 minutes to assess fluid responsiveness in critically ill patients. Unlike Saugel et al (2013) who found the PLR test to be a poor indicator of fluid responsiveness, Duus et al (2015) have more recently reported it to be a promising and feasible tool. The passive leg raising test, which involves the patient being in a supine position with their legs raised to 45˚, returns an estimated 300mls of blood from lower extremities to the heart. This method provides an endogenous and reversible test for preload dependence. This study observational cohort study, conducted in an emergency department setting has a greater generalisability to a RRT review environment when compared to the ICU.

The prediction of fluid responsiveness remains difficult despite a number of tools and technological advancements, with the practice further complicated in a ward setting where such tools are not available. Literature highlights the limited quality of bedside judgement and reliance on clinical parameters which have been considered to be poor indicators of fluid responsiveness.

2.3.5 Heterogeneity in defining a positive response to fluid bolus therapy

Fluid bolus therapy is administered to preload dependant patients to increase stroke volume according the end diastolic pressure volume relationship and the Frank-Starling law. Theoretically a fluid induced increase to end diastolic pressure will result in an improved ventricular contraction and thereby will increase stroke volume and end systolic pressure. It is widely accepted that 15% increase in stroke volume constitutes a positive response to fluid bolus therapy, however in the absence of invasive cardiac output monitoring, a reliable surrogate has been difficult to determine (Lakhal et al. 2013; Monnet et al. 2012; Monnet et al. 2011).

The assessment of hypotensive patients in a ward environment provides limited tools for estimating cardiac output. Largely studies reporting response to fluid bolus therapy have been undertaken in the

perioperative or intensive care environments where invasive haemodynamic monitoring is available (Lakhal et al. 2013). Without cardiac output or stroke volume measurements the response to fluid bolus therapy has been defined by variable increases in mean arterial pressure (MAP), systolic blood pressure (SBP) and pulse pressure (PP), as well as the use of clinical outcomes such as admission to ICU (Eastwood et al. 2015; Glassford et al. 2015; Lakhal et al. 2013; Monnet et al. 2011; Natalini et al. 2012).

A number of studies focused on changes to MAP in order to identify a response to fluid bolus therapy. In a study which aimed to identify cardiovascular and renal predictors of fluid responsiveness, a positive response for fluid was described as restoring the mean arterial pressure to >65mmHg or to increase it by 20%. Using this definition 61% (n=22) of the population were classified as responders to fluid bolus therapy (Natalini et al. 2012). Alteration to MAP was also the focus of fluid response variables in a survey of ICU and ED clinicians. Glassford et al (2015) reported heterogeneity in how clinicians described response to fluid bolus therapy using MAP. Respondents varied in their opinions of minimum MAP change to define a response, with opinion largely ranging from a 0-10mmHg to a 10-20mmHg response from fluid bolus therapy. Neither study provided background on how the definitions were reached. Monnet et al (2011) examined MAP variation as a measure of fluid responsiveness, finding that unlike SBP and PP, changes in MAP could not detect the effect of a fluid challenge.

While there are a number of different definitions used across various studies, only two were identified that compared blood pressure indices against a gold standard. Monnet at al (2011) and Lakhal et al (2013) examined the degree in which systemic blood pressure values could detect a rise in cardiac output in response to administering fluid bolus therapy. In a observational study undertaken within a medical intensive care unit, Monnet et al (2011) evaluated the extent at which invasive pulse pressure, systolic pressure and mean arterial pressure could be used as a surrogate for cardiac output in assessing the effect of fluid bolus therapy and norepinephrine. Defining response as an increase in cardiac output ≥15% the study found that fluid induced changes to cardiac output were correlated with invasive pulse and systolic pressures (r=0.56). An invasive pulse pressure increase of 17% performed best in identifying a positive response to cardiac output following fluid bolus therapy (AUC 0.78 ±.03; sensitivity 65%(56-72); specificity 85%(76-92); *p*0.0001). Similar results were found with a systolic arterial pressure rise of 8% (AUC 0.76±.03; sensitivity 74%(66-81); specificity 67%(57-77). Lakhal et al (2013) performed a similar study, but with the inclusion of non-invasive measurements, thereby making the results more generalisable to a ward environment. This study identified that a large grey zone existed when measuring response to fluid bolus therapy with non-invasive blood pressure. The study found that a positive response was detected with a rise in SBP from 3-22%, which

demonstrates that only a very low/high increase in blood pressure detected a response or non response to cardiac output following fluid bolus therapy. A limitation of this study was its failure to provide a blood pressure cut off which could reliably define fluid responsiveness, rather leaving a wide range of pressure variation which may reflect a change to cardiac output.

The sparse existing data relating to defining fluid responsiveness in the ward patient has highlighted an area where further research should be undertaken. The literature highlights the complications associated with using blood pressure as a surrogate for cardiac output and stroke volume. Reliance on blood pressure may be misleading in a setting where changes to arterial compliance and vascular tone may impact the correlation between stroke volume and systemic blood pressure.

2.3.6 Epidemiology of patients requiring rapid response team review

Much of the literature surrounding the deteriorating patient is centred on assessing the morbidity and mortality outcomes associated with implementing rapid response teams and systems, with limited data on the characteristics and outcomes of the patients themselves (Jones 2014). What is evident is that hypotension is a leading cause for rapid response team activation and fluid bolus therapy is a ubiquitous treatment strategy (Calzavacca et al. 2010; Flabouris et al. 2010; Herod et al. 2014; Jones et al. 2006; Khalid et al. 2014; Weingarten et al. 2012). Furthermore a number of recent studies have identified sepsis as a primary cause for hypotension in this population.

There are few studies which identify the physiological triggers rapid response team activation; with only five studies having been identified as having descriptive data relating to calls for hypotension (Calzavacca et al. 2010; Herod et al. 2014; Jones 2014; Jones et al. 2006; Khalid et al. 2014; Weingarten et al. 2012). Among these studies hypotension is demonstrated as a leading and increasing cause of general and surgical patient deterioration. In a review of calling criteria for rapid response calls of 400 patients within an Australian teaching hospital, Jones et al (2006) identified that hypotension was the cause of 28% of calls during the study period of April to October 2004. In this study, hypotension represented the second most frequent trigger, with hypoxia preceding 41% of activations (Jones et al. 2006). More recently Herod et al (2014) analysed the long term trends in rapid response call triggers in a retrospective observational trial held in an Australian tertiary hospital, finding similar results to those of Jones et al (2006). However there were significant changes to frequency of various triggers over time with hypotension exceeding the formerly prevalent ‘worried’ criteria throughout the 12 year study period (Herod et al. 2014). The proportion of calls triggered for hypotension grew from 21% in2000 to 32% in 2012. While the findings reported by Herod et al (2014) were of a general hospital population, the percentage of calls for hypotension is the same in a study

of rapid response calls in an exclusively post operative patient cohort characterised by Weingarten et al (2012). The highest proportion of hypotensive patients can be seen in a study of patients who re-deteriorated following stabilisation by the RRT, where 38% of all patients with RRT activations between 2009 and August 2011 in a Saudi Arabian Hospital were hypotensive (Khalid et al. 2014). Unlike the findings of Jones et al (2006), Herod et al (2014), Weingarten et al (2012) and Khalid et al (2014) where hypotension triggers approximately one third of all rapid response calls; Calzavacca et al (2010) identified this to be the case in only 15% of RRT reviews. Unlike the other afore mentioned studies, the rapid response triggers reported by Calzavazza et al (2010) includes a category for 'multiple', where the trigger for calling meets two or more criterion, which makes up a further 23.3% of calls.

Only four studies were identified as providing further detail relating to the characteristics or disease states of the patients experiencing rapid response calls (Calzavacca et al. 2010; Cross et al. 2015; Herod et al. 2014; Khalid et al. 2014). As well as reporting the frequency of MET syndrome triggering the call Calzavazza et al (2010) utilised admission diagnosis coding to provide data on the five most represented diagnosis for RRTreview. Utilising the categories of neoplasms, cardiovascular disease, respiratory disorders, gastrointestinal disease, and trauma Calzavazza et al (2010) characterised the entire population, however made no correlation made between disease state and subsequent RRT trigger. Analysis of patients receiving multiple RRT calls found an association between patients admitted with a diagnosis of gastrointestinal disease and/ or a surgical nature and multiple RRT reviews (Calzavacca et al. 2010). In a study of exclusively hypotensive RRT call patients, Khalid et al (2014) provided prevalence of systemic inflammatory response syndrome and sepsis, as well as underlying risk factors including chronic dialysis, malignancy, immunosuppression, congestive heart failure, and liver failure. Sepsis represented a primary cause for hypotension in the study with 59-83% prevalence across the study population (Khalid et al. 2014). In addition there was an increased likelihood of immediate ICU transfer or re-deterioration requiring ICU transfer in patients receiving chronic dialysis or who were septic. In a prospective study Cross et al (2015) further explored the prevalence of sepsis in a ward patient population requiring rapid response activation, finding that 57% of patients fulfilled sepsis criteria in the 24 hours before and 12 hours following the RRT call. The study did not identify the associated RRT trigger but did report that patients who met sepsis criteria around the call had an increased hospital length of stay (Cross et al. 2015). While not reported in the study, Herod et al (2014) hypothesised about an increasing prevalence of sepsis in their cohort, attributing the increased frequency in reviews for hypotension and more patients developing sepsis in hospital.

The high frequency of rapid response calls triggered for hypotension highlights the importance of continued research into this population and interventions performed during the review. Furthermore a high and increasing prevalence of sepsis in this population is potentially indicative of a group who may be unresponsive to fluid bolus therapy.

2.3.7 Factors increasing mortality in rapid response call population

Patients receiving rapid response team review represent a patient population at risk of adverse outcome. In this population increased mortality and hospital length of stay independently associated with delay in rapid response team activation, repeat rapid response team reviews and delay in necessary ICU transfer. Factors increasing the mortality, severity of illness and hospital and ICU length of stay were explored in three of the studies included for analysis (Calzavacca et al. 2010; Khalid et al. 2014; Quach et al. 2008; Stelfox, Bagshaw & Gao 2014).

Khalid et al (2014) found that hypotensive ward patients who were initially stabilised by the MET team only to re-deteriorate eventually requiring ICU transfer faced increased mortality, illness severity and prolonged ICU LOS. In the retrospective study of 410 hypotensive ward patients requiring rapid response team activation those who were to re-deteriorate following initial stabilisation by the MET team face the worst outcomes. Khalid et al (2014) reported higher and prolonged lactic acid elevation, increased prevalence of intubation, and a 15% increase in 28 day mortality compared to those immediately transferred to ICU. This group were categorised as initially showing haemodynamic stability and therefore remained on the ward, however this assessment was made despite commencing dopamine infusions on the ward. While running inotropic infusions in a ward setting is not local practice, it is intuitively plausible that similar patients may remain on the ward with modified rapid response criteria despite being unresponsive to fluid bolus therapy. In a retrospective observational study Calzavacca et al (2010) investigated the features and outcomes of patients receiving multiple rapid response team reviews. Calzavacca et al (2010) reported 22.5% of all patients requiring rapid response team review have multiple activations within 48 hours of the initial call, and that this population have a greater hospital length of stay and increased in hospital mortality rates. This was further demonstrated by Stelfox et al (2014) in a similar retrospective observational study of recurrent clinical deterioration and repeat rapid response activations, with the results demonstrating that repeat rapid response team reviews were associated with higher prevalence of ICU admission, prolonged ICU and hospital length of stay and increased hospital mortality rates. In a retrospective analysis of patients receiving rapid response calls for hypotension and respiratory distress, Quach et al (2008) reported increased mortality when there was a delay in rapid response team activation. The

data for this study was taken between 2000-2002 and is representative of a burgeoning system which may account for the high instance of delay seen (44.5%) (Quach et al. 2008). It is unlikely that such a delay is still seen in more mature rapid response systems, with Herod et al (2014) determining it now to be the case in only 1% of calls.

2.4 Discussion

2.4.1 Synthesis of results

Fluid bolus therapy is a commonplace intervention and frequent first-line resuscitative treatment in the haemodynamically unstable patient (Lira & Pinsky 2014). While discourse relating to fluid resuscitation is long standing and on-going in critical care and peri-operative settings, minimal literature relating to its use in ward patients requiring rapid response team review exists. With limited evidence demonstrating positive physiological response and clinical outcomes associated with fluid bolus therapy in a hypotensive ward patient population requiring rapid response team review, hypothesis must be drawn on assumptions made by researching similar patient populations. Exploring current evidence relating to the use of fluid bolus therapy, primarily from ICU and emergency settings has demonstrated the intervention's questionable efficacy, associated adverse outcomes and heterogeneous classification (Bihari, Prakash & Bersten 2013; Glassford, Eastwood & Bellomo 2014; Lipcsey et al. 2015; Maitland, K. et al. 2011). Largely, the literature regarding deteriorating ward patients relates to epidemiology and factors that are associated with increased length of stay and mortality (Jones 2014). Current literature demonstrates a high prevalence of sepsis in the population and increasing mortality and length of stay, which is associated with re-deterioration and repeat rapid response team reviews (Calzavacca et al. 2010; Khalid et al. 2014).

Sepsis is a primary cause for clinical deterioration in hypotensive ward patients requiring rapid response team review, and their response rate to fluid bolus therapy may be underwhelming (Khalid et al. 2014). Sepsis has been demonstrated by Bihari et al (2013) and Lipscey et al (2015) as a factor predictive of fluid bolus non-responsiveness, with both reporting a limited physiological benefit from the use of fluid bolus therapy to augment the blood pressure of patients with sepsis. Furthermore the adverse outcome which is demonstrated in the work of Maitland et al (2011) and Bihari et al (2013) highlights that the rapid administration of fluid in patients with infection associated hypotension is

not without risk. Moreover it has been demonstrated by Calzavacca et al (2010), Stelfox et al (2014) and Khalid et al (2014) that re-deterioration and repeat rapid response team review following the initial call leads to significantly increased mortality and hospital length of stay in this population. With the high rate of sepsis predicted in the cohort, it is predicted that persistence with fluid bolus therapy may lead to the delayed ICU transfer of a population whom evidence would suggest are likely to be unresponsive to fluid alone.

Additionally there is no literature relating to rapid response teams which describes the fluid type and volumes administered to hypotensive ward patients. Literature relating to the negative associations with the use of 0.9% Saline and starch solutions for resuscitation highlight the need for audit of existing practice regarding fluid bolus administration at rapid response calls (Lira & Pinsky 2014).

Further research into this population will allow investigation into the characteristics and associated clinical outcomes of responders and non-responders to fluid bolus therapy, which may guide treatment at rapid response calls and potentially avoid delays in appropriate ICU transfer.

2.4 2 Limitations of Existing Literature

Almost all of the literature pertaining to rapid response and medical emergency team systems is retrospective and observational in nature, and originates from few hospital sites. The retrospective design of these studies, which utilise existing databases are prone to missing data due to documentation methods and provide a second-hand assessment of the rapid response episode, thereby limiting the internal validity of such studies. Furthermore 40% of selected studies regarding rapid response systems are based at The Austin in Melbourne, Victoria, which despite being an Australian; tertiary teaching hospital does lead to questioning of the external validity in the evidence produced. The benefit of this setting however is the maturity of the hospital's rapid response team, which does prove representative of similar Australian sites where the rapid response system was adopted early.

