

EVALUATION OF CARDIAC SURGERY ASSOCIATED ACUTE KIDNEY INJURY USING ULTRASOUND

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A research report submitted to the Faculty of Health Sciences, under the School of Clinical Medicine, University of the Witwatersrand, in partial fulfilment for the degree of a Masters in Medicine, in the branch of Anaesthesia.

Johannesburg, 2021

DECLARATION

I, Gabriela Pettey, hereby declare that this research report is my own work. It is being submitted for the Degree of Masters in Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any prior examination or degree at any other University.



(Signature of candidate)

21st day of

July 2021 at Sandhurst, Johannesburg

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LIST OF ABBREVIATIONS/NOMENCLATURE

A	Atrial contraction wave	CMJAH	Charlotte Maxeke Johannesburg
AKI	Acute Kidney Injury		Academic Hospital
AKIN	Acute Kidney Injury Network	CO	Cardiac Output
AOR	Adjusted odds ratio	CPB	Cardiopulmonary Bypass
B-mode	Brightness Mode	CRS	Cardiorenal Syndrome
BUN	Blood Urea Nitrogen	CSA AKI	Cardiac Surgery Associated
CABG	Coronary Artery Bypass Grafting		Acute Kidney Injury
CD	Colour Doppler	CTICU	Cardiothoracic Intensive Care
CEO	Chief Executive Officer		Unit
CKD	Chronic Kidney Disease	CVP	Central Venous Pressure
CI	Cardiac Index	D	Diastolic wave (hepatic)
CI	Confidence interval	D1	Day 1 post-operatively
		D4	Day 4 post-operatively

DT	Ventricular filling deceleration time	Na ⁺	Sodium
E	Early ventricular filling wave	NGAL	Neutrophil Gelatinase-Associated Lipocalin
eGFR	Estimated Glomerular Filtration Rate	OR	Odds ratio
ERAS	Enhanced recovery after surgery	PD	Power Doppler
FDA	Federal Drug Administration	PI	Pulsatility Index
GDT	Goal directed fluid therapy	POCUS	Point of care ultrasound
GFR	Glomerular Filtration Rate	PWD	Pulsed Wave Doppler
Hb	Haemoglobin	RAAS	Renal Angiotensin Aldosterone System
HR	Hazards ratio	RAP	Right Atrial Pressure
HREC	Human Research Ethics Committee	RBC	Red Blood Cell
ICU	Intensive Care Unit	RI	Resistive Index
IGFBP7	Insulin-like Growth Factor Binding Protein 7	RIFLE	Risk of renal failure, Injury to the kidneys, Failure of Kidney Function, Loss of kidney function, End-stage renal failure
IL-18	Interleukin 18	RRT	Renal Replacement Therapy
IQR	Interquartile range	RV	Right ventricle
IRVF	Intrarenal Venous Flow	SCr	Serum Creatinine
IVC	Inferior Vena Cava	TAPSE	Tricuspid annular plane systolic excursion
KDIGO	Kidney Disease Improving Global Outcomes	TIMP-2	Tissue Inhibitor of Metalloproteinase 2
KIM-1	Kidney Injury Molecule 1	UOR	Unadjusted odds ratio
K ⁺	Potassium		
L-FABP	Liver Fatty Acid-Binding Protein		
MDRD	Modified Diet in Renal Disease		

DRAFT ARTICLE

ABNORMALITIES IN HEPATIC VEIN FLOW PATTERNS ARE ASSOCIATED WITH DEVELOPMENT OF ACUTE KIDNEY INJURY AFTER CARDIAC SURGERY

Abstract

The contemporary definition of the diagnosis of acute kidney injury (AKI) is neither time-sensitive, nor specific. AKI is notoriously multifactorial in origin and found to occur more commonly in cardiac surgery patients when compared to non-cardiac surgery patients.

