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In emergency department patients requiring resuscitation room care, can Renal Resistive Index measurements predict the development of acute kidney injury?

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In emergency department patients requiring resuscitation room care, can Renal Resistive Index measurements predict the development of acute kidney injury?

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Declaration of any previous submission of the work
The material presented here for examination for the award of a higher degree by research has not been incorporated into a submission for another degree.

Candidate's signature 

Declaration of authorship
I am the author of this thesis, and the work described therein was carried out by myself personally.

Candidate's signature 

Contents

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This thesis is dedicated in loving memory of Gandalf

….who *always* believed.

Abstract

PURPOSE: Doppler renal resistive index (RRI) has emerged in the last decade as a useful prognostic indicator for transient (fluid responsive) and persistent acute kidney injury (AKI). The determinants of RRI are largely systemic and recent studies confirm that RRI measurement could also be a useful early marker for sub-clinical AKI and post procedural AKI risk. This study aimed to determine the feasibility of RRI measurement in an Emergency Department (ED) resuscitation room setting using a point-of-care ultrasound system.

METHODS: In this prospective single centre study, RRI measurement was attempted in 20 non-consecutive patients (meeting the inclusion criteria) by a single expert sonographer. RRI measurements were evaluated against context specific feasibility criteria and target outcomes.

RESULTS: 20 patients (11 male, 9 female) were recruited to the study. Age of patients ranged from 33 years to 91 years (mean 62.3 years). Adequate visualisation of both kidneys was achieved in 60% of patients (n=12). In patients where it was not possible to achieve adequate views of both kidneys (n=8), limiting technical factors were shortness of breath (SOB) (n=6), high BMI (n=2). At least one measurement of RRI was achieved in 70% of patients (n=14). However, in 9 of these patients (64.3%) the Doppler spectral traces achieved were substandard and did not meet the measurement criteria for RRI as specified in the study protocol. In 30% of patients (n=6) no usable spectral trace was achieved and it was not possible to measure RRI. SOB was noted as a technical difficulty in 60% of patients (n=12) including three for whom RRI measurements were achieved. In 9 patients (45%) SOB was recorded as the primary reason for failure to acquire a usable Doppler trace. All criteria for RRI measurements were met in only 3 patients (15%).

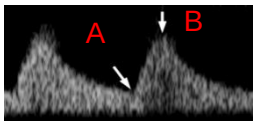
CONCLUSION:
Measurement of RRI was not feasible in patients requiring resuscitation room care using a current point of care ultrasound system. If RRI is to play a useful role in this high priority patient group, adaptation of the available technology is required to mitigate the problem of image blur due to patient breathing movement.

KEYWORDS: Acute kidney injury; Doppler; Resistive index; Feasibility; Emergency Department

Abbreviations, acronyms and glossary of technical terms

AKI	**Acute Kidney Injury**	AKI encompasses a wide spectrum of renal injury mechanisms and is characterised by rapid reduction in renal function over a period of < 48 hours.
AKIN	**Acute Kidney Injury Network**	AKIN is an international interdisciplinary network promoting clinical, research and educational developments around AKI.
ATN	**Acute tubular necrosis**	Death of tubular epithelial cells that form the renal tubules of the kidneys. One of the most common causes of AKI.
CI-AKI	**Contrast induced acute kidney injury**	Decline in kidney function occurring in a narrow time frame after administration of iodinated diagnostic imaging contrast material
$_{c}$PP	**Central pulse pressure**	Difference between the systolic and diastolic blood aortic pressure
ED	**Emergency Department**	A medical treatment facility specializing in emergency medicine and non-scheduled acute care.
EDV	**End diastolic velocity**	Quantitative Doppler measurement of the highest velocity blood flow measured at end diastole.
eGFR	**Estimated glomerular filtration rate**	An estimate of the rate at which fluid is filtered through the kidneys. Based on serum creatinine level, age, sex, and race. eGFR is an estimated value with wide confidence intervals. Inaccurate in people at extremes of body type.
FTE	**Full time equivalent**	Staff - full time equivalent role
KDIGO	**Kidney Disease: Improving Global Outcomes**	KDIGO is an international organisation promoting "*the care and outcomes of kidney disease patients worldwide through the development and implementation of global clinical practice guidelines" (KDIGO 2014).*

MAP	**Mean arterial pressure**	Average arterial pressure. Key determinant of diastolic flow and organ perfusion.
MEW	**Modified Early Warning Score**	Scoring system published by the Royal College of Physicians. Used to standardise the assessment of acute-illness severity.
NEW	**National Early Warning Score**	Revised scoring system published by the Royal College of Physicians and endorsed by NHS England. Used to standardise the assessment of acute-illness severity. December 2017
NGAL	**Neutrophil gelatinase-associated lipocalin**	A protein released by the kidneys following renal insult. Possible early indicator of AKI.
NICE	**National Institute for Health and Care Excellence**	NICE provides national guidance and advice to improve health and social care.
P_o	**Combined interstitial & capillary pressure**	Capillary wedge pressure
PSV	**Peak systolic velocity**	Quantitative Doppler measurement of the highest velocity blood flow measured at peak systole.
POCUS	**Point-of-care ultrasound**	Clinician performed ultrasound at the point of patient care. Used as an adjunct to clinical examination.
R&D	**Research and Development**	NHS Trust based research department
RCEM	**Royal College of Emergency Medicine**	UK professional membership organisation and registered charity representing emergency medicine doctors
RIFLE	**(Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease)**	Classification system for acute kidney injury stage. Pre-dates AKIN classification which is a modified version of RIFLE

RRI	**Renal Resistive Index** 	An ultrasound Doppler measurement of blood flow in the intra-renal arteries. RRI is a ration of peak systolic velocity over peak systolic – end diastolic measurements. $\textbf{RI} = \frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{peak systolic velocity}} = \frac{B - A}{B}$
sCr	**Serum creatinine**	A bi-product of muscle metabolism, excreted by the kidneys and used as an indicator of renal function. Used in estimation of glomerular filtration rate.
SYNTAX	**Scoring system indicating the severity of coronary artery disease**	Combines anatomic and clinical prognostic variables to guide surgical management of coronary artery disease.
U&E	**Urea and electrolytes test**	A commonly performed biochemical blood test that measures urea and electrolytes, including creatinine. A measure of kidney function.

Chapter 1 Introduction and background

This chapter provides a brief introduction to the study and the background from which the focused research question has emerged. Context and target population are explained and a brief rationale for the study is presented.

Acute kidney injury (AKI) is a complex disorder that is characterised by rapid reduction in renal function over a period of < 48 hours. The estimated annual costs associated with AKI exceed those of breast cancer, lung cancer and skin cancers combined and are expected to rise considerably in an aging population (NICE 2013).

In the United Kingdom (UK) in excess of 100,000 in-hospital deaths per year are associated with AKI. However, with the right preventive care and treatment, it is estimated that up to 30% of these deaths could be prevented (Think Kidneys, 2018; NCEPOD, 2009).

In acute admissions, an episode of AKI is confirmed in approximately one in five patients and is linked closely with poor outcome (Wang et al., 2013). Even where patients survive, a minority of patients remain dialysis-dependent (Waikar and Winkelmayer, 2006; Wald et al., 2009; Lahmer et al., 2016; Spatola and Andrulli, 2016). Therefore, the cost of long term community based care can be high. There are no curative therapies for the damage caused by AKI which results in irreversible reduction in renal function. Therefore, outcomes can only be improved by preventive care and early intervention to preserve renal function.

Despite high level focus on this as a research priority, a reliable method of early detection and assessment of individual risk of AKI is still proving to be elusive (Darmon et al., 2017). The current method of AKI diagnosis is based on assessment of changes in serum creatinine level (sCr) which typically will rise 2-3 days after the initial renal insult and on reduced urine output over more than 6 hours (Bagshaw et al., 2010; Chang et al., 2010; Ricci et al., 2011; Lewington and Kanagasundaram, 2011, Darmon et al., 2017). Both of

these markers have poor sensitivity and specificity and are limited by an inherent time lag between observed changes and the time of initial injury to the kidney.

Oliguria may be an indicator for compromised renal function but, can be present due to confounding factors common in acute admissions such as dehydration and hypovolaemia. Rise in sCr level occurs in response to falling eGFR and is a late marker for reduced renal function. sCr level is also highly dependent on a number of patient specific variables such as age, gender, ethnicity and BMI. Assessment of sCr therefore requires a meaningful baseline value for the patient that is rarely available at the time of acute admission.

Acute kidney injury is not a trivial finding. Even stage 1 AKI is essentially a medical emergency that requires early intervention. As definitions of AKI stages have been standardised and their natural progression better understood, the scale of the problem as a global healthcare challenge has emerged. In response, there has been widespread international engagement in the search for an alternative method of early diagnosis of AKI and identification of patients at risk of AKI.

Most of the studies identified by this review focus on development of biomarkers capable of detecting subclinical AKI and on clinical prediction scoring systems to stratify patient risk (Darmon et al., 2017). Exploration of biomarkers in particular has gathered pace in the last decade with multiple studies evaluating their potential (Soto et al., 2010; Nickolas et al., 2012; Schinstock et al., 2012; Vanmassenhove et al., 2013; Kashani et al., 2017). However, these tests remain costly; they are widely unavailable and are yet to be validated. (These alternative approaches to early AKI diagnosis are discussed further in Chapter 9).

Identification of a reliable and cost effective method of early detection of AKI could be particularly beneficial in patients admitted to the Emergency Department (ED). Management of sick patients in this context frequently

requires rapid decision making regarding use of drugs with a known nephrotoxic effect or referral for contrast enhanced imaging. The benefit of these interventions needs to be balanced against the risk of long term irreversible renal damage and associated poor outcome.

1.1 Background

Development of the focused research question explored by this study was prompted initially by discussion with clinical colleagues in critical care regarding the use of ultrasound and its contribution to management of patients with confirmed AKI. In this context, the incidence of AKI is high (Bagshaw, 2010; Darmon, 2011) and ultrasound is used routinely in patient assessment when AKI is confirmed by standard tests.

In critical care patients, prediction of renal recovery is particularly difficult and has significant implications for patient management (Zhou et al., 2006; Bagshaw et al., 2011; Darmon et al., 2011). Early review of the literature focused on the potential role of ultrasound in distinguishing between transient reduction in renal function and persistent irreversible damage.

Against this background, several studies were identified during Phase 2 of the PD Health that establish Doppler ultrasound measurement of Renal Resistive Index (RRI) as a potentially useful prognostic indicator for AKI (Barbani et al., 2010; Darmon et al., 2011; Schnell and Darmon, 2012; Guinno et al., 2013; Viazzi et al., 2014).

Subsequent review during Phase 3 identified a further three studies that explore the potential role of RRI in the early diagnosis of AKI, as well as its performance as a predictor of renal recovery (Bossard et al., 2011; Dewitt et al., 2012; Schnell et al., 2013).

These are summarised in table 1.1 below.

Table 1.1 Summary of key critical care studies

Author, date, country and title	Patient group	Study type	Outcomes	Key results	comments
Barbani et al (2010) Italy *Prognostic value of Doppler based renal arterial RI in critically ill patients with AKI: preliminary results*	Mixed ICU patients	Prospective observational study	Measurement of RI within 24 hours of AKI diagnosis using RIFLE criteria. Renal recovery defined as return to normal renal function parameters.	RRI measured at AKI onset was significantly higher in patients with persistence of renal failure than in patients with complete renal recovery (0.89 (plus or minus) 0.13 vs. 0.72 (plus or minus) 0.14, p<0.001). RRI>0.75 had a sensitivity of 81% (95% CI 67-90%), a specificity of 70% (95% CI 53-82%) and a positive likelihood ratio of 2.75 (95% CI 1.44-5.13) for persistent renal dysfunction at discharge n= 38 At discharge : 18 no AKI 20 persistent AKI mortality rate was 18.4%	Small sample critical care patients RRI measured within 24hours High prevalence (53%) High mortality (18.4%)
Schnell D. et al (2012) France *Renal resistive index better predicts the occurrence of acute kidney injury than cystatin c*	n=58 critically ill patients with sepsis (n=28) or polytrauma (n=30) admitted to ITU	Prospective double-centre descriptive	Measurement of RI and cystatin-c (in serum and urine) within 12 hours of admission	RI > 0.707 on D1 was the only predictor of the development of AKI stag 2 or 3 on D3 (p=0.0004) In patients with AKI stage 2 or 3 on D1, RI was the only predictor of AKI stage 2 or 3 on D3 (p=0.016)	See Soto et al (2010) Cystatin-c as a marker of AKI in the ED High prevalence of AKI 69%
Guinot P. et al (2013) France *Doppler-based RRI can assess progression of AKI In patients undergoing cardiac surgery*	n= 82 patients post cardiac surgery	Prospective study	Serial measurement of RRI pre / post op RIFLE classification of AKI	15 patients (18%) developed persistent AKI 6 patients (7%) developed transient AKI RRI >0.73 distinguishes transient from persistent AKI with good predictive value	RRI 0.72-0.75 *grey zone* (14% patients in this study) Moderate prevalence 22%

Table 1.1 Summary of key critical care studies cont.

Darmon et al (2011) France *Diagnostic accuracy of Doppler renal resistive index for reversibility of acute kidney injury in critically ill patients*	ICU patients with AKI, ventilated but without severe CRD or receiving diuretic therapy.	Prospective observational study Single centre with population of selected high risk patients.	Measurement of RI on admission and repeat serum creatinine.	RI better than urinary indices for predicting persistent AKI. RI> 0.795 has 92% sensitivity and 85% specificity for persistent AKI. n=51 13 transient AKI (37%) 22 persistent (43%)	Delays in initial measurement of RI in some patients. Intra/inter operator variability of RI measurements not tested. Right kidney only assessed. No prospective validation of cut off level. High prevalence of AKI 68%
Barbani et al (2010) Italy *Prognostic value of Doppler based renal arterial RI in critically ill patients with AKI: preliminary results*	Mixed ICU patients	Prospective observational study	Measurement of RI within 24 hours of AKI diagnosis using RIFLE criteria. Renal recovery defined as return to normal renal function parameters.	RI> 0.75 has 81% sensitivity and 70% specificity and +ve likelihood ratio of 2.75 for persistent renal dysfunction on discharge. RRI measured at AKI onset was significantly higher in patients with persistence of renal failure than in patients with complete renal recovery (0.89 (plus or minus) 0.13 vs. 0.72 (plus or minus) 0.14, p<0.001). RRI>0.75 had a sensitivity of 81% (95% CI 67-90%), a specificity of 70% (95% CI 53-82%) and a positive likelihood ratio of 2.75 (95% CI 1.44-5.13) for persistent renal dysfunction at discharge n= 38 At discharge : 18 no AKI 20 persistent AKI mortality rate was 18.4%	Small sample critical care patients RRI measured within 24hours High prevalence (53%) High mortality (18.4%)
Viazzi et al (2014) Ultrasound Doppler renal resistive index: a useful tool for the management of the hypertensive patient.	Target group - Patients with primary hypertension	Review article		RRI value 0.60 +/- 0.01 (mean +/-SD) is usually taken as normal 0.70 considered the upper limit of normal in adults by most authors*	Old data * Tublin ME (2003)

Table 1.1 Summary of key critical care studies cont.

Schnell et al (2013) Renal Perfusion Assessment by Renal Doppler During Fluid Challenge in Sepsis	Consecutive patients receiving mechanical ventilation and requiring a fluid challenge	Prospective cohort study	Resistive index measurement before and after fluid challenge	Renal resistive index was unchanged after fluid challenge in both non-responders (0.72 [0.67–0.75] before and 0.71 [0.67–0.75] after fluid challenge; p = 0.62) and responders (0.70 [0.65–0.75] before and 0.72 [0.68–0.74] after fluid challenge; p = 0.11).	Systemic hemodynamic changes induced by fluid challenge do not affect RRI measurements in patients without AKI, with transient AKI, or with persistent AKI
Dewitt et al (2012) Doppler resistive index to reflect regulation of renal vascular tone during sepsis and acute kidney injury	Patients admitted to ICU with sepsis or shock	Prospective observational study	RRI measurement within 24 hours of admission.	Median renal RIs were 0.72 (0.68-0.75) in patients without AKI and 0.76 (0.72-0.80) in patients with AKI (P=0.001). RIs were 0.75 (0.72-0.79) in transient AKI and 0.77 (0.70-0.80) in persistent AKI (P=0.84).	A poor correlation between renal RI and MAP, age, or PaO2/FiO2 ratio was found in septic and critically ill patients without AKI compared to patients with AKI. These findings suggest that determinants of RI are multiple.
Bossard et al (2011) Early detection of postoperative acute kidney injury by Doppler renal resistive index in cardiac surgery with cardiopulmonary bypass	Patients undergoing elective heart surgery with cardiopulmonary bypass (CPB) and at risk of AK	Prospective, observational study	RRI measured in the immediate postoperative period while subjects were ventilated and sedated. AKI confirmed positive when sCr increased 30% above the preoperative baseline	Post-operative RRI >0.74 predicted delayed AKI with high sensitivity and specificity (0.85 and 0.94, respectively). Multivariate analysis showed that AKI was associated with increased RRI and transfusion.	RRI used in the immediate POP after cardiac surgery with CPB enabled prediction of delayed AKI and anticipation of its severity.

In a meta-analysis of nine related studies (including five of those listed above), Ninet et al (2015) investigated the performance of RRI in predicting the short term reversibility of AKI in critical care patients. The data analysed (n= 449 patients) demonstrate a pooled sensitivity of 0.83 (0.76 – 0.88) and pooled specificity of 0.84 (0.79 – 0.88) for persistent AKI in patients with elevated RRI.

Despite methodological differences and heterogeneity in the data collected (RRI cut off, patient population and definition of renal recovery), in all of these studies RRI performs better than existing tests for AKI in identifying patients with **persistent** reduction in renal function. However, the causative links between AKI outcome and raised RRI were unclear. Ninet et al acknowledge that there are a number of uncertainties regarding the true significance of RRI in these patients and how this relates to renal function. This is exacerbated by some inconsistency between studies in interpretation of the natural progression of AKI from initial insult to full renal failure.

1.2 How exploration of the determinants of RRI shaped the current research question

To gain a better understanding of the potential role of RRI in the diagnosis and management of AKI, results from experimental and clinical studies were explored in an attempt to clarify the determinants of RRI. *(The results of this review are summarised in chapter 3)*.

It became apparent from the evidence reviewed that, the key haemodynamic determinants of (RRI) are systemic rather than renal. Despite the misleading terminology, renal resistive index is **not** an indicator of renal vascular resistance and cannot be interpreted as either a measure of renal perfusion or renal function. A more accurate interpretation would be that RRI is a measure of the **pulsatility** of flow in the renal vessels and is determined primarily by central aortic pulse pressure.

In exploring the determinants of RRI, it becomes apparent that there is significant overlap between the causative mechanisms for AKI, their impact on

systemic and renal haemodynamics and the conditions in which RRI values may be raised. In essence, rise in RRI emerged as a potential indicator of the conditions in which AKI occurs, rather than as a direct result of renal injury.

This led to speculation that RRI may be a useful early indicator of sub-clinical AKI and could potentially act as an indicator of AKI risk. **No** previous studies were identified that explore this potential predictive use of RRI.

1.3 Rationale for the study

If the number of in-hospital deaths associated with AKI is to be reduced, early intervention with these patients to preserve renal function is essential. To achieve this, renal protective care needs to be administered effectively. Most improvement strategies have therefore focused on staff training to raise awareness (Hulse and Davies,2015; Think Kidneys 2018). However, as the scale of AKI as a global health challenge continues to grow, early diagnosis and prediction of AKI risk are likely to be increasingly important.

1.3.1 Rationale for the choice of patient population

As the incidence of AKI is particularly high in acute admissions, exploration of RRI in patients within the emergency department (ED) was proposed. There are well documented operational challenges in emergency care in the UK and non-elective admissions (particularly during winter pressure) are associated with a spike in AKI associated inpatient mortality (Think Kidneys 2018).

If subclinical AKI could be identified at the point of admission, this would allow early implementation of a renal protective care bundle before patient discharge to the ward or community. Stratification of patients to high / low risk groups could also inform clinical decision making in the ED, in particular around the use of nephrotoxic drugs and referral for contrast enhanced imaging.

Patients were recruited from the resuscitation room as the incidence of AKI in this group is high. There is also an increased chance that patients requiring resuscitation room care would be admitted and that follow-up biochemistry would be available.

1.3.2 Point-of-care ultrasound in emergency medicine

To be of value, any new diagnostic test needs to be feasible in the context in which it will be used. Over the past two decades, point-of-care ultrasound (POCUS) in emergency medicine has emerged as an important clinical decision making tool (Brenchley et al., 2006; Thompson, 2008; Katz and Yucel, 2011; Levin et al., 2011).

Local ED practice includes routine use of ultrasound in assessment of patients requiring resuscitation room care. This presented an opportunity to evaluate RRI measurement in the ED without significant disruption to existing care pathways or the need for purchase of additional equipment.

Focused ultrasound in trauma now forms a mandatory part of training for specialist doctors in emergency medicine and sits within the Royal College of Emergency Medicine (RCEM) core curriculum. Recognition of ultrasound renal anatomy and identification of renal vascular landmarks should fall well within the capability of most UK based ED doctors. Part of the reasoning for evaluation of RRI in this context was the existing skill set of ED doctors. If RRI was confirmed as a feasible and useful indicator of AKI in this patient group, introduction of RRI measurement into routine practice could be achievable with limited additional staff training.

Through Phase 2 review of relevant literature, **no** studies were identified that explore the use of RRI as a predictor of AKI risk, or the feasibility of RRI measurement in an ED context. The study objectives were formulated to explore these key questions.

This chapter has outlined the background from which the focused research question emerged and a brief rationale for the study. In the next chapter, the definition, aetiology, diagnosis and health impact of AKI will be discussed. Implications for management of patients presenting to the emergency department and the importance of early diagnosis will be considered.

Chapter 2 Acute kidney injury (AKI)

This chapter provides an overview of the causative mechanisms for acute kidney injury (AKI), predisposing risk factors for AKI and how these may relate to patients presenting to the emergency department (ED). The definition of AKI will be considered along with the limitations of current diagnostic criteria, the health impact of AKI and the importance of early diagnosis in patient outcome.

2.1 What causes AKI?

The aetiology of AKI is complex and includes pre-renal, intrinsic and post-renal causes. (These are summarised in Table 2.1)

In simple terms, the mechanisms for renal damage can be linked to:

- reduction in blood supply to the kidneys (either due to low fluid volume or circulatory disruption)
- concentration of substances within the kidneys that are toxic to renal tissues
- intrinsic damage to the renal parenchyma cause by autoimmune disease

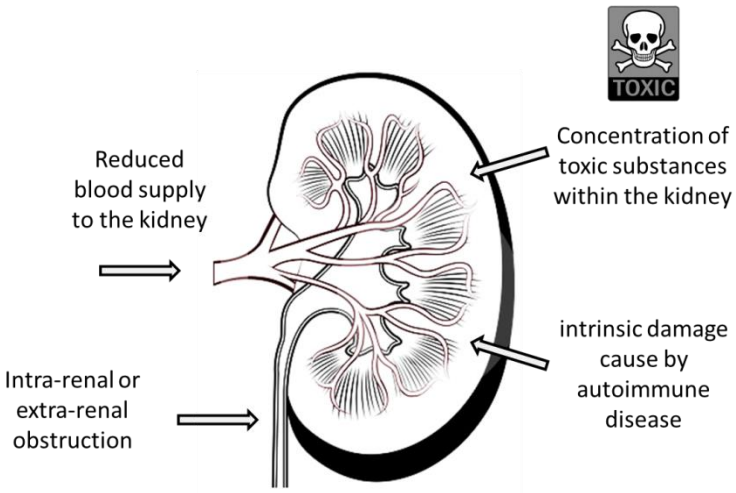


Figure 2.1 : mechanisms for renal damage

2.1.1 Pre-renal causes of AKI

Normal renal function is dependent on maintenance of normal blood supply to the kidneys. Any prolonged or significant disruption to this can result in renal damage. In sick patients, a fall in renal perfusion can occur as a result of volume depletion due to vomiting, diarrhoea, blood loss, burns or concurrent use of diuretics.

Renal perfusion may also fall as a result of systemic vasodilation (triggered by sepsis or neurogenic shock) or by intrarenal vasoconstriction. This occurs as part of the complex feedback mechanisms associated with cardio-renal syndrome, hepato-renal syndrome and abdominal compartment syndrome.

2.1.2 Intrinsic causes of AKI

Intrinsic causes of AKI occur where there is direct damage to renal tissues. This may be due to:

- exposure to medications or substances that are toxic to the kidneys
- medications that increase risk of hypovolaemia or hypotension
- inflammatory diseases of the kidneys
- systemic disease that has an impact on the kidneys

Intrinsic causes of AKI can be considered in broad categories relating to the renal component that is affected [glomerular, tubular, interstitial, vascular] (Rahman et al., 2012).

In-patient episodes of intrinsic AKI are most likely to result in **acute tubular necrosis (ATN)** due to an ischemic event or exposure to a nephrotoxic agent (Ostermann and Joannidis, 2016). Typically, these mechanisms for intrinsic AKI are associated with patients who are more severely unwell. In contrast to pre-renal causes of AKI that typically will respond well to therapy, recovery of renal function in patients with ATN can be limited due to permanent tubular damage. These patients are monitored closely throughout their hospital stay and typically have poor renal outcome.

Tubular ischemia can also be a contributory mechanism for AKI in trauma patients. Muscle injury can result in luminal obstruction caused by rhabdomyolysis. In these patients, early diagnosis of AKI is particularly important if renal function is to be preserved.

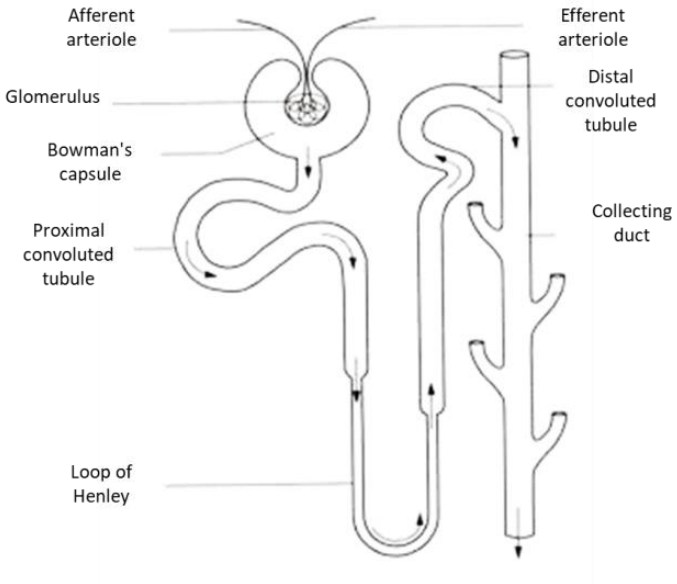


Figure 2.2 : Diagram of the renal nephron

In patients presenting to the ED, AKI can also be triggered by **glomerulonephritis** (inflammation of the glomeruli) resulting from acute infection (for example a simple throat infection) or may be present as a chronic response to long term illness, the underlying cause of which may be difficult to determine (Salifu, M. 2017, para 2).

Acute interstitial nephritis is characterised by inflammation and oedema of the renal interstitium (and renal tubules) and is more commonly associated with an adverse allergic reaction to medication (Kodner et al., 2003).

Acute interstitial nephritis is also associated with primary renal infections (bacterial and fungal) and with a range of systemic immunological and neoplastic pathologies (ibid).

Direct disruption of blood supply to the kidney can also trigger AKI. **Vascular causes** include renal vein thrombus, hypertension and infarction. Underlying atherosclerosis may result in an embolic event causing acute arterial occlusion. This could be triggered by arterial catheterisation, vascular surgery or use of anticoagulants (Dubose TD Jr, Santos RM. 2016).

2.1.3 Post-renal causes of AKI

Post-renal causes of AKI are normally less complex with scope for full renal recovery if diagnosed early.

Extra-renal obstruction mechanisms include prostatic enlargement, neurogenic bladder and pelvic mass.

Intra-renal obstruction is most typically due to the presence of renal calculi. If associated with infection, this can lead to rapid renal cell destruction.

2.1.4 Causative mechanisms for AKI in patients presenting to the Emergency Department

Patients attending the ED will fall into each of these broad categories with further complexity in the underlying trigger for intrinsic renal failure.

In the ED setting, determination of the underlying cause for AKI is always a priority as this trigger mechanism may be in itself an acute condition that requires rapid treatment (for example sepsis). However, in terms of patient recovery of renal function following an episode of AKI, current thinking suggests that the duration and severity of injury appear to be of more importance than the causative mechanism (Ninet et al., 2015). Early definitions of AKI distinguish between transient reduction in renal function (resulting from short term reduced renal perfusion) and persistent AKI that has resulted from permanent damage to renal structures (Ninet et al., 2015). However, AKI is not a ‘binary’ condition and a test +ve / -ve approach is unhelpful. As understanding of AKI has evolved, it has become apparent that AKI is a continuum (Takasu et al., 2013) of progressive renal damage that may be masked in patients with high functional reserve.

In all cases, identification of patients in the earliest possible stage of this process of renal cell destruction is most likely to result in good recovery of renal function. The Kidney Disease Improving Global Outcome Initiative (KDIGO) now classifies AKI as fluid responsive or non-fluid responsive, highlighting the importance of early detection and treatment rather than focus on differentiation of cause. This represents a shift away from focus on differential diagnosis of cause and recognises the importance of early detection and assessment of risk. This is a key driver for this study.