Due to minimal availability in data relating to the use of fluid bolus therapy at rapid response calls, with even fewer studies identifying the outcomes of the treatment, the hypothesis is inferred based on the results of similar settings. Utilising studies from an ICU and emergency department setting is a pragmatic approach to predicting the outcomes of hypotensive patients receiving fluid bolus therapy at rapid response reviews. In many cases however, the specialised nature of such settings means the data is not generalisable. This is the case in the large volume of intensive care studies which use

dynamic cardiac output measurement techniques, as well as invasive methods for predicting fluid responsiveness, with these tools simply not available in a rapid response call setting.

2.5 Conclusion

Fluid bolus therapy represents a ubiquitous treatment strategy for hypotensive ward patients requiring rapid response team review. With emerging evidence highlighting the limitations of the intervention in a number of settings, further investigation into its use in a deteriorating ward patient population is warranted. A retrospective observational study of hypotensive patients receiving fluid bolus therapy at rapid response team reviews will identify characteristics of responders allowing for the identification of factors predictive of fluid responsiveness in the population. As well as characterisation of responders the research can explore the clinical outcomes of responders and non-responders, which may guide future treatment at rapid response calls for hypotension.

Chapter 3

Study Design/ Methods

3.1 Research Paradigm and Methodology

This is a retrospective study using a quantitative and exploratory approach within a post-positivism paradigm. Development of knowledge and research should be based upon a philosophical approach which guides specific methods for measurement (Weaver & Olson 2006; Welford, Murphy & Casey 2011a). Research paradigms or 'world-views' are established by academics with shared beliefs about the relationship between the world and reality, ways of knowing and acquiring knowledge (Welford, Murphy & Casey 2011a). A research paradigm describes practices and beliefs which regulate inquiry within the discipline (Welford, Murphy & Casey 2011a). The paradigms which underpin quantitative methods are positivism and post-positivism (Morgan 2014; Welford, Murphy & Casey 2011a).

Positivism is objective and is based on the belief that the world is real, ordered and regular (Welford, Murphy & Casey 2011a). Utilising scientific method, a positivist approach develops laws which describe and determine patterns in the physical world (Weaver & Olson 2006). The theoretical basis of positivism is the view of universal truth, which exists separate of human perceptions (Weaver & Olson 2006). While the positivist approach has the benefit of generalisability of findings, credibility from enhanced objectivity and researcher detachment, absolute truth which is strived for in positivism is too ridged a framework on which to base this study. 'Value free' observation is impossible because of the prior knowledge and experience the viewer brings to it, and as such a retrospective observational study design will rarely establish the absolute truth the paradigm desires (Weaver & Olson 2006).

Post-positivism continues the positivist emphasis on objective generalisable theory with controlled conditions and empirical testing, however this movement seeks to falsify hypothesis and uncover a probable, rather than absolute, truths (Weaver & Olson 2006). The paradigm acknowledges that reality is never fully known (Welford, Murphy & Casey 2011b). A scientific approach using quantitative research objectively examines the relationships between multiple variables, such as association between physiological characteristics and fluid responsiveness (Welford, Murphy & Casey 2011b). The addition of fallibility in post-positivism takes into account that sophisticated statistical and mathematical models for research alone do not guarantee valid empirical evidence and a theoretically relevant interpretation (Houghton, Hunter & Meskell 2012). A post-positivist approach allows for a more complex scientific method which acknowledges imperfections in the data, and allows for explanation of discrepancies and varied interpretations (Houghton, Hunter & Meskell 2012). This is relevant in a retrospective observational cohort study utilising an existing database could lead

imperfect input data as there has been little control in collection methods and as such may be affected by outside factors.

Post-positivism provides a rigorous, but realistic framework on which to base nursing research and is an appropriate paradigm for this study (Weaver & Olson 2006). Utilising a quantitative approach underpinned by post-positivism will allow for investigation of fluid bolus therapy at rapid response calls for hypotension with a focus on the causes of fluid responsiveness and how the intervention influences patient outcomes.

3.2 Study Design

3.2.1Purpose of Study

The purpose of this single centre, retrospective, observational study is to describe current practice, as well as to examine physiological and clinical outcomes associated with administration of fluid bolus therapy administered at rapid response calls for hypotension.

3.2.2 Aims

To establish current practice, physiological characteristics and clinical outcomes associated with fluid bolus therapy administered at rapid response calls for hypotension.

3.2.3 Study Outcomes

Primary Outcome

To describe current practice relating to the administration of fluid bolus therapy at rapid response calls for hypotension within the study site.

Secondary Outcome

To characterise responder and non-responder populations by age, sex, admission diagnosis, baseline physiological characteristics and volume of fluid administered to identify factors predictive of fluid responsiveness

Tertiary Outcome

To determine if a relationship exists between the administrations of fluid bolus therapy at rapid response calls for hypotension and a number of clinical outcomes, including repeat rapid response calls, ICU admission and in-hospital mortality.

3.2.4 Participants

This is a retrospective observational study of rapid response call data from a single tertiary teaching hospital in South Australia. The study site records all rapid response team (RRT) calls and code blue episodes which occur within the hospital. This patient identified data is locally held at the health unit within a secure database; with management responsibility of this data residing with the rapid response system Clinical practice Consultant and/or ICU Consultant. This dataset includes patient demographic data, reason for MET activation, interventions performed pre and during the MET call, physiological observational data and outcome of the RRT call.

Inclusion criteria comprised all episodes from the rapid response call database identified as having a rapid response call for systolic blood pressure less than 90mmHg, within the 12 month study period 1/07/13 – 30/6/2014.

Exclusion criteria was met for patients who were ≤18 years old and have incomplete data recorded at the rapid response call, or relating to fluid bolus therapy.

3.2.5 Sample size

A priori sample size calculation was not conducted as it required an estimate of the proportion of the primary outcome. This could be achieved by utilising similar published data or pilot study (Farrokhyar et al. 2013). However no published literature measuring fluid bolus response in a hypotensive ward patient population existed, and thereby could not inform the sample size calculation. Furthermore as this was a retrospective observational study a pilot was not feasible. The study period of 12 months was selected to ensure significant case numbers to maintain statistical power in analysis. The initial estimated number of cases for inclusion was 1400, with 1000 of those from the primary study site and 400 from the subsequently excluded site. Upon collecting data and conducting analysis the total number of episodes for inclusion was n=992.

Effect Size

Effect size which addresses the magnitude of difference to achieve clinical importance rather than merely statistical significance. Effect size will be calculate and determines based on Cohen's *d* interpretation where small effect is *d*=0.2, medium *d*=0.5 and large *d*=0.8.

Variability

The variability in the study population would also affect the sample size, with a large sample size required to produce precise inference in a setting of a non-homogenous population (Farrokhyar et al. 2013). This was predicted to be the case when analysing a hypotensive ward patient population requiring rapid response team review, where baseline physiological characteristics, including blood pressure and admission diagnosis would result in an increased variability. The intervention its self did not contribute a great variability as fluid bolus volumes were predicted to be fairly consistent throughout the population.

Confidence Level

The confidence level will be maintained at 95% confidence interval.

Power

The power of the study will be the probability of finding a difference between physiological characteristics in a hypotensive ward patient population requiring RR review who respond or do not respond to fluid bolus therapy.

3.2.6 Study Period

The period of 1/7/13- 30/6/14 was chosen as it represents the commencement of the current patient vital signs and observation record. This form for recording the patient observations now includes guidelines relating to recognising the deteriorating patient and activating a rapid response team call. As well as the introduction of the new observation form, there were also changes to rapid response call criteria, where the trigger for hypotension changed from a SBP less than 80mmHg to less than 90mmHg. This changed aligned the trigger criteria with other Australian tertiary centres and as such performing the study after this time, limits the variability in the study population and increases the generalisability and external validity of findings.

3.3 Study Plan

This study is a single centre retrospective observational cohort study. Cases were identified from the Rapid Response database as detailed above. A retrospective observational study design was appropriate due to the setting and time and budgetary constraints associated with the scope of this Masters of Nursing project.

3.3.1 Data Collected

Data was extracted from the site's RRT database by the Clinical Practice Consultant and downloaded on a secure drive for research purposes. All identifiable information was then removed so that no identity of an individual could be ascertained.

Primary outcome

- Administration of fluid bolus therapy
- Haemodynamic parameters (SBP, DBP, MAP) at commencement and cessation of the rapid response call
- Age
- Sex
- Clinical service (ie. Medical, surgical, renal etc.)
    - Age, sex and admission diagnosis will all be used for characterisation of responders and non-responders
- Patient location/ ward at time of call
    - The collection of data relating to location of the rapid response call and instances of repeat rapid response calls for the same patient to estimate the level of clustering in the data which may need to be controlled for in the logistic regression model.
- Volume of fluid bolus administered
    - The volume of fluid administered is relevant is both reviewing current practice, determining generalisability and may influence the response from treatment.
    - Bihari et al (2013) found a decreased response was associated with high volume fluid administration in septic ICU patients, and as such the volume administered may prove characteristic of response.

- Haemodynamic parameters (SBP, DBP, MAP) at commencement and cessation of the rapid response call
    - Comparing haemodynamic parameters at baseline and cessation of the call will identify responder and non-responder cohorts.
    - Baseline haemodynamic parameters will also be used for physiological characterisation purposes, these variables may be related to the response to fluid bolus. Bihari et al (2013) reported a negative correlation between baseline MAP and fluid bolus administration. Where a lower MAP prior to fluid administration, was associated with a greater response response from the intervention (Bihari, Prakash & Bersten 2013).

Where the admission diagnosis has been omitted from the RRT call documentation these details were obtained using the sites' patient database.

Secondary Outcome

From the rapid response database the following data was collected:

- Oxygenation parameters (SpO2 and FiO2 commencement and cessation of the call)
    - The collection of oxygenation parameters at baseline and following administration of fluid bolus allows for the assessment of respiratory alterations which may be associated with the treatment. As demonstrated by Bihari et al. (2013) fluid bolus therapy was associated with decreased paO2/FiO2 ratios.
- Temperature (at commencement and cessation of the call)
    - Temperature will be collected as a baseline characteristic, as well as being used to identify presence of systemic inflammatory response system (SIRS).
    - To assess the association between fluid bolus administration and decreased temperature in rapid response patients, as this effect was seen in the ICU and ED patients studied by Bihari et al (2013) and Lipcsey et al (2015).
- Outcome of RRT call
- Repeat rapid response review in 24 hour period
    - Repeat rapid response team reviews are associated with increased mortality and length of stay (Calzavacca et al. 2010; Khalid et al. 2014). Collecting this data will allow for assessment of relationships which may exist between response to fluid bolus therapy and instance of repeat rapid response calls.

        - This data is also collected to highlight possible nesting in the data which will need to be controlled for in logistical regression models.
- Type of fluid
    - The type of fluid used for resuscitation is the subject of ongoing debate, with adverse outcome associated with certain solutions (Lira & Pinsky 2014). Collecting this data will not only provide insight into current practice, but fluid choice may also be associated with patient outcome.

Data collected from the RRT database was cross referenced against ICU Adult Patient Database to determine if ICU admission occurred within 24 hours of the initial call and to obtain the following data:

- Acute Physiology and Chronic Health Evaluation (APACHE) II score
- APACHE III score
    - APACHE scores at admission to ICU provide insight into severity of illness.
- ICU length of stay (LOS)

Mortality outcomes were gathered from the hospital's main patient database where death is not the primary outcome of the RRT call.

3.3.2 Data Collection Validity

Content Validity

- The data collected for analysis is completed at the rapid response call and recorded on a Medical Emergency Response Call Data Sheet.
- The Medical Emergency Response Call Data Sheet has undergone expert review by the SA Health Safety & Quality Strategic Governance Committee, as part of its implementation to meet the standard of recognising and responding to clinical deterioration.
- The Medical Emergency Response Call Data Sheet is deemed valid for documentation of clinical parameters, interventions and outcomes associated with rapid response team patient review.

Criterion Validity

- The validity of non-invasive blood pressure (SBP and MAP), obtained using automated intermittent oscillometric devices, as a measure to predict response to fluid bolus is supported in current literature.
- In a study evaluating the extent at which systemic arterial blood pressure is a surrogate for cardiac output to assess the effect of fluid bolus therapy, Monnet et al (2011) demonstrated that systolic arterial pressure could detect changes in cardiac output following fluid administration.

3.3.3 Confounders

Confounding variables which may account for persistent hypotension were also recorded, including the concomitant use of vasopressors, sedative medication, and analgesia, including via epidural routes.

3.4 Results Analysis and Outcomes

Primary Outcome

To describe current practice relating to the administration of fluid bolus therapy at rapid response calls for hypotension within the institution.

Secondary Outcome

To characterise responder and non-responder populations by age, sex, admission diagnosis, baseline physiological characteristics and volume of fluid administered to identify factors predictive of fluid responsiveness

Tertiary Outcome

To determine if a relationship exists between the administrations of fluid bolus therapy at rapid response calls for hypotension and a number of clinical outcomes, including repeat rapid response calls, ICU admission and in-hospital morality.

3.5 Statistical Analysis

Statistical analysis was undertaken using IMB SPSS Statistics version 23, with a number of descriptive and analytical tests utilised.

Continuous data variables were tested for normality of distribution using a number of tests. Initially the variable data was viewed as a histogram with the data visually assessed for normal distribution, ie. symmetry and bell shape. Data was also viewed on a Q-Q plot to determine whether the data points have a linear tendency to lie on the diagonal (Ghasemi & Zahediasl 2012). Kolmogorov-Smirnov and Shapiro-Wilk tests were also conducted to determine normality of distribution (see appendix 4)(Ghasemi & Zahediasl 2012).

Following testing it was determined that the continuous data did not follow a normal distribution and that variances were non-uniform between variables and across ranges (Altman & Bland 2009). T tests were conducted despite the presence of non-parametric baseline variables. While the statistical assumptions of the T-test include normality of distribution, violations of normality do not impact the robustness of the test when used for large samples (Lumley et al. 2002). This is due to the fact that large samples are valid regardless of distribution. The T-test was used to determine differences between independent samples, including responder and non-responders. Logistic regression models were used to identify relationships between the binary responder and non-responder variables and a number of covariates including age, sex and baseline observations. Diagnostic characteristics such as admission diagnosis and clinic codes were omitted from analysis due to reduced sample size. Chi square tests were used to test hypotheses associated with categorical and nominal data.

3.5.1 What is the current practice at this institution related to the administration of fluid bolus therapy at rapid response calls for hypotension?

The RRT observation forms were reviewed for each call during 1/7/13-30/6/14 for details relating to the administration of fluid bolus therapy, including the fluid type, volume, and rate of administration. Data collection from the RRT observation forms (Appendix 5) highlighted issues relating to poor documentation of fluid bolus therapy. The description of the fluid bolus, including the type, volume or speed of fluid administered were frequently omitted. Confirmation of the intervention having been

performed often relied on the person completing the form using a tick box system of treatments administered prior to or at the call. Patients were determined to have received fluid bolus therapy if at least one of the listed determinants were met:

- Fluid bolus tick box indicated a fluid bolus was administered prior to the team arriving or by the team during the call
- The fluid bolus described in the comments section of the form, which may include information relating to the fluid volume, type or speed of administration (When described in the comments section of the form, most frequently the intervention was merely described as a "fluid bolus", with the volume of fluid administered documented in 68.6% of calls and the type of fluid in 46.3%)

Subsequently all analysis relating the fluid bolus administration has been conducted using dichotomous value of yes or no. Upon identifying the administrations of fluid bolus therapy, descriptive statistics were used to analyse frequencies in its use, T- tests were conducted to determine if existence of differences between patients who were administered fluid bolus therapy and those who were not. Levene's test for equality of variances between the two groups were conducted and assumed or not assumed based on the test's significance.

3.5.2 What are the physiological characteristics of patients responsive to fluid bolus therapy administered at rapid response calls for hypotension?