Cardiac surgery associated acute kidney injury (CSA AKI) carries substantial morbidity and mortality. Pursuits to timeously diagnose CSA AKI have, to date, not been actualized. We investigated the use of hepatic venous and right heart ultrasound parameters in predicting CSA AKI.

Methods

The study was a prospective contextual and descriptive two-center study. The sites of the study were Johannesburg, South Africa, and Aarhus, Denmark. Adult patients that satisfied inclusion criteria, between August 2019 and January 2020 were included, with a total of 152 participants. Blood tests, clinical and ultrasound data were obtained pre-operatively, day-1 and day-4 post-operatively. Hepatic vein, Inferior vena cava and right heart Doppler ultrasound parameters were obtained and analysed for abdominal venous hypertension and the development of AKI.

Results

The median (IQR) age of patients was 68 (55-73) years, predominantly male and the majority were hypertensive. Of 152 patients analysed, 54 (35 %) patients developed AKI. Among these, 37 (69 %) were classified as KDIGO stage I, 11 (20 %) in stage II, whilst 6 (11 %) were in stage III. Age [AOR 1.05, 95%CI 1.00-1.10 P=0.031], EuroSCORE II [AOR 1.43, 95%CI 1.14-1.80, P=0.005] and pre-operative serum creatinine [AOR 1.04, 95%CI 1.01-1.08, P = 0.013] were predictive of AKI. Those who developed AKI had experienced longer cardiopulmonary bypass (CPB) times (P<0.001). Pre-operatively hepatic vein S wave measurements were significantly higher in patients with AKI (P<0.05). On post-operative

day-1, hepatic vein flow ratios of patient with AKI were significantly decreased, driven by low S waves and high D waves, accompanied by significantly elevated central venous pressure (CVP) levels. CVP levels on day-1 (D1) post-operatively were predictive of AKI [AOR 1.31, 95%CI 1.11-1.55, P = 0.001].

Conclusion

Pre-operative hepatic vein S waves were higher in those who developed AKI. This phenomenon seemed to precede the decrease in D1 hepatic flow ratios driven by low S waves and high D waves. The element of venous congestion was reflected by significantly elevated CVP values which were independently associated with AKI on D1. These parameters may reflect peri-operative circumstances including prolonged CPB times, and potential fluid management aspects that can be modified peri-operatively.

Keywords: Cardiac surgery associated acute kidney injury, ultrasound, venous hypertension, venous congestion, hepatic vascular ultrasound, goal directed fluid therapy, IVC

Introduction

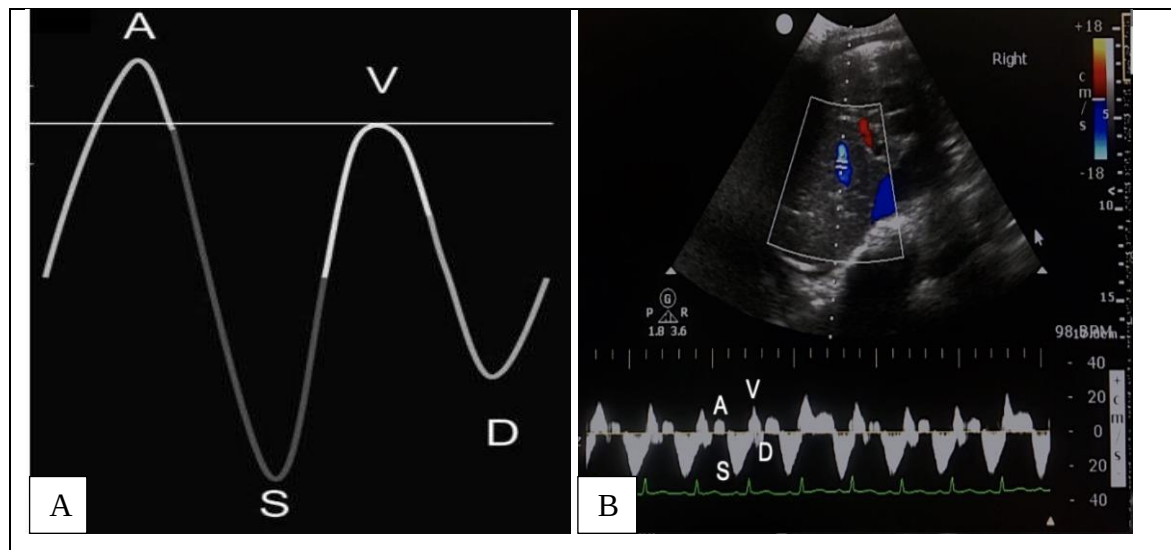
Cardiac surgery associated acute kidney injury (CSA AKI) is a well-recognised post-operative complication^{1–11}. It occurs in up to 40 % of adults post cardiac surgery¹. CSA AKI may complicate into the need for renal replacement therapy (RRT)^{1,10}, develop into chronic kidney disease (CKD), and result in mortality if not managed effectively^{3,4,6,7,12}. CSA AKI has been shown to increase hospital mortality five-fold¹ with rates ranging from 50 – 80 % once RRT has been instituted¹³. Given the magnitude of its complications, improved methods of predicting and diagnosing CSA AKI are essential.