Table 2.1 :Summary of the causes of AKI

Pre-renal	Intrinsic	Post-renal
Drop in renal perfusion due to volume depletion: • vomiting • diarrhoea • blood loss • burns • diuretics Drop in renal perfusion due to systemic vasodilation: • Sepsis • neurogenic shock • intrarenal vasoconstriction (associated with cardio-renal syndrome, hepato-renal syndrome &abdominal compartment syndrome)	Acute tubular necrosis (ATN) due to: • ischemic event • exposure to nephrotoxic agent Tubular ischemia • Muscle injury (rhabdomyolysis) Glomerulonephritis due to: • acute infection • long term illness Acute interstitial nephritis • allergic reaction to medication • primary renal infections • systemic immunological pathology • neoplastic pathology Vascular causes • renal vein thrombus • hypertension • infarction • embolic event • (causing acute arterial occlusion - triggered by arterial catheterisation, vascular surgery or use of anticoagulants)	Extra-renal obstruction caused by: • prostatic enlargement • neurogenic bladder • pelvic mass • ureteric or urethral obstruction

2.2 Definition, diagnosis and classification of Acute Kidney Injury

One of the challenges in review of studies relating to the diagnosis and epidemiology of this condition is lack of historic consensus on definitions of AKI. In recent years, international consensus has led to refined classification of AKI presence and severity (KDIGO 2012, NICE 2013). However, current detection methods are still based on identified changes in serum creatinine level (sCr) and on reduced urine output.hours (Bagshaw et al., 2010; Chang et al., 2010; Ricci et al., 2011; Lewington 2011).

Both of these indicators are problematic in the ED where baseline sCr level may be unknown and rapid decision-making is required. In the absence of a known baseline, raised sCr is generally assumed to be attributed to possible AKI. This leads to low test specificity. However, patients may also present following recent significant renal insult but before sCr change occurs. As the symptoms of AKI are vague (or can be absent) in these patients, potentially preventable progressive renal damage may be missed.

Typically, in the ED, estimated glomerular filtration rate (eGFR) (based on sCr, patient age, sex, and race) is used to assess AKI risk on initial patient presentation. All patients admitted to the local Trust ED have a Urea and Electrolytes Test (U&E) on arrival. (Fig. 2.3) Follow up care includes check of U&E daily in those who are acutely unwell and remain at risk of AKI.

Electronic reports are issued on a Trust wide clinical management IT platform for all inpatients with a rise in creatinine consistent with AKI. An electronic care bundle is also available and is completed for every patient with suspected AKI. (Fig. 2.4)

	26Apr13 21:45	2 0
Biochemistry		
Biochemistry		
Acute Kidney Injury Comment	*Acute I...	
Sodium	* 133	
Potassium	↑ * 5.4	
Urea	↑↑ * 21.7	
Creatinine	↑ * 357	
eGFR	* 15	
Acute Kidney Injury Stage	↑↑ * 3	
Present Creatinine Result	* 357	
Baseline Used to Calculate AKI	* 158	
Date of Baseline Sample	* 260313	

Figure 2.3: Local Trust electronic report of patient biochemistry

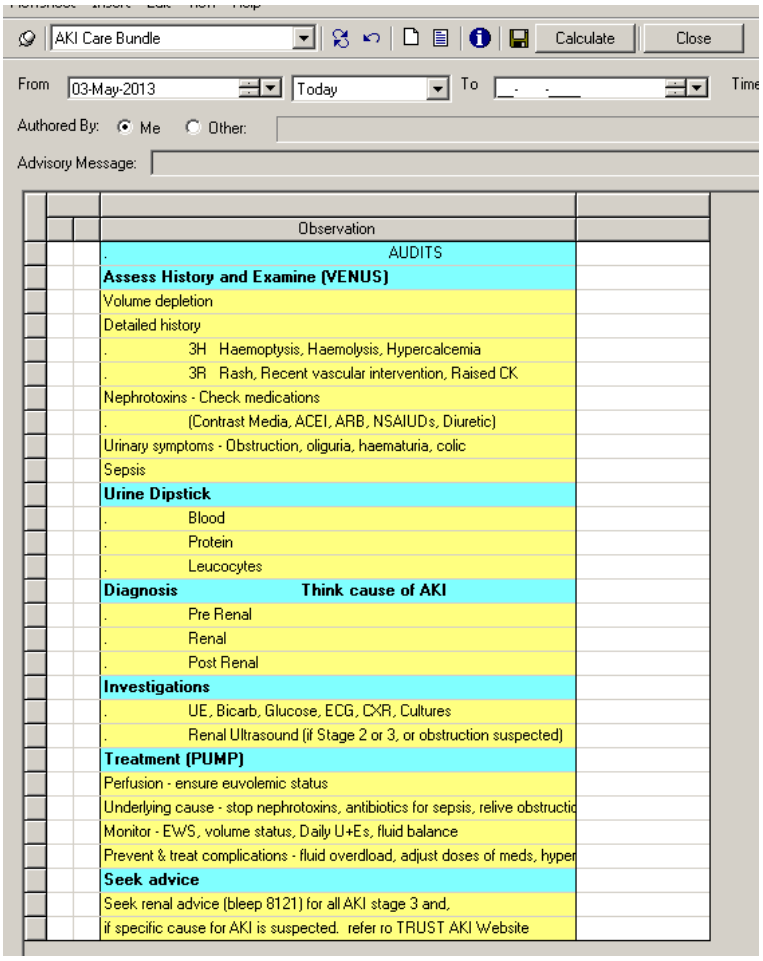


Figure 2.4: Local Trust electronic clinical management system – AKI care bundle

Staging to indicate severity of AKI is based on the current diagnostic criteria detailed in Fig. 2.5. However, there is well documented evidence that sCr is a poor marker of early renal dysfunction (Soto et al., 2010; KDIGO 2012). eGFR may remain within the normal cut off range of > 60 even where up to 50% of nephrons are lost (Sharma et al., 2014). This limits the value of eGFR as a measure of renal functional reserve. eGFR also lacks the specificity to distinguish between AKI, chronic renal failure and prerenal azotemia (volume depletion) that may be reversed through early fluid administration (Di Somma et al., 2010).

Whilst consensus on AKI definition and staging is helpful, review of current literature confirms that the status of sCr based evaluation of patient risk has been largely unchanged for several decades. Current protocols remain susceptible to delayed diagnosis and missed decline in renal function (Bagshaw et al., 2013). This is a key driver in the search for alternative approaches to early diagnosis, prognosis and decision-making

- The AKI staging system is based on change in serum creatinine and urine output. If these lead to different AKI stages, use the highest.
- iCM will issue reports on all patients who sustain AKI (see below). These reports only take account of changes in creatinine and it is up to you to consider changes in urine output.

Stage	Serum creatinine	Urine output
1	Increase in serum creatinine of >26μmol/L from baseline within a 48hr period **or** Increase of 1.5 to 1.9 times baseline	< 0.5 mL/kg/hour for > 6 hours
2	Increase in serum creatinine of 2 to 2.9 times baseline	< 0.5 mL/kg/hour for > 12 hours
3	Increase in serum creatinine to 3 times baseline **or** Increase in serum creatinine to >354μmol/L **or** Initiation of renal replacement therapy	< 0.3 mL/kg/hour for > 24 hours **or** no urine output > 12 hours

- Baseline creatinine is taken as the most recent stable creatinine value, extending back to twelve months if necessary. When no previous creatinine measurements are available, an estimated baseline creatinine can be back-calculated using an eGFR of 75ml/min (this will be performed automatically in iCM). In these circumstances, a clinical decision has to be made as to whether a raised creatinine indicates AKI or whether the patient has CKD. Repeating the creatinine to look for subsequent acute change and taking account of the clinical picture may help.

Figure 2.5: Local Trust criteria for recognising and staging AKI (2017)

2.3 Health impact of AKI

AKI is recognised internationally as a major public health concern (Silver et al., 2017). The incidence of AKI continues to increase and is expected to more than double over the next decade (Bedford et al., 2014; Arias-Cabrales et al., 2017: Darmon et al., 2017; Medcalf et al., 2016). Although rarely the solitary cause of death, AKI is associated with significant mortality and has been associated with in excess of 40,000 avoidable deaths per annum in the UK alone (Kerr et al., 2014). The financial burden of AKI on the UK National Health Service has been estimated at £1.02 billion (just over 1% of the total NHS budget.) In-hospital costs are associated with increased length of hospital stay, use of critical care services and increased use of complex interventions (Challiner et al., 2014).

AKI is seen in 5-15% of all hospital admissions and is particularly common in the elderly. One in five patients with AKI will die during their hospital admission and mortality rates rise to above 30% in those with more severe AKI (stages 2 and 3).

Incidence of AKI in patients presenting to the Emergency Department (ED) is unknown. In unselected UK emergency admissions it has been estimated at 25% (Challiner et al., 2014) with approximately one third of cases confirmed on initial presentation. In patients where a baseline for renal function tests was available at the time of admission, the incidence of AKI in these patients was 38%. In this study by Challiner et al (2014), as in previous studies (Zhou et al., 2006; Akcay, 2010; Bagshaw et al., 2011; Darmon et al., 2011), AKI was associated with increased hospital stay (more than double), admission to critical care and increased mortality (odds ratio for death : stage 1 AKI - 2.0, stage 3 AKI –10.1).

A limitation of all studies exploring the incidence of AKI in acute admissions is the absence of a credible baseline creatinine level. Ideally this should be the lowest SCr recorded > 90 days prior to an acute admission (Bedford et al., 2014). Where pre-morbid renal function is unknown, it is not possible to distinguish between acute and pre-existing chronic renal disease.

In practice, pre-hospital measurement of SCr may not be available. In a retrospective review of 66,829 admissions to a UK based district general hospital, baseline SCr was available in 87% of patients (Challiner et al., 2014). However, the authors note that this percentage is likely to be significantly lower in most contexts as the Trust at which the study was performed has implemented routine increased frequency of testing due to heightened awareness of AKI risk.

The extent to which true incidence of AKI in unplanned admissions is over or under estimated is unknown. However, it is estimated that, in up to two thirds of UK emergency patients, AKI will remain undetected until after admission (Challiner et al 2014). This is largely due to the limitations of creatinine based tests. For these patients, potentially avoidable delay in preventive treatment will have implications for both cost and outcome.

There is also some indication that the number of patients discharged with undiagnosed AKI may be increasing. The extent to which this may be due to changes in the classification and reporting of AKI is difficult to determine. However, following the NCEPOD report (2009), review of patients dying post discharge suggests that failure in AKI may be a contributory factor in around 50% of cases (Meran et al., 2014).

In an aging population, use of recognised nephrotoxic agents that act as triggers for AKI (non-steroidal anti-inflammatory and anti-hypertensive drugs etc.) is increasing (Akcay et al., 2010). The financial burden associated with short and long term treatment of AKI will rise accordingly. When extended hospital stays and long term community based care for these patients are considered, the overall costs are eye-wateringly high. Even a modest reduction in the number of patients with a delayed diagnosis could provide non trivial financial savings. The flurry of research activity around this goal is therefore no surprise despite a general lack of public awareness of the condition.

2.4 Risk factors for AKI

AKI does not occur in isolation. It has been considered a marker of ill health, the risk of which increases as patient wellbeing deteriorates (Darmon et al., 2017). Patients requiring resuscitation room care are invariably unwell. However, there are multiple factors that may be unrelated to the patients presenting condition that increase individual risk of AKI.

In patients who are pre-morbidly well (e.g. trauma patients) risk of AKI may be directly related to their immediate illness. (e.g. crush injury, bleeding, burns etc.) However, the majority of patients attending the ED will have some relevant risk factors that pre-date their current admission. It has been estimated that approximately 65% of acute kidney injury starts in the community (Selby et al., 2012).

Multiple risk factors that predispose patients to an episode of AKI are well documented and high risk groups can be identified (Bagshaw et al., 2005; Challiner et al., 2014). These are summarised below.

Table 2.2 :Summary of risk factors for AKI

Age ≥65 years	Hypovolaemia	Current or recent medication with nephrotoxic potential - eg, NSAIDs, ACE inhibitors, AIIRAs, aminoglycosides, diuretics
Chronic kidney disease - eGFR <60	Liver disease	Use of iodinated contrast agents within the previous week
Past history of AKI	Diabetes	Neurological impairment or disability that may impact on self-care and hydration
Cardiac failure	Sepsis	Deteriorating early warning scores (NEWS)
Peri-operative patients	Hypertension	Cerebrovascular disease
Dementia	Malignancies	Chronic lung disease
Alcohol abuse	Stroke	Connective tissue disease

(Bagshaw et al., 2005; Challiner et al., 2014)

Undoubtedly, the primary risk factor for AKI is age and is associated closely with the long term conditions that are more common in the elderly. Poor outcome is noted in the frail or elderly in particular as they are more likely to lack the functional reserve to cope with further renal damage. The impact of multiple co-morbidities (such as heart failure, diabetes and chronic renal

disease) may be exacerbated by dehydration due to poor self-care. In these patients, there may be no single cause for AKI but rather a pattern of multiple risk factors including long term exposure to nephrotoxic drugs, vascular disease, poor cardiac output, chronic renal disease and a short term trigger such as fluid depletion.

In response to the National Confidential Enquiry into Patient Outcome and Death report (2009), the “Think Kidneys Acute Kidney Injury (AKI) Programme” was established in 2013 by the UK National Patient Safety team (now part of NHS Improvement). The central aim of this initiative was to improve the management of AKI. Building on NICE guidance (2013) one of the work streams within this programme focused on identification of patient risk factors. Better understanding of the relationship between underlying contributory factors and the trigger mechanisms that result in an episode of AKI may improve risk prediction. By combining detailed patient data with real time hospital wide electronic reporting systems, this will inform both preventive strategies and individual patient management decisions. These initiatives remain a strong focus for further research and enquiry. However, the Think Kidneys Report (2017) concludes that, to date there are no reliable, validated AKI risk scores for patients presenting in primary or secondary care. Therefore, for patients presenting to the ED, we remain reliant on sCr based tests.

This chapter has outlined the triggers for AKI, why this is a major public health concern and the importance of early diagnosis in improving outcomes.

In the next chapter, renal resistive index (RRI) will be considered as a semi-quantitative indicator of renal blood flow characteristics. Results from theoretical models and experimental data will be considered in an attempt to understand the relative importance or renal and systemic haemodynamic factors as determinants of RRI and how these may relate to renal pathology.

Chapter 3 Doppler Renal Resistive Index

This chapter provides an overview of the key haemodynamic determinants of renal resistive index (RRI) and aims to clarify their relative importance. With reference to a simplified theoretical model, evidence from experimental and clinical studies will be considered and early interpretation of RRI will be challenged. By exploring the impact of systemic and renal factors, we gain a better understanding of the potential value of RRI as a predictor of renal damage.

Doppler ultrasound has been used extensively for many decades in the assessment of vascular disease, haemodynamics and organ perfusion.

The *Doppler Effect* was first described in 1842 by the Austrian mathematician Christian Doppler in his landmark paper "*On the coloured light of the double stars and certain other stars of the heavens"*. Whilst this paper described frequency shift in light from stars, similar effects are observed when sound waves are emitted from or reflected by moving structures. This is perhaps most widely recognised in the shifting frequency of an emergency siren as the vehicle travels towards or away from the observer.

Medical ultrasound systems utilise the shift in frequency that occurs when sound is reflected from a moving target (red blood cells) to determine the direction and velocity of blood flow in target vessels. By comparing the frequency profile of a reflected wave with the frequency spectrum of the transmitted pulse, flow within the vessel can be quantified and a range of flow parameters calculated.

3.1 Doppler assessment of blood flow

3.1.1 Colour Doppler

The Doppler signal can be displayed as either a colour-coded overlay superimposed on the brightness mode image (Figure 3.1a), or as a graphical representation of velocity profile over time (Figure 3.1 b) (Venables, 2011). Colour coded Doppler techniques allow identification of target vessels from which a spectral trace can be captured by placing a sample gate within the position of the vessel lumen.

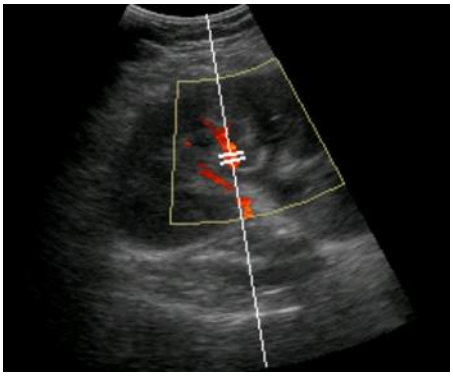


Figure 3.1a *LS section of upper pole of the kidney: Colour Doppler box is placed over the renal hilum. The Doppler sample gate is located over the lumen of an interlobar artery from which a spectral trace can be captured.*

3.1.2 Spectral Doppler

Through repeated sampling along a single line of sight, a spectral trace is generated that corresponds to the changing profile of blood flow though the vessel throughout the cardiac cycle. This is achieved by transmission of multiple pulses along the selected line within the image frame. Analysis of the return signal allows extraction of Doppler shift values corresponding to movement of reflecting targets (red blood cells) within the sample gate. These signals are then displayed along a time base as brightness values (determined by signal amplitude) at each velocity. The resultant spectral trace corresponds to the flow profile across the vessel throughout the cardiac cycle. Typically this will be parabolic with slow moving blood close to the vessel walls due to frictional drag.

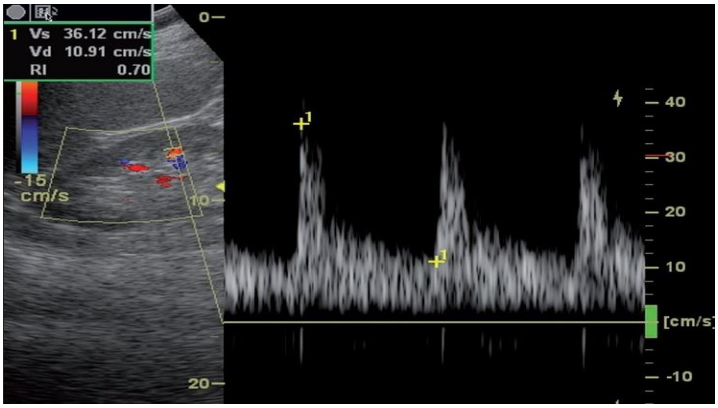


Figure 3.1 b *Colour Doppler is use to identify the interlobar vessels from which a spectral trace is captured. Peak systolic and end diastolic measurements are recorded by placing the measurement calliper at the relevant position within the cardiac cycle.*

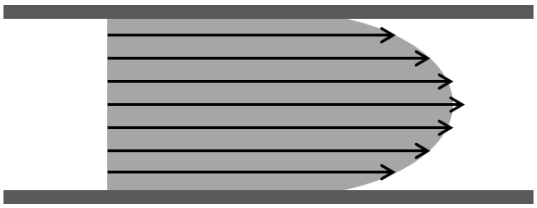


Figure 3.1c *Flow profile across vessel: parabolic profile due to frictional drag at vessel walls*

3.1.3 Quantitative assessment of blood flow

From the spectral trace, a range of parameters can be calculated to quantify flow characteristics, including peak systolic (PSV) and end diastolic (EDV) velocities.

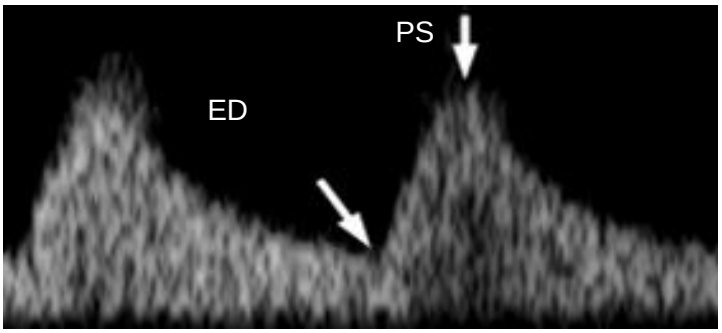


Figure 3.1d *Peak systolic velocity (PSV) and end diastolic velocity (EDV) measurements can be captured from the spectral trace*

3.2 Definition of resistive index

Doppler Resistive Index (RI) was first proposed in the mid-1970s by French medical doctor / electrical engineer Léandre Pourcelot.

RI is an expression of the percentage reduction in end diastolic flow in relation to maximum flow at peak systole.

$$RI = \frac{PSV - EDV}{PSV}$$

PSV = peak systolic velocity
EDV = end diastolic velocity

3.3 Renal resistive index (RRI)

Renal resistive index (RRI) has been used for several decades as a potential indicator for renal disease and progression (Darmon et al., 2011; Barbani et al., 2010; Scnell et al., 2012; Viazzi et al., 2013; Guinno et al., 2013). Emerging initially as a measure of renal function in patients with renal artery stenosis (Radermacher et al., 2001) RRI was assumed to be directly associated with altered resistance to flow within the kidney and associated with a range of renal pathological structural changes. Despite this, subsequent experimental and in vivo studies have demonstrated that RRI is more closely associated with systemic factors (Boddi et al., 2015; Cauwenberghs and Kuznetsova, 2016).

Ironically, repeated clinical studies have demonstrated that RRI appears to have very little dependence on renal vascular resistance (Hashimoto and Ito, 2011; Naesens et al., 2013; Chirinos et al,. 2014; O'Neill 2014; Kuznetsova et al., 2015; Lee et al., 2015). For this reason, use of RRI as a useful (direct) indicator for renal disease has been challenged. However, RRI has been shown to be affected by a number of extra-renal factors that explain the observed value of RRI as a strong prognostic indicator for patients with renal damage and a potential predictor of AKI risk. (See chapters 1 & 4)

3.4 What are the theoretical determinants of RRI?

Despite the term '***resistive index'***, this dimensionless ratio is more accurately an indicator of flow pulsatility. Simplified analysis (O'Neil, 2014) demonstrates that this model of RI is largely independent of vascular resistance.

$$RI = \frac{PSV - EDV}{PSV} \qquad RI = 1 - \frac{EDV}{PSV}$$

$$\text{Velocity (V)} = \frac{\text{Flow}}{\text{Lumen area (LA)}}$$

$$\text{Flow} = \frac{\text{difference in blood pressure } (\Delta P)}{\text{Vascular resistance (R)}}$$

Therefore: $V = \frac{\Delta P}{R \times LA}$

As

$$RI = 1 - \frac{EDV}{PSV}$$

$$RI = 1 - \frac{\left[\frac{\Delta P}{R \times LA}\right]_{Diast}}{\left[\frac{\Delta P}{R \times LA}\right]_{Syst}}$$

Although luminal cross sectional area and pressure within the vessel will change during systole and diastole, renal vascular resistance is unlikely to alter during the time frame of a single cardiac cycle (O'Neil, 2014, Chirinos et al., 2014).

Therefore, if R remains constant between systole and diastole, then

$$RI = 1 - \frac{\left[\frac{\Delta P}{LA}\right]_{Diast}}{\left[\frac{\Delta P}{LA}\right]_{Syst}}$$

Whilst this simplified model explains in part the relative independence of RRI from vascular resistance, this does not take into account the complexity associated with distal vascular compliance (capacitance) or non-uniform flow throughout the cardiac cycle. Once impedance of the distal vascular bed is considered, RI does demonstrate some dependence on resistance. (O'Neil, 2014)

3.5 What are the key haemodynamic determinants RRI?

Whilst, experimental and in vivo studies demonstrate an inconsistent relationship between RRI and vascular resistance, three haemodynamic parameters emerge that appear to have a direct impact on RRI.

- Ratio of diastolic to systolic blood pressure
- Combined effect of interstitial and venous pressure
- Ratio of lumen area in systole and diastole at the sample site

O'Neil (2014) clarifies the mathematical relationship between these factors and the simplified flow equation below.

$$RI = 1 - \frac{\left[\frac{\Delta P}{LA}\right]_{Diast}}{\left[\frac{\Delta P}{LA}\right]_{Syst}}$$

$$RI = 1 - \left[\frac{\Delta P_{Diast}}{\Delta P_{Syst}}\right] \times \left[\frac{LA_{Syst}}{LA_{Diast}}\right]$$

OR

$$RI = 1 - \left[\frac{P_{Diast} - P_0}{P_{Syst} - P_0}\right] \times \left[\frac{LA_{Syst}}{LA_{Diast}}\right]$$

P_0 Combination of interstitial and venous pressure

3.5.1 Ratio of diastolic to systolic blood pressure (P_{diast} and P_{syst})

The ratio of P_{diast} and P_{syst} is an inverse function of pulse pressure and is affected primarily by cardiac output and systemic arterial compliance (vessel stiffness).

$$RI = 1 - \left[\frac{P_{Diast} - P_0}{P_{Syst} - P_0}\right] \times \left[\frac{LA_{Syst}}{LA_{Diast}}\right]$$

Experimental data confirm a strong correlation between RI and aortic pulse pressure (Hashimoto and Ito, 2011; Chirinos et al., 2014; O'Neil, 2014).

There is also strong support from a number of clinical studies where pulse pressure appears to be the main determinant of RRI (Naesens et al., 2013; Lee et al., 2015)

Pulse pressure is affected by:

- Cardiac output
- Fluid volume
- Systemic arterial compliance (vascular stiffness)
- Heart rate
- Blood pressure
- Renal artery disease
- Distal vascular disease

These factors are explored further in this chapter.

3.5.2 Combined effect of interstitial and venous pressure P_o

(Essentially this is the renal capillary wedge pressure)

$$RI = 1 - \left[\frac{P_{Diast} - P_0}{P_{Syst} - P_0} \right] \times \left[\frac{LA_{Syst}}{LA_{Diast}} \right]$$

Anything that changes interstitial or venous pressure will affect RI.

The kidney is encapsulated by a thin fibrous sheath that provides a degree of stability and protection for the organ. In the presence of hydronephrosis, acute

inflammation, oedema or haematoma, the kidney volume increases. However, this expansion of the kidney is limited, with the renal capsule providing the major opposing force (Hebert et al., 1975). Intrarenal pressure therefore increases under these conditions.

Similarly, venous pressure may change due to renal vein thrombosis, hypovolaemia or vasoplegia (due to sepsis or post-surgery).

3.5.3 Ratio of lumen area in systole and diastole at the sample site

$$RI = 1 - \left[\frac{P_{Diast} - P_0}{P_{Syst} - P_0} \right] \times \left[\frac{LA_{Syst}}{LA_{Diast}} \right]$$

Vessel lumen cross sectional area (LA) changes throughout the cardiac cycle.

The relative cross sectional area at systole and diastole is a theoretical determinant of RRI and is affected by

- vascular wall stiffness
- vessel compliance
- Interstitial pressure (increased recoil during diastole if iP raised)

3.6 Determinants of RRI: Evidence from clinical and experimental studies

Numerous clinical and experimental studies demonstrate the complexity of associations between RRI and systemic haemodynamic factors.

Early investigations (primarily of patients presenting with renal artery stenosis) focused on renal recovery, identifying poor outcome in patients with raised RRI (Radermacher et al., 2001; Chirinos et al., 2014). Subsequent studies in critical care have generated a wealth of evidence supporting the close association of RRI with a number of outcome measures including renal recovery, need for long term renal replacement therapy and death (Ninet et al., 2015; Boddi et al., 2016).

Despite the promising role of raised RRI in patient prognosis and predication of renal recovery, a growing body of research confirms that **systemic factors** are the key determinants of RRI and that RRI cannot be considered a useful **direct** indicator of renal disease. Interpretation of these somewhat contradictory findings requires a better understanding of the complex association between non-renal haemodynamic factors, individual patient characteristics, how these affect renal blood flow and their potential influence on risk of renal damage. The impact and relative contribution of these factors as determinants of RRI are explored in the following sections.

3.6.1 Systemic factors - How is RRI affected by blood pressure?

The observed relationship between RRI and the components of blood pressure (steady and pulsatile) are consistent with our theoretical understanding of RRI and also offer some insight into how these systemic factors may result in renal injury.

3.6.1.1 Influence of mean arterial pressure on RRI

General population studies (Kusnetzova et al., 2014;) and studies of hypertensive patients (Calabia et al., 2014; Chirinos and Townsend 2014) demonstrate a consistent **inverse** relationship between RRI and **mean arterial pressure** (MAP) that appears to be independent of other co-variables (Cauwenburghs et al., 2016). Whilst this is not a direct indicator of renal function, reduced MAP over time would be consistent with a pattern of poor renal perfusion.

$$RI = 1 - \frac{\left[\frac{\Delta P}{LA}\right]_{Diast}}{\left[\frac{\Delta P}{LA}\right]_{Syst}}$$

↓ MAP ⟶ ↓ diastolic pressure ⟶ ↓ EDV ⟶ ↑ RRI

However, this relationship does not appear to hold in critically ill patients with sepsis where poor correlation between RRI and MAP is noted (Dewitt et al., 2012; Lahmer et al., 2016). This suggests that, in these patients, other factors affecting renal circulation may have a more dominant role in RRI. (Whilst this effect is poorly understood, this does limit the use of RRI in management of fluid balance in these patients.)

3.6.1.2 Influence of pulse pressure on RRI

A key determinant of **pulse pressure** is compliance of the large arteries. In a normal patient, as blood is ejected from the heart, expansion of the aorta effectively dampens the pulse. This effect contributes to maintenance of continuous steady flow to the kidneys. Where compliance of the aorta is reduced due to vessel wall stiffening, this damping effect is absent and the renal microvasculature is exposed to high pulse pressure. In a review of studies exploring the association between aortic stiffening and microvascular

disease, O'Rourke et al (2005) propose that these high pressure fluctuations (increasing markedly with age of the patient) may result in epithelial damage leading to renal insufficiency.