All continuous physiological variables were entered in a logistic regression model with fluid response as the dependant variable. As the constant in the model represents the baseline odds ratio assuming all entered covariates are zero, the physiological variables were entered as their 'centred' value. Centring the predictors on the mean, would result in a baseline OR based on the mean of each continuous variable, such as the OR of being a responder based on a mean SBP and HR, rather than a SBP or HR of zero. Due to missing data across a number of variables estimation maximisation methods were used to impute missing values for the logistic regression. This ensured the inclusion of enough episodes to power the logistic regression model. Covariates which were not significant were removed from the model. Subsequently there were enough episodes for analysis without resorting to inclusion of imputed data. MAP was not included in the model due to missing data and multicollinearity with SBP. Both age and SBP were significant and remained in the model.

3.5.3 What is the outcome of administering fluid bolus therapy on repeat RRT calls for hypotension, ICU admission and in hospital mortality?

992 RRT calls for hypotension were included for main analysis, these call were made up of repeat patients across repeat admissions. Repeat calls were omitted and only the primary RRT call for hypotension for each patient was included for analysis. Where a patient had several admissions throughout the study period, with numerous calls for hypotension during their stay, only the primary call for hypotension was included for each admission. 188 repeat RRT calls for hypotension were excluded to analyse incidence of repeat RRT call and ICU admission per patient admission. Descriptive statistics, mean comparison and logistic regression were utilised to determine the clinical outcomes associated with administering fluid bolus therapy at the primary hypotensive RRT call.

3.6 Strengths and Limitations

3.6.1 Contribution to sparse existing literature

The strengths of the project lie in the potential contribution to sparse existing literature, by examining the outcome and response to fluid bolus therapy in a large hypotensive ward patient population requiring rapid response team review. The limitations stem from its retrospective design, the use of an existing database, and the inability to accurately determine the prevalence of sepsis in the population.

3.6.2 Retrospective data usage

Utilising a retrospective observational study design was most appropriate in a setting of budgetary and time constraints associated with a masters project; despite being less rigorous when determining causal inferences (Healy & Devane 2011). Utilising the retrospective RRT database, rather than prospective data collection proved comparably quick and cost effective (Healy & Devane 2011). In the setting of a 24-hour rapid response system often attending multiple calls at once, it was not feasible to perform prospective data collection for this project where there is a single, unpaid primary investigator. Using the databases also allows for the inclusion of a large volume of subjects and an extended study period (12 months). Doing this increased the generalisability of the results and may have helped to overcome limitations associated with the accuracy and comprehensiveness of the

previously recorded data (Healy & Devane 2011). The documentation of observation at the review is typically completed by the critical care registered nurse attending the rapid response call, and as such there is validity in the collection methods due to the individual's role and experience recording such data. The setting and acuity of the call may require that another nurse perform the documentation, however it is likely to also be within their scope of practice. Missing data is a limitation and may have arisen due to the nature of situation where the data is collected, as responding to the critical event may prove distracting and lead to minimal documentation. Typically, the data entry into the database is performed by the RRT Clinical Practice Consultant or an ICU Registered Nurse and as key stakeholder there is a presumption that the process would be highly accurate. Upon extracting the cases from the database it was identified that the entry of observations during the study period had not been inputted, rather only the episode with minimal detail was present. It was likely organisational factors which meant that the data entry had not been fully completed during this period. As a result of incomplete entry it was required that the primary investigator enter the data from the original RRT observation forms. One benefit of retrospectively collected data is the avoidance of bias which could occur if the documentation at the rapid response call was knowingly performed by the primary investigator. Despite the primary investigator entering the data, bias was still avoided due to the initial documentation having been performed independent of their involvement.

3.6.3 Unable to identify SIRS/Sepsis

Sepsis has been demonstrated to have an association with fluid responsiveness and as such determining the rate of sepsis present in the population would further support this evidence (Bihari, Prakash & Bersten 2013; Lipcsey et al. 2015). Reliance on the RRT databases means that the prevalence of sepsis cannot be determined accurately due to the data that is recorded. It was predicted that using the observational parameters SIRS criteria would be met in many cases and could be used as a surrogate for a true diagnosis of sepsis, with sepsis prevalence predicted from supporting literature. However due to the large volume of missing data the ability to reliably indicate the prevalence of SIRS in the population was not possible.

3.6.4 Inability to evaluate definition of responsiveness

This study defined fluid response as a systolic blood pressure increase of ≥20% following the administration of a clinician determined fluid bolus. The definition was based upon previously published literature which reported 8-22% as a cut off for detecting a 15% increase in cardiac output (Lakhal et al. 2013; Monnet et al. 2011). Evaluation of a diagnostic test is conducted to determine the

tests ability to confirm the presence of the event, but also its ability to identify negative cases. Evaluation of a test with a dichotomous outcome uses sensitivity and specificity as measures of the test's accuracy when compared against a gold standard (Hajian-Tilaki 2013). The gold standard for measuring a positive response to fluid bolus therapy is to identify a 15% increase in cardiac output or stroke volume. It was not feasible to utilise invasive monitoring techniques on a ward based patient population, and therefore cardiac output and stroke volume could not be measured. In the absence of a gold standard for comparison, the study definition of fluid response could not be evaluated.

3.7 Ethical Considerations

This retrospective observational study qualified as negligible risk research based upon the guidelines outlined in chapter 2.1.7 by NHMRC in the National Statement on Ethical Conduct in Human Research (2007). The definition was applicable as this study carried 'no foreseeable risk of harm or discomfort to participants', 'and that any foreseeable risk is no more than inconvenience'. Participant involvement was limited to the use of information collected from an existing database. There was no occurrence of direct patient contact, exposure to radiation, drugs or other devices. There were no implications of this study to the patient cases involved. Data was transferred from an existing source with all identifiers removed so that no identity of a specific individual could be reasonably ascertained. No more data than was necessary and relevant to the study aims was collected or stored. All information was kept confidential, non-identified and accessible only to the primary investigators. The project ethical approval by the appropriate human research ethics committee on 16/6/15 (reference: HREC/15/RAH/249), see appendix 2. The study also received site specific approval to be conducted at the study site (reference: SSA/15/RAH/292), see appendix 3.

3.8 Conclusion

Fluid responsiveness in a hypotensive ward patient population requiring rapid response team review is poorly documented. Given the negative associations with fluid bolus therapy which have been demonstrated in sepsis literature, the use of the intervention in a deteriorating patient population

warrants further investigation (Bihari, Prakash & Bersten 2013; Glassford, Eastwood & Bellomo 2014; Lipcsey et al. 2015; Maitland, K. et al. 2011). A potential non-response to fluid bolus therapy in this population may be associated repeat rapid response calls and delays in appropriate ICU transfer, both of which are independently associated with increase mortality and prolonged length of stay (Calzavacca et al. 2010; Khalid et al. 2014; Stelfox, Bagshaw & Gao 2014). Retrospective analysis of the use of fluid bolus therapy at rapid response calls for hypotension may allow for characterisation of responders and non-responders and identify clinical outcomes associated with the intervention.

Chapter 4

Results of analysis

4.1 Introduction

Fluid bolus therapy is a ubiquitous intervention in the treatment of hypotension, however limited evidence detailing the physiological and clinical outcomes associated with its to a hypotensive ward patient population requiring RRT review highlights the need for further research. This single centre, retrospective, observational study explored the current practice of, as well as the physiological and clinical outcomes associated with, fluid bolus therapy administered at RRT calls for hypotension. This study aimed explore the clinical outcomes associated with the treatment, including repeat RRT calls and admission to ICU, as well as to establish the baseline physiological characteristics of 'responders' and 'non-responders' to fluid bolus therapy administered at rapid response calls for hypotension. Responding to the research questions below, this chapter will describe and display the results of statistical analysis of the data.

4.1.2 Research Questions

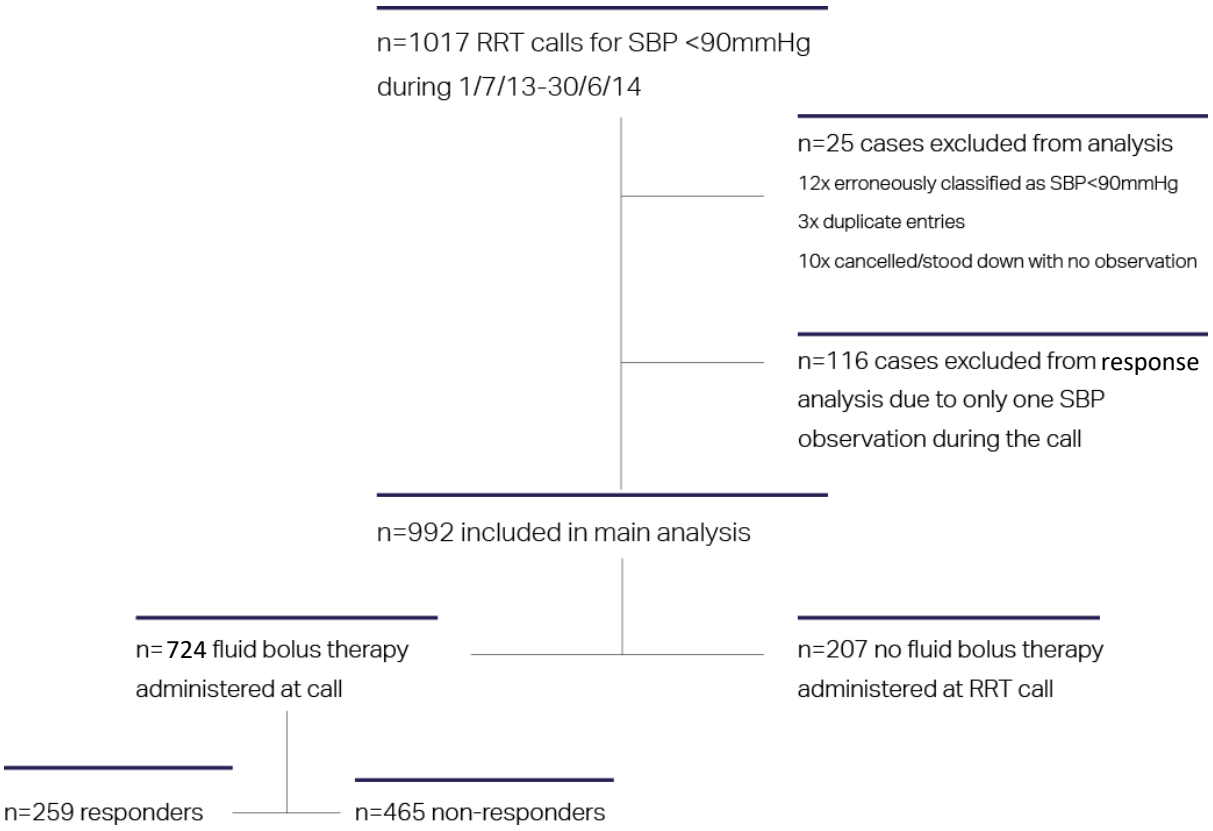
1. What is the current practice at this institution related to the administration of fluid bolus therapy at RRT calls for hypotension?
2. What are the physiological characteristics of patients responsive and non-responsive to fluid bolus administered at rapid response calls for hypotension?
3. What is the outcome of administering fluid bolus therapy on repeat RRT calls for hypotension, ICU admission and in-hospital mortality?
4. What are the demographic and baseline characteristics of hypotensive ward patients who receive fluid bolus therapy at a RRT call and are admitted to ICU within 24 hours?
5. What are the demographic and baseline characteristics of hypotensive ward patients who receive fluid bolus therapy at a RRT call and are not admitted to ICU within 24 hours?

During the study period of 1/7/13-30/6/14 there were 1017 calls triggered for hypotension (SBP<90mmHg). A number of cases were removed from analysis. These case included 12 episodes where the call was erroneously classified for hypotension, this occurred for a number of reasons including carbon transfer from previously completed forms, and invalid initial blood pressure recording by ward staff. Three cases which were removed as they had been entered into the databases as duplicates. 10 calls which were 'stood down' or cancelled upon the team's arrival with

no subsequent observations recorded. 116 cases were excluded from response analysis due to only one blood pressure being recorded and as such no comparison could be made to determine response to therapy. Following exclusions 992 episodes were included in the main analysis.

Figure 1.

RRT calls for SBP<90mmHg during 1/7/13-30/6/14



4.2 What is the current practice at this institution related to the administration of fluid bolus therapy at rapid response calls for hypotension?

The RRT observation forms were reviewed for each call during 1/7/13-30/6/14 for details relating to the administration of fluid bolus therapy, including the fluid type, volume, and rate of administration. Analysis relating the fluid bolus administration has been conducted using dichotomous value of yes or no. Upon identifying the administration of fluid bolus therapy, descriptive statistics were used to analyse frequencies in its use, T- tests were conducted to determine differences between patients who were administered fluid bolus therapy and those who were not. Levene's test for equality of variances between the two groups were conducted and assumed or not assumed based on the test's significance.

Fluid bolus therapy was administered at 785 (79.1%) of the 992 RRT calls for hypotension analysed during the study period of 1/7/13-30/6/14. Patients who received fluid bolus therapy at the RRT call for hypotension were older (68 (17.7) vs 64 (19.3) years, p 0.012) and had lower SBP (85 (12.8) vs 89 (14.7)mmHg, p <0.001) and MAP (63 (10.1) vs 68 (12.7)mmHg, p <0.001) on arrival as indicated in table 1. While these variables showed a statistically significant difference between the two groups, these small differences in mean have a small effect, and are not likely to be clinically significant (cohen's d = <0.5).

The physiological effect of the fluid bolus was measured by the difference in each variable during the call. The effect to each variable was calculated by subtracting the value documented at conclusion from that taken at the start of the RRT call. The difference in variables (SBP, MAP, HR, SpO2, SpO2/FiO2 ratio) throughout the call were the same on comparison regardless of fluid bolus administration during the call (table 2). Therefore there was no additional physiological benefit seen when comparing the administration of fluid bolus and no fluid bolus.

Patients typically (76.1%) received a single fluid bolus, as demonstrated in table 3, which shows the number of fluid blouses administered throughout the call. The total volume of fluid administered throughout the call ranged from 100 – 6000mls. The most frequent total volumes administered were between 500 - 750mls seen in 39.7%, followed closely by boluses ≥1000mls in 31.5% and 250-400ml volumes in 26.9% of calls. 0.09% Sodium chloride solution was the most frequently bolused fluid, and used for more than 65% of boluses. Other fluid varieties including colloids and balanced solutions were infrequently used, as described in table 5.

Analysis of fluid bolus administration by the RRT found that the treatment was common among calls for hypotension. Fluid bolus therapy was administered in almost 80% of calls despite physiological data showing no difference when compared to those who did not receive fluid. Saline solution (0.09% sodium chloride) was favoured by the team and was typically administered in volumes of 500-750mls.