The current consensus for the diagnosis of AKI is by Kidney Disease Improving Global Outcome (KDIGO) group⁴ classification, which combines serum creatinine (SCr) and urine output values⁴. This has proven to be non-specific and ineffective in predicting early kidney stress^{3–6,8,9,11,14}. The clinical use of novel biomarkers^{15–18} and ultrasound assessment for vascular congestion have been areas of recent research focus^{2,5,14,15,19–30}.

The cause of CSA AKI is multifactorial^{2,19,31}. It is associated with abnormalities in perfusion of the kidneys and imbalances between the arterial and venous pressures^{24,32–36}. Current evidence guiding the enhanced recovery after cardiac surgery (ERAS Cardiac) recommendations puts emphasis on protection against kidney stress and injury, and on goal directed fluid therapy (GDT) as part of an effort to improve post-operative outcomes³⁷. Fluid overload leads to venous congestion and increased right atrial pressure (RAP)^{33,38,39}. RAP is transmitted retrogradely into systemic veins including hepatic veins.

Hepatic venous waveforms are characterised by four waves; two are retrograde (“A” and “V”) and two are anterograde (“S” and “D”)⁴⁰ (**Figure 1A and 1B**). They can be categorised as continuous/normal ($S > D$), biphasic/venous congestion ($S < D$) and monophasic/pathological/severe congestion^{23,32–34,41}. Retrograde waves are described as flow away from the inferior vena cava (IVC) and anterograde waves as flow toward the IVC⁴². When venous congestion occurs, increased RAP is transmitted into the hepatic veins resulting in a less negative S wave⁴⁰, and as the pressure increases, S wave deflections approach the baseline, with a resultant decrease in S:D.

Figure 1A. Normal hepatic venous trace ⁴², **1B.** Normal hepatic venous waveform



It is imperative to diagnose kidney stress early before kidney injury sets in, in an effort to improve outcomes. The dilemma remains in finding modalities with assessment capabilities that can be used in diagnosing kidney stress timeously. Point-Of-Care ultrasound (POCUS) allows for assessment of fluid status, flow patterns and Doppler parameters ³². POCUS is useful for quantification of haemodynamic parameters in the heart, the major vessels such as the IVC, and hepatic vessels ^{32,43}. In this study, we sought to describe the relationship between hepatic venous flow patterns and the development of acute kidney injury.

Methods

This was a prospective, contextual, and descriptive two-centre study. The study was a multimodality study investigating association between several ultrasound vascular parameters and development of AKI. Consecutive convenience sampling was used. The study locations were Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), University of the Witwatersrand, South Africa (55 participants) and Aarhus University Hospital, Denmark (100 participants). Approval to conduct the study was obtained from the human research ethics committees of the University of the Witwatersrand (M190310) and the Region Central Denmark Ethical Committee (identifier: 1-10-72-267-18). Adults (age > 18 years) presenting for cardiac surgery were recruited. The exclusion criteria was: isolated aortic valve, reoperation surgery, insufficient ultrasonographic imaging, aortic balloon pump use intraoperatively, pre-operative dialysis or known end-stage renal disease, prior participation in the study, refusal to partake in the study and inability to give informed consent. The data collection process is shown in flow diagram (**Figure 2**).