These findings have led to a plethora of studies that explore the relationship between RRI and central pulse pressure (cPP) or peripheral pulse pressure (pPP) (Tedesco et al., 2007; Hashimoto and Ito, 2011; Stea et al., 2013; Ponte et al., 2014; Kusnetzova et al., 2015). In all cases, a consistent and significant positive association is noted. (These are summarised in Table 3.8)

↑ $_c$PP → ↑ systolic pressure → ↑ PSV → ↑ RRI

(cPP = Central pulse pressure)

One of the key challenges of studies exploring this association is the difficulty of separating the contributory effects of renal and non-renal factors. This is further complicated by the fact that a high proportion of recent studies have been undertaken in critical care, where patients have multiple confounding co-morbidities and high incidence of chronic renal disease.

This has been resolved (at least in part) by studies of transplant kidneys where RRI is also noted to be strongly dependent on aortic pulse pressure of the **recipient** rather than the donor (Tublin et al., 1999; Akgul et al.,2009; Hashimoto and Ito, 2011; Naesens et al., 2013; et al., 2013).

In a landmark study in 2013, Naesens et al compared baseline RRI and RRI at the time of biopsy in 321 transplant recipients. Unlike studies of native kidneys, in transplant patients, the relative contribution of renal and systemic factors on RRI can be explored. This allowed close scrutiny of the relationship between RRI measurements and renal histology.

In this study, the strongest independent factor for increased RRI was recipient age ($P<0.001$). However, there was also close association with increased pulse pressure and reduced MAP. The authors conclude that serial

measurements of RRI at the time of biopsy reflect characteristics of the recipient rather than the graft. This important study supports the conclusion that RRI is of limited use as a **direct** indicator of renal function. However, in the same study population, RRI was closely associated with recipient survival. This supports the usefulness of RRI for prognostic stratification in sick patients.

3.6.2 Relationship between RRI and Cardiac output

Normal renal function is dependent on a constant blood supply which is, in turn, dependent on cardiac output. Renal autoregulation is essential in maintaining stable glomerular filtration rate (GFR). The heart and kidneys also play a closely associated role in maintaining haemodynamic stability and severe dysfunction in either of these organs is unlikely to occur in isolation (Bock et al., 2010).

The amount of blood available to the kidney (roughly 20% of total cardiac output) is dependent on total blood volume and on left ventricular output. Kuznetsova et al (2015) explored the relationship between RRI and left ventricular outflow in a general population study (n = 171). Doppler assessment of left ventricular outflow tract (LVOT) and transmitral peak velocities demonstrated significant association of RRI with central pulse pressure and left ventricular systolic and diastolic Doppler blood flow indexes. (RRI was significantly and positively associated with LVOT and E peak velocities ($P \leq 0.012$) and VTIs ($P \leq 0.010$).)

Although the precise causal relationship is unclear (acknowledged by the authors), this study demonstrates that, in an unselected population, the Doppler spectral profile within the intrarenal arteries is influenced by cardiac hemodynamic factors. However, in the same study, the correlation between RRI and cardiac factors was not as strong as that observed with central pulse pressure ($P < 0.0001$).

The findings of this study (of well patients) are difficult to translate to a sick or elderly in-hospital population where cardiac output is likely to be

compromised. No studies are identified that explore simultaneous longitudinal changes in cardiac and renal haemodynamics. However, altered cardiac output in a critically unwell or ED population is likely to be of more significance than this study suggests. This could be particularly relevant in older patients presenting with reduced left heart function in combination with hypovolaemia or vasoplegia associated with fluid loss or sepsis.

3.7 Renal causes of altered RRI

The experimental and clinical studies reviewed provide compelling evidence that changes in RRI are determined predominantly by systemic haemodynamics rather than isolated renal pathology. However, there are instances where a direct causal link with renal factors has been demonstrated.

3.7.1 Interstitial pressure and vascular compliance

RRI clearly reflects renal artery pulsatility (Cauwenberghs et al., 2016; Kuznetsova et al., 2015) and as such may be a useful indicator of early stage renal microvascular damage. From the mathematical model outlined by O'Neil (2014), raised interstitial pressure (iP) will also affect RRI. The impact of moderately increased iP may be masked by autoregulation. However, where iP is more markedly increased, luminal cross sectional area and end diastolic velocity (EDV) are likely to be affected. These predicted findings are confirmed by experimental study of ex-vivo hydronephrotic kidneys (Murphy and Tublin 2000).

Although RRI appears to be largely independent of vascular resistance (the ratio of pressure to flow) (Bude et al., 1999; Tublin et al., 1999; Chirinos et al., 2014) experimental evidence supports the hypothesis that changes in **compliance** of the renal vascular bed and interstitium are contributory factors in the raised RRI values observed where renal disease is present. Direct evaluation of the stiffness and elasticity of intrarenal arteries is problematic. However, in an elegant study of isolated perfused rabbit kidneys, Murphy et al

(2000) explored this effect indirectly by inducing raised interstitial pressure via incremental increase in ureteral pressure.

As a surrogate measure of overall distensibility of the vascular bed, vascular conductance (ratio of flow to pressure) was measured (along with mean flow, mean pressure and RRI) under different driving arterial pressures. They hypothesized that the raised iP caused by obstruction of the kidney would restrict distension of the intrarenal arteries and arterioles.

In this landmark study, increase in ureteral pressure was associated with:

- consistent and reproducible increase in RRI
- increase in RVR (overall mean renal vascular resistance)
- significant reduction in flow
- significant reduction in mean conductance

($P < 0.05$ for all values)

Of particular note was the relative reduction of conductance measured at systole and diastole. A greater proportional reduction (and hence flow) was observed during diastole.

The kidney is inherently a low resistance structure, evidenced by the positive flow throughout diastole seen in a normal spectral waveform.

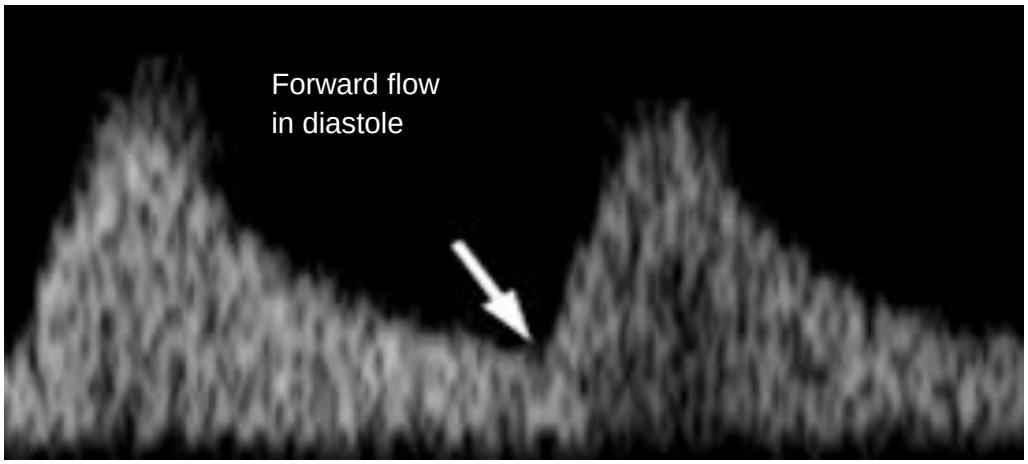


Figure 3.7: *Renal inter-lobar artery spectrum. Positive flow throughout the cardiac cycle with high end diastolic flow evidences low vascular bed resistance.*

In a normal kidney, iP is approximately zero. Arterioles have high cross sectional area and these small compliant vessels are free to expand during systole.

The distensibility of a vessel is dependent on wall stiffness, the pressure exerted through the wall (transmural pressure) and the compliance of the surrounding interstitium. In this study, Murphy et al (2000) hypothesised that, when iP is raised, arterioles will dilate to approximately full extension during systole, but will collapse down to close to occlusion during diastole. End diastolic flow is therefore reduced.

As RRI is a ratio of peak systolic to end diastolic flow (PSV – EDV / PSV) this would account for the observed increase in RRI.

The relative contribution of renal vascular resistance and compliance in raising RRI is difficult to determine from this study. However, previous experimental work by the same authors confirmed that even marked increase in vascular resistance (through pharmacologically induced vasoconstriction) resulted in only minimal increase in RRI (Tublin et al., 1999; Murphy et al., 2000). They conclude that the impact of raised iP on conductance (particularly at diastole) seems to be the reason why RRI rises with increased ureteral pressure.

Results from these important studies suggest that, in addition to pulse pressure, raised interstitial pressure has an important role in increasing RRI. This raises the possibility that RRI could be a direct indicator of renal pathologies that increase interstitial pressure or reduce vessel distensibility.

3.8 Patient characteristics affecting RRI

In addition to the haemodynamic factors considered in this chapter, a number of patient anthropometric characteristics have also been linked with RRI.

General population studies (Ponte et al., 2014; Kuznetsova et al., 2015) show a strong positive correlation between RRI and subject age, female gender and body weight and a negative correlation with height.

In addition to these independent patient characteristics, in large studies of hypertensive patients (Tedesco et al., 2007; Hashimoto and Ito, 2011; Stea et al., 2013) multi-variate analysis demonstrates a positive correlation between RRI, hypercholesterolemia and use of renin-angiotensin system (RAS) inhibitors.

In general, patient age is identified in all studies as the strongest independent determinant of RRI.

First author (year)	Study population	↑ RRI cut off	Independent correlation with patient characteristics
Ponte et al 2014	General population (n=726	0.64 ± 0.05 (female) 0.62 + 0.05 (male)	↑ age, female, BMI
Kuznetsova 2015	General population (n=171)	0.61 + 0.06 (female) 0.59 + 0.06 (male)	↑ age, female, weight ↓ height
Stea 2013	Hypertensive (n=216)	0.63 + 0.07	↑ age, BMI
Tedesco 2007	Hypertensive	0.69 ± 0.05	↑ age
Hashimoto 2011	Hypertensive (n=133)	0.65 + 0.07	↑ age ↓ height
Lin 2003	Healthy subjects (n=135)	0.59 + 0.04	↑ age
Trovato 2010	Hypertensive (n=124) Non-hypertensive (n=97)	0.65 + 0.05	↑ age, body mass, insulin resistance ↓high coffee consumption

(Adapted from Cauwenberghs p.174; 2016)

Table: 3.8 Independent population and patient determinants of RRI

3.9 Factors affecting AKI risk reflected by raised RRI

Review of the studies referenced in this chapter identifies significant historic confusion regarding the determinants of RRI, which was long regarded as a direct reflection of renal vascular resistance (Boddi et al., 2015; Wybraniec et al., 2016). This view of RRI, based on early experimental data from animal studies, led to speculation that RRI could provide a useful non-invasive measure of renal perfusion and intrarenal pathology. However, as a better understanding of the influence of systemic haemodynamic factors has emerged, it is perhaps more useful to think of raised RRI as a *'red flag'* marker for the conditions in which AKI risk is increased.

The aetiology of AKI is highly complicated with multiple contributory factors and complex associations between pathological conditions, acute events and renal auto regulatory response. Individual risk of the rapid functional decline associated with AKI is dependent on pre-existing chronic renal damage and the severity of acute insult.

In broad terms, the picture emerging from review of current literature is that there is significant overlap between the determinants of RRI and age related risk factors (such as arterial stiffening) that result in gradual functional decline. This pattern is consistent with evidence from critical care that indicates that raised RRI performs better than other independent patient characteristics at predicting outcome of an episode of AKI.

Although the key determinants of RRI discussed in this chapter are systemic, there is compelling evidence that RRI can also be influenced directly by raised interstitial and venous pressure. This suggests that, as well as acting as a marker for chronic reduced functional reserve, raised RRI may also have potential as a marker for sub-clinical AKI in patients who are acutely unwell.

The association between systemic and renal determinants of RRI and raised risk of AKI are summarised in tables 3.9a and 3.9b.

Table 3.9a *Systemic determinants of RRI associated with renal functional decline*

Patient factor	Key haemodynamic determinant	Impact on intrarenal blood flow	Impact on RRI	Significance of factor as determinant of RRI	Potential link to immediate (or future) AKI risk
Hypertension	↑ systolic pressure	↑ PSV	↑ RRI	major	Microvascular trauma over time → ↓ functional reserve
Increased central pulse pressure	↑ systolic pressure	↑ PSV	↑ RRI	major	Microvascular trauma over time → ↓ functional reserve
Increased systemic arterial stiffness	↓ aortic compliance	↑ PSV	↑ RRI	major	Microvascular trauma over time → ↓ functional reserve
Left heart failure → decreased flow LVOT	↓ diastolic pressure	↓ EDV	↑ RRI	minor	Long term hypo-perfusion → ischemic damage → ↓ functional reserve
Reduced mean arterial pressure (MAP)	Poor renal perfusion over time	↓ EDV	↑ RRI	minor	Long term hypo-perfusion → ischemic damage → ↓ functional reserve
Bradycardia	Increased diastolic duration	↓ EDV	↑ RRI	minor	Long term hypo-perfusion → ischemic damage → ↓ functional reserve

End diastolic velocity (EDV) Peak systolic velocity (PSV)

Table 3.9b *Acute determinants of RRI associated with rapid renal functional decline*

Patient factor	Key haemodynamic determinant	Impact on intrarenal blood flow	Impact on RRI	Potential link to immediate (or future) AKI risk
Hydronephrosis Acute inflammation Oedema Haematoma	↑ interstitial pressure	↓ EDV ↑ ratio of luminal CSA	↑ RRI	Impact may be masked by auto-regulation.
Renal vein thrombosis Hypovolaemia Vasoplegia (sepsis or post-surgery).	↑ venous pressure	↓ EDV	↑ RRI	Tubular ischemia due to hypo-perfusion
Trauma Rhabdomyolysis ± hypovolaemia	*renal vaso-constriction ↓ renal blood flow	↓ EDV	↑ RRI	Tubular ischemia due to hypo-perfusion

End diastolic velocity (EDV) Cross sectional area (CSA)

In this chapter, the key haemodynamic determinants of (RRI) and their relative importance have been explored. This provides a better understanding of why the factors affecting AKI risk may be reflected by raised RRI.

In the following chapter, the literature search strategy used to explore the evidence base for use of RRI as a predictor of AKI will be outlined. Relevant studies will be reviewed to determine if there is evidence to support the use of RRI in identification of patient risk of AKI in an ED context.

Chapter 4 Review of current literature

This chapter explores relevant literature to determine if there is evidence to support the use of renal resistive index (RRI) in the identification of patients at risk of renal injury at the point of admission to the Emergency Department (ED).

4.1 Development of the search strategy

This search strategy builds on previous phases of the study (PD Health Unit 5 and Unit 8) and seeks to identify papers relevant to the research question that have been published in the intervening period (2016-2018).

The primary aim of this review was to determine if there is evidence to support the use of renal resistive index (RRI) in the identification of patients at risk of renal injury at the point of admission to the Emergency Department (ED).

The research question was framed initially in three parts in line with Royal College of Emergency Medicine (RCEM) guidance for review of best evidence (RCEM 2018).

- Patient Characteristic
- Intervention(s) or Defining Question
- Relevant Outcome(s)

This approach is used extensively in Best Evidence Topic (BET) reports (http://bestbets.org/background/bets-and-cats.php) and builds on established review strategies such as the Population, Intervention, Comparator and Outcomes (PICO) model (Richardson et al., 1995; Sayers et al., 2007).

4.1.1 General question

Can RRI predict AKI in patients presenting to resus?

4.1.2 Derived three part question

In patients admitted to the resuscitation room, is RRI superior to existing sCr based tests at predicting AKI risk?

Specific objectives of the search were to identify studies that:

- establish the current evidence base for the role of RRI in the diagnosis of AKI.
- relate directly to the diagnosis and management of AKI in emergency department patients.
- relate directly to the use of RRI to identify patient risk of AKI in an ED context. (ie Has this study already been done?)

A range of subject-specific electronic data bases were used to identify relevant papers including EMBASE, Pubmed, Web of Science, Scopus, BioMed Central, EBSCO Medical databases, Medline and the Cochrane library.

Whilst coverage is similar, it has been demonstrated that using two or more data bases will identify a greater percentage of available citations (Wilkins T, Gillies R & Davies K 2005).

4.1.3 Developed keywords

Key search terms emerged from an initial scoping search and development of the focused 3 part research question. Subject specific terms were identified that reflect the research topic and the varied terminology used in ultrasound related papers.

The term '***acute kidney injury***' (AKI) is now recognised internationally (KDIGO 2017). However, in earlier phases of the study, numerous inconsistencies in use of terminology were identified within the literature

reviewed. The current search strategy was formulated using a range of key words and truncations that reflect these observed variations.

English language papers reporting the use of ***Doppler renal resistive index*** use a variety of synonymous terms and abbreviations including ***renal RI****,* ***renal resistive index, renal Doppler, RI*** and ***RRI.***

In subsequent stages of the search these terms were used to identify studies of Doppler ultrasound investigation of renal blood flow parameters and the terms **"*emergency*"** and **"*ED*"** were used to search for emergency department context specific studies.

4.2 Initial search

An initial search was performed in each database using the Boolean operators "AND" and "OR" to identify papers with the words "***acute kidney injury***" OR "***acute renal failure***" OR "***acute renal injury***" OR "***acute kidney failure***" in the title / abstract.

A repeat search for ***renal RI****,* ***renal resistive index, renal Doppler, RI*** and ***RRI*** was undertaken using the same limits.

Limits were activated to include **Humans**, **Clinical Trial, Review, Meta-analysis**, **All Adult: 19+ years**, published in the **last 5 years**. No language restrictions were used.

The initial search terms for AKI were then combined separately with ***emergency department*** OR ***ED*** (or other synonymous terms) in a title/abstract search.

The Cochrane Central Register of Controlled Trials was used to search for AKI studies that had not been identified by combined searches within the other data bases. This identified **30 review articles** all of which focus on the evaluation of drugs for the prevention and treatment of AKI and comparative methods of renal replacement therapy. None of the studies identified evaluated methods of AKI diagnosis. Further exploration of the Cochrane data

base for relevant trials identified only one relevant study of renal resistive index (Marty et al., 2015) but no additional studies.

Review of Cochrane Renal Review Group activity (including protocols currently undergoing referee scrutiny) identified two protocols in progress that explore the use of biomarkers in the assessment of renal function. No protocols are identified that link directly to either the role of RRI in this patient group or an ED context.

Inclusion and exclusion criteria were developed from the focused research question and refined through the initial scoping search.

Inclusion criteria	Exclusion criteria
• Primary research studies investigating the role of RRI in the diagnosis of AKI	• Primary research studies investigating the role of RRI in the prognostic stratification of patients with known AKI
• Primary research studies investigating the role of RRI in the prediction of post procedural complications (including AKI)	• Primary research studies investigating the role of biomarkers in the diagnosis of AKI
• Primary research studies investigating the role of RRI in an ED population	• Primary research studies investigating the treatment of AKI
• Systematic reviews of the role of RRI in the diagnosis of AKI	• Primary research studies investigating renal failure in patients post renal transplant
• Humans	• Animals
• Adult	• Children
• Clinical trials	
• Published in last 5 years	

Table: 4.1 Summary of search inclusion and exclusion criteria

Despite the obvious advantages of electronic data bases, it is recognised that they are not infallible. (Aveyard H. 2010). However, in this instance, manual review of the reference lists for each of the papers identified above produced no further records of new clinical trials relevant to the search. None of the studies identified related directly to an ED context. The originality of the proposed study is therefore confirmed.

(A summary of the search strategy is included as Appendix 1.)

4.3 Review of studies

The majority of studies identified by the above search report on the predictive role of RRI for clinical outcome in patients where an episode of AKI has already been confirmed (Bruno et al 2014, Lee et al 2015, Schnell 2015, Boddi et al., 2016; Lahmer et al., 2016, Di Nicolo, P., & Granata, A. 2016). These studies, largely from a critical care context, offer further important insight into the complex determinants of RRI and how these relate to the development of AKI. (See chapter 3)

The primary focus of the search is on the role of RRI in prediction of AKI in a specific ED patient group. None of the studies identified meet both of these criteria.

Five studies in total met the inclusion criteria for *prediction* of AKI. Four of these consider pre-procedural RRI as a predictor of AKI in patients following major surgery (Giustiniano et al., 2014; Marty et al., 2015; Marty et al., 2016; Hertzberg et al., 2016) and one paper evaluated RRI in prediction of contrast induced AKI following coronary angiography (Wybraniec et al., 2017).

One further study identified within the Phase 2 review is included here due to relevance to the search question. (Guinot et al., 2013)

No studies were identified that explore use of RRI in an ED patient population.

4.3.1 Pre-operative assessment of AKI risk prior to surgery

Peri-operative AKI is a known risk factor for significant surgical interventions and is associated with prolonged hospital stay and poor outcome (Boddi, M., Natucci, F., & Ciani, E. 2015, Doyle, J. F., & Forni, L. G. 2016). Five of the studies included in this review explore the use of RRI to predict AKI risk in patients presenting for major surgery. These studies include pre and post-operative assessment of patients undergoing major orthopaedic, general and cardiac surgery.

Giustiniano et al (2014) explored whether RRI could predict complications (including acute renal failure) in patients recovering from high risk surgery. In this prospective dual centre trial, RRI was measured in consecutive patients in the immediate post anaesthetic recovery period following surgery (including cardiac, thoracic, abdominal, brain and vascular interventions).

Of the 205 patients enrolled, RRI > 0.70 was measured in 60 patients (29.3%). They note a significant correlation between raised RRI (>0.70) and complications at 1 week post-surgery [acute renal failure (P = 0.001), pneumonia (P = 0.016), septic shock (P = 0.003)].

RRI> 0.70 was also closely associated with longer ICU stay (P = 0.001) and extended period of mechanical ventilation (P = 0.004.)

In a similar study, **Marty et al. (2016)** explored the predictive value of RRI for early detection of AKI in patients presenting for surgical repair of hip fractures. RRI was measured pre and post-operatively in a selected group of 48 patients with known risk factors for AKI (age, gender, hypertension, arteritis, diabetes, cardiac failure, use of angiotensin-converting enzyme (ACE) inhibitor and sCr.)

Multi-variate analysis was used to compare the statistical significance of individual patient rise in pre / post-operative RRI and in absolute cut off values. A significant grey zone was noted for both pre and post-operative prediction of AKI with (0.59 – 0.75 and 0.64 – 0.71 respectively). However, high value post-operative RRI (> 0.706) performed better that all other preoperative measures of AKI risk.

These findings are consistent with those of a previous study by the same group where pre and post-operative measurements of RRI were taken in 50 patients presenting for hip or knee replacement (Marty et al 2015). Again, in this study, the most accurate cut-off value for prediction of AKI was a

postoperative RRI of 0.705 (sensitivity=94%, specificity=71%, LR+=3.19 and LR-=0.09).

AKI in this patient group is closely associated with increased hospital stay and both short and long term morbidity and mortality (Ulucay et al., 2012). The key trigger for surgically induced AKI is hypo-perfusion of the kidneys arising from hypovolaemia and hypotension (Goren, O., & Matot, I. 2015). This may be further exacerbated by post-operative use of nephrotoxic drugs. Where there is reduced functional renal reserve due to pre-existing renal disease or other risk factors, rapid reduction in renal function may occur in the post-operative period leading to poor outcome.

However, it is interesting to note that early diagnosis of renal impairment (using standard tests) in these patients appears to offer little benefit (Lejus et al., 2012; Marty et al., 2016). Whilst this seems counterintuitive, this may be due primarily to low test sensitivity and specificity of existing tests that are based on sCr level and urine output. Sub clinical AKI in these patients and delay of more aggressive preventive therapies could account for poor outcome rather than ineffective treatment interventions.

The results of these studies by Marty et al (2015, 2016) suggest that raised RRI post-operatively may provide a useful alternative method of stratification of patients into a high risk group for whom early intervention could be beneficial. This may be particularly helpful in patients where onset of AKI is delayed.

A further study by **Hertzberg et al** (2016) explores the value of pre-operative measurement of RRI in patients undergoing cardiac surgery. In this prospective cohort study, RRI was measured in 96 patients the day before surgery. Multiple participant characteristics were recorded including patient specific data (age, gender, BMI etc), measurements of cardiac function (ejection fraction) and type of operative procedure. Logistic regression was used to analyse the association between RRI and AKI. Variables that were

closely associated with AKI were included in multi-variate analysis and results were adjusted for age, sex and eGFR.

In the study group, 27 patients (28%) developed AKI by Acute Kidney Injury Network (AKIN) criteria stage 1 (or worse). The broad finding of the study was that patients with preoperative RRI ≥ 0.7 had a threefold increased risk of AKI.

Positive predictive value for RRI ≥ 0.7 was 0.36 (0.24-0.5). Negative predictive value for RRI<0.7 (95% CI) was 0.84 (0.69 - 0.94). Sensitivity and specificity were 0.78 (0.58 - 0.91) and 0.46 (0.34 - 0.59) respectively.

These results indicate a significant grey zone, and low positive predictive value. However, the negative predictive value of 0.84 and relatively high sensitivity could enable useful pre-surgical identification of a low risk group. When combined with additional markers of AKI risk, raised RRI could enable targeted protective therapy for the higher risk group.

The study by Hertzberg et al builds closely on work undertaken by Guinot et al (2012) who evaluated RRI in a similar post-cardiac surgical group of patients. In this earlier study, (identified by the Phase 2 review) RRI was measured pre and post-surgery in 82 patients presenting for cardiac surgery with cardiopulmonary bypass. The primary aim of the study was to evaluate RRI in distinguishing between transient (fluid responsive) and persistent AKI in this group of ICU patients. Patients were not selected on the basis of known AKI risk factors as the authors were keen to present a more representative group. The demographic of this study therefore differs from others in this review.

In this patient group there was significant heterogeneity in pre-operative RRI and post-operative RRI performed better. RRI >0.73 distinguished transient from persistent AKI with good predictive value (95% CI 0.73- 0.75)

4.3.2 Contrast induced AKI

The final study identified by the search (Wybraniec et al 2017) analyses the association between pre-procedural RRI and onset of contrast induced AKI (CI-AKI) in patients presenting for coronary angiography. This prospective

observational study investigated 95 consecutive patients for whom 128 pre and intra-procedural variables were collected. These include multiple intra-renal blood flow Doppler measurements acquired immediately prior to and repeated 1 hour after the procedure.

The primary outcome measure was CI-AKI as defined by AKIN criteria (≥50% relative or ≥0.3 mg/dL absolute increase in SCr concentration) 48 hours after the procedure. CI-AKI was confirmed by these criteria in 9 patients (9%).

Pre and intra-procedural data were compared in the CI-AKI and non-affected groups. Univariate analysis was used to identify odds ratios (OR) with 95% confidence intervals (CIs) for all parameters. Patient variables achieving statistical significance at $p<0.1$ were then used in logistic regression analysis, from which RRI and SYNTAX* score emerged as the strongest predictors of CI-AKI.

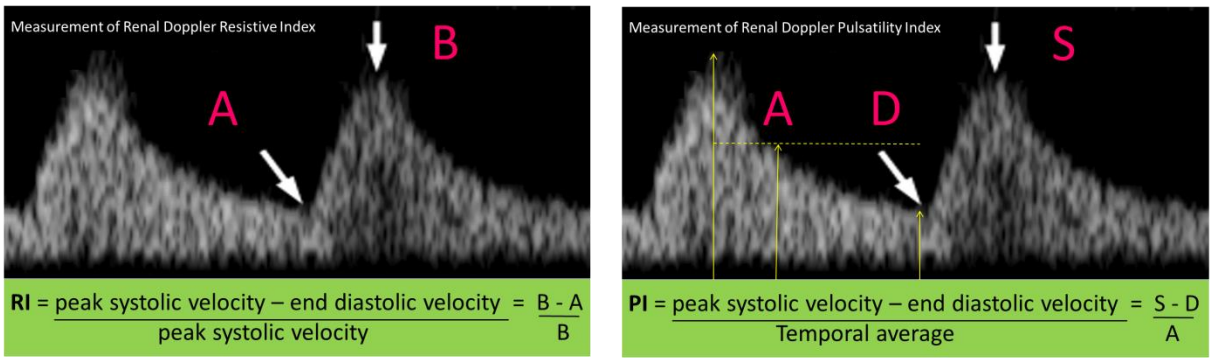
(*SYNTAX – scoring system indicating the complexity of coronary artery disease)

In this analysis, patient age, presence of peripheral artery disease and diabetes were also associated with CI-AKI.

At a threshold of RRI > 0.69 , pre-procedural RRI achieved sensitivity and specificity of 78% and 81% respectively, positive likelihood ratio of 4.18 (95% CI 2.4 – 7.3) and negative likelihood ratio of 0.27 (95% CI 0.08 – 0.9) for prediction of CI-AKI.

From these combined results, the authors conclude that the greatest potential benefit in use of pre-procedural RRI would be found in elderly patients with advanced cardio-vascular disease and type 2 diabetes.

In contrast to the other studies in this group, Wybraniec et al (2017) investigate multiple renal vascular parameters. These include peak systolic velocity (PSV), end diastolic velocity (EDV), renal resitive index (RRI) and renal pulsatility index (RPI) in both extra and intra renal vessels.



Measurement of Renal Resistive Index *Measurement of Renal Pulsatility Index*

Figure 4.1 Calculation of Renal Resistive and Pulsatility Indices

Although RRI and RPI were both significantly higher in patients developing CI-AKI, in multivariate analysis intra-renal RRI was the only renal flow measurement to emerge as an independent predictor of CI-AKI onset.