Table 1 - Baseline variables for fluid bolus administration vs no fluid bolus administration

	Fluid bolus (n=785, 79.1%) Mean (SD)	No fluid bolus (n=207, 20.9%) Mean (SD)	P - value	CI 95%
Age, years	68.1 (17.7)	64.4 (19.3)	**0.012**	.79 – 6.3
Female/male	410/370	109/91	0.625	
SBP on arrival, mmHg	84.8 (12.8)	89.1 (14.7)	**<0.001**	-6.6 - -2.1
MAP on arrival, mmHg	63 (10.1)	68 (12.7)	**<0.001**	-7.5 - -2.4
HR on arrival, beats/min	82.1 (20.7)	82.3 (20.95)	0.896	-3.6 – 3.1
RR on arrival, breaths/min	18.7 (4.7)	19.1 (5.1)	0.393	-1.2 - .45
SpO2 on arrival, %	96.4 (3.5)	96.2 (4.5)	0.510	-.40 - .81
FiO2 on arrival, %	32.3 (12.96)	33.2 (15.97)	0.512	-3.6 – 1.8
Temperature on arrival, ˚Celsius	36.8 (.83)	36.8 (.72)	0.634	-.14 - .23

Note: statistically significant *p* values are in bold

Table 2 - Difference between baseline and end of call observations for patients who received fluid bolus therapy vs. those who were not administered fluid bolus therapy

	Fluid bolus therapy (n=785, 79.1%) Mean (SD)	No fluid bolus therapy (n=207, 20.9%) Mean (SD)	P - value	CI 95%
SBP, mmHg	↑14 (14.7)	↑14.6 (17.5)	0.800	-3.8 – 2.9
MAP, mmHg	↑8.6 (11.3)	↑8 (12.2)	0.717	-2.63 – 3.8
HR, bpm	↓0.1 (11.2)	↑0.2 (11.7)	0.755	-2.69 – 2.0
SpO2, %	↑1.2 (3.2)	↑0.5 (3.0)	0.054	-0.02 – 1.3
SpO2/FiO2	↓1.6 (50.4)	↑0.3 (63.9)	0.754	-13.6 – 9.9

Table 3 - The number of bolus administered throughout the RRT call
(587/785 (75%) calls had detailed information relating to the number of boluses administered throughout the call.)

1 bolus	2 boluses	3 boluses	4 boluses	5 boluses	6 boluses
(n=447) 76.1%	(n=111) 18.9%	(n=19) 3.2%	(n=5) 0.9%	(n=4) 0.7%	(n=1) 0.2%

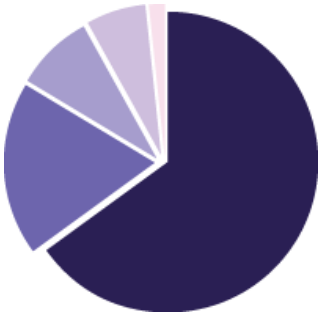
Table 4 - Volume of fluid administered throughout RRT call

(539/785 (69%) calls had detailed information documenting the volume of fluid administered throughout the call.)

≤250ml	n=10 (1.9%)
250ml up to 500ml	n=145 (26.9%)
500ml up to and including 750ml	n=214 (39.7%)
≥1000mls	n=170 (31.5%)

Table 5 - Type of fluid administered

368/785 (45%) boluses had details relating to the type of fluid used.



0.09% Sodium Chloride	n=240 (65.2%)
Gelofusin	n=68 (18.5%)
Blood Products	n=31 (8.4%)
Compound Sodium Lactate	n=23 (6.3%)
Unspecified Crystalloid	n=6 (1.6%)

4.3 What are the physiological characteristics of patients responsive and non-responsive to fluid bolus administered at rapid response calls for hypotension?

Classifying a positive response to fluid bolus therapy as a rise in SBP greater than 20%, yielded a response rate of 35.8% as indicated in table 6. There was no difference in response rates among those who did not receive fluid bolus therapy, where 36.8% of patients had a 20% rise in SBP throughout the RRT call, despite not receiving fluid. Those who responded to fluid bolus therapy were older and more hypotensive upon RRT arrival, as described in Table 7. The mean age of responders as higher when compared to non-responders, 70 (17.6) vs 67 (17.7) years old (p0.024). Patients who responded to fluid bolus therapy had a baseline SBP 10mmHg lower than non-responders (8.7, 12, 11.8; <p0.0001). Responders MAP was also lower on RRT arrival, 58mmHg (8.5) compared to that of non-responders, 65mmHg (9.6) (<p0.001). There was no significant difference in the volume of fluid or number of boluses administered to each group.

All continuous physiological variables were entered in a logistic regression model with response as the dependant variable. As seen in table 10 the OR of being a responder based on average age and SBP is 0.4 (p<0.001). Logistic regression found that for each 10 year increase in age the OR for being a responder increases by 14% (95%CI 3.1-26.2, p0.011), at any given initial SBP. Decreased SBP as a predictor of response was identified, where for a 10mmHg increase in SBP the OR for being a responder decreased by 70% (95%CI 40.0-77.0, p<0.001), at any given age.

The physiological effect of fluid bolus therapy administration was marked in responders, where the rise in SBP and MAP was significantly different to those who did not exhibit a positive response. The increase in SBP among responders was 29mmHg higher than for those who were non-responders (13; 7.3; p<0.0001). Similarly, responder's MAP rose by 18mmHg more than non-responders (9; 6.8; p<0.0001).

Less than half of patients who received fluid bolus therapy responded to treatment and similar numbers exhibited a response despite not being administered fluid. Of those who did respond to fluid bolus therapy, increasing age and more severe hypotension were predictive of response. The physiological outcome of responders was greater when compared to those who were deemed to be non-responders, this was especially true for SBP and MAP increase.

Table 6 - Response to fluid bolus therapy

	Responders	Non-responders
Systolic response		
20% increase in SBP at end of event	35.8% (n=259)	64.2% (n=465)
Pulse pressure response		
35% rise in pulse pressure by end of event	29.8% (n=113)	70.2% (n=266)

Table 7 - Blood pressure rise with no fluid bolus therapy administered

	Responders	Non-responders
Systolic response		
20% increase in SBP at end of event	36.8% (n=56)	63.2% (n=96)

Table 8 - Baseline variables for SBP responder vs SBP non-responder

	Responder (n=259, 35.8%) Mean (SD)	Non-responder (n=465, 64.2%) Mean (SD)	P - value	CI 95%
Age, years	70 (17.6)	67 (17.7)	0.024	.42 – 5.8
Female/male	152/106	224/238	0.008	
SBP on arrival, mmHg	77 (8.7)	88 (11.8)	<0.0001	-12.1- -9.1
MAP on arrival, mmHg	58 (8.5)	65 (9.6)	<0.001	-8.8 - -5.6
HR on arrival, beats/min	83 (23.3)	82 (19.2)	0.592	-2.3 - 4.0
RR on arrival, breaths/min	19 (4.7)	19 (4.7)	0.698	-.59 - .88
SpO2 on arrival, %	96 (3.8)	96 (3.3)	0.054	-1.1 - .01
FiO2 on arrival, %	33 (12.7)	32 (12.8)	0.203	-.71 - 3.3
Temperature on arrival, ˚Celsius	36.8 (.81)	36.8 (.83)	0.628	-.20 - .12
Fluid volume administered	715 (612.2)	687 (598.6)	0.615	-80 - 135.5
Number of boluses administered	1.3 (.61)	1.3 (.71)	0.495	-.15 - .08

Table 9 - Physiological measure of response among responders and non-responders to fluid bolus therapy

	Responder (n=259, 35.8%) Mean (SD)	Non-responder (n=465, 64.2%) Mean (SD)	P - value	CI 95%
SBP difference, mmHg	↑28 (11.7)	↑5 (7.6)	**<0.0001**	21.2 - 24.0
MAP difference, mmHg	↑17 (11.1)	↑3 (7.5)	**<0.0001**	11.7 - 15.9
HR difference, bpm	↓.2 (12.5)	↓.6 (10.7)	0.640	-1.4 - 2.2
SpO2 difference, %	↑1 (3.4)	↑.8 (3.0)	0.061	-.02 - 1.0
SpO2/FiO2 difference	↓5 (52.9)	↑.3 (46.2)	0.201	-14.2 - 3.0

Table 10 - Logistic regression for SBP responder

	S.E	Wald	Odds Ratio	P-value	CI 95%
Age	.005	6.463	1.013	**0.011**	1.0 - 1.0
SBP	.012	108.4	0.887	**<0.001**	.87 - .91
Constant	.096	77.23	0.431	**<0.001**	

	S.E	Odds Ratio	P-value	CI 95%
10x Age	.052	1.140	**0.011**	1.03 – 1.26

	S.E	Odds Ratio	P-value	CI 95%
10x SBP	.115	0.301	**<0.001**	0.24 – 0.38

4.4 What is the outcome of administering fluid bolus therapy on repeat RRT calls for hypotension, ICU admission and in-hospital mortality?

There were 992 RRT calls for hypotension included for main analysis, these call were made up of repeat patients across repeat admissions. Repeat calls were omitted and only the primary RRT call for hypotension for each patient was included for analysis. Where a patient had several admissions throughout the study period, with numerous calls for hypotension during their stay only the primary call for hypotension was included for each admission. 188 repeat RRT calls for hypotension were excluded to analysise incidence of repeat RRT call and ICU admission. Of the 804 primary calls analysed, n= 104 (13%) were followed by repeat call(s) for SBP<90mmHg within 24 hours, n=144 (18%) were followed by repeat call(s) during the admission, and n=56 (7%) resulted in an admission to ICU within 24 hours of the RRT call for hypotension. There was no relationship seen between administration of fluid bolus therapy at RRT calls for hypotension and in-hospital mortality.

Of the 104 calls which were followed by recurrent calls for SBP<90mmHg within 24 hours 85.6% were administered fluid bolus therapy at the first call (see figure 2). Logistic regression found no significant relationship between the administration of fluid bolus therapy and prevention or risk for repeat calls for SBP<90mmHg within 24 hours (OR 1.4, 95%CI 0.8-2.6, *p*0.221). Logistic regression of repeat RRT calls and volume number of boluses administered found so significant relationship

Of the 56 calls which resulted in ICU admission within 24 hours, fluid bolus therapy was administered in 85.7% of cases (see figure 3). Logistic regression of fluid bolus therapy administration found no relationship with whether the patient was later admitted to ICU (OR 1.5, 95%CI 0.7-3.2, *p*0.348). Fluid therapy was predictive of ICU admission when the number and volume of boluses were analysed. Univariate logistic regression of volume and number of boluses both significantly positively predicted ICU admission. For those receiving an additional 500mls at the RRT call, there was a 43% (95%CI 7.6 – 73.7, *p*<0.02) increased odds of ICU admission.

When analysed as a dichotomous value there was no relationship identified between the administration of fluid bolus therapy and prevention of repeat RRT calls for hypotension or ICU admission. Further analysis of fluid bolus volume did find that increasing volume of fluid bolus therapy was associated with increased likelihood of ICU admission, but not repeat RRT calls for hypotension.

Figure 2 - RRT calls for SBP<90mmHg and instance of repeat calls for SBP<90mmHg within 24 hours

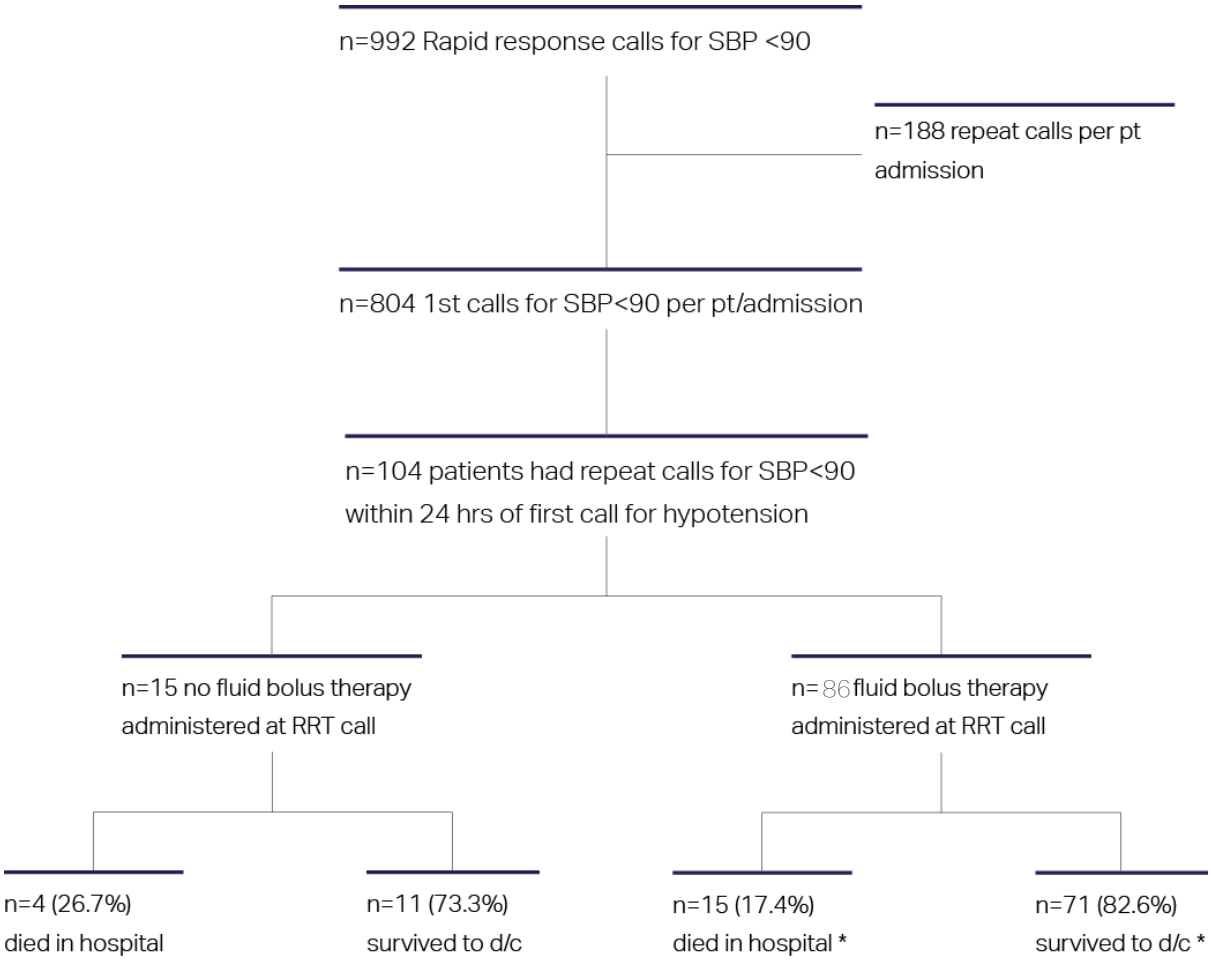


Figure 3 - RRT calls for SBP<90mmHg and instance of ICU admission within 24 hours