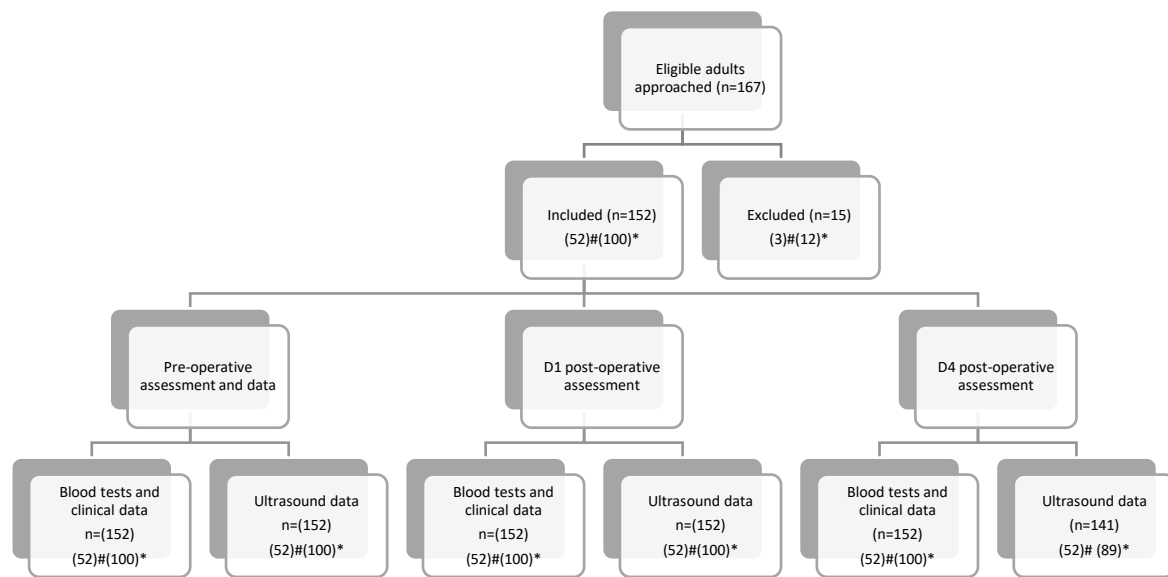


Figure 2. Flow chart depicting the process of data collection

#South Africa, *Denmark. Reasons for exclusion: 3 poor ultrasonographic data, 8 patients refused participation, 4 were unable to provide consent. 11 participants not scanned D4 post-operatively due to: 6 declined further participation, 3 transferred to another facility, 2 no operators available to perform scan

Ultrasound assessments were performed using a GE Healthcare S6 or S70 ultrasound system (Denmark) and Philips CX C50 (South Africa). Ultrasound data was collected by (SN) in South Africa and (JH) in Denmark. Hepatic venous ultrasound measurements were obtained with the patient lying supine, the curvilinear transducer aligned from the seventh to the tenth intercostal spaces on the right side, lateral to the midclavicular line. The hepatic vein was identified using Colour Doppler (CD), and Pulse-wave Doppler (PWD) applied to delineate flows. Hepatic venous flow waveforms were analysed, and flow classified into three patterns: normal, venous congestion and severe congestion. eGFR was calculated using the Cockcroft-Gault equation.