Of note in the CI-AKI group, was a tendency towards low intra-renal end diastolic flow (EDF). The authors speculate that this may indicate that the dominant mechanism for raised RRI in the high risk group is raised intra-vascular resistance due to endothelial dysfunction. This could in part explain the increased likelihood of tubular injury in the presence of a highly viscous contrast medium.

4.4 Discussion of studies exploring RRI as a predictor of AKI

To date, only a small number of studies have explored the ability of RRI to predict a future AKI event. In each of the studies reviewed RRI is measured in a controlled (selected) group of patients prior to or following interventions with a known associated risk of AKI.

In each of the above studies, baseline or post procedural RRI values were significantly higher in patients with confirmed AKI. Whilst the context,

intervention and patient groups vary, the observed association between raised RRI and AKI appear to be surprisingly consistent. This would support the view that RRI is influenced closely by the underlying risk factors for AKI and that RRI has potential as an independent test of AKI risk. However, multiple variations in the methodology, measurements and definition of outcome parameters are noted.

With the exception of Giustiniano et al (2014), in the studies reviewed, AKI is defined by AKIN or RIFLE criteria. Both systems classify AKI by serum creatinine (SCr) increase from a base level. Marty at al (2016) use lowest recorded SCr for each patient during their hospital stay. However, they acknowledge that this may be an inaccurate reflection of normal baseline SCr level for patients within their study group. Assessment of AKI risk on initial patient presentation may therefore be misleading. Similarly, in an ED context, normal baseline level of SCr would be unknown.

Giustiniano et al (2014), offer no information regarding classification of acute renal failure.

A further limitation of the studies is the time limit for patient observation. In five of the six studies, urine output and SCr level were monitored up to 48 hours post procedure. This may have underestimated the rate or AKI in each study group. Schnell et al (2012) defined AKI at 72 hours and observed no additional episodes of AKI after day 3. Giustiniano (2014) monitored patients for a range of complications over 1 week. However, ARF criteria and timing of diagnosis are not defined.

There is wide variation in the patient populations studied by these authors. In all studies, exclusion criteria include known chronic renal disease and renal replacement therapy (RRT). Obesity, respiratory distress, tachycardia, patient agitation or confusion were listed as additional exclusion criteria across most of the studies. All of these factors may affect the feasibility and reproducibility of RRI measurement due to technical difficulty in achieving an adequate

Doppler spectral trace. This may be problematic in a non-selected ED population.

In the studies reviewed, these limitations were acknowledged and mitigated in part by use of a single operator and close adherence to a clearly defined measurement protocol. By taking repeat measurements and using arithmetic mean values for RRI, previous studies have demonstrated fairly high reliability of RRI measurements (Gao J.B. 2015; Ninet at al., 2015). Whilst there remains some uncertainty regarding lack of intra and inter-operator reproducibility, there seems to be a consensus between key authors that RRI performs well in the assessment of short term prognosis (Schnell, D., & Darmon, M. 2015)

4.4.1 Results of studies exploring RRI as a predictor of AKI

Cut off values for RRI vary between studies but, are closely in agreement with RRI > 0.70 as an upper limit of normal. This value is surprisingly consistent between studies of patient groups presenting for cardiac surgery, orthopaedic surgery, general surgery, sepsis and contrast enhanced angiography. However, there is wide variation in the confidence intervals and most authors note a significant grey zone around this value. The number of patients falling within the grey zone varies between 14% (Guinot P. et al., 2013) and 23% (Marty et al., 2016).

This is consistent with earlier studies that evaluate RRI as a predictor of persistent AKI (Schnell et al., 2012; Darmon et al., 2011).

In the studies reviewed, RRI does not appear to correlate with pre procedural eGFR or SCr. Wybraniec note that 17 of 95 patients presented with borderline eGFR 50 – 60 mL/min / 1.73m2. All of these had RRI measurement below the 0.7 cut off. This is consistent with Hertzberg's findings where no statistical difference was seen between eGFR values in RRI < 0.7 and RFI ≥0.7 groups. This would support the view that raised RRI is an indicator of AKI **risk** rather than a marker of impaired renal function.

This is consistent with the findings of earlier studies from critical care settings where RRI is evaluated as a predictor of renal recovery and patient outcome.

In a meta-analysis of studies exploring the predictive value of RRI for reversibility of renal dysfunction, Ninet et al (2015) pooled results from 9 studies. Elevated RRI was associated with significantly increased risk of persistent renal damage. Pooled sensitivity and specificity were 0.83 (95% ci, 0.77 – 0.88) and 0.84 (95% ci 0.79 – 0.88) respectively. Again, methodological differences between studies and heterogeneity across patient characteristics, AKI definition and RRI cut off present limitations to this meta-analysis. However, in line with previous studies, the authors conclude that, whilst RRI is unsuitable as a measure of renal perfusion, RRI is a helpful indicator of the short term reversibility of AKI and has some potential as an indicator of AKI risk.

Interestingly, in critically ill patients, there appears to be a close correlation between RRI and general recovery, not just irrevocable renal damage. A number of studies have explored the relationship between raised RRI and adverse outcomes including mortality. This is consistent with the prospective studies identified by this review.

Boddi et al (2016) undertook a prospective study of 125 patients admitted to ICU, exploring the association between RRI, persistent AKI and patient mortality. RRI (measured at the time of AKI diagnosis) was 0·77 (0·70-0·88) in survivors and 0·85 in non-survivors (0·79-0·94) (P = 0·002). In this study, multivariate analysis identified raised RRI >0.77 as the strongest independent predictor of both persistent AKI on discharge and of in-hospital death, regardless of diagnosis on admission. This association remained significant even after correction for AKI scoring (RIFLE), need for renal replacement therapy and AKI aetiology. In the ICU population, there are multiple confounding factors that make it difficult to attribute AKI as the precise cause of death in these patients. However, these findings are consistent with those of earlier studies and provide insight into the determinants of RRI in sick patients and causative links with AKI.

4.4.2 Not just about the kidney…

The term RRI implies a direct relationship with renal vascular resistance. However, this is misleading. The correlation between RRI and renal resistance is weak and it has been recognised for some time that RRI is a poor indicator of renal perfusion (Ward, S. P., Taylor, M. G., & Gosling, R. G., 1993: Bude, R. O., & Rubin, J. M. 1999; Ninet et al., 2015; , Di Nicolo, P., & Granata, A. 2016). This is confirmed by earlier studies of transplant patients where RRI reflects haemodynamic features of the host (primarily cardiac output and systemic vascular compliance) rather than renal perfusion (Naesens et al., 2013).

The determinants of RRI are complex and include multiple renal and systemic vascular factors such as age, gender, fluid status, use of anti-hypertensive and non-steroidal anti-inflammatory drugs and pre-existing co-morbidities (Naesens et al., 2013; Chirinos, J. A., & Townsend, R. R. 2014; Viazzi et al., 2014; Joslin, J., & Ostermann, M. 2012; O'Neill, 2014; Boddi et al., 2015). The theoretical and experimental evidence for these are explored in depth in Chapter 3.

However, there is both experimental and clinical data confirming that RRI is markedly affected by renal interstitial and venous pressure and does therefore reflect altered renal microcirculation (Ward, S. P., Taylor, M. G., & Gosling, R. G., 1993; Boddi et al., 2015: Chirinos eta l., 2014; O'Neill, 2014, Ninet et al., 2015). Despite the complexity of cause, in native kidneys, numerous studies continue to support the role of RRI as a predictor of progressive renal dysfunction and increased likelihood of persistent renal damage (Sugiura et al, 2009; Dewitte et al., 2012; Guinot et al., 2013; Viazzi et al., 2014; Granata et al., 2014).

Whilst raised RRI is not a direct indicator of altered renal function, it does appear to be influenced closely by the underlying risk factors and systemic vascular changes that lead to progressive renal damage. This is consistent with the findings of the studies reviewed and may support the use of RRI as a potential early indicator of sub-clinical AKI.

Whilst there is variation in patient characteristics, methodology and outcome measures, from the studies reviewed, RRI appears to perform consistently as an independent predictor of AKI. The broad confidence intervals noted suggest a grey zone approach may be useful with stratification of patients into high / low risk groups where RRI falls outside of this zone.

No studies are identified by the review that evaluate RRI in ED patients.

In this chapter, review of current literature confirms that RRI may be a useful independent predictor of AKI risk in patients undergoing surgical or contrast enhanced procedures. The extent to which this is a clinically useful approach to AKI prediction in an ED population is explored in the current study.

In the following chapter, the study aim and objectives are defined. Study methodology is described and the process (and requirements) for ethical approval are outlined. Measurement protocols, method of data collection and technical factors are detailed and reproducibility of measurements is considered.

Chapter 5 Methodology and methods

In this chapter, the underpinning methodology for the study is considered. The study aim, objectives and outcome measures are defined and the study design is described. The process for ethical approval is outlined and the study method is detailed.

5.0 Underpinning methodology for the study

The current study emerged as a collaborative partnership between an expert sonographer and colleagues in emergency medicine. Historically, in both diagnostic imaging and emergency care, research has been strongly positivistic and quantitative in methodology and underpinning philosophy. In both of these professional disciplines research studies follow a typical 'medical model' that focuses on quantifiable data, defined outcome measures and statistical analysis of findings. This largely quantitative approach, founded in post-positivism but, acknowledging the subjective interpretation of data, forms the basis for evidence based practice in emergency medicine (Adam, 2014).

The methodological approach and data collection methods developed are consistent with those used in existing studies that explore links between RRI and renal function. This allows comparison of test performance and test characteristics across patient sample groups and increases scope for future meta-analysis.

The RRI measurement tool used is adapted from previous studies for use in the Emergency Department (Deruddre et al., 2007; Darmon et al., 2011; Murphy, M. E., & Tublin, M. E., 2000; Kusnetsova 2014). All technical amendments to the technique used for Doppler measurements have been tested through normal volunteer practice and are designed specifically to improve the reliability of RRI in this patient group.

Development of criteria to assess the feasibility and clinical usefulness of RRI in this context was through an iterative approach. The feasibility and 'usefulness' measures identified are context specific, emerging from combined review of existing literature, informal feedback from clinical colleagues and scrutiny of key national drivers for diagnosis and management of AKI. No previous studies were identified that test measurement of RRI in this patient group.

5.1 Research question

5.1.1 Aim

The aim of this study was to evaluate whether ultrasound measurement of Renal Resistive Index (RRI) is a feasible and clinically useful method of early identification of Acute Kidney Injury in patients requiring resuscitation room care.

5.1.2 Research objectives

1. To determine if RRI measurement is feasible in an Emergency Department (ED) resuscitation room setting using a point-of-care ultrasound system.
2. To determine the sensitivity, specificity, positive and negative predictive values of ED bedside measurement of RRI in the identification of AKI in patients requiring resuscitation room care.
3. To compare the performance of RRI and conventional indicators of AKI risk in this context.
4. To assess the performance of RRI as a predictor of persistent AKI in this patient group
5. To identify the additional training needs of ED doctors who are experienced ultrasound users to enable them to perform RRI measurement.

5.2 Study design

Building on evidence from early landmark papers in critical care, the study design was developed in consultation with senior colleagues in emergency medicine and critical care. Expert methodological and statistical input was provided by Department for Health faculty at the University of Bath.

This single centre prospective cohort study assesses the diagnostic and prognostic value of RRI in a selected population of adult Emergency Department (ED) patients admitted to the resuscitation room.

As the feasibility and utility of RRI was not established in an ED context, inclusion of patients who lack capacity to consent or the randomisation of patients to alternative treatment groups on the basis of these measurements was not justified. However, as early intervention to prevent progressive renal damage remains a key national driver, exploration of RRI in this high risk population was supported by the Trust Research Department (who acted as the local sponsor for the study) and regional ethics committee.

5.3 Definitions and outcome measures

Prior to exploration of test characteristic of RRI in prediction of AKI in this patient group, the first objective of the study was to evaluate the feasibility of RRI measurement in this context.

Context specific feasibility criteria and target outcomes were proposed as outlined in Table 5.3a. Ensuring minimal disruption of standard care pathways was central to this.

	Question	Target outcome
Performance of the scan	How reliably can ED sonographer visualise the kidneys in this patient group?	Kidneys adequately imaged in 90% of patients?
	In what proportion of patients recruited can RRI be measured? (3 consecutive waveforms)	RRI measurements comply with study protocol in 90% of patients
	What are the limiting factors in achieving RRI measurement?	Patient, context or equipment related factors are identified
	Can these be mitigated?	Are there any technical / other solutions?
Time for scan	How long does it take to achieve RRI measurement? Is this reasonable in this context?	90% of RRI measurements completed in target limit to 5 mins
	Does the scan delay standard patient care pathway?	Minimal disruption / delay of standard care pathway. (Will vary between patients. Can we quantify this?)

Table 5.3a Test feasibility criteria and target outcomes

5.3.1 Test characteristics

The primary outcome measure for the study was confirmed diagnosis of AKI (AKIN criteria) at 7-14 days (or prior to patient demise) and return to normal biochemistry / urine output in line with local and international guidelines [sCr and urinalysis at 48hrs and 7-10 days (or prior to discharge or demise)] (Lopes, J. A., & Jorge, S. 2013).

Stage	Serum creatinine	Urine output
1	Increase in serum creatinine of >26μmol/L from baseline within a 48hr period **or** Increase of 1.5 to 1.9 times baseline	< 0.5 mL/kg/hour for > 6 hours
2	Increase in serum creatinine of 2 to 2.9 times baseline	< 0.5 mL/kg/hour for > 12 hours
3	Increase in serum creatinine to 3 times baseline **or** Increase in serum creatinine to >354μmol/L **or** Initiation of renal replacement therapy	< 0.3 mL/kg/hour for > 24 hours **or** no urine output > 12 hours

Figure 5.3b *Whilst alternative reference standards are reported (KDIGO 2012, NICE 2013), management of AKI within the study setting is in line with AKIN criteria.*

For each patient, routine follow-up biochemistry results were accessed from the Trust clinical management data base and stored in accordance with Trust data protection policy.

5.3.2 Clinical usefulness of RRI as a predictor of AKI risk

Beyond standard definitions of test reliability and validity, the clinical usefulness of a diagnostic test is tricky to measure (Nelson et al 2001). In addition to parameters such as sensitivity, specificity and predictive values, the test must demonstrate context specific feasibility in the target patient group, provide some tangible advantage over existing tests and should be acceptable to patients. Ultimately, the test must facilitate patient care pathways that improve outcome.

To determine the clinical usefulness of RRI in this patient group the following evaluation checklist was proposed:

Question	Check list	Outcome
Is AKI risk common in these patients?	Is there any documented evidence of the prevalence of this condition in this patient group?	What is the prevalence of this condition in local ED resus patient group?
How good are the current routine tests?	eGFR has low specificity and un-known sensitivity in this patient group.	Does RRI perform better than eGFR in prediction of AKI
How good is RRI at predicting AKI?	What are the test characteristics of RRI for the detection / prediction of AKI?	Sensitivity, specificity. Predictive values for RRI
Can we believe the result of the new test?	Is RRI a reliable indicator of AKI risk in this patient group?	Intra-operator and inter-operator reliability.
Is this change in the patient's best interest?	Could use of RRI as a predictor of AKI improve patient outcomes?	Is there evidence that earlier detection of AKI risk could reduce progressive renal damage in some patients.
Will it change patient management?	Only if we believe the results	Renal protective care bundle may be advised. Follow up study needed?
What are the risks of NOT doing the test?	High morbidity / mortality if AKI undiagnosed. eGFR based on sCr known to be a poor indicator of reduced renal function.	Possible preventable renal damage
What are the risks of doing the test?	Potential delay in immediate patient management during the scan? Un-necessary withdrawal of nephrotoxic drugs if false +ve?	Target - No delay in fluid management or other significant interventions.

Table 5.3c* Clinical usefulness criteria

5.4 Ethical approval

Ethical approval for the study was gained through joint application to the regional NHS Ethics Committee and local Trust Research Department.

In an emergency department context, a key priority was to ensure minimal disruption to patient care. In patients with significant illness, any additional intervention may be considered burdensome. The time dependent nature of some medical interventions in this context was also considered. Both aspects are reflected in the study design.

A key ethical challenge for the study was the necessity to balance the level of information needed for patients to make a fully informed decision and the capacity of these acutely unwell patients to read and process the information provided. This is explored further in Chapter 8.

5.5 Setting

The setting for this study was a 1139 bedded acute teaching hospital serving a population of approximately 660,000 across rural and urban areas. The 24 hour Emergency Department receives on average approximately 400 patients a day.

Patients were recruited to the study from a six bedded resuscitation room that receives, on average, 35* patients per day.

(*Estimated from 21 day sample: Jan 2017/June 2017)

The Trust is classified as a trauma unit.

5.6 Study protocol

All scans were performed to a strict study protocol and in compliance with the British Medical Ultrasound Society Safety Guidelines (Ter Haar 2017) and Trust infection control policy.

The scan results were non-contributory and did not influence patient care or subsequent treatment in any way. The doctor responsible for the patient's resuscitation room care was blinded to the RRI measurement.

To minimise the potential impact of the study on patient well-being, patients requiring time dependent interventions were excluded from the study and target scan time was a maximum of 5 minutes. (The full study protocol is summarised in Figure 5.12 below.)

5.7 Sample

20 patients admitted to the resuscitation room and meeting the inclusion criteria were recruited over approximately 50 non-consecutive days.

Principal inclusion criteria

- Adult ED patients requiring resuscitation room care
- Capacity to consent confirmed

Principal exclusion criteria

- Cardiac arrest
- Lack of capacity to consent
- Age <18
- Known history of chronic kidney disease

Level of patient illness in this context varies considerably. Patients with high Patient Modified Early Warning (MEW) score or high National Early Warning (NEW) score were excluded at the discretion of the doctor responsible for their care.

5.8 Recruitment and consent

Recruitment to the study was by individual approach by the doctor responsible for participant's resuscitation room care. Following verbal explanation of the study, patients expressing an interest in participation were invited to read a short patient information sheet (Appendix 2a) and opportunity to ask further questions was provided.

A more detailed version of the study information document (Appendix 2b) was given to recruited patients for them to read on discharge. This included

contact details for the research team and for the Trust Patient Advice & Liaison Service. (PALS offers help, support and advice to patients, relatives or carers, about any issues relating to their experience of the Trust.)

Verbal check of patient consent to proceed was undertaken by the Chief Investigator (an independent expert sonographer) immediately prior to the scan and consent was documented.

Due to the context of the study and the time dependence of ED patient management, it was not feasible to allow an extended period of time for patients to consider participation in the study. For this reason, consent was approached as an on-going process with multiple opportunities for patients to ask questions and consider their participation or possible withdrawal. In all cases, the timing of initial approach and decision making was governed by the patient's immediate and on-going care needs.

Resuscitation room patients are monitored constantly and their capacity to consent may vary over time. In all cases, routine clinical interventions took precedence over the research intervention. Where initial consent to participate was gained and the patient's clinical condition later deteriorated, the decision to proceed with the study intervention was discussed with the ED doctor responsible for their care. Where the patient was deemed to have lost capacity to consent, or urgent medical intervention was needed, a scan was not performed.

Due to the time dependent nature of both clinical and research interventions in an emergency context, potential participants who may have difficulties in adequately understanding written or verbal information in English were excluded from the study.

5.9 Data collection period

The target data collection period was restricted initially to one day per week for 10 months. (This was determined by expert sonographer availability and release from other duties.) In response to poor recruitment to the study, the total recruitment period was extended to 15 months. Throughput of patients in

the ED is variable with seasonal changes placing significant additional pressure on staff. The current crisis of emergency care in the NHS is well documented. This placed significant restrictions on research activity in the unit and recruitment to the study was halted temporarily during periods of high pressure.

5.10 Method

Following recruitment and consent, patients were scanned by a single independent expert sonographer (not the doctor responsible for patient care). All patients were examined in a supine or semi-sitting position. Using a SonoSite EDGE Portable Ultrasound system, with a C60X 60mm 5-4 MHz broadband curved array transducer, the right kidney was imaged and assessed for gross abnormality.

Colour Doppler was used to identify the interlobar arteries. Pulsed Doppler was used to capture a spectral trace and RRI was measured using a standardised technique as described in previous studies (Deruddre et al., 2007; Darmon et al., 2011; Murphy, M. E., & Tublin, M. E. 2000; Kusnetsova et al., 2014).

Doppler gain and scale settings were adjusted to optimise the spectral trace, avoiding signal saturation and enabling clear identification of peak systolic and end diastolic velocities for accurate calliper placement.

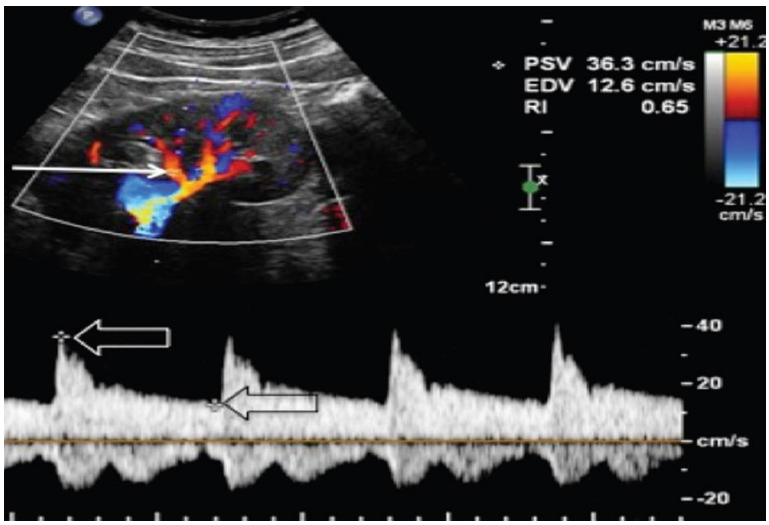
RRI was measured where the spectral trace from a minimum of three cardiac cycles could be captured. RRI measurement was repeated three times, from different interlobar arteries at upper mid and lower poles where feasible and mean RRI values were recorded. Images were captured for analysis.

RRI was calculated as PSV – EDV / PSV using an automatic on-screen measurement package (Sonosite 2016).

The full RRI measurement protocol is detailed in **Figure 5.11**

Interlobar artery

Peak systolic velocity



End diastolic velocity

Figure 5.10 Renal inter-lobar artery RRI measurement from spectral trace.

The left kidney was then imaged and assessed for gross abnormality only. RRI measurements were not recorded from the left kidney. In the absence of unilateral renal obstruction (or other gross renal abnormality), previous studies report insignificant difference in RRI between the two kidneys (Mostbeck, G. H., Zontsich, T., & Turetschek, K. 2001; Deruddre et al., 2007). By restricting RRI measurement to the right kidney only, total scan time was kept to a minimum.

Figure 5.11 ED AKI - RRI measurement protocol V 1.0 25.02.14

Equipment	• SonoSite EDGE Portable Ultrasound system • 5-4 MHz 60mm curved array transducer • Renal RI pre-set (Study specific to include optimised PRF and lowest wall filter) • Image depth 15cm • Study Participant Number entered to new patient Field. • Use lowest PRF without aliasing to ensure optimal display of waveforms • Reduce gain to remove noise from PW spectrum without loss of information
Patient position	• Supine (head raised) • Patient comfortable
Image acquisition	• Intercostal / subcostal image of the right kidney • View achieved on passive expiration where feasible • Colour box positioned over renal hilum • Fine adjustment of transducer position to identify arcuate / interlobar arteries at the level of the renal pyramids.
Measurement	• PW Doppler selected and RRI measured when a minimum of three reproducible waveforms are demonstrated. • Calliper placement at peak systolic and end diastolic for automated calculation of RRI [(PSV-EDV) / PSV] • Measurement repeated 3 times (upper, mid and lower pole) • Images demonstrating RRI measurements saved to system hard drive. • RRI measurements documented on data collection sheet
Left Kidney	• The left kidney should be identified • Any evidence of hydronephrosis or possible structural abnormality? • Representative image saved to hard drive

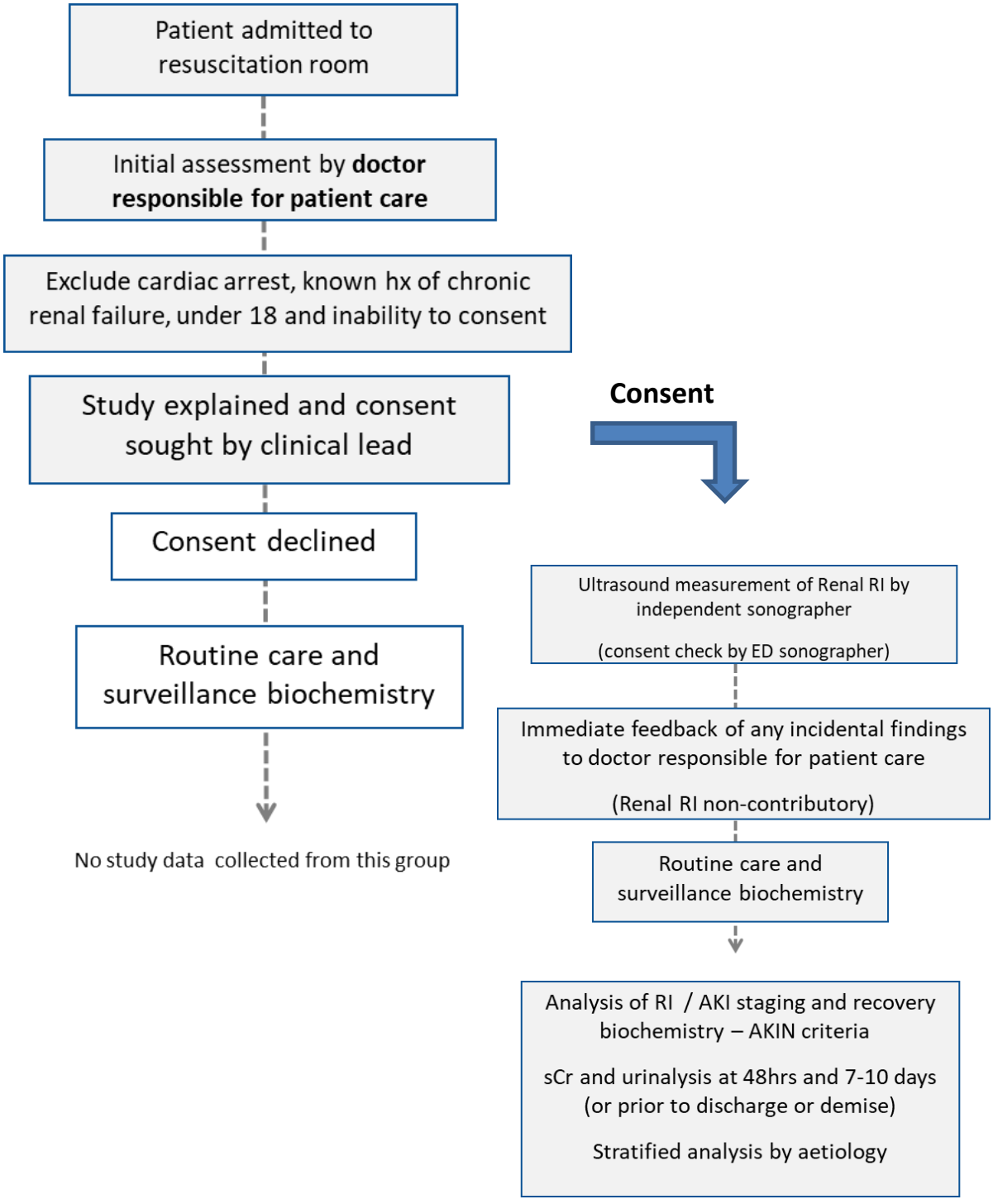


Diagram 5.12 Study protocol and recruitment process

RRI measurements were undertaken by a single expert sonographer who was blinded to routine biochemistry to avoid interobserver variability.

Where a spectral trace consistent with the study protocol could not be achieved within the target time limit of 5 minutes (and where patient condition was stable), scan time was extended to a maximum of 10 minutes. Where patient condition was either deteriorating or not compatible with further attempts) the scan was abandoned and no further measurements were recorded.

For each patient, age, gender, primary diagnosis on admission, NEW (or MEW) score, baseline eGFR, creatinine and urea were recorded. Any complications or technical difficulties with the scan were noted. Any incidental findings were recorded and reported to the doctor responsible for patient care.

5.11 Data collection tool

The data collection tool was designed to be completed at the bedside (at the time of the scan) and to provide a paper based record of relevant patient details, scan findings and any technical challenges. Patients were identified on the form by their ED number only. No patient names were recorded. The completed paper based forms were stored in a secure cabinet in the resuscitation room. Immediately after the scan, all data from the form were anonymised and recorded by the chief investigator on a non-networked encrypted data base with password access. (Appendix 3)

Patient primary diagnosis on admission and MEW / NEW score were recorded from the patient care notes and baseline eGFR, creatinine and urea for each patient were retrieved from the Trust clinical management IT platform.

5.12 Confidentiality and data handling

In line with Caldicott Principles, minimal patient identifiable data were recorded. All data were anonymised, stored in accordance with Trust data protection regulations and accessible only to the principal and chief investigators.

Any person-identifiable information, such as patient hospital number , were stored separately to the data collected as part of the study. These details were only identifiable by a 'research study number' and were accessed only by the chief investigator and the doctor supervising the study.