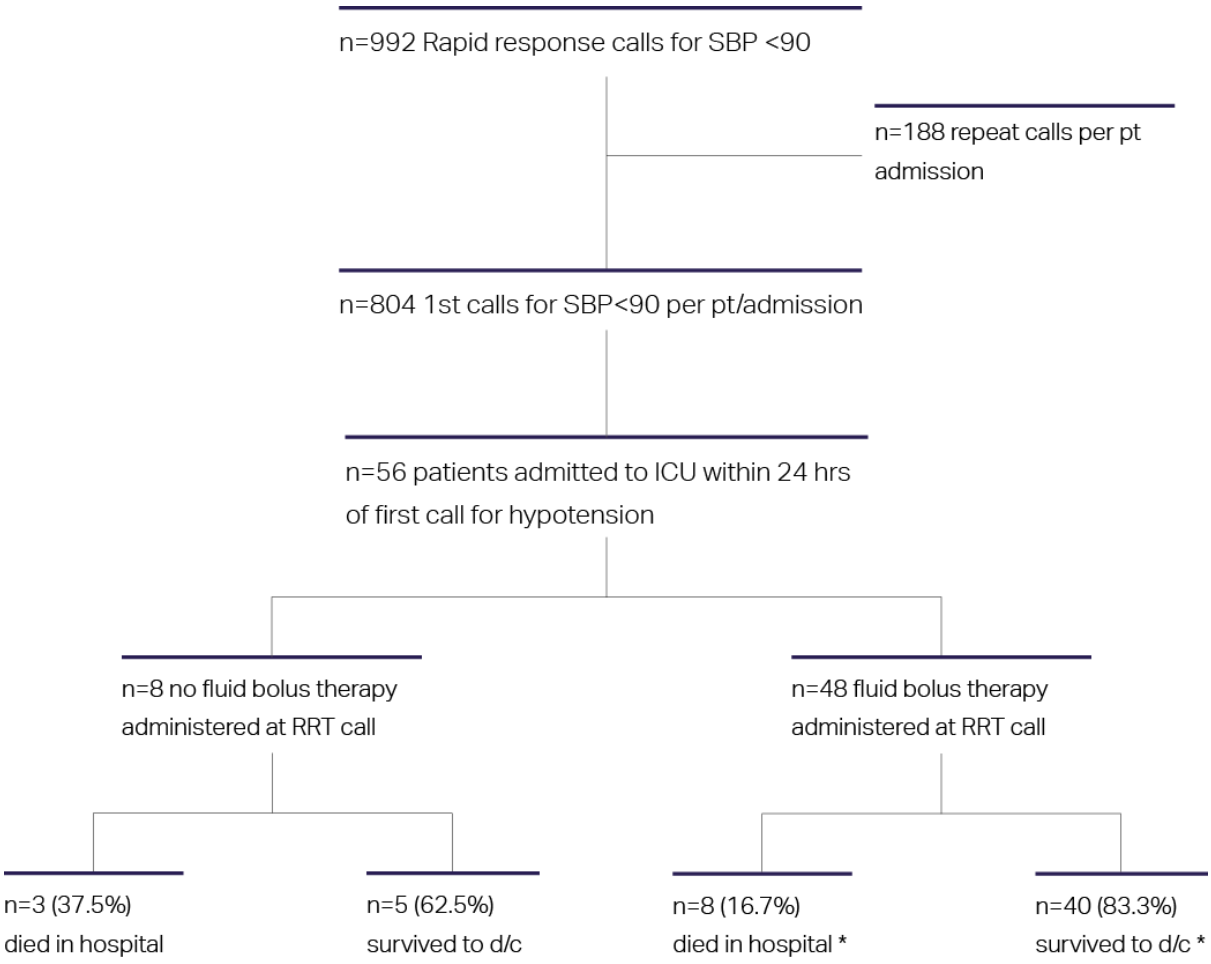


Table 10 - Logistic regression for administration of fluid bolus therapy at rapid response call for SBP<90

	S.E	Wald	Odds Ratio	P-value	CI 95%
Admission to ICU within 24 hrs of first RRT call for SBP<90	.397	.881	1.451	0.348	.67 – 3.2
Repeat RRT call for SBP<90 within 24 hrs of first call	.298	1.5	1.442	0.221	.80 – 2.6
In-hospital mortality	.247	1.93	.709	0.165	.44 – 1.2
Constant	.105	177.47	4.05	<0.001	

Table 11 - Univariate logistic regressions for repeat RRT calls for SBP<90mmHg 24 hours following first call

	S.E	Wald	Odds Ratio	P-value	CI 95%
Total bolus volume at RRT call (mls)	.000	0.001	1.00	0.978	1.0 – 1.0
Number of boluses administered at RRT call	.159	2.387	1.279	0.122	0.9 – 1.7

Table 12 - Univariate logistic regressions for ICU admission within 24 hours following RRT call for SBP <90mmHg

	S.E	Wald	Odds Ratio	P-value	CI 95%
Total bolus volume at RRT call (mls)	.000	12.9	1.001	**<0.001**	1.0 – 1.0
Number of boluses administered at RRT call	.179	23.2	2.367	**<0.001**	1.7 – 3.4

	S.E	Odds Ratio	P-value	CI 95%
500x Total volume of fluid administered	.099	1.430	**<0.001**	1.18 – 1.74

4.5 Compare the demographic and baseline characteristics of hypotensive ward patients who receive fluid bolus therapy at a RRT call and are admitted to ICU within 24 hours, vs those who are not admitted to ICU within 24 hours?

Fluid bolus therapy was administered 80% of the 804 primary calls for hypotension and of these, 48 resulted in an admission to ICU within 24 hours of the first call. Using T-test analysis the baseline variables of patients who received fluid bolus therapy, but still required ICU admission within 24 hours were compared to patients who were given fluid and avoided ICU admission. Patients who required ICU admission despite fluid administration were more hypotensive and had an increased oxygen requirement at the RRT's arrival. The mean SBP and MAP (88 vs 86mmHg, *p*0.005; 59 vs 63mmHg, *p*0.045) of patients who progressed to ICU were lower. The mean heart rate of those who were admitted to ICU was 13 beats per minute faster than patients who avoided ICU. Furthermore, FiO2 and SpO2/FiO2 ratios were worse at baseline for patients requiring ICU admission (41 vs 32, *p*0.003; 281 vs 337, *p*0.003).

The clinical significance of these variables were tested in logistic regression with ICU admission the dependant variable with subsequent hypothesis testing by specifying null hypotheses as linear combinations of parameters performed. Logistic regression analysis found that SBP had a negative predictive value and HR and FiO2 had a positive predictive value for ICU admission (see table 14). For every 10mmHg increase in SBP at baseline the odds of ICU admission decrease by 26% (OR.74, 95%CI 57-96, *p*0.025). A 10bpm increase in HR resulted in a 22% increase in odds of ICU admission (OR1.2, 95%CI 6.8-39, *p*0.003). Similarly, a fractional increase of 10 to the FiO2 at baseline increased the odds of ICU admission by 38% (OR1.38, 95%CI 14-67, *p*0.001).

Patients who required ICU admission despite the administration of fluid bolus therapy were more acutely ill with a number of physiological variables deranged when compared to those patients who avoided ICU. 48/642 patients were administered fluid bolus therapy at their primary RRT call for hypotension but still required ICU admission within 24 hours. These patients were more hypotensive, tachycardic, had poor oxygenation and required increased

FiO2 upon review by the RRT. This group was also administered almost twice the volume of fluid bolus therapy than those who remained in the ward.

Table 13 - Baseline variables for ICU Admission with 24 hrs vs no ICU admission among those administered fluid bolus therapy at RRT calls for SBP<90

	ICU admission (n=48, 7.5%) Mean (SD)	No ICU admission (n=594, 92.5%) Mean (SD)	P - value	CI 95%
Age, years	65 (15)	68 (17.9)	0.186	-8.7 – 1.7
Female/male	20/28	329/260	0.057	
SBP on arrival, mmHg	80 (13.7)	86 (12.8)	**0.005**	-9.3 - -1.6
MAP on arrival, mmHg	59 (10.3)	63 (10.2)	**0.045**	-7.5 - -0.08
HR on arrival, beats/min	94 (22.5)	81 (20.6)	**<0.001**	6.7 – 19.0
RR on arrival, breaths/min	20 (6)	19 (4.6)	0.143	-0.5 – 3.1
SpO2 on arrival, %	96 (4)	96 (3.3)	0.777	-1.2 – 0.88
FiO2 on arrival, %	41 (19)	32 (12.7)	**0.003**	3.4 -15.4
SpO2/FiO2 Ratio	282 (122.6)	337 (99.8)	**0.007**	15.5-94.7
Temperature on arrival, ˚Celsius	37 (1.2)	36.8 (0.8)	0.308	-0.19 - 0.60
Fluid volume, mls	1161 (1132)	673 (550)	**0.018**	89.4 – 885.7

Table 14- Logistic regression for ICU Admission

	S.E	Wald	Odds Ratio	P-value	CI 95%
SBP	.013	5.06	0.970	**0.025**	0.9 – 1.0
HR	.007	8.53	1.020	**0.003**	1.0 – 1.0
FiO2	.010	10.95	1.033	**0.001**	1.0 – 1.0
Constant	.196	203	0.061	**<0.001**	

	S.E	Odds Ratio	P-value	CI 95%
SBPx10	.133	0.741	**0.025**	0.57 – 0.96
HRx10	.068	1.221	**0.003**	1.06 - 1.39
FiO2x10	.097	1.380	**0.001**	1.14 – 1.67

4.6 Missing Data Analysis

The use of an existing retrospective database has led to an abundance of missing data across a number of variables. As illustrated in figure 4, only 81 (8.2%) of episodes have all demographic and observational data recorded. Of the variables analysed, the type of fluid (was missing in 63% of episodes) volume of fluid administered (46%), temperature (44%) and diastolic blood pressures (44%) were most frequently omitted. There was no correlation found between the date of the RRT call and the number of valid observations recorded (R^2 linear = 0.002) (see figure 5). While a scatterplot graph found that there was no correlation between the degree of hypotension and the number of valid observations recorded (R^2 linear = 0.002), there was a trend towards fewer observations in less hypotensive patients (see figure 6). T-test comparison of the baseline variables of patients who had multiple observations documented vs those with only one set of observations, found that multiple observations were documented for patients with lower SBP and MAP. The SBP and MAP were 6mmHg and 10mmHg higher in patients with only one set of observations documented. Of the 116 patients with only one set of valid observations recorded 61 received fluid bolus therapy. Due to there only being one SBP measurement this patient group's response to fluid bolus therapy could not be measured. It is possible that the exclusion of the 116 episodes from analysis of fluid responsiveness may have created a bias, however the degree to which this may be true can not be measured. Performance of the Little's MCAR test across the remaining data identified that it was missing completely at random (MCAR), and as such any bias is unlikely. As the data was MCAR the major issue was related to the study having sufficient power. As the logistic regression model utilised listwise deletion, the inclusion of several baseline variables meant that more than 70% of episodes were excluded from analysis. In order to power the logistic regression model, data was imputed using estimation maximisation technique. Subsequently, the imputed data was not included for analysis and only two variables were of significance and remained in the model.

Figure 4 - Analysis of missing data

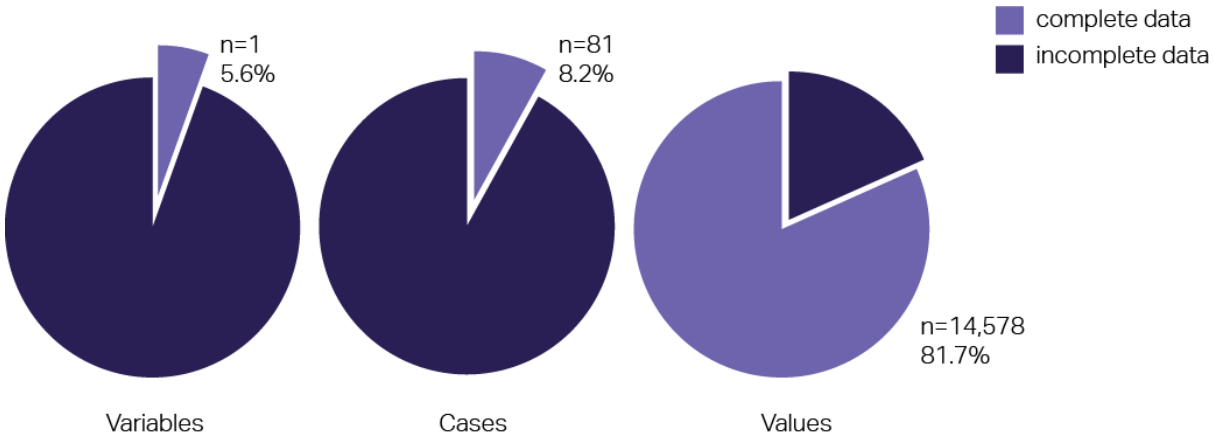


Figure 5

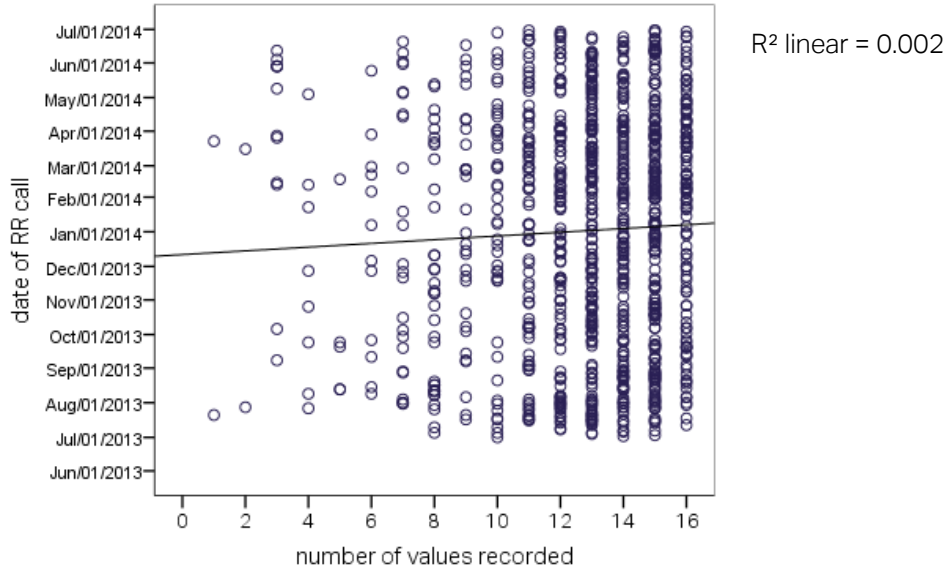


Figure 6

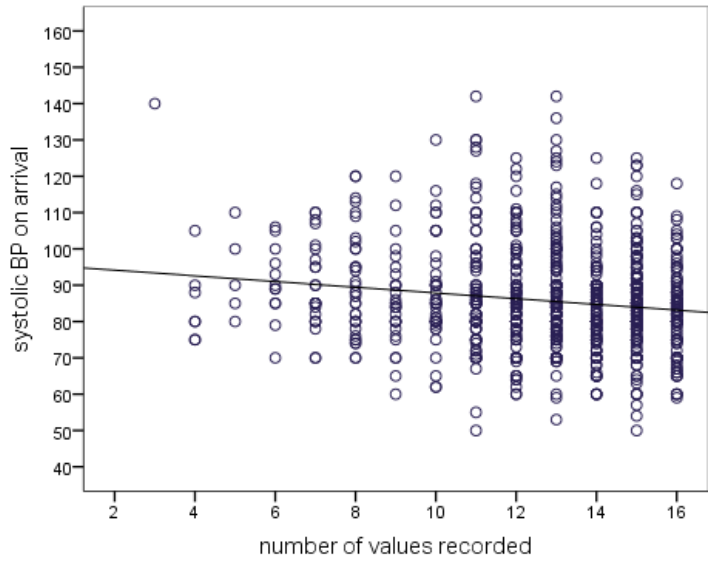


Table 15 - Baseline variables for one vs >two sets of observations recorded at RRT call

	One observation (n=116) Median (IQR)	More than one observation (n=876) Median (IQR)	P - value
Age, years	67 (79.5-56)	71 (82-55)	0.223
SBP on arrival, mmHg	90 (105-85)	84 (90-78)	**<0.001**
MAP on arrival, mmHg	71.6 (81.6-60)	61.7 (68.3-56.7)	**<0.001**
HR on arrival, beats/min	80 (92-67)	80 (94-64)	0.499
RR on arrival, breaths/min	18 (22-16)	18 (20-16)	0.231
SpO2 on arrival, %	97 (99-95)	97 (99-95)	0.688
FiO2 on arrival, %	28 (36-21)	28 (36-21)	0.643
Temperature on arrival, ˚Celsius	36.8 (37.5-36.5)	36.7 (37.2-36.4)	0.512
Length of event, hh:mm	0:11 (0:18-0:06)	0:24 (0:34-0:16)	<0.001
Fluid bolus administered	n=61, 52.6%	n=724, 82.6%	<0.001

Chapter 5

Discussion

5.1 Introduction

Fluid bolus therapy is a cornerstone intervention in the treatment of the hypotensive patient. This remains so despite limited evidence which details the physiological and clinical outcomes associated with its use. As hypotensive ward patients contribute to the largest proportion of RRT reviews, and represent a population where the evidence of fluid bolus therapy and its associated outcomes is poorly documented. This single centre explorative study of the administration of fluid bolus therapy to hypotensive patients requiring RRT review contributes to limited existing evidence on the physiological and clinical outcomes associated with its use in this population. This study found that the administration of fluid bolus therapy is a frequent intervention performed by the RRT, with the data contributing new detail into the practice of the RRT relating to fluid administration. While less than half of hypotensive patients responded to the administration of fluid bolus therapy, a number of variables were identified as being predictive of response, including increasing age and low SBP. Analysing possible associations between fluid bolus therapy and clinical outcomes found there was no beneficial effect of its administration in reducing instance of repeat RRT calls for hypotension or admission to ICU, and rather that ICU admission was associated with greater volumes administered. A subsequent finding in this study was incomplete and poor documentation at the RRT call. This chapter aims to detail and discuss the major findings of this study and their contribution to the existing literature base.

5.2 Current practice relating to fluid bolus therapy

This study adds new detail to sparse existing literature relating to the practice of fluid bolus therapy at RRT calls for hypotension. While it had been established that the administration of fluid bolus therapy was a common intervention performed by the RRT, there was little description of its practice, including techniques of predicting fluid responsiveness, fluid type, volume or outcome.

5.2.1 Predicting fluid responsiveness

Fluid bolus therapy was frequently administered at RRT calls for hypotension despite less than half of patients having a positive response to the intervention. The complexity of predicting fluid responsiveness in critically ill patient has been well established in the literature. In a ward setting with limited tools available determining preload dependence is difficult. While this study has not specifically investigated the methods used by RRT to predict how patients will respond to fluid bolus therapy, the data may be suggestive of certain technique. A number of studies have previously estimated fluid responsiveness to be around 50%. In this study population a positive response was seen in 301 (42%) of cases, with fluid administered at 79% of episodes. With the high frequency of fluid administration relative to response, it is intuitively plausible that the RRT typically utilise a fluid challenge test to determine patients' fluid responsiveness, where the outcome of the bolus is assessed following administration of an initial volume. The practice of using a fluid challenge is supported in the literature, as the difficulty in predicting response based on other values is widely acknowledged.

5.2.2 Constituents of fluid bolus therapy (fluid type, volume)

Fluid type

Due to incomplete documentation at the RRT reviews, descriptive data relating to the fluid bolus administered was limited. The type of fluid was documented in less than 50% of calls and the volume in less than 70%. Based on the data available 0.09% Sodium chloride (65%) was the most commonly administered fluid despite its use being associated with development of hyperchloraemic acidosis and increased risk of AKI in certain patient populations (Lira & Pinsky 2014). The synthetic colloid, Gelofusin made up (18.5%) of boluses and while there has been no harm associated with its use, there is also no evidence of benefit from administration of such solutions (Lira & Pinsky 2014). Synthetic colloid molecules are relatively small and their duration in the intravascular space is relatively short (Plumb & Brown 2015). Due to the lack of evidence, and the possibility of adverse effect, the use of synthetic colloids is not recommended in the literature. Surprisingly, given a growing body of evidence linking the use of balanced solutions with decreased incidence of AKI and need for RRT their administration was rare, only accounting for (6%) of boluses (Lira & Pinsky 2014). A number of factors are likely to have contributed to the distribution of solutions used, including availability and clinician preference. During the study period the IV fluid stock on the RRT trolley were 2 litres of 0.09% Sodium chloride and 500mls of Gelofusin, therefore it is not surprising that these

were frequently administered. This is supported by a number of studies that have identified that local practice, economic consideration and product availability are more likely to dictate choice of fluid rather than the patient's individual characteristics (Lira & Pinsky 2014). It is likely the distribution of fluid administered by the RRT will change over time, and it is predicted there will be decline in the use of Gelofusin due to limited evidence and that it has since been removed from the RRT trolley.

Volume and treatment endpoints

As a total volume administered over the call, patients most frequently (40%) received 500-750mls of fluid. The volume of fluid administered did not vary between responders and non-responders. Volumes over 1000mls were given in 31.5% of calls. Patients typically (76%) received one bolus, with a second bolus administered in 18.9% of calls. The literature supports goal directed administration of fluid rather than a liberal approach. While initial fluid bolus therapy may increase cardiac output and therefore improve oxygen delivery, persistant bolus administration can lead to oedema, contributing to an enlarged oxygen diffusion distance resulting in a reduction of diffusion oxygen transport capacity. Increasing fluid volumes were predictive of intensive care admission within 24 hours of the first RRT call for hypotension which supports evidence which links indiscriminate fluid administration with adverse outcome.

From the data available little conclusion can be reached relating to the end points used by the RRT to determine the volume administered at the call. Infrequent recording of DBP and MAP may demonstrate that the RRT rely heavily of SBP as an end point for fluid administration. SBP as a goal for treatment is also likely as it is the basis for RRT call criteria (SBP<90mmHg). In an aging population where increasing pulse pressure has been widely documented, reliance on SBP alone may leave a number of patients with a MAP not compatible with adequate organ perfusion. The mean DBP in patients over 65 year old in this study had a mean DBP of 51mmHg (10). Therefore simply aiming for a SBP >90mmHg in older patients where there is a high prevalence of decreased diastolic pressure would result in patients remaining on the ward despite maintaining a MAP<65mmHg. In this study population the instance of repeat RRT call for hypotension, ICU admission within 24 hours of the first call and mortality were increased in a setting of MAP <65mmHg at cessation of the RRT call. Compared to the entire study population, this group faced a 9% increase in instance of repeat RRT calls, 4% increase in ICU admissions and 3% more in hospital mortality.

There is little consensus in what constitutes fluid bolus therapy and as such there is limited evidence in which to compare the practice recorded at RRT calls for hypotension.

5.3 Response to fluid bolus therapy

Fluid bolus therapy is typically administered upon identifying clinical signs of impaired organ perfusion, with the primary goal being to increase cardiac output and oxygen delivery (Veenstra, Ince & Boerma 2014). A positive response to fluid bolus therapy is defined by an increase in stroke volume by more than 10-15% and achieved in preload dependent patients. In the ward setting the prediction of preload dependence relies on bedside judgement using clinical parameters and physical examination. These methods provide a relatively poor indication of fluid status which contributes to the difficulty in predicting patients response to fluid bolus therapy (Duus et al. 2015). Utilising a rise of systolic blood pressure as a definition of response, this study found that less than half of patients who received fluid bolus therapy had a positive response. Furthermore, the rate of systolic pressure rise in patients who did not receive fluid bolus therapy at their RRT were the same as those who were administered the therapy. Analysis of clinical parameters of patients requiring RRT review for hypotension identified increasing age and decreasing systolic blood pressure as predictors of responsiveness for fluid bolus therapy.

5.3.1 Increasing age

Analysis of the population identified increasing age as a variable independently associated with response to fluid bolus therapy. Upon mean comparison age proved significant, where responders were on average three years older than those who did not respond to fluid bolus therapy. While reaching statistical significance, this minor age difference did not initially appear to be clinically significant. The predictive value of age in determining fluid response was however further supported in logistic regression, where for every 10-year increase in age the odds of responding to fluid bolus therapy increased by 15%. While the data did not reveal a cause for this effect, it could be hypothesised that the association between age and a positive systolic response may relate changes in arterial tone and stiffening associated with aging, concomitant use of cardiac medications which may affect cardiac output, or restrictive fluid administration due to assumption of cardiac impairment. (Monge Garcia, Gil Cano & Gracia Romero 2011). Additonally, increasing SBP and pulse pressure seen in an aging population may suggest these parameters may be less suitable as treatment end points.

Increasing age is related to arterial stiffening, and subsequently increased systolic and pulse pressures (Hermeling et al. 2011). Arterial stiffening with age is a result of degeneration of arterial media,

fracturing and fragmentation of elastic lamina, increasing collagen and calcium content, and remodelling of large arteries and the aorta (Sakuragi & Abhayaratna 2010). Furthermore, repetitive distention and recoil of the arteries as well as advanced glycation end products accumulating in the arterial wall contribute to the development of arterial stiffness with aging (Sakuragi & Abhayaratna 2010). These changes to arterial elastane will affect the stroke volume in accordance with cardiac pressure volume relationships, where reduced arterial elastance will result in reduced stroke volume and increased end systolic pressure. Arterial stiffness reduces the Windkessel function in the aorta, thereby resulting in less cushioning of the stroke volume in the arterial bed during systole (Sakuragi & Abhayaratna 2010). As such it is possible that small changes to stroke volume are highlighted by marked systolic pressure changes resulting from reduced arterial elastance. This idea was tested by utilising a difference definition for response which is less affected by changes to pulse or systolic pressure. Despite limited numbers due to missing data, the logistic regression model was re-run utilising a MAP based definition for responsiveness. When a positive response to fluid bolus therapy was defined as in increase in MAP ≥ 17% age was no longer a predictive variable of fluid responsiveness. This outcome questions the validity in using systolic blood pressure changes as a means of describing response to fluid bolus therapy, especially in older patients where the pressure changes may be amplified. The association between systolic pressure rise and administration of fluid in an older patient population requires further investigation.

In this study data relating to patient's medication regime was not collected, unless the medication was administered during and/or impacted the events at the RRT call (use of vasopressors, and antiarrhythmic drucs etc). As such it a relationship between patients' regular medications and how they respond to fluid cannot be confirmed. Co-morbid conditions associated with aging including hypertension and arrhythmias mean that this population is likely to have regular medications administered which may affect how they respond to fluid bolus therapy. Multiple studies have reported increased incidence of atrial fibrillation (AF) with aging (Sheikh et al. 2015). Incidence of AF in individuals under 50 is minimal (0.5 per 1000 person years), however after the seventh decade the risk exponentially increases (9.7 per 1000 person years (Sheikh et al. 2015). First line therapy for these patients is rate control, usually achieved with administration of beta-blockers(Sheikh et al. 2015). Beta-blocker administration in this population may impact how the administration of fluid bolus therapy increases stroke volume. The loss of sympathetic drive and negative chronotropic effect associated with beta-blockers impact the compensatory mechanisms required to respond to falling cardiac output. Cardiac output is determined by heart rate and stroke volume, however in a setting where the rate is controlled by beta-blocker therapy, patients may be more responsive to volume expansion due to their inability to otherwise compensate.

Anecdotal clinical experience would demonstrate a trend towards more conservative approaches to fluid administration in older patients. A reluctance to administer fluid, possibly due to concern of further exacerbating potential cardiac impairment and failure, could lead to hypovolaemia in older patients. As such the increased responsiveness in older patients may be attributed to the increased incidence of hypovolaemia rather than other hypotensive states, such as pump failure or vasoplegia.

A number of factors may account for the relationship which exists between increasing age and responsiveness to fluid bolus therapy. Age related changes to the arterial structure, concomitant medication therapy and clinical practice are factors which require further investigation to determine their involvement in fluid responsiveness in an older population.

5.3.2 Systolic blood pressure

A positive response to fluid bolus therapy was related to the degree of hypotension in the patients studied, where the baseline SBP and MAP recorded for responders was 10mmHg and 7mmHg lower than that of non-responders. Logistic regression found that increasing systolic pressure was predictive of non-responsiveness, such that for every 10mmHg increase in SBP the OR for being a responder decreased by 67%. The relationship between profound hypotension and responsiveness may be attributed to the increased likelihood of the patient's preload dependence.

The Frank-Starling law describes the positive relationship between preload and systolic volume (Sabatier et al. 2012). An increase to preload and thereby ventricular stretch strengthens the force of contraction, which results in greater systolic volume (Sabatier et al. 2012). This relationship however is not linear, but rather follows a curve. The ascending portion of the curve identifies a preload dependant state (Sabatier et al. 2012). The administration of fluid bolus therapy at this point would result in an increased preload giving rise to a marked increase in systolic volume. As the curve flattens, increases in preload have little effect on increasing the ejection volume (Sabatier et al. 2012). Patients presenting with a greater degree of hypotension have an increased likelihood of being preload dependant and therefore responsive to fluid. Bihari et al (2013) found a similar relationship to arterial blood pressure and physiological effect from fluid bolus therapy, reporting that the lower the MAP the greater the response.

5.4 Fluid bolus therapy and ICU admission and repeat RRT calls for hypotension

Repeat RRT calls and delayed admission to ICU are independently associated with increased mortality and hospital LOS in patients requiring review by the RRT. This study explored the relationship administering fluid bolus therapy had on the incidence of repeat RRT calls for hypotension and ICU admission in the 24 hours following the first call. The data was unable to demonstrate that administering fluid bolus therapy prevented the recurrence of RRT review for further hypotension, ICU admission or in-hospital mortality. The volume of fluid and number of boluses administered at the call was predictive of ICU admission however. Furthermore this study has identified a number of physiological variables predictive of ICU admission independent of the administration of fluid bolus therapy.

Of the 104 patients who required repeat RRT calls for hypotension 86% (n=89) received fluid bolus therapy, with 74/89 (83%) administered additional boluses at subsequent calls. Logistic regression of fluid bolus therapy administration and occurrence of repeat RRT call for hypotension found no relationship. With no reduction is repeat RRT calls for hypotension seen with the administration of fluid bolus therapy, its continued administration is likely contributing to a positive fluid balance and potential harm. If the patient was not initially responsive or managed to avoid further hypotensive RRT reviews, it stands to reason that progression with further fluid bolus therapy would be futile.

The administration of fluid bolus therapy in patient requiring ICU admission was the same as for those who had recurrent RRT calls and similarly there was no relationship between its administration and preventing admission. Of the 56/840 (7%) patients who required ICU 86% received fluid bolus therapy at the initial RRT call for hypotension. The mean volume of fluid administered to these patients was almost half a litre more than for those who avoided ICU admission. The fluid volume was predictive of ICU admission, where for every additional 500mls administered the odds of ICU admission increased by 43%. Indiscriminate fluid administration is associated with adverse outcome. Goal directed administration of fluid is supported in the literature to avoid adverse outcomes. A number of baseline variables were identified as being predictive of ICU admission independent of fluid bolus administration, including a greater degree of hypotension, increased tachycardia and increasing oxygen requirement. It is possible these changes in physiology are due to systemic inflammatory response (SIRS) and sepsis, however with missing data the criteria for SIRS and sepsis cannot be met in many cases. The temperature is missing in more than 50% of cases, which limits the analysis of it as

a predictive variable. As Bihari et al (2013) found limited response to fluid bolus therapy in septic patients, the presence of SIRS and sepsis in hypotensive ward patients requiring RRT for hypotension may be predictive of ICU admission regardless of fluid bolus therapy administration.

5.5 Poor Documentation at RRT calls

Analysis of the data highlighted issues with missing data and poor documentation at RRT calls. The database consisted of the first and last set of observations taken at the call. Where a full set of observations should be taken at these times values were frequently missing. Observations are prospectively collected during the rapid response call. It is typically the responsibility of the rapid response nurse to document the events and frequent patient observations at the call, however depending on the patient acuity and workload this task if often delegated to the ward nursing staff. A number of factors may have contributed to the level of missing data seen in the database, including unfamiliarity with rapid response form, high work load, and patient acuity.