5.13 Management of incidental findings

Measurement of RRI requires visualisation of the kidney and adjacent organs on ultrasound. Where an incidental finding (such as dilatation of the kidney or a possible mass) was noted, the study protocol required findings to be documented and communicated to the doctor responsible for the patient's care and images captured for radiology review where indicated. Processes for management and referral of incidental findings were agreed prior to the start of the study to ensure a robust approach to clinical governance and record keeping.

In all instances, the doctor responsible for patient care remained blinded to the RRI measurement. Standard care pathways were not altered.

In this chapter, the underpinning methodology for the study has been considered. The study aim, objectives and outcome measures have been defined and the study design described along with the process for ethical approval and method.

In the next chapter, results are presented and the feasibility of RRI in this patient group is evaluated.

Chapter 6 Results and analysis

In this chapter, results from the study are presented and analysed. The feasibility of RRI in this patient group is evaluated using pre-defined criteria and the technical limitations of RRI measurement are discussed.

6.1 Patient characteristics

A total of 20 patients requiring resuscitation room care (11 male, 9 female) were recruited to the study. Age of patients ranged from 33 years to 91 years (mean 62.3 years). (See Table 6.1)

6.1.2 Baseline biochemistry

Baseline sCr, urea and eGFR were recorded from the Trust clinical management database after measurement of RRI. The sonographer undertaking the scan was blinded to these results at the time of scan.

(See Table 6.2)

6.1.3 Visualisation of both kidneys

Adequate visualisation of both kidneys was achieved in 60% of patients (n=12). In patients where it was not possible to achieve adequate views of both kidneys (n=8), limiting technical factors were shortness of breath (SOB) (n=6), high BMI (n=2). In one patient, the scan was abandoned due to patient distress and no attempt was made to image the left kidney.

Table 6.1 Patient characteristics and primary diagnosis on admission

Pt no.	Age	M / F	MEW score	Primary diagnosis on admission	Admitted / discharged	AKI this visit	Outcome
1	74	M	3	AAA	Discharged	No	Survived
2	56	M	1	AF	Discharged	No	Survived
3	74	F	4	Upper GI bleed	Admitted (Gen)	No	Died
4	72	M	1	AAA	Admitted (SAU)	No	Survived
5	48	F	1	Angioedema	Discharged	No	Survived
6	33	F	1	Fall ? spinal injury	Admitted (Gen)	No	Survived
7	63	M	0	pneumonia	Admitted (MAU)	No	Survived
8	60	M	0	Chest pain	Admitted (MAU)	No	Survived
9	65	M	0	AF	Admitted (ACC)	No	Survived
10	79	M	1	?GI bleed – SOB & vomiting. Ca pancreas	Admitted (MAU)	No	Survived
11	74	F	1	Spontaneous pneumothorax	Admitted (MAU)	No	Died
12	47	F	0	Abdominal pain	Admitted (SAU)	No	Survived
13	54	F	1	Arrhythmia + chest pain	Discharged	No	Survived
14	67	M	1	Chest pain – aortic valve rep.	Admitted (MAU)	No	Survived
15	53	M	2	SOB ?lung mass	Admitted (MAU)	No	Survived
16	73	F	2	COPD	Admitted (MAU)	No	Died
17	59	F	1	SOB – chest pain	Admitted (MAU)	AKI stage 1 day 4	Survived
18	91	F	1	Atrial fibrillation and SOB	Admitted (MAU)	No	Survived
19	42	M	5 (NEWS)	Sepsis	Admitted (MAU)	AKI stage 1 day 2	Survived
20	63	M	3 (NEWS)	Atrial fibrillation	Admitted (MAU)	No	Survived

6.1.4 Renal resistive index

At least one measurement of RRI was achieved in 70% of patients (n=14). However, in 9 of these patients (64.3%) the Doppler spectral traces achieved were substandard and did not meet the measurement criteria for RRI as specified in the study protocol.

In 30% of patients (n=6) no usable spectral trace was achieved and it was not possible to measure RRI. (Table 6.2)

6.1.5 Follow-up biochemistry

Follow-up biochemistry was recorded for 16 patients. The remaining 4 patients were discharged following ED assessment and no further results were available.

In 2 patients (10% of the study sample) AKI stage 1 was recorded (at day 2 and day 4 respectively) by AKIN* criteria. (*Appendix 4)

													Follow up biochemistry							
Pt No.	Age	M / F	MEW score	Baseline eGFR	Baseline sCr	Baseline Urea	scan time (mins)	Both kidneys imaged	RRI upper pole	RRI mid pole	RRI lower pole	RRI mean	Days post scan	eGFR	sCr	Urea	Days post scan	eGFR	sCr	Urea
1	74	M	3	51	121	8.5	6	No	0.68	0.7	NM	0.69								
2	56	M	1	>60	76	5.7	10	Yes	0.54	0.57	NM	0.55								
3	74	F	4	46	101	21.9	10	Yes	0.79	NM	NM	0.79	3	55	87	5.7				
4	72	M	1	>60	90	5.2	9	Yes	0.6	0.6	0.59	0.596	6	58	109	4.5	15	>60	84	4.9
5	48	F	1	>60	73	4.2	9	Yes	0.64	0.66	0.65	0.65								
6	33	F	1	>60	46	2.2	6	Yes	0.56	0.56	0.56	0.56								
7	63	M	0	>60	79	5.6	10	Yes	NM	NM	NM	NM								
8	60	M	0	>60	64	4.4	9	yes	0.54	0.64	0.62	0.6	31	>60	68	3.9				
9	65	M	0	>60	96	9.5	8	yes	0.54	0.54	0.54	0.54								
10	79	M	1	>60	74	15	14	yes	0.59	0.52	NM	0.55	7	>60	58	11	14	>60	59	6.1
11	74	F	1	>60	46	3.6	7	No	NM	NM	NM	NM								
12	47	F	0	>60	80	5.7	5	yes	0.57	0.56	0.56	0.563								
13	54	F	1	>60	71	5.5	8	yes	0.5	0.51	NM	0.505								
14	67	M	1	>60	65	4.8	5	No	NM	NM	NM	NM	6	>60	60	5.3				
15	53	M	2	>60	57	4	4	No	NM	0.62	NM	0.62	7	>60	66	2.4	14	>60	61	2.8
16	73	F	2	>60	51	2.4	4	No	NM	NM	NM	NM	12	>60	59	4.6				
17	59	F	1	>60	54	2.5	6	No	0.75	0.74	0.74	0.74	5	>60	67	2.9				
18	91	F	1	54	85	8	12	No	NM	NM	NM	NM	2	49	92	6.8				
19	42	M	5 (NEWS)	39	167	8.4	8	No	NM	NM	NM	NM	2	60	108	6	7	>60	83	3.5
20	63	M	3 (NEWS)	>60	90	6.4	7	Yes	0.64	0.64	0.63	0.636								
	Mean 62.3	11 M 9 F					Mean 7.8													

Table 6.2 Results

6.2 Performance of the scan

6.2.1 Scan time

Recorded scan time for all patients ranged from 4 – 14 minutes. In patients where at least one measurement of RRI was achieved, scan time ranged from 5 – 10 minutes. Mean scan time was 7.7 minutes (± 2.3)

One scan was abandoned after 4 minutes due to patient distress.

6.2.2 Technical limitations of the scan

Where technical difficulty was experienced, the reason for failure to acquire high quality Doppler spectra was documented at the time of scan. RRI measurements were further evaluated retrospectively through review of stored images. (Table 6.3)

In 5 of the 6 patients where no usable RRI measurement was achieved, patient shortness of breath (SOB) was noted as a key technical factor. The remaining patient where no measurement was obtained was noted to be morbidly obese.

Shortness of breath (SOB) was also noted as a key technical factor in 4 patients where suboptimal Doppler traces only were achieved. In the remaining 2 patients with suboptimal Doppler, the scan was abandoned as the 10 minute target time limit had been exceeded.

In total, shortness of breath was noted as a technical difficulty in 60% of patients (n=12) including three for whom RRI measurements were achieved.

In 9 patients (45%) SOB was recorded as the primary reason for failure to acquire a usable Doppler trace.

Table 6.3 Technical limitations of the scan

Pt no.	Age	M / F	MEW score	Technical difficulty?	Measurement of RRI achieved
1.	74	M	3	High BMI SOB	Limited
2.	56	M	1	Time limit	Limited
3.	74	F	4	SOB - Difficult to track vessels	Limited
4.	72	M	1	None recorded	**Yes**
5.	48	F	1	SOB	**Yes**
6.	33	F	1	None recorded	**Yes**
7.	63	M	0	High BMI SOB - Six attempts but no measurement achieved	No measurement
8.	60	M	0	None recorded	**Yes**
9.	65	M	0	None recorded	**Yes**
10.	79	M	1	Limited views left kidney	Limited
11.	74	F	1	Severe SOB – Patient in pain. No usable views	No measurement
12.	47	F	0	Limited views left kidney.	**Yes**
13.	54	F	1	SOB	Limited
14.	67	M	1	SOB - no usable trace	No measurement
15.	53	M	2	SOB patient distressed. Very limited views. Scan abandoned	Limited
16.	73	F	2	COPD Severe SOB – no usable trace	No measurement
17.	59	F	1	SOB Lt kidney difficult to image	Limited
18.	91	F	1	SOB rapid shallow breathing – no usable traces	No measurement
19.	42	M	5 (NEWS)	Morbidly obese. No intrarenal flow seen on colour Doppler.	No measurement
20.	63	M	3 (NEWS)	A little SOB but able to cooperate	Limited

Table 6.4 Evaluation of RRI measurements from stored images

RRI measurement criteria	Participant number																		
	1	**2**	**3**	**4**	**5**	**6***	**7***	**8**	**9***	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Interlobar artery identified	✓	✓	✓	✓	✓	*No images	*No images	✓	*No images	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓
Doppler gain optimised	✓	✓	✓	✓	✓			✓		✓	No usable spectral trace	✓	✓	No usable spectral trace	✓	No usable spectral trace	✓	No usable spectral trace	No usable spectral trace	✓
Doppler scale optimised	✓	✓	✓	X	✓			X		✓		✓	✓		✓		✓			X
Minimum of three cardiac cycles	X	✓	X	✓	✓			X		X		✓	✓		X		✓			✓
Correct calliper placement at peak systole	✓	✓	X	✓	✓			NA		✓		✓	✓		✓		✓			✓
Correct calliper placement at end diastole	✓	✓	X	✓	✓			NA		✓		✓	✓		✓		✓			✓
Measurement repeated 3 times (upper, mid and lower pole)	X	X	X	X	✓			X		X		✓	X		X		✓			✓
Measurements meet criteria	N	N	N	N	**Y**			N		N	N	**Y**	N	N	N	N	**Y**	N	N	N

***Participants 6,7 and 9 -** Images stored to the ultrasound system hard drive were lost before backup due to an equipment fault.

6.3 Evaluation of RRI measurements

RRI measurements were evaluated against the study criteria by review of stored images. For three participants, images were lost prior to backup due to an equipment malfunction.

The remaining 17 participant image sets were graded using pre-determined measurement criteria. (Table 6.4)

From the image sets reviewed, the stored spectral traces met **all** criteria for RRI measurement in only **3** patients (15%). In a further 2 patients, measurement criteria were met for at least one interlobar vessel but, were not repeatable for three vessels (upper, mid, lower pole) as specified in the measurement protocol.

Individual RRI evaluation criteria were met in at least one measurement in a total of 5 patients (25%).

6.4 Analysis of RRI measurements

Insufficient data were collected to allow meaningful statistical analysis of the relationship between RRI and patient biochemical markers on arrival. For the small number of patients where at least one measurement of RRI meets the defined measurement criteria (n=5), there is no obvious correlation between RRI and sCr on presentation or between mean RRI and urea. This is consistent with previous studies (Giustiniano et al., 2014; Marty et al., 2015; Marty et al., 2016; Hertzberg et al., 2016).

Results from pre-operative studies (discussed in Chapter 4) suggest a cut off value of **RRI ≥ 0.7** as a predictor of increased AKI risk (Giustiniano et al., 2014: Marty et al., 2016: Hertzberg et al., 2016).

In the current study, RRI measurements from only two patients exceed this RRI ≥ 0.7 cut off.

In one patient, a single measurement of RRI = 0.79 was recorded. However, on review of the stored image, the spectral trace from which RRI is calculated

failed to meet the study measurement criteria. In particular, peak systolic velocity (PSV) is over estimated due to poor signal quality and incorrect calliper placement. The recorded RRI of 0.79 will therefore be overestimated. Follow-up biochemistry at day 3 did not confirm AKI by AKIN criteria. However, this patient presented with reduced baseline eGFR of 46 ml/min/1.73m2 that may indicate underlying chronic renal disease.

In one further patient, three high quality measurements of RRI were imaged and a mean RRI = 0.74 recorded. AKI stage 1 was confirmed at day 4.

It is interesting to note that this is one of only two patients within the study sample with confirmed AKI (stage 1) shortly after admission. One additional patient with confirmed AKI at day 2 was morbidly obese and no RRI measurement was achieved.

No further statistical analysis was attempted for this small data set. Test characteristics for RRI as a predictor of AKI could not be determined and this study objective has not been met.

6.5 Feasibility of RRI measurement in this context

Performance of RRI measurement was evaluated against the performance criteria outlined in Chapter 5.

	Question	Target outcome	Outcome	Target criteria met
Performance of the scan	How reliably can ED sonographer visualise the kidneys in this patient group?	Kidneys adequately imaged in 90% of patients?	60% (n=12)	**No**
	In what proportion of patients recruited can RRI be measured? (3 consecutive waveforms)	RRI measurements comply with study protocol in 90% of patients	15% (n=3) meet **ALL** measurement evaluation criteria. 25% (n=5) meet criteria for at least one measurement	**No**
	What are the limiting factors in achieving RRI measurement?	Patient, context or equipment related factors are identified	SOB 60% of patients (n=12) High BMI 15% of patients (n=3)	Key limiting factor is SOB
	Can these be mitigated?	Are there any technical / other solutions?	No. Not with current equipment capability	**No**
Time for scan	How long does it take to achieve RRI measurement? Is this reasonable in this context?	90% of RRI measurements completed in target limit to 5 mins	Mean scan time 7.7 mins	**No**
	Does the scan delay standard patient care pathway?	Minimal disruption / delay of standard care pathway. (Will vary between patients. Can we quantify this?)	No recorded disruption	Yes

Table 6.5 Feasibility criteria

In this context, reliable measurement of RRI (to the agreed protocol) was not feasible in 85% of patients. In 20% of patients (n=5), no Doppler spectral trace was obtained despite multiple attempts. The primary limiting factor was patient inability to hold their breath throughout capture of Doppler readings. This is discussed further in chapter 7.

Chapter 7 Discussion of findings

In this chapter, the technical factors limiting feasibility of RRI measurement in this patient group are discussed and potential technical solutions are explored.

The aim of this study was to determine whether ultrasound measurement of Renal Resistive Index (RRI) is a feasible and clinically useful method of early identification of Acute Kidney Injury in this patient group.

When the study was proposed, no previous studies had been identified that explore either measurement of RRI in an **ED** point of care setting or the potential use of RRI as a **predictor** of AKI. To our knowledge, at the time of writing, this remains the only study to explore the potential use of RRI in this context.

7.1 Feasibility of RRI measurement in the resuscitation room

The first objective of the study was to determine if RRI measurement is feasible in an ED resuscitation room setting using a point-of-care ultrasound system.

Multiple studies in critical care demonstrate that, with minimal additional training, ultrasound skilled intensivists are able to perform RRI measurements in high dependency patients (Barbani et al., 2010; Darmon et al., 2011; Schnell et al., 2012; Viazzi et al., 2013; Guinno et al., 2013; Schnell et al., 2013).

However, in patients requiring ED resuscitation room care, performance of RRI measurement was technically challenging. In this study, where RRI measurements were achieved, only 15% (n=3) met the full feasibility performance criteria outlined in Chapter 5.

The key technical challenge was patient inability to hold their breath during capture of the spectral trace from which RRI is calculated.

7.2 RRI measurement technique

The operator dependence of Doppler RRI measurement is well recognised (Gottlieb et al., 1997; Deruddre et al., 2006; Ninet et al., 2015; Darmon et al., 2011). However, with careful measurement technique, excellent levels of interobserver and intraoperator reliability can be achieved (Knapp et al., 1995; Darmon et al., 2011; Lee et al., 2015).

From the critical care studies reviewed, reported intraoperator errors for RRI range between 2.1% (+2.6) to 3.29% (± 2.18). The measurement protocol used for this study was adapted from the validated approach proposed by these early authors. (see Figure 5.11)

Following localisation of the intrarenal vessels on colour Doppler, the Doppler sample gate is placed within the lumen of the vessel. This is achieved by selecting the pulsed wave (PW) spectral Doppler mode and using the track pad on the machine control panel to align the PW sample line with the selected vessel. The sample gate is then moved to the lumen of the vessel at the required sample site using a track pad keyboard function.

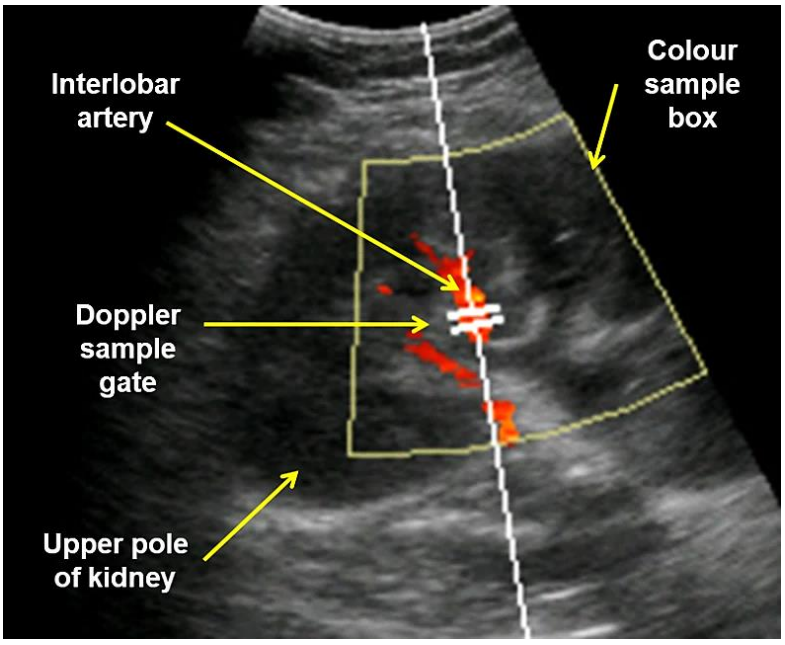


Figure 7.2 : *Spectral Doppler sample gate is placed over the lumen of the target vessel. Transducer is positioned to align the sample beam and vessel to eliminate need for angle correction.*

Doppler estimates of blood flow velocity are affected by the angle dependence of the Doppler shift.

$\Delta f = 2f_o V\cos\theta / C$ Where Δf = Doppler shift
f_o = transmitted frequency
V = velocity of flow
C = speed of sound
θ = beam to vessel angle

Error resulting from poor beam to vessel angle can be reduced by use of an angle correction function or by aligning the Doppler sample beam along the lumen of the vessel to ensure an angle of 0^o. (See Figure 7.2)

As a ratio (PSV – EDV / PSV), resistive index (RI) is largely independent of angle of insonation. However, measurement reliability can be improved by careful transducer positioning and alignment of the sample beam and vessel to eliminate the need for angle correction.

PW mode is then selected, Doppler gain and velocity scale settings are optimised and a spectral trace captured.

This process must be completed whilst keeping the target vessel within the field of view. The vessel must then remain stationary relative to the Doppler sample gate for the duration of the sample period (minimum of 3 cardiac cycles).

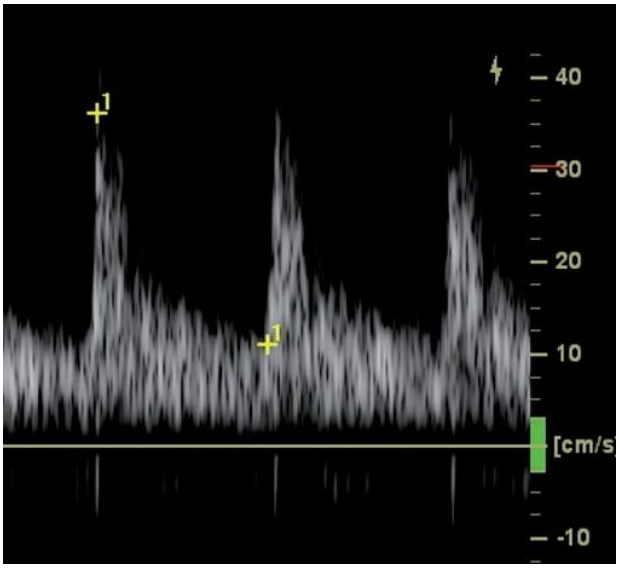


Figure 7.2c RRI *measured from the spectral trace captured over a minimum of three cardiac cycles*

This sequence of image optimisation and capture of a spectral trace requires a high degree of operator dexterity and patient cooperation. The kidney is a mobile structure that moves in response to changing diaphragm position as the patient breathes. Once the target intrarenal vessel is identified, the patient must be able to hold their breath as the Doppler sample gate is placed and the spectral trace captured. Breathing movement during this period typically will result in complete loss of the Doppler signal. For a patient with even a moderate degree of breathing difficulty, this may be problematic.

Typically, the process of initial Doppler image acquisition, optimisation of settings and capture of the trace will take place over several breath holds. Throughout this period, any other movement of the patient will result in loss of alignment between the ultrasound sample beam and the target vessel.

During capture of the spectral trace, magnification of the real time image of the kidney is reduced and a small static image is displayed on the screen above the Doppler waveform (Figure 7.2d). Fine adjustment of the scan position to ensure correct placement of the sample gate is maintained is difficult during this spectral capture phase. Successful capture of a high quality spectrum is therefore dependent on successful patient breath hold and elimination of patient or transducer movement.

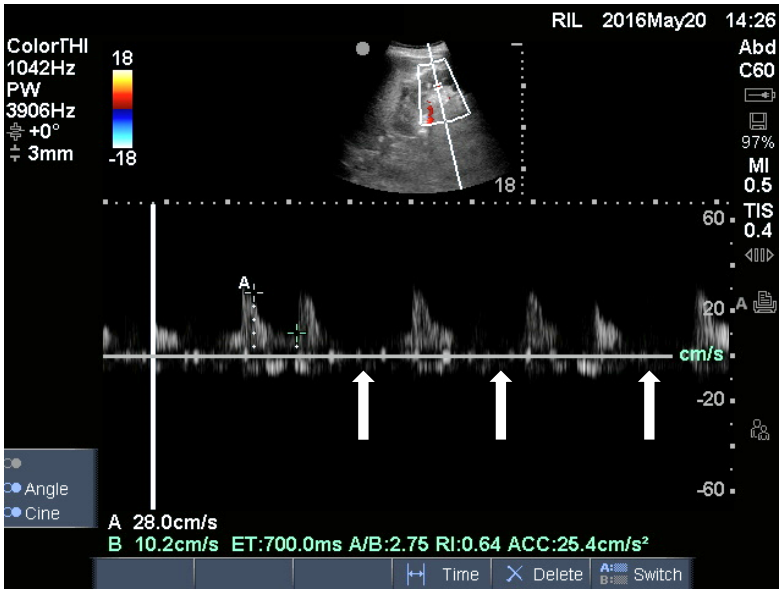


Figure 7.2d *Doppler sample gate moves in and out of the vessel lumen with movement of the kidney during breathing motion. This results in loss of the Doppler signal and gaps within the spectra trace (**bold arrows**).*

7.2.1 Adaptation of scan technique

Prior to commencement of the scan, the importance of breath hold was explained to the patient. Normal scan technique when imaging the kidney normally requires the patient to hold their breath on inspiration. This pushes the kidney lower into the abdomen improving visualisation from a subcostal or intercostal approach. However, breath hold on inspiration can be tiring for the patient. For the purpose of this study, an adapted scan technique was used to minimise patient fatigue and improve patient cooperation.

To identify the intrarenal vessels and capture a spectral Doppler trace, it is not necessary to visualise the kidney in its entirety. Imaging on **passive expiration** will normally enable good visualisation of the kidney and requires less patient effort to maintain breath hold. This technique (***breathe in – breathe out – stop breathing***) was demonstrated to the patient by the operator and each patient was invited to practise the technique (as a check of understanding) prior to Doppler imaging.

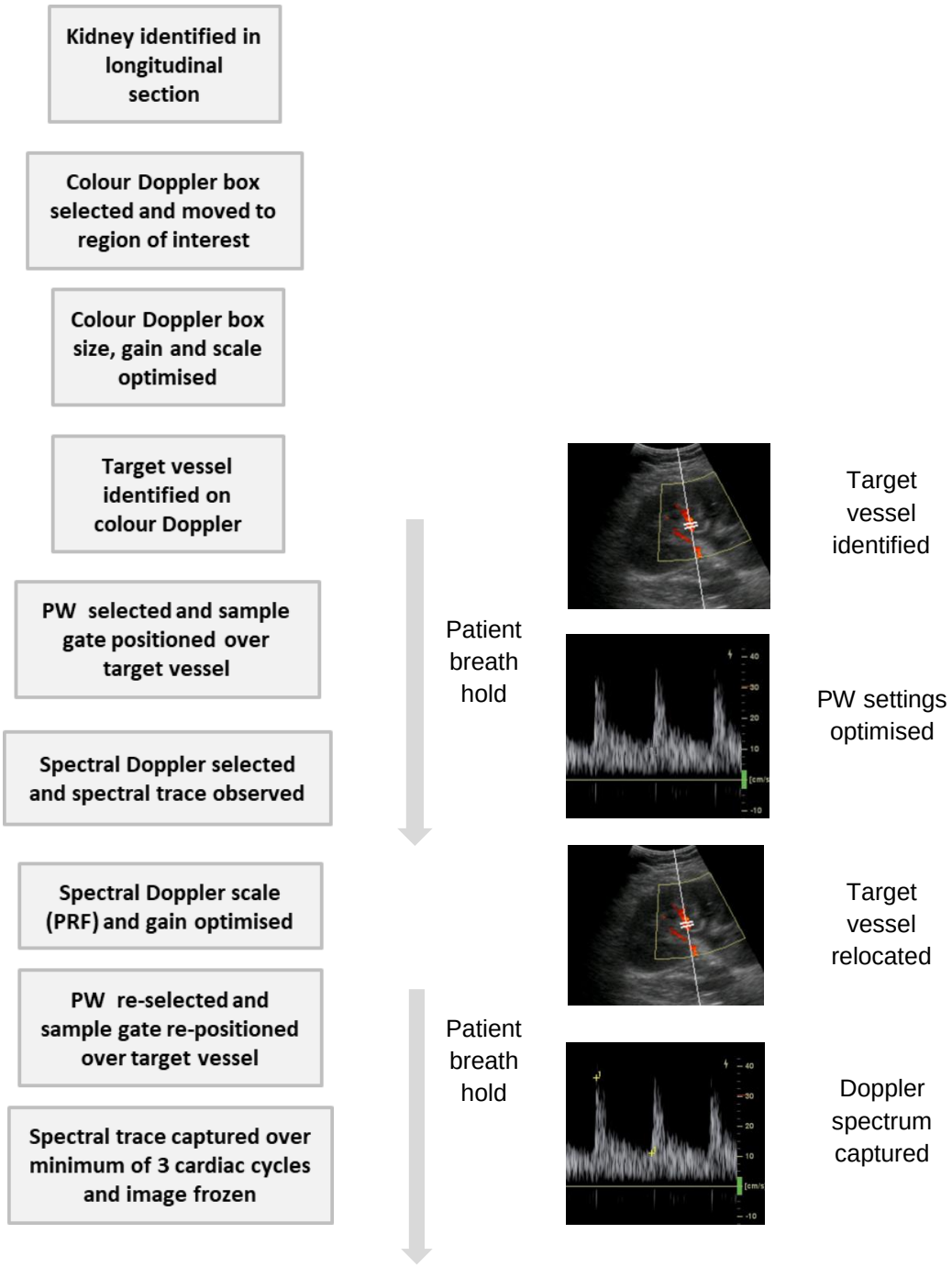


Figure 7.2e Scan sequence for Doppler RRI measurement.

Typically, the process of Doppler image acquisition, optimisation of settings and capture of the trace will take place over several 'breath holds' and may take several attempts.

7.3 Measurement of RRI in patients requiring resuscitation room care

Review of the images acquired from the ED patient sample demonstrates incomplete spectral traces (fewer than 3 complete waveforms captured) in **85%** of measurements (n=17).

In 30% of patients (n=6) **no** usable spectral trace was achieved and it was not possible to measure RRI. Patient shortness of breath (SOB) was noted as a limiting factor in **all** cases.

Whilst RRI measurement requires operator dexterity and a good understanding of equipment controls, in a cooperative patient, this measurement is achievable and used extensively in routine general ultrasound practice. In critical care patients, breathing movement is avoided by pausing mechanical ventilation as the spectral trace is captured. This eliminates movement of the kidney and avoids need for patient cooperation. This would explain the lack of technical difficulties reported (other than high BMI) and the limited additional operator training required in early studies in a critical care context (Darmon et al., 2011; Barbani et al., 2010; Schnell et al., 2012; Viazzi et al., 2013; Guinno et al., 2013; Schnell et al., 2013).

More recent studies (exploring the **predictive** value of RRI for AKI) focus on patients who are undergoing planed surgical intervention (Giustiniano et al., 2014; Marty et al 2015; Marty et al., 2016; Hertzberg et al., 2016). Pre-surgical measurement of RRI was performed during pre-operative assessment, with follow-up measurement during the immediate post-surgical period. Consistent with the current study findings, respiratory distress is noted as an exclusion factor in recruitment to these perioperative studies. Post-operative measurements were taken either while mechanical ventilation was paused or during the recovery period. Again, patients who were unable to cooperate (due to SOB or confusion) were excluded from follow-up.