The study period selected coincided with the introduction of a new rapid response call observation form and changed call criteria with lowered call triggers. The new paperwork on which to record observations may have contributed to the missed data. It was predicted that a relationship may exist between the date of the call and the number of valid observations recorded, however this was not supported. Using a scatterplot graph of the date of call and number of valid variables, no linear relationship existed. This may suggest that the quality of documentation is not time sensitive, and it was not likely a cause of the new form's release.

Changes to call triggers in this period resulted in an increase in the volumes of calls. This resulted in a change to RRT nursing attendance. Where two critical care nurses would have previously attended a rapid response call, it has now been reduced to a single role unless in the incidence of a code blue. Adjustment to the increased work load associated with only one critical care nurse in attendance may have meant that recording of observations was more frequently delegated to staff who were inexperienced in scribing acute events. This could be further investigated by comparison of the number of valid observations documented prior to the changes made to RRT staffing.

It was also considered that with increasing patient acuity there is less available time to document patient observation resulting in more missing data. However this was not supported when using

systolic blood pressure as a surrogate for patient acuity, where there was no relationship with systolic blood pressure and the number of valid data points recorded. More likely it is that case that when patients are perceived to be or lower acuity, less importance is placed on thorough documentation of patient observation. This was demonstrated when comparing the baseline variables of patients who received one set of observations vs those with repeated observation documented, where the SBP and MAP of those with only one set of observations recorded were significantly higher. This effect may have become more pronounced with the changing to nurse staffing for RRT calls. With the aforementioned increase in calls, which arose from lowering of call triggers, an additional two RRT nurses were allocated for each shift. Unlike the primary RRT nurse, the remaining roles are staffed by critical care ICU nurses who also have a patient allocation. The need to return to the ICU to attend to their ICU patient allocation may discourage RRT nurses from remaining at a low acuity RRT call to conduct further observation.

These qualitative theories relating to the lack of complete documentation seen in the RRT database require further investigation. A grounded theory research could be conducted to determine factors associated with the documentation of observations at the RRT calls.

5.6 Recommendations for further research

This study has identified that while the administration of fluid bolus therapy by the RRT at calls for hypotension is common, less than half of patients respond to treatment. When the proportion of responders to fluid bolus therapy was compared to those who did not receive fluid, the instance of SBP rise is the same. This study was unable to identify positive clinical outcomes associated with the administration of fluid bolus therapy to this cohort, including a reduction in repeat RRT calls for hypotension or admission to ICU within 24 hours. Furthermore, deleterious outcomes were identified, where increasing volume of fluid bolus administration was associated with admission to ICU. A number of results of this study have highlighted areas where further research is recommended, including exploration of the factors related to increasing age and increased systolic response, the role of recording MAP at RRT calls,

5.6.1 Predicting and defining of fluid responsiveness

The design of this study was limited in the setting of lack of consensus on an existing definition of fluid responsiveness. The ward environment represents an area where the prediction and assessment of fluid responsiveness is difficult to determine. A lack of invasive and complex diagnostic tools including invasive haemodynamic monitoring techniques mean that defining a response to fluid bolus therapy is largely theoretical. From the documentation collected at RRT calls for hypotension, it would appear that the RRT largely utilise blood pressure variation to determine a response to fluid bolus therapy. This is reasonable in a setting with limited monitoring resources, however the reliability of such measures to detect a change in cardiac output or stroke volume is questionable. Further research into adjunct tools for assessing response may improve the accuracy in which the RRT identify potential fluid responders. The validity and feasibility of devices such as the Non-Invasive Cardiac Output Monitor, which was recently utilised in an emergency department environment, could be investigated for use in a ward/ RRT call setting (Duus et al. 2015).

5.6.2 Examining factors associated with aging and systolic response to fluid

This study identified increasing age as a predictor of fluid responsiveness as defined by an increase to systolic blood pressure by greater than 20% following the administration of fluid bolus therapy. The exact mechanism of aging and fluid responsiveness could not be determined by this study. A number of hypotheses have been suggested, including age related changes at arterial compliance, factors associated with clinical practice when ordering maintenance fluid or fluid bolus therapy to older patients, and concomitant use of beta-blockers in the population. These theories should be tested with further research, which may include additional observational studies which collect more detailed patient characteristics including cardiac history, regular medications and prior fluid balance. A more thorough approach to patient characterisation and variable analysis may provide additional insight into factors associated with a positive response to fluid in a RRT setting. Furthermore important information could be obtained through continued experimental research which further examines the relationship between fluid response and vascular tone.

5.6.3 Explore the relationship of SIRS/Sepsis to fluid responsiveness

The presence of sepsis has been shown to be associated with fluid non-responsiveness in a number of studies (Bihari, Prakash & Bersten 2013; Lipcsey et al. 2015). Furthermore the administration of fluid bolus therapy to septic children was associated with an increase in all cause mortality (Maitland, K. et al. 2011). Sepsis induced changes to endothelial glycocalyx and vascular permeability may increase the incidence of adverse outcome from the administration of fluid bolus therapy (Glassford, Eastwood & Bellomo 2014; Lira & Pinsky 2014). This study aimed to investigate the relationship between fluid responsiveness, repeat RRT calls and ICU admission and the presence of SIRS in a hypotensive ward patient population. Due to missing data, the presence of SIRS in this population could not be reliably detected and subsequently any association which may exist was not able to be found. Cross et al identified SIRS in more than 70% of patients requiring RRT review, with more than 60% of this population meeting the criteria for sepsis. This is a significant population who are potentially non-responders to fluid bolus therapy, who may face worse outcome from indiscriminate fluid bolus therapy administration. The limitation of this study to identify associations of sepsis and fluid non-responsiveness mean that this is this an area which requires further investigation and warrants continued research.

5.6.4 Documentation at RRT calls

This study highlighted issues related to poor documentation at RRT calls within this institution. This area warrants further exploration to determine if this is a widespread or isolated problem. This study proposed a number of factors which may have contributed to limited documentation at the RRT, including unfamiliarity with the observation chart, and limited time due to increased patient acuity. No relationship or contributory cause for poor documentation could be identified in the data. A qualitative approach may be more effective in identifying factors which contribute to limited data being recorded at the RRT call and will assist in overcoming the problem. As well as sparse documentation, this study identified a trend towards the RRT only reporting the systolic blood pressure at RRT calls. Measuring the systolic blood pressure only, restricts the RRT's ability to assess the patients' MAP, and PP. This study identified that a focus on systolic pressure alone, meant that a number of patients remained on the ward with a MAP not compatible with sufficient organ perfusion (<65mmHg). While small, this population faced increased incidence of ICU admission and mortality. Further investigation into the outcomes faced by patients who remain on the ward with a MAP <65mmHg is warranted.

5.7 Recommendations for clinical practice

Fluid bolus therapy is a commonplace intervention preformed in the ward environment and represents the first line treatment for hypotension. Despite its frequent use the physiological and clinical outcomes associated with fluid bolus therapy in a hypotensive ward patient population are poorly documented in the literature. This study, which was primarily explorative, investigated the use of fluid bolus therapy for hypotensive ward patients requiring RRT review. The study aimed to describe current clinical practice, assess physiological response and determine clinical outcomes associated with the use of fluid bolus therapy in this population. Due to the exploratory nature and observational design of this study, the results are not able to strongly influence current practice, but rather support current recommendation.

5.7.1 Predicting fluid responsiveness

Current literature supports the use of administering a mini fluid bolus or fluid challenge to assess the patient's responsiveness to fluid bolus therapy (Marik & Lemson 2014). While this approach could lead to indiscriminate fluid administration and potentially cause harm, there is limited option in a ward/ RRT setting. This study identified increasing age and a greater degree of hypotension were predictive of fluid responsiveness, however this is relationship is limited in its ability to guide future practice. The causal factors associated with aging and its validity as a predictor need further investigation before it can be used to assess a patient's likely response to fluid bolus therapy. This study found limited harm related to the administration of fluid bolus therapy, with the only adverse outcome being associated with administration of large volumes of fluid. While increasing fluid volume was predictive for admission to ICU, this relationship does not impact existing recommendations. The results of this study do not oppose the existing literature surrounding the fluid challenge and support that when fluid boluses are administered in a judicious nature there is not likely to be harm to the patient.

Chapter 6

Conclusion

6.1 Conclusion

Fluid bolus therapy is a ubiquitous intervention within the critical care setting. It is administered to restore impaired organ perfusion by increasing stroke volume. Fluid bolus therapy remains the first line treatment in responding to the hypotensive patient, despite a paucity of evidence describing reliable and positive clinical outcomes. Hypotension among ward patients is the leading cause of deterioration and represents the most frequent trigger for review by the RRT. While fluid bolus therapy is frequently administered by the RRT, the physiological effect and clinical outcomes associated with its use are poorly documented in a hypotensive ward patient population. A growing body of evidence which demonstrates a limited effect and adverse event associated with fluid bolus therapy highlights the need for further investigation into its use in a hypotensive ward patient population. This retrospective observational study aimed to document the current practice of fluid bolus therapy performed by the RRT, as well as to explore the physiological and clinical outcomes associated with its use within the population.

Retrospective analysis of RRT calls for hypotension over a 12 was undertaken to describe current clinical practice relating to the administration of fluid bolus therapy, as well as to explore the physiological and clinical outcomes associated with its use. While experiencing some methodological limitations, which include the use of retrospective data, the inability to evaluate the definition of fluid responsiveness, and a lack of data required to identify SIR and sepsis in the population; this study does contribute to sparse existing literature describing the use of fluid bolus therapy in a hypotensive ward patient population. This study was successful in describing current practice, identifying significant characteristics of responders, and determining factors associated with ICU transfer in the population.

This study found that while fluid bolus therapy was frequently administered, less than half of recipients exhibited a physiological response, and furthermore there was no reduction in adverse clinical outcome associated with its use. The physiological effect produced by the fluid bolus was minimal when compared to the physiological outcomes of who did not receive fluid bolus therapy. The responders to the therapy were older and more hypotensive, with increasing age and worse hypotension both identified as predictive for fluid responsiveness. There was no evidence demonstrating that administering fluid bolus therapy had positive effects on the reduction of repeat RRT calls for hypotension or ICU admission within 24 hours of the first call. What was evident was that

increasing volume administration at the RRT call predicted ICU admission. The results described the in this study highlighted a number of areas which require further research, including the causal relationship between increasing age and fluid responsiveness, factors associated with the poor documentation at RRT calls and defining fluid response in a ward setting. Due to the exploratory nature of this study, there is minimal scope for the results to change clinical practice. The outcomes studied support the continued use of fluid bolus therapy when administered in a judicious manner.

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Appendix 1

Critical Appraisal of the Literature

Citation	Aims	Sample and setting	Study design and methods	Findings	Strengths and limitations	Significance
Bihari, S, Prakash, S & Bersten, AD 2013, 'Post Resuscitation Fluid Boluses in Severe Sepsis or Septic Shock: Prevalence and Efficacy (PRICE Study)', Shock, vol.40, no.1, pp.28-34	To investigate the prevalence, efficacy and possible harmful effects of fluid bolus therapy administered to septic ICU patients in the days following initial fluid resuscitation.	Single centre, South Australian, tertiary ICU. 102 patients admitted with severe sepsis/septic shock during the study period	Prospective observational study	Post resuscitation fluid boluses are common in septic patients, meet limited success, and may be harmful.	There is a small sample size, however there is also reduced variability in the population, (all septic ICU patients). Single centre setting which uses predominantly 4% Albumin for resuscitation – which limits the external validity of the study and questions generalisability of results.	Highlights the deleterious effects and limited benefit of fluid bolus therapy. Identifies severe sepsis/septic shock patients in post resuscitation period as potential non-responders to fluid bolus therapy.
Calzavacca, P, Licari, E, Tee, A, Mercer, I, Haase, M, Haase-Fielitz, A, Jones, D, Gutteridge, G and Bellomo, R 2010, 'Features and Outcome of Patients Recieving Multiple Medical Emergency Team Reviews', *Resuscitation*, 81, 7	To establish the characteristics and outcomes associated with patients receiving multiple rapid response calls.	Single centre, Australian, tertiary hospital. (The Austin) 1664 patients over all with 374 requiring multiple rapid response team reviews.	Retrospective observational study	Patients requiring multiple rapid response team reviews were more likely to be surgical, have gastrointestinal disease and trigger for arrhythmia. This population faces increased LOS and in-hospital mortality.	Large population and mature rapid response system. Single centre - ?external validity Retrospective study design utilising existing data base with missing data.	Identifies factors associated with increased mortality in ward patient population requiring rapid response team review.

Chen, J, Bellomo, R, Hillman, K, Flabouris, A and Finfer, S 2010, 'Triggers for Emergency Team Activation: A Multicentre Assessment', *Journal of Critical Care/Journal of Critical Care*, 25, 7	Examine the triggers for Medical Emergency Team review across hospitals with and without a MET system.	2414 calls from 23 Australian hospitals. Interventional hospitals were those with MET system implemented vs control hospitals without a MET system.	Cluster randomised controlled study.	Triggers for calls in control hospitals were more likely to be related to respiratory distress or drop in GCS, whereas hospitals with a MET system were 35 times more likely to call if 'worried'.	Due to analysis of old data, the features of rapid response systems studied may no longer be relevant to the mature systems of today. The baseline characteristics of control and interventional sites are not made clear. Questionable validity in cluster RCT design.	Provides some evidence of frequency of triggers for rapid response team review.
Cross, G, Bilgrami, I, Eastwood, G, Johnson, P, Howden, B and Jones, D 2015, 'The Epidemiology of Sepsis During Rapid Response Team Reviews in a Teaching Hospital', *Anaesthic Intensive Care/Anaesthic Intensive Care*, 43, 2, 6	Assess the proportion of rapid response team reviews associated with SIRS and sepsis.	Single centre, Australian, tertiary hospital. (The Austin)	Retrospective observational study	77.4% of all calls met SIRS criteria, with 57.4% going on to fulfil criteria for presumed sepsis. 57.2% of infections were nosocomial in nature with respiratory tract and abdominal cavity being the most common sites.	Single centre - ?external validity Retrospective study design utilising existing data base with missing data. Diagnosis of sepsis relied exclusively on objective data, where clinical assessment may capture more cases.	Demonstrates high incidence of sepsis in ward patient population requiring rapid response team review. Relevant due to evidence suggesting that this population may not be responsive to fluid bolus therapy.
Duus, N, Shogilev, D, Skibsted, S, Zijlstra, H, Fish, E, Oren-Gringberg, A, Lior, Y, Novack, V, Talmor, D, Kirkegaard, H & Shapiro, N 2015, 'The Reliability and Validity of Passive Leg Raise and Fluid Bolus to Assess Fluid Responsiveness in Spontaneously Breathing Emergency Department Patients', *Journal of Critical Care*, vol. 30, pp. 217-22.						