These studies demonstrate that, in patients who are either ventilated or pre-morbidly well, RRI is consistently achieved. However, whilst not explicitly stated by any of these authors, RRI was **not** measurable in patients who lack capacity to cooperate by breath hold during capture of the Doppler spectral trace. This is confirmed by the current ED study where SOB was identified as the most likely cause of measurement failure.

7.4 Operator training

To be clinically useful in an ED context, there must be sufficient operators trained in the technique of measuring RRI. Bedside ultrasound is performed routinely by UK Emergency Medicine doctors for a range of trauma and acute clinical indications. Ultrasound competencies have formed part of the formal credentialing for ED specialist trainees since 2013 (RCEM 2018). Therefore, it was anticipated that ED staff that have completed RCEM competencies would require minimal additional training for measurement of RRI in a cooperative patient.

In the critical care studies reviewed, discussion of operator training and background is limited. In a letter to the *Journal of Critical Care*, Schnell et al (2015) acknowledge that level of prior ultrasound experience required to "… *allow adequate RRI measurement is unclear*". However, for intensivists with experience of focused echo in life support, they propose that a half day, Radiology led, training event (1 hour didactic, 2-3 hours hands on practice) was sufficient.

This level of training would be consistent with that required for other point of care ultrasound techniques used extensively in emergency medicine. However, it is of note that Schnell et al are referring to measurement of RRI in patients where ventilation can be paused.

In their earlier study, Schnell et al (2014) compared RRI measurement from junior operators with half-day training and senior operators (intensivists with 5 years + experienced of renal Doppler). They report reasonably good

agreement between senior and junior staff (interclass correlation coefficient 89%; 95% confidence interval 82% - 93%) with negligible systematic bias (p=0.001). They note also that the 95% limit of agreement for this study was consistent with previous studies using only experienced operators. Inter-operator reproducibility was acknowledged as a limiting factor by these authors but, they conclude that RRI still performs well as a predictor of overall patient outcome in a critical care context.

Within the limitations of the current study, the training required by ED doctors to undertake renal Doppler measurements was not explored due to the technical difficulties outlined above. However, it is worth considering if RRI measurement in this patient group could be improved by additional operator training.

In the current study, RRI measurement was performed by a single expert sonographer with extensive experience of renal ultrasound and Doppler measurement technique. Despite this level of operator expertise, adequate RRI measurement was not achieved in 85% of patients (n=17). Even high intensity targeted training for ED point of care ultrasound users is therefore unlikely to provide the skills required to deliver reliable measurement of RRI in these patients.

7.5 Could the feasibility of RRI measurement be improved by use of a higher specification ultrasound system?

The ultrasound equipment used is a laptop based system designed explicitly for the point of care market. As such, some of the system software packages and user operator controls are somewhat simplified compared to the high end systems used in central imaging departments. However, key Doppler operator controls are standard between most commercially available systems. The sequence of control adjustments that needs to be made to capture a spectral trace (as detailed in Figure 7.2e) is common to both high specification and point of care systems.

The improved spatial and contrast resolution offered by a high end ultrasound system may enable better visualisation of the kidney and easier identification of intrarenal vessels. However, this would not resolve the issue of patient breathing movement.

7.6 Possible technical solutions

7.6.1 Pulsatile flow detection

Pulsatile Flow Detection (**PFD**) is a manufacturer specific equipment function launched in 2000 by GE Medical and is specific to the GE Logiq 700 Expert ultrasound system (GE 2000)

PFD provides real-time analysis of blood flow dynamics to identify vessels in which pulsatile flow is detected. The Doppler signal is analysed to identify flow characteristics such as high temporal variance (rapid velocity change) consistent with pulsatile arterial flow.

In a standard colour Doppler system, mean Doppler frequency is displayed by colour hue within the region of interest (as defined by the colour box) with directional information colour coded as red and blue.

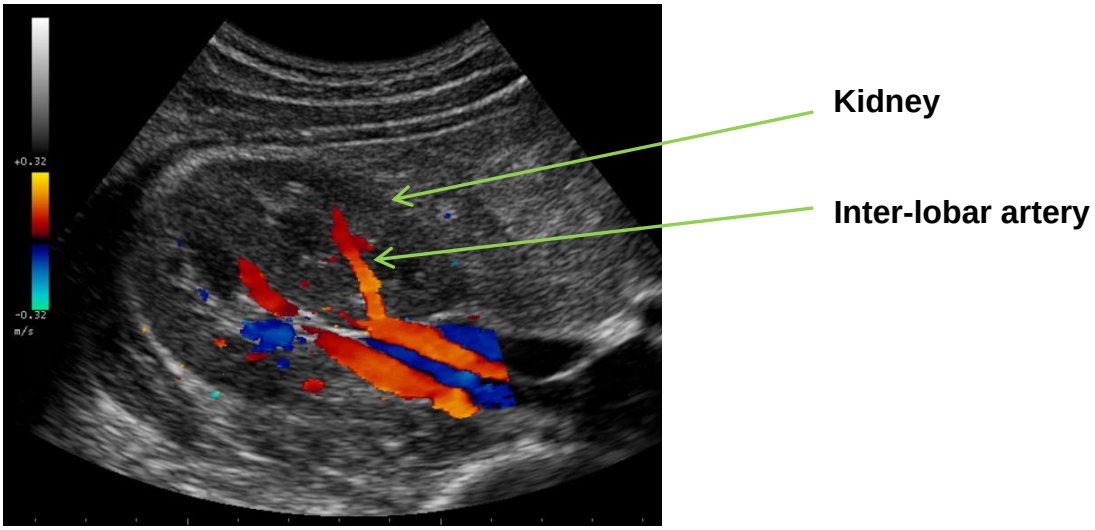


Figure 7.6a *Conventional colour Doppler. Flow towards the transducer is coded as red. Flow away from the transducer is coded as blue.*

In this conventional colour Doppler system (Figure 7.6a), blood flow characteristics can be visualised using fast Fourier transform (FFT) analysis. However, in patients with limited ability to hold their breath, visual perception of pulsatile flow is limited by relative movement of the colour sample box and target vessels. The Pulsatile Flow Detection (**PFD**) facility tracks flow characteristics and highlights areas demonstrating characteristics of pulsatile flow as a separate colour map superimposed over the standard colour box.

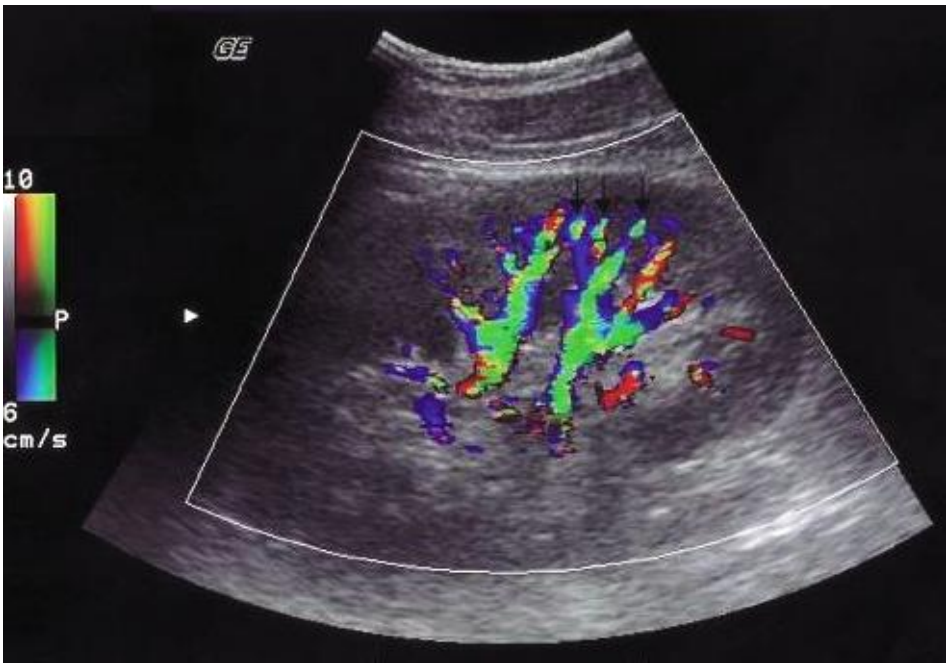


Figure 7.6b *Pulsatile Flow Detection map (green) superimposed over a conventional colour Doppler map of renal blood flow. (From Kim SH et al., 2002)* *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2713986/*

Early clinical studies of this technique include an evaluation of PFD in measurement of renal resistive index (Kim SH et al., 2002). Using conventional CFM and PFD guided techniques; Kim compared time to acquire RRI measurement and quality of the spectral trace in 56 native kidneys. In this study of healthy volunteers, they conclude that, the time to acquire RRI can be reduced with PFD guidance with no change in the quality of spectral trace.

However, this is a time reduction (mean of 30 seconds) for the **overall scan**. Essentially, the benefit offered by this technique is easier differentiation between arterial and venous flow. This could allow more rapid identification of target intrarenal arteries, particularly for an inexperienced operator. However, the duration of patient breath hold required during capture of the spectral trace is not affected. Overall scan time may be reduced but, there would be no obvious benefit of this technique in a breathless patient.

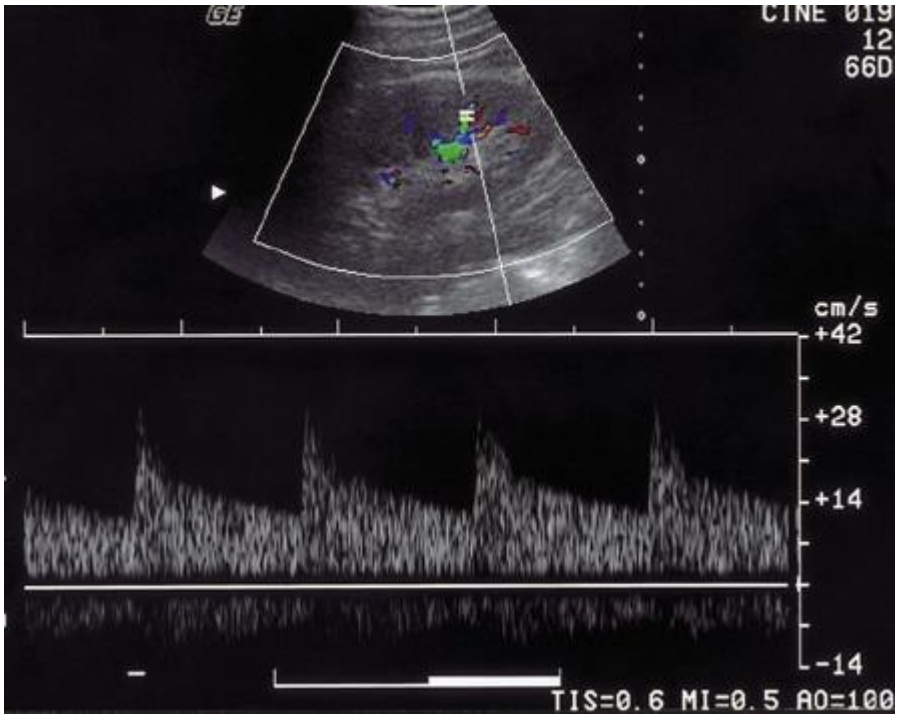


Figure 7.6c *Pulsatile Flow Detection map (green) used to locate an intrarenal vessel from which a conventional measurement of RRI is captured. (From Kim SH et al., 2002)* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2713986/

No further references to PFD techniques were identified through targeted literature review.

7.6.2 Two-dimensional flow index mapping (2D-FIM)

Only one study was identified that offers a potentially credible alternative to the standard approach to capture and manual measurement of RRI.

Building on an earlier feasibility study by Sikdar et al (2007), Zhang et al (2010) propose a **two-dimensional flow index mapping function** for rapid quantitative imaging of flow indices. This method provides automated estimates of RI directly from the **power Doppler** signal.

Using a thresholding technique and a clutter filter to remove signals from static tissues, vessel wall movement and low velocity venous flow, the **power of the filtered Doppler signal** ($\mathbf{P_{filt}}$), is extracted as a function of the Doppler shift at each image location.

By synchronising signal capture with an ECG trace, values for $\mathbf{P_{filt}}$ are captured at peak systolic and end diastolic image frames.

They demonstrate that, as $\mathbf{P_{filt}}$ is linearly related to estimated Doppler shift ($\mathbf{\Delta f}$). Therefore $\mathbf{P_{filt}}$ at peak systole and end diastole can be used as surrogate measures from which resistive index (RI) can be calculated.

$$\mathbf{RI} = \frac{\mathbf{PSV - EDS}}{\mathbf{PSV}} \approx \frac{\mathbf{P_{filt}^{systole} - P_{filt}^{diastole}}}{\mathbf{P_{filt}^{systole}}}$$

PSV = peak systolic velpcity
EDV = end diastolic velocity
$P_{filt}^{systole}$ = power of the filtered Doppler signal at systole
$P_{filt}^{diastole}$ = power of the filtered Doppler signal at diastole

In an original feasibility study by Sitkar et al (2007), RRI values acquired by standard measurement technique and by **2D-FIM** were compared in 9 transplanted kidneys and 4 normal volunteers (upper, mid and lower pole interlobar arteries). **2D-FIM** acquired indices showed a high level of correlation ($r=0.8$, $P<0.0004$) with those generated by manual capture and measurement of a PW spectral trace.

A follow-up study by the same group (Zhang et al., 2010) confirmed these findings in a further 8 normal volunteers and 8 transplant kidney. Again, a high level of correlation ($r=0.84$) was found between **2D-FIM** and standard acquired RRI values.

Unlike the standard measurement of RRI from a single target vessel, **2D-FIM** provides a two dimensional map of **resistive index** within the selected region of interest. From this, post-acquisition quantitative values for RRI in specific vessels can be calculated.

Using **2D-FIM**, mean time to acquire RRI values was 10 seconds. Total scan time was 5 minutes including location of the kidney and orientation of the required section. This capture time for mapping of simultaneous RRI calculation across multiple vessels is impressive. However, the authors note that motion blur may still be problematic.

In the original feasibility study (Sikdar et al., 2007) a static clutter filter was used to reduce noise but, no motion correction was applied to the captured 2D data set. An inherent feature of power Doppler is the need for low pulse repetition frequency (PRF) and hence an associated low temporal resolution (9-13 frames per second in this study).

Although no statistical difference was seen between **2D-FIM** and manually acquired RRI measurements, Zhang et al (2010) acknowledge that low PRF could in theory lead to an underestimate of RRI as there is the risk that peak systole (the time of maximum flow velocity) could be missed.

Of more significance to the current study is the impact of image blur due to poor temporal resolution. This is not addressed in the studies by Sikdar and Zhang but, it is of note that, in these studies, **2D-FIM** was evaluated in normal healthy volunteers and in transplant kidneys. In both groups, inability to maintained breath hold was not an issue. However, it may not be possible to replicate these findings in an ED population.

The system described combines **2D-FIM** processing with a conventional image formation technique that is limited by a standard pulse transmission / reception sequence. In newer systems, full field transmission techniques offer increased PRF and rapid image capture from a single pulse transmission. This could reduce motion blur as temporal resolution would be improved.

Further improvement could be achieved by limiting the power Doppler sample box size to encompass a single target vessel. This would allow increased PRF by reducing the area over which multiple power Doppler sample gates are employed.

7.7 Measurement of resistive index in an alternative vascular bed

As the potential technical solutions explored fail to resolve the challenge of breath hold in sick patients, it may also be worth exploring the potential value of resistive index measurement in an alternative vascular bed (i.e. not the renal vessels).

From the experimental and clinical evidence reviewed, it is clear that the determinants of RRI are systemic rather than renal and that a strong correlation exists between RRI and factors such as aortic pulse pressure. Logically, other abdominal vascular beds that are also affected by cardiac output and systemic arterial compliance may offer an alternative to measurement of RI in the kidney.

Building on early experimental evidence from animal studies (Norris and Barnes, 1984; Seiler et al., 2012), a number of authors speculate that RRI

should correlate with resistive index measured in the spleen (**SRI**) and that the clinical significance of raised SRI would be similarly indicative of systemic risk factors for renal disease (Seiler et al., 2012; Grün et al., 2012; O'Neill, 2014; Grupp et al., 2017). The research questions addressed by these authors differ in focus from the current study but, they provide useful evidence of close correlation between determinants of haemodynamics in these related abdominal vascular beds.

In a study of stable transplant recipients (n=87) Seiler et al (2012) measured RRI, SRI and carotid artery intima-media thickness (IMT). Interestingly, this is one of only three studies identified that examine RRI prospectively in stable transplant recipients and the first study to consider SRI as a potential surrogate measure to predict patient and allograft outcome.

In this study, IMT and RRI were measured using standard techniques. SRI measurement was repeated three times in the segmental branches of the splenic artery at their entry to the splenic parenchyma and SRI values averaged.

Seiler et al claim a strong association with IMT (as an established marker for systemic vascular disease) and with patient mortality for both RRI and SRI. However, their results indicate a fairly weak correlation between these factors. [RRI: r=0.203 (P=0.006); SRI: r =0.315 (P<0.001)].

Interestingly, they note that, as a predictor of overall patient outcome, SRI performs slightly better than RRI in this study. However, raised RRI and raised SRI both failed to predict clinically significant decrease in eGFR or need for dialysis and neither ratio performed better than recipient age as an independent risk factor for allograft outcome. The findings of this study appear to be somewhat over stated. However, they are consistent with evidence from other studies of transplant kidneys that confirm the relationship between resistive indices and the recipient rather than the donor kidney.

Grün et al (2012) explored the difference between RRI and SRI as a potential marker for renal parenchymal damage in native kidneys. In this larger prospective study, the difference of resistive indexes (RIs) in the spleen and kidney (**DI-RISK**) was compared in unmatched cohorts of healthy volunteers (n=152) and in patients with known chronic renal disease (n=290).

In this study, a slightly stronger correlation between RRI and SRI was confirmed (r = 0.54, P= 0 .001) and both demonstrated a weak association with patient age (RRI: r = 0.18, P = 0.027; SRI: r = 0.33, P = 0 .001) and with common carotid artery IMT (RRI: r = 0.19, P =0 .022; SRI: r = 0.23, P = 0.005).

Both studies demonstrate that RRI and SRI are similarly influenced by systemic cardiovascular factors that are known markers for renal disease. However, consistent with previous studies, neither predicts specific renal outcomes.

A more recent study by Grupp et al (2018) explores the difference between RRI and SRI as a potential marker for renal artery stenosis (RAS). Both indices were measured in hypertensive patients with no evidence of renal artery stenosis (n=181) and in patients with suspected stenosis who were followed up by angiogram (n=24).

In the cohort where RAS was not suspected, they note an age related steady rise in absolute values for both RRI and SRI (from age of 30) with values for SRI consistently slightly lower across all ages with a median difference of 0.055. In patients with confirmed RAS on angiogram, the difference between RRI and SRI was significantly lower [(median - 0.05) P= 0.002].

For SRI to offer a viable surrogate measure for RRI there must be a predictable and constant relationship between these respective flow indices. Of note from the study by Grupp et al was the consistent relationship

demonstrated between RRI and SRI across age groups. The slope of age dependency was absolutely parallel for RRI and SRI with both indices independent of gender and kidney location (left v right).

The primary question addressed by this study was diagnosis of RAS. However, confirmation of the constant relationship between splenic and renal flow indices does confirm the dependence of both on systemic factors (where RAS is absent) and suggests that use of SRI may be a viable alternative to RRI measurement.

No studies were identified that explore alternative vascular beds other than the spleen.

Measurement of splenic resistive index

In the context of the current study in an ED population, the technique used to measure SRI and its feasibility is worth considering. Ultrasound identification of the spleen in patients requiring resuscitation room care is within the normal skill set of ED point of care ultrasound users. The spleno-renal space is examined routinely as part of the focused assessment with sonography in trauma (FAST) protocol to identify intra-abdominal bleeding in blunt trauma and forms part of standard trainee credentialing. However, visualisation of the splenic perihilar arteries can be challenging. In a supine patient, this region is frequently obscured by overlying bowel gas in the stomach and an adapted technique (requiring patient movement and cooperation) may be required to visualise the splenic hilum. Visualisation also varies considerably with patient body habitus and is challenging in patients with high BMI.

In the studies reviewed, patients and normal volunteers were fasted to reduce gastric contents and overlying bowel gas. Patients were examined in both supine and decubitus positions and all subjects were ambulatory. All of these technique adaptations may be problematic in patients requiring resuscitation room care. Splenic perihilar arteries are slightly larger than renal interlobar arteries and are arguably easier to identify and localise if the spleen is visualised. However, both renal and splenic arteries are subject to movement

with the diaphragm as the patient breathes. Whilst this was not explored within the remit of the current study, SRI measurement may be worth further exploration in an ED patient sample. However, patient inability to achieve adequate breath hold is not necessarily addressed by use of SRI as a surrogate for RRI.

Conclusion

Pulsatile Flow Detection (PFD) may offer some benefit in speeding up localisation of intrarenal vessels, particularly for inexperienced operators. However, this technique offers no benefit in sick patients where a high quality spectral trace cannot be achieved.

2D-FIM does not offer a complete solution to the challenge of RRI measurement where SOB is a limiting factor. However, adaptation of this technique for **targeted single vessel sampling** could be worth exploring as a method of rapid acquisition of RRI estimate in patients who have difficulty with breath hold.

There is some evidence supporting the use of SRI as a surrogate measure for RRI and this may be worth further exploration in relation to prediction of AKI. However, technique adaptation required for SRI measurement may be limited in patients requiring resuscitation room care and both measurements are affected by patient ability to hold their breath.

A technical solution is likely to be a more promising approach if adoption of RRI or SRI as a predictor of AKI is to be considered. Even where patients are pre-morbidly well, these measurements require a degree of operator skill and may be prohibitively time consuming to be used in an acute setting.

In this chapter the technical limitations of RRI measurement in this context are discussed along with potential technology focused solutions.

Currently available commercial systems do not have the functionality to allow reliable and rapid RRI measurement in a breathless patient. However, in newer (post 2010) systems with high temporal resolution, use of an adapted version of the power Doppler signal processing technique 2D-FIM for targeted RRI measurements may be worth exploring.

Use of flow indices in alternative vascular beds offers some promise, particularly where unilateral renal disease is suspected. However, use of SRI as a surrogate measure is unlikely to resolve the challenge of breath hold in an ED population.

The study findings need to be interpreted in the context of the challenges presented by research in an emergency department setting with an acutely unwell patient population. These factors are explored in depth in Chapter 8.

Chapter 8 Ethical considerations and patient consent

Patients requiring resuscitation room care are acutely unwell and are, by definition, a vulnerable population. Informed consent for research participation in this context is both controversial and ethically unclear (Schmidt et al 2004). In this chapter, the ethical issues relevant to research in emergency medicine are explored and their impact on the current study is discussed.

Research in an emergency or acute care context is difficult (Hirshon et al., 2013; Kraus et al., 2012; Levine et al., 2017; Sahan et al., 2016; Tucker et al., 2014). Conflicting ethical priorities may stifle research and lead to practices for which the evidence base is uncertain. There are also multiple additional factors that may disrupt standard approaches to research, not least of which is the current unrelenting pressure on front line clinical services.

As formal research governance procedures have emerged, along with considerable legislative confusion, there is growing concern that many acute conditions, urgent treatments and interventions are under-researched. The pressing need for high quality research in emergency medicine needs to be balanced alongside the decision to involve vulnerable individuals in research activity. Central to this is the question of patient capacity to consent and how this can be interpreted in the context of an acute presentation.

8.1 Review of ethics literature relevant to research in an Emergency Department context

A focused literature review was undertaken to gain a better understanding of current legislation and best evidence for management of ethical issues and consent in an emergency context. In addition to the legislative documents outlined, the papers identified are focused largely around patient attitudes to consent, barriers to patient enrolment, deferred consent, surrogate decision makers, proxy consent and non-voluntary enrolment. The broad findings from this review are detailed below with discussion of how they have influenced ethical review and approach to consent for the current study.

8.2 Legislative framework

The current UK position regarding patient consent for emergency research has emerged against a backdrop of complex and at times contradictory European Union (EU) and non-EU international legislation (Kompanje et al., 2014; Mentzelopoulos et al., 2015)

Directive 2001/20/EC in particular was criticised widely for effectively halting research in an emergency setting by requiring consent prior to enrolment for all research participants. Before revision of 2001/20/EC in 2014, some member countries (including the UK) introduced the option of **deferred consent** and this was adopted as part of Good Clinical Practice (GCP) standards (NHS Health Research Authority 2017). https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/good-clinical-practice/

In response to widespread challenge, EU legislation 2001/20/EC was amended to include the option of deferred consent (EU Regulation 536/2014).

8.2.1 How is consent defined in legislative guidance?

The European Commission Clinical trials - Directive 2001/20/EC defines informed consent as

"…the decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation." *(https://ec.europa.eu/health/human-use/clinical-trials/directive_en)*

The 2001 European Clinical Trials Directive (2001/20/EC) forms the basis of national law in the member countries including the UK. In the document *Good Medical Practice* (2013) the UK General Medical Council provide guidance on good practice in health research. Subsection 33-35 details consent requirements for research into treatment in emergencies (https://www.gmc-uk.org/guidance/ethical_guidance/6477.asp)

Guidance here is based on recognition within the Mental Capacity Act 2005 that urgent research in emergency medicine may require retrospective consent. Where this is necessary, agreement from a doctor not involved in the research is required and consent must be gained retrospectively where this is feasible.

UK guidance on legislation relevant to research in the ED is published by the Health Research Authority via the NRES website. Based on scrutiny by the National Institute of Health Research (NIHR) *Injuries and Emergencies National Specialist Group*, the guidance provided seeks to translate the complex EU legislation into practical *'real world'* recommendations.

A clear distinction is made by NIHR between trials involving drug products - Clinical Trials of Investigational Medicinal Products (CTIMPs) and trials of "*other intrusive emergency research*".

In adults who are unable to consent, English (and Welsh) law allows them to be recruited to emergency studies (other than CTIMPs) without prior advice from a consultee if:

- treatment needs to be given urgently
- it is also necessary to take urgent action to administer a drug for the purposes of the trial
- it is not reasonably practicable to seek advice from a consultee
- the procedure is approved by a NHS Research Ethics Committee
- a consultee is consulted as soon as possible to seek advice on the participant's likely views and feelings.

8.2.2 Non-European guidance on consent for emergency research

Many of the studies reviewed refer to emergency research carried out in the United States of America where legislation governing consent is provided by the Food and Drug Administration (FDA).

For the purpose of research in emergency medicine in the US, a series of fairly narrowly defined exemptions from the principle of offering an *"informed and free decision"* are adopted, as outlined in the FDA document *Exception from Informed Consent Requirements for Emergency Research (FDA 2013).*

Within the scope of these non-binding recommendations, ethics panels may decide that, where research is justified and prospective consent cannot be gained from the patient (or their authorized legal representative), this can be waived.

This complex, detailed document was produced by the FDA in response to growing concern that, due to patient lack of capacity to consent, much of the standard therapies and interventions used in emergency medicine had not been adequately evaluated through robust clinical trials.

By offering some scope for exception from informed consent, the FDA was seeking to promote research activity that would:

- evaluate potentially lifesaving therapies
- explore the effectiveness and safety of existing therapies
- improve interventions for conditions that currently have poor outcomes

To meet the FDA requirements for prospective informed consent to be waived, studies must also meet a series of defined criteria (21 CFR 50.24 APPENDIX A pg. 49).

In broad terms these stipulate that:

- *subjects must be in a life threatening situation, intervention is required and available treatments are unproven*
- *subjects must be unable to consent as a result of their medical condition*
- *contact with a legally authorized representative is not feasible*
- *prospective recruitment of participants is not possible*
- *participants may benefit directly from intervention*
- *evidence from experimental studies supports the potential for this intervention in this patient group*
- *risks associated with the study investigation are reasonable in the context of this condition*

The FDA stipulates additional responsibilities for research parties that offer explicit protection to participants when informed consent is not gained prior to study intervention.

These include:

- *consultation with representatives of the community(ies) in which the research will take place and from which the subjects will be drawn*
- *public disclosure of information before the start of the study and following its completion*
- *a commitment by the investigator to try to locate the subject's legally authorized representative or contact a family member to determine whether the family member objects to the subject's participation*
- *study oversight by an independent data monitoring committee.*

(FDA regulation 21 CFR 50.24 2013)

8.3 Gaining consent in sick patients

The central ethical challenge in research in an emergency context is patient inability to provide informed consent and time constraints that make contact with a legal representative non-feasible (Sahan et al., 2016).

Capacity to consent is measured by individual ability to

- *understand the information relevant to the decision*
- *retain the information*
- *use or weigh the information*
- *communicate his or her decision (by any means)*

(Mental Capacity Act 2005)

In patients attending the ED and requiring resuscitation room care, capacity in all four of these broad areas may be compromised and difficult to assess. Arguably, normal mental status is highly unlikely in this context. Therefore, it is questionable whether fully informed consent is *ever* achievable in this patient group. This raises the difficult question of how consent in emergency care patients should be approached.