Flabouris, A, Chen, J, Hillman, K, Bellomo, R and Finfer, S 2010, 'Timing and Interventions of Emergency Teams During the MERIT Study', *Resuscitation/Resuscitation*, 81, 5	To examine the timing and interventions performed at rapid response calls in hospitals with and without and MET system.	2376 calls from 23 Australian hospitals. Interventional hospitals were those with MET system implemented vs control hospitals without a MET system.	Cluster randomised controlled study.	Nearly all calls required a critical care type intervention. Ward level interventions were more common in MET hospitals	Data in MET hospitals may no longer be relevant to mature MET systems. The baseline characteristics of control and interventional sites is unclear	Demonstrates that fluid bolus therapy is an intervention administered at a high proportion of calls, which thereby supports a predicted high prevalence of use in the rapid response setting.
Eastwood, G, Peck, L, Young, H, Paton, E, Glassford, NJ, Zhang, L, Zhu, G, Tanaka, A & Bellomo, R 2015, 'Intensive care nurses' self-reported practice of intravenous fluid bolus therapy', *Intensive and Critical Care Nursing*, vol. 31.	To describe the self-reported practice of fluid administration by intensive care nurses	A multi-choice questionnaire was used to survey nurses from a single centre over a one-month period	Survey	The most frequently administered fluid was 4% Albumin, in boluses of 250mls. Respondents identified hypotension as the leading trigger for administration of fluids. Physiological response was likely over estimated.	Survey conducted in a single centre which limited the validity of findings. The practice described by respondents is likely to be different in other institutions, for example chiefly Albumin boluses used.	Identifies variability in clinician opinion of what constitutes a fluid bolus, and a positive response to the therapy.
Glassford, NJ, Jones, SL, Martensson, J, Eastwood, G, Baileey, M, Cross, AM, Taylor, D & Bellomo, R 2015, 'Characteristics and expectations of fluid bolus therapy: a bi-national survey of acute care physicians', *Anaesth Intensive Care*, vol. 43, no. 6.						

Glassford, NJ, Eastwood, GM and Bellomo, R 2014, 'Physiological Changes After Fluid Bolus Therapy in Sepsis: a systematic review of contemporary data', *Critical Care/Critical Care*, 18, 696, 21	To review contemporary evidence relating to the physiological outcome of administering fluid bolus therapy in sepsis.	33 studies describing fluid bolus therapy	Systematic review	Heterogenity in triggers, volume, and fluid choice for administration of fluid bolus therapy. Variable physiological targets, with no relationships made between physiological changes and clinically relevant outcomes. No RCT comparing fluid bolus therapy to alternate treatment.	Article search strategy is thorough and clearly described.	Demonstrated ambiguity in what constitutes fluid bolus therapy, highlights heterogeneity in fluid volume, type, and duration in both local and international practice.
Herod, R, Frost, S, Parr, M, Hillman, K and Aneman, A 2014, 'Long Term Trends in Medical Emergency Team Activations and Outcomes', *Resuscitation*, 85, 5	To analyse the long term operational tends of the MET system, including number of calls, triggers, and outcome.	Single centre, Australian, tertiary hospital. 19,030 MET calls, activated over 12 years.	Retrospective observational study	Frequency of MET calls increased over the study period. Frequency of physiological trigger for call changed over the period, with hypotension becoming the most common reason for review.	Mature MET system. Single centre design limits external validity of the study and generalisability of results. However prolonged study period and large population does limit this effect. Retrospective study design utilising existing data base potential for missing data.	Highlights high prevalence of ward patients requiring rapid response team review for hypotension, thereby identifying a significant population worthy of continued study.
Jones, D, Duke, G, Green, J, Briedis, J, Bellomo, R, Casamento, A, Kattula, A and Way, M 2006, 'Medical Emergency Team Syndromes and an Approach to Their Management', *Critical Care/Critical Care*, 10, 4	To investigate the most common causes for MET calls and determine approaches for the subsequent management.	Single centre, Australian, tertiary hospital. (The Austin) 400 MET calls over 7 month study period in 2004	Retrospective observational study	Determined the underlying causes fro MET calls with hypotension leading to 28% of calls. Formulation of a system for the management of MET calls.	Single centre design questions external validity of the study. Retrospective study design utilising existing data base potential for missing data.	Contributes to evidence indicating hypotension as a leading cause of rapid response team review.

Khalid, I, Qabajah, MR, Hamad, WJ, Khalid, TJ & DiGiovine,B 2014, 'Outcome of Hypotensive Ward Patient Who Re-Deteriorate After Initial Stabilisation by the Medical Emergency Team', Journal of Critical Care, vol.29, pp.54-59	In this study Khalid et al evaluate the outcomes of hypotensive ward patients who re-deteriorate following initial stabilisation by the Medical Emergency Team.	Single centre, tertiary care teaching hospital. 410 adult patients during the study period, who had an episode of acute hypotension on the ward for which MET was activated, were evaluated.	Retrospective observational study	Hypotensive ward patients who re-deteriorate after initial stabilisation face increased mortality and are more acutely unwell on admission to ICU.	Large sample size. Proportion of hypotensive patients requiring review is similar to other studies. Clinical practice of MET team is not representative of Australian protocol (Dobutamine infusion on the ward) which Limits generalisability of results to an Australian setting	Contributes to evidence indicating hypotension as a leading cause of rapid response team review. Contributes to evidence of sepsis as a primary cause for hypotension. Supports reoccurring theme of sepsis as a factor indicative of fluid bolus non-responsiveness. Indicates delay in ICU transfer increases mortality.
Lakhal, K, Ehrmann, S, Wolff, M & Boulain, T 2013, 'Fluid challenge: tracking changes in cardiac output with blood pressure monitoring (invasive or non-invasive)', *Intensive Care Med*, vol. 39, pp. 1959-62.						
Lipcsey, M, Chiong, J, Subiakto, I, Kaufman, MA, Schnider, AG & Bellomo, R 2015, 'Primary Fluid Bolus Therapy for Infection-Associated Hypotension in the Emergency Department', Critical Care and Resuscitation, vol.17, pp.6-11	To investigate the physiological outcomes of FBT in the first 6 hours (primary FBT) for patients presenting to the ED with infection-associated hypotension	Single-centre metropolitan emergency department. (The Austin) 101 consecutive ED patients with infection and a systolic blood pressure (SBP) <100 mmHg who underwent FBT in the first 6 hours.	Retrospective observational study	The average mean arterial pressure (MAP) did not change from admission to 6 hours in the whole cohort, or in patients who were hypotensive on arrival at the ED. When noradrenaline was used in 10 patients, hypotension was corrected and the MAP reliably increased	Single centre design limits the external validity of the study Small sample size. Generalisability of results improved by the study auditing practice against current guidelines to determine that fluid volumes administered are comparable to current practice in similar settings.	Highlights limited physiological effect of FBT. Supports reoccurring theme of sepsis sepsis as a factor indicative of fluid non-responsiveness.

Lira, A and Pinsky, M 2014, 'Choices in Fluid Type and Volume During Resuscitation: Impact on Patient Outcomes', *Annals of Intensive Care/Annals of Intensive Care*, 4, 38, 13	To summarise emerging literature relating to physiological principles underlying fluid resuscitation and current recommendations regarding fluid type and volume	5 randomised controlled trials and 10 meta-analysis and systematic reviews.	Systematic review	There is no evidence of Albumin as a superior resuscitative solution. Hydroxyethyl stage is associated with increased harm. Normal saline is associated with hyperchloraemic acidosis and AKI. Balanced solutions have shown no harmful effects.	Article search strategy is thorough and clearly described.	Summarises debate regarding fluid choice and volume.
Maitland et al 2011, 'Mortality after Fluid Bolus in African Children with Severe Infection', New England Journal of Medicine, vol.364, no.26, pp.2483-2495	To investigate the practice of early resuscitation with a saline bolus as compared with no bolus (control) and with an albumin bolus as compared with a saline bolus.	6 Hospitals in Kenya, Tanzania, and Uganda. 3170 Children between 60 days and 12 years of age presenting with a severe febrile illness complicated by impaired perfusion.	Randomised controlled trial	Children resuscitated with boluses of normal saline or 5% human albumin had a 3.3% increased risk of absolute death by 48 hours, when compared to their no bolus controls.	Only RCT comparing fluid bolus therapy to alternate treatment. Poor generalisability to a first world, adult critical care setting. Methodological limitations including broad inclusionary criteria no final diagnosis.	Landmark study questioning decades of practice (early fluid resuscitation) in resource-rich countries as well as the current understanding of the pathophysiology of shock.
Monnet, X, Letierce, A, Hamzaoui, O, Chemla, D, Anguel, N, Osman, D, Richard, C & Teboul, J 2011, 'Arterial pressure allows monitoring the changes in cardiac output induced by volume expansioon but not by norepinepherine', *Critical Care Medicine*, vol. 39, no. 6, pp. 1394-9.						

Natalini, G, Rosano, A, Militano, CR, Di Maio, A, Ferretti, P, Bertelli, M, De Giuli, F & Bernardini, A 2012, 'Prediction of arterial pressure increase after fluid challange', *BMC Anesthesiology*, vol. 12, no. 3, pp. 1-7.						
Quach, JL, Downey, AW, Haase, M, Haase-Fielitz, A, Jones, D and Bellomo, R 2008, 'Characteristics and Outcomes of Patients Receiving Medical Emergency Team Review for Respiratory Distress or Hypotension', *Journal of Critical Care/Journal of Critical Care*, 23, 325-331	To identify characteristics and explore the outcomes of patients receiving rapid response calls triggered for hypotension and respiratory distress.	Single centre, Australian, tertiary hospital. (The Austin) 200 patients receiving a rapid response call for hypotension or respiratory distress from 2000-2002	Retrospective observational study	Sepsis was present in 58% of cases, delayed MET calls significantly increased mortality and was the case in present in 39% of call calls for hypotension	Single centre - ?external validity Small sample size limited statistical significance in patient characteristics. Study conducted at the start of the rapid response program which means results may no longer be representative of practice seen in a mature rapid response system.	Highlights the prevalence of sepsis in the hypotensive deteriorating patient. Identifies recurrent rapid response reviews as a factor associated with increased mortality in a hypotensive population requiring rapid response team review.
Saugel, B, Kirsche, S, Hapfelmeier, A, Philip, V, Schultheiss, C, Schmid, R & Huber, W 2013, 'Prediction of fluid responsiveness in patients admitted to the medical intesive care unit', *Journal of Critical Care*, vol. 28, pp. 537-46.						

Stelfox, H, Bagshaw, S and Gao, S 2014, 'Characteristics and Outcomes for Hospitalised Patients With Recurrent Clinical Deterioration and Repeat Medical Emergency Team Activations', *Critical Care Medicine/Critical Care Medicine*, 42, 7, 9	To identify the prevalence recurrent rapid response calls and associated patient outcomes.	Canadian multi-centre study, featuring two community hospitals and two tertiary care hospitals. 3200 rapid response patients with 337 of those experiencing multiple reviews.	Retrospective cohort study	Recurrent clinical deterioration and repeat rapid response calls are common and associated with increased hospital length of stay and mortality.	Large sample size and multi-centre design provide internal and external validity and help to overcome limitations associated retrospective design.	Identifies recurrent rapid response reviews as a factor associated with increased mortality in deteriorating patient population
Weingarten, T, Venus, S, Whalen, F, Lyne, B, Temple, H, Wilczewski, S, Narr, B, Martin, D, Schroeder, D and Sprung, J 2012, 'Postoperative Emergency Response Team Activation at a Large Tertiary Medical Centre', *Mayo Clinica Proceedings/Mayo Clinica Proceedings*, 87, 1, 9	To explore characteristics and outcomes of post operative patients requiring rapid response team activation.	Single centre , American, tertiary hospital 181 patients requiring rapid response calls in their post operative period	Retrospective observational study	Rapid response calls in the post operative period are associated with intra-operative haemodynamic instability and hypotension is the leading trigger for review	Single centre and small sample size limit the generalisability of findings. Reduced population variability increases statistical significance of results. Retrospective study design utilising existing data base potential for missing data.	Identifies hypotension a primary trigger for rapid response team review in post operative patients.

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Approval Date: 16 June 2015

Ms Sarah Doherty
Intensive Care Unit
ROYAL ADELAIDE HOSPITAL

Dear Ms Doherty

HREC reference number: **HREC/15/RAH/249**

Project Title**: "Fluid bolus therapy in MET calls for hypotension; a retrospective observational study."**

RAH Protocol No: 150616.

Thank you for submitting the above project for ethical review. This project was considered by the Chairman of the Royal Adelaide Hospital Human Research Ethics Committee.
I am pleased to advise that your protocol has been granted full ethics approval and meets the requirements of the *National Statement on Ethical Conduct in Human Research*. The documents reviewed and approved include:

- **LNR Application: AU/15/617F115 Sites covered by this approval:**
  - **Royal Adelaide Hospital: CPI – Ms Sarah Doherty**
  - **Flinders Medical Centre: Dr Shailesh Bihari**
- **Protocol, Version 1, 11/06/2015**
- **Curriculum Vitae – Sarah Doherty**

Please quote the **RAH Protocol Number, 150616** and the **HREC number, HREC/15/RAH/249** allocated to your study on all future correspondence.

GENERAL TERMS AND CONDITIONS OF APPROVAL OF AUDIT:

- Adequate record-keeping and data security is important. The duration of record retention for all clinical research data is 15 years.
- Confidentiality is important. The data collected should as much as possible protect the identity of individuals. Where this is not possible, a separate file of subject identifiers should be maintained such that clinical information is kept separately from subject identifiers.
- You must notify the Research Ethics Committee of any changes which might warrant review of the approval.
- Approval is ongoing. Annual or final reports are ***not*** required.
- The REC must be advised within 30 days of completion so that the file can be closed.

Should you have any queries about the HREC's consideration of your project, please contact Ms Heather O'Dea on 08 8222 4139, or rah.ethics@health.sa.gov.au .

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a SA Health site until separate authorisation from the Chief Executive or delegate of that site has been obtained.

This Committee is constituted in accordance with the NHMRC's *National Statement on the Ethical Conduct of Human Research* (2007).

The HREC wishes you every success in your research.

Yours sincerely,

for

A/Prof A Thornton
CHAIRMAN
RESEARCH ETHICS COMMITTEE

Appendix 3

Skewness, kurtosis and normality tests for continuous variables of all RRT calls for SBP<90mmHg

Variable	Sample (n)	Skewness	SEskewness	Zskewness	Kurtosis	SE Kurtosis	Z Kurtosis	Kolmogorov-Smirnov*		Shapiro-Wilk	
								stats	p-value	stats	p-value
Age	981	-.687	0.78	-0.880	-.179	.156	-1.147	.095	<0.001	.951	<0.001
sBP_1	973	.891	0.78	1.142	1.701	.157	10.834	.134	<0.001	.948	<0.001
sBP_2	878	.775	0.83	0.934	2.767	.165	16.769	.101	<0.001	.955	<0.001
dBP_1	587	1.008	.101	9.980	3.439	.201	17.109	.120	<0.001	.945	<0.001
dBP_2	629	.168	.097	1.731	2.561	.195	13.133	.105	<0.001	.969	<0.001
HR_1	944	.977	.080	12.212	1.600	.159	10.062	.091	<0.001	.849	<0.001
HR_2	813	.786	.086	9.139	.999	.171	5.842	.099	<0.001	.965	<0.001
RR_1	898	1.272	.082	1.551	2.817	.163	17.282	.169	<0.001	.909	<0.001
RR_2	705	.943	0.092	10.25	2.730	.184	1.484	.152	<0.001	.921	<0.001
SpO2_1	928	-2.880	.080	-36	15.673	.160	97.96	.172	<0.001	.770	<0.001
SpO2_2	774	-2.844	.088	-32.32	16.085	.176	91.39	.171	<0.001	.774	<0.001
FiO2_1	850	1.879	.084	2.236	3.970	.168	23.63	.249	<0.001	.769	<0.001
FiO2_2	756	1.803	.089	20.26	3.749	.178	21.062	.254	<0.001	.786	<0.001
Temp	559	.157	.103	1.524	2.671	.206	12.966	.098	<0.001	.960	<0.001
Bolus vol.	539	3.685	.105	35.10	21.863	.210	104.11	.269	<0.001	.655	<0.001

* Lilliefores significance correction