8.4 What are the alternatives to prospective patient consent?

8.4.1 Use of a Legal Authorised Representative

Where an individual is incapacitated and unable to provide consent, the Mental Capacity Act defines conditions in which advice may be sought from a Legal Authorised Representative (LAR) acting on behalf of the patient. In the studies reviewed, it is evident that use of a proxy or surrogate decision maker is common practice (Bryant et al., 2012; Mentzelopoulos et al., 2015). However, it is recognised that in an emergency setting, it may not always be feasible to contact a LAR or next of kin.

There are also uncertainties regarding the extent to which relatives are able to accurately predict patient preferences. Bryant (2012) investigated preference discrepancies between surrogate decision makers (n=200) and suspected stroke patients (n=200) presenting to an acute stroke assessment unit. In this

study, high levels of agreement were observed in prediction of preferences regarding standardised interventions (80.2% accuracy). However, agreement regarding preference for research participation was much lower (49% - 74% accuracy depending on the type of clinical trial).

In a follow up study of out of hospital cardiac arrest patients, Kamarainen et al (2012) explored the opinions of patients and their spouses (surrogated decision makers) on the policy of surrogate consent for research participation. High levels of agreement were noted between patients and relatives. However, as an interesting foot note to this study, the clinicians consenting patients to research participation were sceptical about the ability of surrogates to provide valid consent. All of the spouses surveyed reported a high level of confidence in their ability to decide on study participation on their partner's behalf. However, it could reasonable be argued that, in the context of pre-hospital cardiac arrest, the patient's spouse is also likely to be incapacitated to some extent. This could account for the lack of confidence in surrogate consent expressed by the recruiting doctors.

A study by Dutton et al (2008) explored capacity to consent in a cohort of 2011 consecutive patients presenting to a large trauma centre at the University of Maryland. Potential to consent to a hypothetical research study was assessed at 1 hour post admission in all patients and whether consent could be gained by proxy (LAR) within 3 hours. Complete data were captured for 1734 patients. Of these 982 (57%) were judged to have capacity to consent. Of the remaining 752 patients, LAR consent was not available for 348 (20% of total).

Of particular relevance to the current study of RRI is Dutton's retrospective review of patients who were assessed as able to provide consent on initial presentation. In two thirds of these patients, findings "*strongly suggestive of* (mental) *impairment*" were noted. Although the patients assessed by Dutton et al were severe trauma patients, this study does call into question the perceived capacity to consent in patients requiring high level care and the limited feasibility of LAR consent.

For the current study of RRI, consent by surrogate was rejected. Next of kin are not always available and patients lacking capacity to consent would be unlikely to cooperate with the scan.

8.4.2 Deferred consent

Revision of 2001/20/EC in 2014 to permit deferred consent recognised that research in emergency medicine may require retrospective consent. Where this is necessary, agreement from a doctor not involved in the research is required and consent must still be gained retrospectively where this is feasible. This approach requires researchers to build into a research proposal a strategy for contacting participants after the research intervention has taken place. This has clear resources implications.

Offerman et al (2013) explore the use of follow up telephone contact to gain delayed consent for patients enrolled to a prospective multi-centre study of outcomes in anticoagulated patients with blunt head trauma (n=506). In this example of deferred consent, patients were not informed of the study during their initial hospital visit. The patient (or their legal representative) was contacted by telephone a minimum of 14 days after ED discharge. Five patients were lost to follow up but, in 500 of the remaining 501 patients consent was confirmed. They conclude that this approach was both effective and well received by subjects and their representatives.

The study by Offerman et al is purely observational. Outcome data were collected (along with patient contact details). However, there was no direct patient contact or need for consent to an immediate intervention. Although RRI measurement is non-contributory in the current study, ultrasound is still an intervention for which patients would normally be asked to consent and it requires patient cooperation at the time of scan. Consensus was reached that deferred consent was therefore inappropriate for the current study.

8.4.3 Consent waiver

Where research interventions involve rapid decision making (for example in trauma, stroke or cardiac arrest), the current regulatory framework provides scope for consent to be waived (GMC 2018). However, this approach still requires subjective judgement of patient mental state and their lack of capacity to consent. Each individual must be assumed to have capacity unless there is clear evidence that this is lacking.

The broad pattern emerging from review of the literature suggests that consent waivers are most likely to be applied for purely observational studies of time critical interventions (Wright et al., 2008; Fox et al., 2013) or where there is low chance of patient survival. The argument for consent waiver where there is no change to patient management is relatively easy to resolve. However, non-voluntary enrolment of critically ill patients does raise the question of whether this is ever morally justifiable.

Tigard (2016) presents an interesting philosophical discussion that essentially turns this question around to examine the moral implications of stifling research into interventions that could improve patient outcome. Tigard argues that there is a strong moral case for pursuing innovation in emergency medicine but, only where this occurs as a "*by-product of pursuing therapeutic success*". This condition for consent waiver (described by Tigard as a "*double-effect*" principle) is consistent with the American Food and Drug Administration (FDA) requirement that, for prospective informed consent to be waived, "..*subjects must be in a life threatening situation, intervention is required and available treatments are unproven…. and participants may benefit directly from intervention*".

For example, UK studies meeting this "*double-effect*" principle include early studies of focused ultrasound assessment of blunt abdominal trauma where consent was waived (Brenchley et al., 2006).

8.4.4 Community consultation

A small number of studies were identified by the review that explore the efficacy of community consultation and the attitudes of clinical staff to tests of community perception (Biros, Sargent & Miller, 2009; Dickert et al., 2014). Whilst public consultation is not required for approval of consent waivers, research ethics panels are expected to consider questions and potential concerns from the public.

In a survey exploring public attitudes to emergency medicine research (Biros et al., 2009), 1901 participants were asked their views on different approaches to consent. Whilst 88% of respondents supported research in an ED context, this fell to 35% for studies where consent was waived. This increased to 51% when applied to the respondent in person and their attitude to personal research involvement. A limitation of this study is that level of patient illness and urgency of care decisions were not defined. The authors acknowledge that responses may have been different if time critical scenarios (for example trauma) had been specified.

Biros et al also report a high number of '*no opinion'* responses on returned questionnaires and note that these are disproportionately associated with respondents on low income or with low educational achievement. This could indicate lack of understanding of the questions. They suggest that two way conversation within a community group may be of benefit. However, this needs to be balanced against the risk of observed opinions being swayed by lone dissenting voices.

Concerns regarding public understanding of consent waivers in an ED context are echoed by Dickert et al 2013. They undertook a retrospective survey of patient (n=24) and next of kin (n=37) experience of research participation for which prospective consent was not obtained. 95 % of respondents supported research in an ED context and 73% were in favour of consent waiver. However, 62% of interviewees did not appear to understand several key questions despite opportunities for questions and probing of their answers.

These findings bring into question the validity of *consent by public opinion* and are consistent with discrepancies in opinions amongst healthcare

professionals and patient participants. Ripley et al (2012) explored attitudes, beliefs and experiences of emergency care providers who were involved directly in studies requiring consent waiver. Findings confirmed support for research activity in all respondents. However, discussion of consent waiver identified complex and divergent opinions with a predominant feeling that individual patient right to decide outweighs decisions based on community consultation.

8.5 Could prospective consent have been waived for the current study?

In the context of this observation study, it is difficult to argue that ultrasound measurement of RRI (unproven and non-contributory) meets the criteria for prospective consent to be waived. The proposed intervention is not time critical (as for example a FAST scan for blunt trauma) and offers no immediate benefit to the patient. Therefore, despite concerns regarding patient capacity, formal consent was required prior to scan.

In discussion with the Trust Research and Development (R&D) advisor and with reference to the Regional Research Ethics Committee (REC), the study protocol was designed to reflect the challenges of consent in this context. Central to this was the need to approach consent as an ongoing process rather than a 'one off' decision. Even in patients who respond positively to initial recruitment, capacity to consent is likely to change over time and may be altered by pain and use of analgesia or sedatives (Sahan et al., 2016). In evaluation of patient capacity in the resuscitation room, patient general level of illness, the likelihood of rapid deterioration and the need for urgent time dependent interventions must also be considered. For this reason, the initial approach to patients was by the doctor responsible for their care. This is consistent with GMC Good Medical Practice (2013).

8.6 Consent not coercion

A number of the studies reviewed highlight the additional risk of coercion and question how voluntary 'voluntary consent' is in practice (Schmidt et al., 2004; Halila, R. 2007; Baren et al., 2010). By using a doctor who is not involved in the research study to make the first approach to patients, it can be argued that risk of coercion is reduced. Their primary concern is with management of the patient's urgent and ongoing care needs rather than research participation.

This approach is consistent with the basic principles outlined in the World Medical Association Declaration of Helsinki (1996) as outlined in the Good Clinical Practice document (2017). This advises that, when obtaining informed consent, if there is any risk of duress, consent should be *"obtained by a physician who is not engaged in the investigation"*.

8.7 Consent as an ongoing process

The initial approach to patients was by a brief verbal explanation of the study given by the recruiting doctor. This was followed by introduction of the patient to the primary investigator (an expert sonographer) who provided a one page study information sheet for the patient (and any attending relatives) to read. The study proposal and implications of participation were then discussed and opportunity for questions provided.

In an interesting study exploring the behaviours of ED research participants, Baren et al (2010) observed a large cohort of 1609 during the consenting process. They noted whether participants read the study and consenting information provided, how long they spent reading it and whether questions were asked. The authors note minimal engagement with information provided during consenting from approximately half of the study participants. 53% read the information provided but, only 13% spent more than 2 minutes considering a 2 page document. Only 20% of patients asked any questions to clarify the research or consenting process. 47% did not read the information provided prior to consenting.

It is difficult to generalise from this study but, these findings suggest that a significant proportion of ED patients may pay limited attention to written information provided as part of the consenting process. It is therefore important that check of understanding is included in the protocol with opportunity for question and verbal review of the implications of study participation.

For the current study, once the patient had indicated their initial willingness to participate, the PI and recruiting doctor signed the study consent form to confirm their agreement that the patient demonstrated capacity to consent. This provided an opportunity to check for any concerns regarding capacity at an early stage of the recruitment process.

The patient was then presented with the paper based consent form (Appendix 5) and consent checks were read aloud by the PI. Understanding was checked and the patient was asked to initial each section and add their signature to the form. Right to withdraw at any time was emphasised throughout this process.

Patients in an emergency context are likely to be distracted, with shortened attention span. In discussion with Trust R&D and following feedback from the REC, study information sheets were provided in short and long versions (Appendix 2a / 2b)

The initial information sheet given to patients was restricted to one page with large text and bullet point information only. This was supplemented by a verbal description by the PI of what participation would entail and opportunity for withdrawal at any time was explained. A detailed version of the information form was provided for patients to take away with them and for any attending relatives to read.

Throughout the scan, patients were offered further opportunity to ask questions. Through this, the PI was able to provide additional information about the study whilst monitoring patient understanding and capacity to consent.

In this chapter, the ethical issues relevant to research in emergency medicine have been explored and their impact on the current study discussed.

In the next chapter, the limitations of the study are considered and conclusions and recommendations are presented.

Chapter 9 Further discussion

In this concluding chapter, limitations of the study are considered, conclusions are presented and recommendations are made for further study.

The aim of this study was to evaluate whether ultrasound measurement of Renal Resistive Index is a feasible and clinically useful method of early identification of AKI in patients requiring resuscitation room care. The rationale for the study emerged initially from review of a wealth of supportive evidence from critical care studies reporting the prognostic value of RRI in patients with confirmed AKI and from discussion with clinical colleagues about the challenge of AKI diagnosis in the ED. In the intervening period from initial proposal of the study, further compelling evidence from critical care studies has emerged supporting the role of RRI as a useful prognostic indicator for sick patients with known AKI.

In gaining a better understanding of the haemodynamic determinants, it became apparent that RRI is largely a reflection of systemic factors rather than a direct indicator of renal perfusion or renal function. This led to speculation that RRI may be a useful early indicator of sub-clinical AKI and could potentially act as an indicator of AKI **risk**. Further in-depth review of the literature (at the time of study proposal) identified no previous studies that explore the potential use of RRI as a **predictor** of AKI.

As a population, patients admitted to the ED and requiring resuscitation room care are at increased risk of AKI. However, individual patient risk varies (Thomas et al., 2015; Hodgson et al., 2017). Despite extensive evaluation of renal bio-markers and the introduction of real time electronic reporting systems, initial diagnosis of AKI in ED patients remains dependent on standard tests of sCr and urine output, where lack of baseline measurements, and a recognised lag between change and initial renal insult may delay diagnosis and treatment.

A high proportion of resuscitation room patients are admitted to hospital and their renal function will be monitored carefully throughout their hospital stay. However, earlier detection of sub-clinical AKI at the point of admission would allow implementation of a renal protective care bundle prior to discharge to the ward or for community based care (Kolhe et al., 2015; Bagshaw, 2015; Kolhe et al., 2016). Although at present unproven, given the dismal outcome for patients in whom AKI has resulted in permanent renal damage, these benefits could be considerable.

Identification of a simple test that can accurately predict individual patient **risk** of AKI would be of significant benefit in the ED. Existing tests of AKI are based on changes in biochemistry and urine output that signal that damage to the kidneys has already occurred. However, these tests tell us little about patient renal functional reserve or risk of a future episode of AKI. At present, clinical decision making around use of known nephrotoxic drugs or contrast enhanced imaging investigation is supported by risk assessment algorithms (based on multiple risk factors such as patient age, gender BMI and ethnicity). The local Trust clinical management system combines detailed patient data with real time hospital wide electronic reporting systems. However, to date there are no reliable, validated AKI risk scores for patients presenting in primary or secondary care (Think Kidneys Report 2017). Identifying a simple, reliable test that can accurately estimate individual patient risk of AKI is therefore a research priority.

9.1 Have the study research questions been answered?

The first research objective of this study was to determine the **feasibility** of RRI measurement in the ED. Essentially, the study findings indicate that, using a standard point of care ultrasound system, RRI **cannot** be reliably achieved in patients requiring resuscitation room care. Training requirements for ED doctors to perform RRI measurement were not explored as the test, in its current form, was not found to be fit for purpose.

The remaining study objectives (as outlined in Chapter 5) were focused on evaluation of test characteristics for RRI (in the diagnosis of AKI and prediction of AKI risk), and on the potential training requirements of ED doctors to perform these measurements.

Due to the small sample size and lack of reliable measurements achieved, it has not been possible to characterise RRI as an indicator of AKI in these patients.

9.2 Limitations of the study

Research in emergency medicine is beset with challenges and there are well documented issues including slow participant recruitment, small sample size and premature discontinuation of trials (Schandelmaier et al., 2016; Thomsen, 2015). This study is no exception and has highlighted the difficulty of patient recruitment in this context and the impact of high workload on recruitment strategies.

9.2.1 Sample size

The final sample size is too small to allow meaningful analysis of the test characteristics of RRI as an indicator of AKI. Research objectives 2-4 that explore the performance of RRI in diagnosing and predicting AKI cannot be answered by this study.

The importance of a priori calculation of study sample size and anticipated study power is well documented (Suresh et al., 2012; Peeling et al., 2010; Bacchetti et al., 2010 ;Fozgate et al., 2009). However, during development of the initial proposal for this feasibility study, a formal power calculation was rejected due to the extent of unknown factors. This is consistent with National Institute for Health Research guidance (NETS-CC Annex A 2018) for studies that test the feasibility of an intervention not previously validated in the study population.

In general, when assessing diagnostic test characteristics, the larger the sample size, the narrower confidence intervals are likely to be. However, in an

Emergency Department setting, where patients are un-well and disruption to care pathways needs to be minimised, a large sample size may be ethically unjustified.

One of the key challenges was estimating how well RRI was likely to perform in the study population. Sensitivity and specificity were unknown, as was prevalence of the condition in the study population. A priori power calculation would therefore be based on ‘best guesses’.

A pragmatic approach was taken with a defined target recruitment period (10 months) and planned review of patient recruitment at key stages.

The small final sample size (n=20) reflects the stringent exclusion criteria (particularly around patient capacity to consent), difficulty of recruitment in the ED and the limited feasibility of RRI measurement in this patient group.

9.2.2 Barriers to recruitment in emergency medicine

Barriers to recruitment in emergency medicine are well documented (Johnson et al., 2016; Schandelmaier et al., 2016). Practical challenges such as staff time, staff training and availability of local resources may be exacerbated by high work pressure, need for urgent clinical intervention and critical over-crowding in the ED.

For the purpose of this study, impact on clinical services was minimised by restricting data collection to a single (supernumerary) expert sonographer who was seconded to the department for approximately one day per week for 10 months. However, input was still required by each doctor responsible for patient care during initial recruitment and consenting. It was therefore important that clinical staff understood the protocol including exclusion / inclusion criteria and were supportive of the broad study aim.

9.2.3 Staff engagement

Before recruitment began, the study was promoted by the PI and by the ED research lead via staff newsletters, closed ED group social media and PI

attendance at regular team briefings. Ongoing individual briefings were time consuming but essential to maintain staff engagement.

Overall, the study proposal was well received and most staff expressed enthusiasm for the broad study aim. However, pressure on clinical staff resulted in their cautious approach to recruitment, particularly in the early stages, rather than general lack of engagement or unwillingness to participate.

Ripley et al (2012) comment on the conflict between the role as clinician and the role as researcher in emergency medicine doctors and note that this can impact on participant recruitment. In all cases, patient care was prioritised and, in busy periods in particular, this resulted in very slow recruitment. During periods of atypical high pressure within the department, recruitment was paused completely.

In an evaluation of research capacity among ED clinicians, Lawlor et al (2014) identified insufficient time (71.2%), lack of support [training or supervision] (61.8%), lack of interest in a topic (42.0%), and inadequate resources (23.6%) as the four barriers most likely to influence research involvement. Staff support for the current study was encouraged by promoting the importance of the topic and by minimising impact in the remaining areas. This was vital for a study that was non-portfolio (not supported financially by the Trust) and undertaken by an honorary visiting researcher. However, resource related barriers could not be fully addressed and, in the current climate of high workload in the ED, these were undoubtedly a significant limitation, affecting recruitment in particular.

9.2.4 Patient population

A further uncontrollable factor affecting recruitment was the population demographics for patients admitted to the resuscitation room, with a high proportion unable to demonstrate capacity to consent. Factors such as patient general confusion and agitation, combined with other exclusion criteria

(history of known renal disease, cardiac cause for admission, non-English speaking) reduced the potential pool of participants considerably.

The combined limiting effects of patient demographics and ED staff time/availability to check capacity to consent resulted in very low recruitment over the initial 10 month target period. This included a period of approximately 3 months where recruitment was paused due to atypical pressure on the department. The recruitment period was then extended for a further 4 months before data collection was halted.

9.2.5 Stop criteria

One of the ethical challenges of research in emergency medicine is the widely reported issue of premature study discontinuation.

In a retrospective review of 894 clinical trials, Schandelmaier et al (2016) compared discontinuation in studies carried out in acute and non-acute settings. They report a four-fold higher risk of early discontinuation in studies in an acute setting with slow recruitment highlighted as the most common cause. This raises the question of how this effect can be mitigated in study design for research in the ED. For a small scale study that is non-portfolio (and hence cannot expand paid staff involvement), an extended recruitment period was the only feasible pragmatic response.

One of the weaknesses of the current study is that recruitment '**stop criteria'** were not defined at the time of study proposal. Tyson et al (2016) note that "*stopping guidelines are often vague or unspecified*" in the design of clinical trials and that this is a long standing challenge that is often not addressed during ethical review.

In a large scale review of published randomised controlled trials, Stegert et al (2016) found that approximately two-thirds of protocols did not include clear stopping rules. Tyson (2016) focuses on the importance of planned expert statistical interim review of data with analysis of conditional power and predictive probabilities. However, for the current study, where a priori power calculation had been rejected and the feasibility of the intervention was

unproven, this was of limited value. It is also interesting to note that, even in the large scale clinical drug trials reviewed by Stegert, 80.4% were discontinued *without* reference to a pre-defined mechanism or evidence of planned interim analyses. Clearly this issue is not limited to research in emergency medicine.

Where conventional stop criteria for *futility* are discussed, these generally relate to clinical trials that evaluate the effectiveness of drug therapies (Vickers, A. J., Kattan, M. W., & Daniel, S., 2007, Tyson et al., 2016; Stegert et al., 2016). They conclude that, even where no effect is seen, premature discontinuation should be avoided as this is likely to reduce the statistical power of later meta-analysis. Whilst this makes sense for therapeutic drug trials, this approach is unhelpful where the study intervention is a diagnostic test that is demonstrably not feasible in the study population. Indeed, in a vulnerable patient cohort, it could be argued that, continuation in these circumstances is not ethically justified.

The decision to halt recruitment for the current study was taken in consultation with the supervising clinician and on expert ethics advice.

9.2.6 How representative was the final study sample?

By eliminating patients who lacked capacity to consent, the study protocol limited evaluation of RRI measurement to a small sub-set of the resuscitation room population. To gain a better understanding of how representative the study sample is, background data were analysed for **all** resuscitation room admissions over a sample period of four weeks (2 weeks in June, 2 weeks in January).

No significant difference was noted in mean age of all attendees (62.0 years) and the study sample (62.3 years). However the age range was slightly narrower for the study group (33 - 91 years) compared to overall resuscitation room admissions (22 – 96 years).

In the study sample, there was a slightly more even split between male and female (55% male, 45% female study sample. 60% male 40% female all admissions).

In a relatively high proportion of patients in the study sample, respiratory problems were noted as the primary reason for admission (30%). By comparison, in the sample period for 'all admissions', the primary diagnosis on admission was classified as a respiratory related problem in 19.2 % of patients. The small final sample size makes it difficult to interpret the significance of this difference but, as SOB was a key factor in limiting the feasibility of RRI measurement, this may be an important feature of the sample group.

However, the '*all admissions'* data reviewed provides only the **primary** diagnosis on admission. This fails to capture the breadth of patient symptoms experienced on presentation. In practice, although difficult to quantify, SOB is likely to be a presenting symptom in a much higher proportion of patients admitted to the resuscitation room. This would be consistent with the finding that SOB was noted at the time of scan as a technical difficulty in 60% of patients in the sample group.

9.2.7 Is RRI measurement likely to be feasible in the patients who were not recruited to the study?

Patients were excluded from recruitment on the basis of one or more of three broad exclusion criteria.

i. Lack of capacity to consent
ii. History of renal disease
iii. Cardiac arrest / too ill to participate (high MEW score)

Lack of capacity to consent does not necessarily mean that patients would lack capacity to cooperate with the scan. However, exclusions for reasons of capacity to consent included patients who were confused, agitated, in pain, under the influence of drugs (prescribed or recreational) or a combination of

the above. In patients requiring resuscitation room care, these characteristics are not uncommon. Although not tested by this study, it is reasonable to assume that cooperation with the scan would be compromised in these patients, perhaps more so than in patients demonstrating full capacity to consent.

Patients admitted with cardiac arrest, with high MEW score or with reduced levels of consciousness were excluded from the study. The primary reason for exclusion was to minimise risk to the patient. Even where consent to scan may have been theoretically feasible, performance of a non- urgent, non-contributory test was contraindicated due to the high risk of rapid deterioration or need for urgent medical intervention. From the study findings, it is reasonable to predict that RRI measurement would not be achievable in these patients with a standard point of care system.

AKI is a significant risk factor for developing chronic kidney disease (CKD) and can present as an acute on chronic kidney injury (Wilson et al 2017). A prior history of CKD is a key predictor of AKI risk with the incidence of AKI risk increasing by up to six-fold in CKD patients (Porta et al 2016).

The overarching aim of the study was to explore the performance of RRI as a predictor of AKI risk, primarily in patients where this might be missed. Patients presenting with a known history of renal disease were excluded from this initial feasibility study as baseline biochemistry and RRI values would be difficult to interpret. However, in patients with reduced functional reserve (due to known chronic renal disease), an episode of AKI is associated with high morbidity and mortality. If a revised measurement method is validated that eliminates the issue of motion blur, it would be worth exploring RRI as an early indicator of acute on chronic kidney injury.

9.3 Is the use of RRI measurement as a predictor of AKI in this patient group worth further investigation?

AKI remains a serious health problem with associated spiralling costs and dismal patient outcomes where diagnosis and treatment are delayed. The impact of AKI on use of health resources is predicted to increase with an aging population.

For an individual patient, an episode of AKI (even at Stage 1) is non-trivial and this potentially preventable condition is associated with a high risk of mortality. Innovations such as Trust wide data sharing initiatives improve outcome but, impact is still limited by delayed diagnosis due to the inherent lag in response time for existing tests based on sCr rise and fall in urine output. To improved outcomes, early diagnosis is key but, this remains challenging.

9.3.1 Bio-markers

In the last decade, there has been considerable attention focused on the development of bio-markers (such as urinary or serum neutrophil gelatinase-associated lipocalin (NGAL) and cystatin-c) as alternative early indicators of renal damage (Soto et al., 2010; Bennett et al., 2011; Nickolas et al., 2012; Bagshaw et al., 2013; Vanmassenhove et al., 2013; Alge J. and Arthur J.M. 2017).

Schiffl & Lang (2012) present a review of the clinical impact of urinary biomarkers for the detection of AKI. They conclude that routine use of even the most promising of these markers in the ED is as yet unwarranted and that none of the markers studied have a clear advantage beyond established clinical decision making approaches. Despite considerable investment and initial enthusiasm, the role of biomarkers remains uncertain. Schiffl & Lang warn that indiscriminate use of biomarkers may in fact distract from adequate clinical evaluation and could worsen patient outcome.

From review of more recent literature, biomarkers seem to be viewed as something of a magic bullet. However, there is a risk that a strong focus on biomarkers could inhibit evaluation of alternative approaches to early AKI diagnosis. This view is supported by Vanmassenhove et al (2013) who

highlighted the cumbersome nature of early diagnosis of AKI using these methods, and in particular the difficulties that arise where timing and aetiology of AKI are not well defined. However, their use in management of renal replacement therapy and the evaluation of disease progression from AKI to chronic renal failure looks more promising (McCullough et al., 2013; Alge J. and Arthur J.M. 2017).

The extent to which bio-markers may eventually provide individualised patient management of AKI remains to be seen, despite promising early results in ED patients (Soto et al., 2010; Nickolas et ., 2012; Schinstock et ., 2012). However, identification of a sensitive and specific early marker for renal injury has proved elusive. These tests remain costly, widely unavailable and are yet to be validated in large prospective studies; particularly where their contribution to decision making is evaluated. Unlike the use of troponins for confirmation of myocardial infarction, identification of a single marker for AKI seems unlikely as the aetiology of AKI itself is so complex.

9.3.2 Evidence that RRI can predict AKI

Since the initial proposal for this study, a number of papers have been published that support the hypothesis that RRI can act as a predictor of AKI risk. The studies reviewed in Chapter 4 all conclude that RRI performs better than existing tests as an independent predictor of AKI risk in the patient groups in which this was evaluated (Marty et al., 2016; Hertzberg et al., 2016; Giustiniano et ., 2014; Marty et ., 2015; Wybraniec et al., 2016).

In all of these studies, **RRI > 0.70** (measured prior to surgery or contrast enhanced imaging) was closely associated with increased risk of AKI, length of in-hospital stay and overall patient outcome. Whilst there is variation in the patient populations studied and a sizable grey zone around the cut off of RRI> 0.70, collectively these authors present compelling evidence that the hypothesis for the current study was correct.

A distinctive feature of the patients studied by these authors is that they were all pre-morbidly well. Inability to comply with breath hold (respiratory distress)

was cited amongst the exclusion criteria but not quantified. However, measurement of RRI in ambulatory patients (presenting for pre-operative / pre-contrast assessment) appears to be a feasible and useful marker for increased risk of AKI.

9.4 Measurement of resistive index in other vascular beds

As outlined in previous chapters, there is compelling experimental and clinical evidence that the determinants of RRI are systemic and that aortic pulse pressure is a key factor. If this is the case, it is possible that measurement of resistive index in an alternative vascular bed could act as a surrogate measure of RRI. Further exploration of RRI measurement in the splenic hilar vessels as outlined in the previous chapter may be worth considering. However, measurement in these vessels is unlikely to offer a credible alternative to renal measurement if patient breath hold is problematic.

9.5 Technology solutions

The ultrasound systems employed in point of care settings are necessarily compact. Most will lack some of the new design features and signal processing techniques that are emerging in high end systems. However, as novel applications of ultrasound have emerged that are specific to an ED context (for example ultrasound diagnosis of pneumothorax), equipment adaptations and bespoke software packages are also gradually emerging that support point-of-care specific tasks.

Development of the technologies discussed in Chapter 7 to resolve the issue of motion blur should be well within reach. Two-dimensional flow index mapping (2D-FIM) in particular could be combined with image formation techniques that improve temporal resolution to make auto-capture of RRI feasible in patients who have difficulty with breath hold.

Availability of a system that facilitates rapid automatic capture of RRI (with minimal operator training) could have wide potential outside of the ED. This would certainly strengthen the commercial case for development of an

automated measurement package. An estimated 65% of AKI episodes start in the community (Selby, et al. 2012). In an aging population where use of known nephrotoxic drugs and other risk factors continue to increase, it may also be worth exploring community based use of RRI to monitor risk of renal injury, particularly in hypertensive patients.

9.6 Conclusions

In the context of this study, measurement of RRI was **NOT** feasible in patients requiring resuscitation room care using a current point of care ultrasound system. Image blur due to patient breathing movement prevented reliable measurement of RRI in a high proportion of patients and this could not be mitigated without adaptation of the available technology.

Review of studies published since the current study commenced provides some compelling evidence that RRI performs better than existing tests in early diagnosis of AKI and in **prediction** of AKI risk prior to surgery and contrast enhanced imaging. These are significant findings that support further evaluation of RRI in high risk patient groups.

As AKI remains a significant global health challenge, the imperative to identify a more effective method of early detection is still a research priority. As a standard test on admission to the ED, eGFR has significant known limitations and may give false reassurance in patients at high risk due to loss of renal functional reserve. The technology ‘fix’ required to allow automatic capture of RRI measurements in patients with breathlessness is, at least in theory, trivial. Although beyond the scope of this study, at the time of writing, early dialogue with one of the relevant commercial manufacturers and academic partners is ongoing.

9.7 Recommendations

The primary aim of this study was to evaluate the feasibility and usefulness of RRI as an indicator of AKI risk in an ED point of care setting. Whilst it is not possible to generalise from the limited data captured, if further evaluation of RRI in this patient group is to be considered, development of an alternative measurement algorithm is recommended. This should be well within the scope of current ultrasound systems with adapted Power Doppler based estimation of RRI, using maximum and minimum power of the Doppler signal as surrogate measures of peak systolic and end diastolic parameters. (See Chapter 7)

Exploration of RI measurement in the splenic hilar vessels may be worth further exploration, particularly where unilateral renal abnormality is suspected. However, measurement of RI in an alternative abdominal vascular bed is unlikely to offer a useful substitute in acutely unwell patients with limited capacity for cooperation.

The current study speculated that RRI could be a useful indicator of AKI **risk.** At the time of the initial proposal, no other studies were identified that explore this predictive use of RRI. Subsequent studies (identified in Chapter 4) confirm a link between the causative mechanisms for rise in RRI and post procedural AKI risk. This is an important finding that may have significant implications for future use of RRI, particularly prior to planned surgery or contrast enhanced imaging of patients who are pre-morbidly well.

An ongoing challenge associated with AKI in an aging population is lack of meaningful individual baseline data. A number of the studies reviewed identify a close link between long term use of antihypertensives (and other nephrotoxic drugs) and life time risk of renal failure. In these patients, a gradual reduction in renal functional reserve places them at increased risk of renal injury during an episode of acute illness. Although a stand-alone

measurement of RRI tells us relatively little about renal function, it is worth speculating that serial measurement of RRI, possibly within the community, may be useful in identifying patients at high risk. RRI may also perform better than current definitions of return to ‘normal’ (eGFR and sCr) as an indicator of future risk where renal functional reserve has been diminished following an episode of AKI.

Use of RRI measurement on this scale would require a more cost effective and accessible approach than that offered by expert hospital based ultrasound services. Ultimately, if further research supports RRI as a clinically useful predictor of AKI, this could be the driver required for commercial development of an automated measurement system. However, further large scale prospective studies are needed to confirm the predictive value of RRI for AKI if this investment is to be justified.

As a broad principle, research activity involving patients in an acute setting should only be undertaken if the research questions cannot be answered elsewhere (Sahan et al 2016). There should be evidence to support the likelihood of improvement in diagnosis or therapy in this group, and a reasonable assumption that the intervention will be feasible in this context.

This study has confirmed that, using a state of the art point of care ultrasound system, RRI measurement is not feasible in patients requiring resuscitation room care. However, these patients remain a high priority group where rapid clinical decision making is required and there is opportunity for early implementation of a renal protective care bundle.

It is recommended that validation of RRI for AKI prediction and risk stratification should be explored further in alternative patient groups before implementation in an ED patient population can be considered.

“It always seems impossible until it's done.” Nelson Mandela

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Appendices

Appendix 1

Detailed summary of Phase 2 literature Search strategy (2014)

Outlined below are details of the initial Phase 2 literature search. It is from this review of relevant literature that the current study original research question emerged.

In emergency department patients requiring resuscitations room care, can Renal Resistive Index predict the development of acute kidney injury?

Specific objectives of the search strategy were to identify current literature that:

1. establish the evidence base for the role of RRI in the diagnosis and prognostic stratification of AKI.
2. relate directly to the diagnosis and management of AKI in emergency department patients.
3. relate directly to the use of RRI to identify patient risk of AKI in an ED context. (ie Has this study already been done?)

Terminology

The term ‘acute kidney injury’ is recognised internationally. However, there are numerous inconsistencies in use of terminology within current literature. The search strategy was formulated using a range of key words and truncations that reflect these observed variations.

English language papers reporting the use of ***Doppler renal resistive index*** use a variety of synonymous terms and abbreviations including **renal RI**, **renal resistive index, renal Doppler, RI** and **RRI.**

In subsequent stages of the search these terms were used to identify studies of Doppler ultrasound investigation of renal blood flow parameters and the

terms **“emergency”** and **“ED”** were used to identify emergency department context specific studies.

Initial search

An initial search was performed in each database using the Boolean operators “AND” and “OR” to identify papers with the words “**acute kidney injury**” OR “**acute renal failure**” OR “**acute renal injury**” OR “**acute kidney failure**” in the title / abstract.

A repeat search for **renal RI**, **renal resistive index, renal Doppler, RI** and **RRI** was undertaken using the same limits.

Limits were activated to include **Humans**, **Clinical Trial**, **All Adult: 19+ years**, published in the **last 5 years**. No language restrictions were used.

In Pubmed, a combined search for these terms identified two papers by **Schnell**, D., L. Camous, et al. (2013) and **Schnell**, D., S. Deruddre, et al. (2012). Neither of the two papers fit the search criteria of an emergency department context.

The search was then repeated with an extended time limitation of 10 years. No additional **papers** were identified. Repeat of the search with the clinical trial limit removed again identified **no additional papers** matching the remaining criteria.

The initial search terms for AKI were then combined separately with **emergency department** OR **ED** in a title/abstract search. This identified 7 papers.

Of these, 3 papers (Nickolas et al. 2012, Ruedinger et al.2012 and Schinstock et al 2013) explore the diagnosis and prognostic stratification of AKI in an ED context. Manual review of these papers confirms no direct reference to renal resistive index.

The above search strategy was repeated in EMBASE (restricted to **humans** and time limited from **2009**). This identified 3 further papers meeting all

criteria, Barbani et al. (2010), Fremin et al. (2012) and Ngai et al. (2011) However none of these related directly to an ED context.

Combined search for AKI and RRI (and alternative terms) returned 90 papers. Manual review of these identified 34 papers that relate to the use of RRI as a predictor of AKI.

AKI diagnosis and management updated search

To gain an overview of the current evidence base for AKI diagnosis and management, the strategy used in the Phase 2 (Unit 8) literature search was repeated to identify papers published in the intervening period.

Search terms were revised to target papers with the term ‘acute kidney injury’ or the abbreviation ‘AKI’ in the title. When limited to **Humans, Clinical Trial, All Adult: 19+ years, published in the last 5 years,** this identified **177 papers** in total in pubmed.

Manual review of these identified 73 papers relating to the initial diagnosis of AKI.

Exclusion criteria included narrow focus on comparative renal replacement therapies, peri-operative risk of AKI associated with alternative surgical interventions and assessment of transplanted kidneys.

Search of the 73 papers identified above combined with (**emergency department [Title/Abstract]**) identified no additional relevant studies.

Author searches for the key papers identified in the initial stage of the search identified Bagshaw S.M, as a prolific author with 37 AKI related papers listed in PUBMED for this 5 year period. Manual review of these identified no additional relevant clinical trials.

Repeat of the above search in EMBASE for AKI or acute kidney injury and RRI identified 9 papers when limited **to human and clinical trial and last 5 years**.

EMBASE search for AKI or acute kidney injury in combination with “emergency department” identified 138 papers, manual review of which identified 5 additional studies of AKI diagnosis in an ED population.

The Cochrane Central Register of Controlled Trials was used to search for AKI studies that had not been identified by combined searches within the other data bases. This identified **21 review articles** all of which focus on drug treatments for the prevention and treatment of AKI and comparative methods of renal replacement therapy. None of the studies identified evaluated methods of AKI diagnosis or prognostic stratification. Further exploration of the Cochrane data base for relevant trials identified only one further study of renal resistive index (Naesens et al 2014).

Review of Cochrane Renal Review Group activity (including protocols currently undergoing referee scrutiny) identified two protocols in progress that explore the use of biomarkers in the assessment of renal function. No protocols are identified that link directly to either the role of RRI or an ED context.

Repeat search in Web of Science [Title=(acute kidney injury) AND Title=(“resistive index”)] identified 8 references including 2 previously unidentified conference abstracts (An et al 2013, Sinning et al 2013). Review of the conference proceedings in which these abstracts were published identified one further abstract (Youngsoo Kim et al 2013) that explores diagnosis and progression of AKI in ED trauma patients.

Despite the obvious advantages of electronic data bases, it is recognised that they are not infallible. (Aveyard 2010). However, in this instance, manual review of the reference lists for each of the papers identified above produced no further records of new clinical trials relevant to the search.

Conclusion

Building on the search undertaken during Unit 5, combined searches in PUBMED, EMBASE, Web of Science and Cochrane Central Register of

Controlled Trials identified a small number of new studies that add additional support to the use of RRI as a predictor of AKI.

However, no studies were identified that explore this measure in an ED population. The originality of the proposed study is therefore confirmed.

PUBMED 17/02/14

Limits Activated: Humans, Clinical Trial, All Adult: 19+ years, published in the last 5 years

1	(((acute kidney injury[Title]) OR acute renal failure[Title]) OR acute renal injury[Title]) OR acute kidney failure[Title]	**Results 488**
2	("renal RI"[Title/Abstract] OR "renal resistive index"[Title/Abstract] OR "renal Doppler"[Title/Abstract] OR RI[Title/Abstract] OR RRI [Title/Abstract])	**Results 166**
3	1 AND 2	**Results 2**
4	1 AND ("emergency department"[Title/abstract] OR ED[Title/abstract])	**Results 7**

PUBMED 17/02/14

1	("renal resistive index"[Title/Abstract]) **Limits Activated:** Humans, Clinical Trial, All Adult: 19+ years, published in the last 5 years	**Results 4**
2	"acute kidney injury"[Title/Abstract] **Limits Activated:** Humans, Clinical Trial, All Adult: 19+ years, published in the last 5 years	**Results 271**
3	1 AND 2 ("renal resistive index"[Title/Abstract]) AND "acute kidney injury"[Title/Abstract]	**Results 2**

PUBMED 17/02/14

Limits Activated: Humans, Clinical Trial, All Adult: 19+ years, published in the last 5 years

1	(AKI[Title/Abstract])	**Results 184**
2	"acute kidney injury"[Title/Abstract]	**Results 271**
3	emergency OR ED[Title/Abstract])	**Results 3250**
4	1 AND 3 Search (AKI[Title/Abstract]) AND (emergency OR ED[Title/Abstract]	**Results 8**
5	2 AND 3 Search ("acute kidney injury"[[Title/Abstract]) AND (emergency OR ED[Title/Abstract]	**Results 13**

EMBASE 21/03/14

1	'acute kidney injury'/exp OR 'acute kidney injury' OR 'acute renal injury'/exp OR 'acute renal injury' OR 'acute renal failure'/exp OR 'acute renal failure' OR 'acute kidney failure'/exp OR 'acute kidney failure'	**Results 76244**
2	'resistive index' OR ‘renal RI’	**Results 1886**
3	#1 AND #2	**Results 90**
4	“Emergency department” OR ED	**Results 88714**
5	#3 And #4	**Results 3**

Combined search for AKI and RRI (and alternative terms) – manual review of 90 papers identified 32 papers that relate to the use of RRI as a predictor of AKI.

Pubmed 17April2014

1	AKI[Title] Limits: **Humans, Clinical Trial, All Adult: 19+ years, published in the last 5 years**	**Results 6**
2	“acute kidney injury”[Title] Limits: **Humans, Clinical Trial, All Adult: 19+ years, published in the last 5 years**	**171**

Manual review of 171 papers identified 73 studies relating to the initial diagnosis of AKI.

EMBASE 17April2014

1	“acute kidney injury” OR “acute renal failure” OR “acute renal injury” OR “acute kidney failure”	**Results 55122**
2	#1 AND [adult]/lim AND (2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py) AND ('clinical article'/de OR 'cohort analysis'/de OR 'human'/de OR 'major clinical study'/de OR 'observational study'/de OR 'prospective study'/de OR 'retrospective study'/de)	**Results 5482**
3	“resistive index”	**Results 1875**
4	2 AND 3	**Results 9**
5	“emergency department”	**69259**
6	2 AND 5	**138**

Manual review of 138 papers identified 5 additional studies of AKI diagnosis in an ED population..

Appendix A2a PARTICIPANT INFORMATION SHEET PISv1.1b
(Short version)

Study Title: Can measurement of renal resistive index identify risk of acute kidney injury in emergency department patients requiring resuscitation room care?

We would like to invite you to take part in a research study. Before you decide to take part we would like to provide you with some information about the research and what it will involve for you. **Take as long as you need to read the information and please ask us to explain anything you do not understand or if you have any further questions.**

What is the purpose of this research study? We want to know if an ultrasound scan can help us to identify patients who are at risk of a condition known as **acute kidney injury**. It is important that we treat this condition quickly to prevent permanent damage to the kidneys. However, in its early stage it can be difficult to detect.

Why have I been invited to take part? You are being asked to take part in the study as your current illness means that you **may** be at risk of acute kidney injury.

Who is doing the research? A PhD student from the University of Bath, working under the supervision of one of the Consultant doctors in the Emergency Department.

What will happen if I agree to take part? You will be required to sign a consent form to say that you are happy to take part in the study.
We will do an ultrasound scan of your kidneys. This will take around five to ten minutes. It will involve putting a small amount of gel onto your upper abdomen and you will be asked to hold your breath briefly while we take the measurements.

How will this affect my treatment?
Taking part in the study **will not change your treatment in any way**.

Do I have to agree to take part? No. Taking part in the study is entirely voluntary.

Are there any risks involved? No. Ultrasound is a very safe imaging technique that does not involve ionising radiation or any known risk used in this way. The research team are all qualified ultrasound users.

Can I change my mind? Yes. You are free to withdraw at any time up to the stage where we analyse the results of the study. You do not need to give a reason for your withdrawal.

Further information Before you leave the department you will be given a more detailed information sheet about the study. You will be able to ask more questions and consider if you want to take part.

Heather Venables (Principle Researcher)

Appendix A2 b PARTICIPANT INFORMATION SHEET PISv1.1b

(Long version)

Study Title: Can measurement of renal resistive index identify risk of acute kidney injury in emergency department patients requiring resuscitation room care?

We would like to invite you to take part in a research study. Before you decide to take part we would like to provide you with some information about the research and what it will involve for you. **Take as long as you need to read the information and please ask us to explain anything you do not understand or if you have any further questions.**

What is the purpose of this research study? We want to know if an ultrasound scan can help us to identify patients who are at risk of a condition known as acute kidney injury. It is important that we treat this condition quickly to prevent permanent damage to the kidneys. However, in its early stage it can be difficult to detect.

In patients with this condition, there is a sudden change in how well their kidneys are working. This study will explore if an ultrasound scan to measure blood flow in the kidney could be a better way of detecting these changes.

Why have I been invited to take part? You are being asked to take part in the study as your current illness means that you **may** be at risk of acute kidney injury.

Who is doing the research? The research is being undertaken by a postgraduate student from the University of Bath, working under the supervision of one of the Consultant doctors in the Emergency Department here at The Royal Derby Hospital. The study has been approved by both the University of Bath and by the local NHS ethics committee.

What will happen if I agree to take part? You will be required to sign a consent form to say that you are happy to take part in the study.

As well as the routine blood and urine tests that we take to check how well your kidneys are working, we will do an ultrasound scan of your kidneys. This will take around five to ten minutes. It will involve putting a small amount of gel onto your upper abdomen and you will be asked to hold your breath briefly while we take the measurements.

Who will do the scan? If you agree to take part in the study, the doctor in charge of your care will ask **another member of the study research team** to complete the scan. This will be **either** the lead researcher who is a qualified sonographer or one of the Emergency Department doctors.

How will this affect my treatment? Taking part in the study **will not change your treatment in any way**. The doctor in charge of your care will **not** be told the scan

results and these **will not be used** to alter how we manage your current illness or future treatment.

Are there any risks involved? No. Ultrasound is a very safe imaging technique that does not involve ionising radiation or any known risk used in this way. The research team are all trained ultrasound users who hold a recognised ultrasound qualification.

Are there any benefits if I decide to take part? There are **no** known benefits for you in this study. Your care will not be altered in any way. However, we are hopeful that the results of the study will be of benefit to future patients.

Do I have to agree to take part? No. Taking part in the study is entirely voluntary. Whatever you decide, this will not change your treatment in any way.

Can I change my mind? Yes. There will be further opportunities to ask more questions and consider if you want to take part. You are free to withdraw at any time up to the stage where we analyse the results of the study. You have the right to ask that any data you have supplied to that point be withdrawn. You do not need to give a reason for your withdrawal.

Confidentiality The results of your scan and the data that we collect from your medical notes will be kept confidential. We will not collect any personal details about you except your age, gender, blood and urine test results and relevant history of kidney disease. All data will be anonymised, stored in accordance with Trust data protection regulations and will only be accessible to the research team.

Any personal details, such as your hospital number or date of birth will be kept separately to the data collected as part of the study. These details will only be identifiable by a 'research study number' and will only be accessed by the principle investigator and the doctor supervising the study. .

What will happen to the results of the study?
The final report will be submitted to the University of Bath, for journal publication and for presentation nationally / internationally.

Further information If you, or a member of your family need any further information about the study, a member of the study research team will be glad to answer your questions.

I can be contacted at any time by email at h.venables@derby.ac.uk or you can contact Dr Iain Lennon (the doctor who is supervising the study) on **01332 787859**

If you would like to find out about the final results of this study, you are welcome to email h.venables@derby.ac.uk

Heather Venables (Principle Researcher)

Study ref. number

Appendix 3 Data collection sheet - Derby RRI Study 2016

Please ensure the patient has received and read the patient information sheet, and has signed consent.

Inclusion Criteria:	Adult patient requiring resuscitation room care Consent confirmed	**Exclusion Criteria:**	Unable to consent Confirmed or suspected cardiac arrest History of chronic kidney disease

ED Number:	**Age:**	**Sex:** **M / F** (Circle appropriate)	
Preliminary diagnosis on admission:			**MEW score:**
			eGFR
Recruited by: ***(treating doctor)***			
Consented by:			

RRI Measurement

Scanned by: ***(N.B. this should not be the treating doctor)***		***Grade*** Consultant ☐ Middle Grade ☐ FY1-ST2 ☐ Other ☐
Scan start time	***Scan end time***	

IVCCI if measured:	
RRI measurements In which kidney? (Right preferred)	Right / Left
• Upper pole	
• Mid pole	
• Lower pole	

Both kidneys imaged? Y / N

Any incidential findings? Y / N

(Please specify)

Any technical difficulties?

Y / N

(Please specify)

Please return this form to the Collection Box in Cubicles Area

Appendix 4 Diagnosis and staging criteria for AKI

AKIN diagnostic criteria for AKI (Mehta et al. 2007)

1. Rapid time course (less than 48 hours)
2. Reduction of kidney function
    - Rise in serum creatinine
        - Absolute increase in serum creatinine of ≥0.3 mg/dl (≥26.4 µmol/l)
        - Percentage increase in serum creatinine of ≥50%
    - Reduction in urine output, defined as <0.5 ml/kg/hr for more than 6 hours

RIFLE criteria for staging of AKI (Ricci et al. 2011)

- Risk: serum creatinine increased 1.5 times or urine production of <0.5 ml/kg for 6 hours
- Injury: doubling of creatinine or urine production <0.5 ml/kg for 12 hours
- Failure: tripling of creatinine or creatinine >355 µmol/l (with a rise of >44) (>4 mg/dl) OR urine output below 0.3 ml/kg for 24 hours
- Loss: persistent AKI or complete loss of kidney function for more than 4 weeks
- End-stage renal disease: complete loss of kidney function for more than 3 months

Appendix 5 Patient Consent FORM PCF1.3

Derby Hospitals NHS Foundation Trust

Centre Number:

Study Number:

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: In emergency department patients requiring resuscitation room care, can Renal Resistive Index measurements predict the development of acute kidney injury?

Name of Researcher: **Heather Venables**

Please initial all boxes

1. I confirm that I have read and understand the information sheet [dated 11th OCT 2015] version **[PISshortv1.1]** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw (up to the point of data analysis) without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by the research team where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of recruiting Doctor.	Date	Signature
Name of Person taking consent.	Date	Signature

Appendix 6 Phase 2 : Reflection on sample size estimate

The importance of a priori calculation of study sample size and anticipated study power is well documented (Suresh 2012, Peeling 2010, Bacchetti 2010, Fozgate 2009). However, this key stage of study design is frequently missing from studies that evaluate the characteristics of diagnostic test (ibid). Study power of anything less than 80% appears to be a standard measure by which most review committees would consider a study to be unethical. However, this appears to be an almost arbitrary cut off and the assumptions on which power and sample size calculations are made may be inherently difficult to determine at the outset of a study (Bacchetti 2010).

To extent to which estimates of diagnostic parameters such as test sensitivity, specificity, predictive value etc. can be viewed as precise is dependent on confidence intervals. In general, the larger the sample size, the narrower these intervals are likely to be. However, in an Emergency Department setting, where patients are un-well and disruption to care pathways needs to be minimised, a large sample size may be ethically unjustified.

Prevalence of the condition in the total study population will also affect the precision of estimates. Where prevalence is low, sensitivity estimates may be misleading. Predictive values are also population specific with PPV increasing and NPV decreasing as prevalence of the condition in the population increases.

Sensitivity and Specificity

For the proposed study, one of the key challenges has been estimating how well RRI is likely to perform in the study population. Sensitivity and specificity are as yet unknown, as is prevalence of the condition in the study population. A priori power calculation must therefore be based on ‘best guesses’.

RRI is a continuous variable and in the studies reviewed, cut off points for normal vary and are context specific. Standard deviation for these values in an ED population is unknown and small changes in estimated values have a marked impact on sample size calculation.

Reported test characteristics from previous studies of RRI are based almost exclusively in a critical care context where patients are very unwell and the prevalence of AKI is high (53% - 69%).

Audit of available local data suggests that approximately 32% of patients will be identified as at risk of AKI at admission (eGFR < 60). However at follow-up (eGFR < 60 at 48 hours) this falls to approximately 7%. **(See table T1.10c)**

Poor specificity is a known limitation of sCr based calculation of eGFR (where a baseline value is not known). The fall in confirmed AKI numbers at 48hrs would therefore be anticipated. However, these numbers will also be influenced by successful preventive treatment and reversal of renal dysfunction.

Sensitivity of eGFR in this population is unknown. However, as change in sCr level is known to lag behind the initial renal insult, risk at presentation based on sCr level is likely to be underestimated. This would imply low sensitivity of the standard test.

Follow-up data on patients with eGFR >60 (normal) at admission are not yet available. From the audit data analysed to date, it is not possible to establish an accurate prevalence of AKI in this population.

Best guesses

The College of Emergency Medicine recommend a fairly pragmatic approach to sample size calculation using a simple two way table, ‘best guess’ estimates of sensitivity / specificity and prevalence and required confidence intervals (CEM 2014).

NICE (2013) report AKI in 13–18% of all UK hospital admissions.

For the purpose of calculation of confidence intervals for this study, an estimated prevalence of 15% has been assumed. This is consistent with Trust data on **all** hospital admissions. (The actual prevalence is likely to be higher in a resuscitation room population as these patients are typically quite unwell.)

A **conservative** target recruitment of 200 patients (based on discussion of feasibility with the department lead) and a reported range of values of sensitivity and specificity (Appendix A1.3) have been used as the basis for estimation of predictive values.

	AKI +	AKI -
RRI +	a 27	b 34
RRI -	c 3	d 136

200 patients Prevalence 15%
Sensitivity 90% Specificity 80%

True +ve 27 True –ve 136

False +ve 34 False –ve 3

	AKI +	AKI -
RRI +	a 24	b 51
RRI -	c 6	d 119

200 patients Prevalence 15%
Sensitivity 81% Specificity 70%

True +ve 24 True –ve 119

False +ve 51 False –ve 6

These estimates of predictive values were used to calculate confidence intervals using MedCalc Software, (On-line) Version 13.2.2 - Last modified: May 22, 2014

http://www.medcalc.org/calc/diagnostic_test.php

(See tables **T1.10 a & T1.10 b)**

Conclusion

The extent to which the confidence intervals calculated above are accurate or acceptable remains to be seen. Negative predictive values appear to be encouraging but are dependent on accurate prediction of prevalence. Increasing risk of AKI is closely associated with severity of illness. As patients lacking capacity to consent (sicker or unconscious patients) will be excluded, the prevalence of AKI is therefore likely to be lower in the study population

than in a typical resuscitation room population. Predictive values in an unselected population are likely to be higher.

For RRI to be clinically useful in this context, improved test characteristics will need to be sufficiently better than the existing screening test to justify the associated resource implications. Where ultrasound is used in an ED context, it is generally used as a 'rule in' tool rather than to exclude patients from routine clinical follow up. Specificity (important for a rule in test) needs to be high enough to enable clinicians to make a meaningful risk benefit judgement re implementation of a renal care protective bundle in patients with a positive test result. This may for example include withdrawal or avoidance of drugs such as anti hypertensives, NSAIDs, gentamicin etc that would otherwise be used routinely. However, the specificity of eGFR (the current 'gold standard') is remarkably low. So low in fact that it is use simply to flag the need for further monitoring rather than to change management.

Confidence intervals for RRI sensitivity appear to be fairly wide. However, they appear to be considerably smaller than the acknowledged confidence intervals for eGFR. Recent studies suggest that the sensitivity of RRI in this context is likely to be better than eGFR.

Inaccuracies in sample size calculation appear to be an acknowledged feature of a high percentage of published studies (Ayeni et al 2011, Giraudeau 2009, Bacchetti 2010). Yet this seems to be regarded as a 'make or break' stage of study design within the ethical review process. In considering the design of this particular study, numerous approaches to power and sample calculation have been explored and I feel I now have a far better appreciation of the interdependence of the variables used. However, the degree of estimation necessary in some of these parameters leaves me questioning the extent to which a meaningful conclusion can be reached. If I was an accountant I would be asking " ….what number did you have in mind?".

A time limited recruitment period is a pragmatic response.

References

Ayeni, O., L. Dickson, et al. "A systematic review of power and sample size reporting in randomized controlled trials within plastic surgery." Plast Reconstr Surg(10): 2012 Jul;2130(2011):2078e-2086e.

Bacchetti, P. "Current sample size conventions: flaws, harms, and alternatives." BMC Med(10): 2010 Mar 2022;2018:2017.

Charles, P., B. Giraudeau, et al. "Reporting of sample size calculation in randomised controlled trials: review." Bmj(10): 2009 May 2012;2338:b1732.

Table T1.10 a

200 patients Prevalence 15% Sensitivity 90% Specificity 80%

	Disease				
Test	**Present**	**n**	**Absent**	**n**	**Total**
Positive	True Positive	a= 27	False Positive	b= 34	a + b = **61**
Negative	False Negative	c= 3	True Negative	d= 136	c + d = **139**
Total		a + c = **30**		b + d = **170**	

Results

Sensitivity	$\frac{a}{a+c}$	= **90.00 %**	95% CI: **73.44 %** to **97.77 %**
Specificity	$\frac{d}{b+d}$	= **80.00 %**	95% CI: **73.19 %** to **85.73 %**
Positive Likelihood Ratio	$\frac{\text{Sensitivity}}{100 - \text{Specificity}}$	= **4.50**	95% CI: **3.26** to **6.22**
Negative Likelihood	$\frac{100 - \text{Sensitivity}}{\text{Specificity}}$	= **0.12**	95% CI: **0.04** to **0.37**

Ratio			
Disease prevalence	$\frac{a + c}{a + b + c + d}$	= **15.00 %** (*)	95% CI: **10.36 %** to **20.72 %**
Positive Predictive Value	$\frac{a}{a + b}$	= **44.26 %** (*)	95% CI: **31.55 %** to **57.55 %**
Negative Predictive Value	$\frac{d}{c + d}$	= **97.84 %** (*)	95% CI: **93.81 %** to **99.53 %**

MedCalc Software, (On-line) Version 13.2.2

Table T1.10 b

200 patients Prevalence 15% Sensitivity 81% Specificity 70%

	Disease				
Test	**Present**	**n**	**Absent**	**n**	**Total**
Positive	True Positive	a= 24	False Positive	b= 51	a + b = **75**
Negative	False Negative	c= 6	True Negative	d= 119	c + d = **125**
Total		a + c = **30**		b + d = **170**	

Results

Sensitivity	$\frac{a}{a + c}$	= **80.00 %**	95% CI: **61.42 %** to **92.24 %**
Specificity	$\frac{d}{b + d}$	= **70.00 %**	95% CI: **62.51 %** to **76.78 %**
Positive Likelihood Ratio	$\frac{\text{Sensitivity}}{100 - \text{Specificity}}$	= **2.67**	95% CI: **1.99** to **3.57**

Negative Likelihood Ratio	$\frac{100 - \text{Sensitivity}}{\text{Specificity}}$	= **0.29**	95% CI: **0.14** to **0.59**
Disease prevalence	$\frac{a + c}{a + b + c + d}$	= **15.00 %** (*)	95% CI: **10.36 %** to **20.72 %**
Positive Predictive Value	$\frac{a}{a + b}$	= **32.00 %** (*)	95% CI: **21.70 %** to **43.78 %**
Negative Predictive Value	$\frac{d}{c + d}$	= **95.20 %** (*)	95% CI: **89.84 %** to **98.21 %**

MedCalc Software, (On-line) Version 13.2.2