Statistical analysis

Using information from an article published by Beaubien-Souligny and colleagues²⁴, it was determined that to obtain a power of 80 %, with an α of 0.05, a sample size of 152 patients would be adequate. Data was collected for 167 patients to allow for loss to follow up. Three patients were later excluded due to poor quality ultrasound data in South Africa and 12 in

Denmark. Data analysis was performed with the assistance of a biostatistician, using Stata version 16 (StataCorp®, USA). Normally distributed data were reported as means and standard deviations whilst non-normally distributed data was reported as medians and inter-quartile ranges. Categorical data were presented as counts and proportions on a contingency table. A comparative summary of ultrasound and haemodynamic parameters was done between those who developed AKI and those who did not, at baseline, day-1 (D1) and day-4 (D4) post-operatively. Comparisons between continuous independent variables were done using the Mann-Whitney test. Categorical variables were compared using Chi-square test. Where relevant, Fisher's exact test was used to determine non-random associations between categorical variables. A univariable regression analysis was performed to determine association with AKI following which all parameters with a P value ≥ 0.1 and those deemed clinically relevant were included in a multivariable logistic regression analysis.

Results

Data for 152 patients were analysed. Their median (IQR) age was 68 (55-73) years. They were predominantly male (72 %), and the majority were hypertensive (67 %). The median (IQR) EuroSCORE II was 1.84 (1.22-3.5). Baseline ultrasound and clinical data is tabled (**Supplementary Table 1**). A summary of ultrasound data for both groups over the 4-day period are shown (**Supplementary Table 2**). The majority of patients had normal hepatic vein flow patterns pre-operative (75 %), on D1 (84 %) and D4 post-operatively (79 %). Overall, 54 (35 %) participants developed AKI. Among those who developed AKI, 37 (69 %) were classified as KDIGO stage I, 11 (20 %) in stage II, whilst 6 (11 %) were in stage III.

Patients who developed AKI had significantly lower pre-operative eGFR ($P=0.010$), higher pre-operative serum creatinine ($P=0.028$) and EuroSCORE II values ($P<0.001$) (**Table 1**). Pre-operative hepatic vein flow patterns were comparable (**Table 1**). Patients who developed AKI presented with significantly higher hepatic vein S wave flow measurement while all other ultrasound parameters were comparable (**Table 2**). Those who developed AKI had experienced longer cardiopulmonary bypass times $P<0.001$.

Table 1. Comparison of baseline characteristics between those with AKI and No AKI

	AKI (n=54)	No AKI (n=98)	P Value
Parameter	N (%), mean (SD), median (IQR)		
Median Age (IQR) in years	68 (59-73)	67.5 (53-73)	0.67
Gender (Female)	16 (29.6)	27 (27.6)	0.79
IDDM	18 (33.3)	20 (20.4)	0.08
Smoker	25 (46.3)	46 (46.9)	0.94
Hypertension	37 (68.5)	65 (66.3)	0.78
Hypercholesterolaemia n	27 (50.0)	47 (48.0)	0.81
Pre-operative eGFR	71 (56-84)	84 (70-90)	0.01
Euro SCORE II	3.06 (1.48-6.16)	1.675 (1.15-2.43)	<0.001
Pre-operative Hb (g/dL)	9.1 (7.90-12.50)	9.15 (8.5-11.9)	0.40
Pre-operative SCr (mmol/L)	90 (78-107)	81.5 (67-99)	0.03
CPB time (minutes)	151 (112 – 207)	114 (89 -143)	<0.001
Pre-operative Hepatic flow pattern	Normal Venous congestion Severe congestion	7 (13.2) 17 (17.9) 10 (10.5) 68 (71.6)	0.45
Pre-operative IVC (mm)	Minimum Maximum Variation (%)	15.5 (14-17) 17.5 (17-21) 16.0 (11.8-42.3)	0.07 0.10 0.57
Pre-operative TAPSE (mm)		22 (18- 24)	0.33
Pre-operative RV Base (mm)		37 (33 – 41)	0.06

*(Pre-op) Pre-operatively; (D1) Day 1; (D4) Day 4; (TAPSE) Tricuspid annular plane systolic excursion; (RV) Right ventricular; (CVP) central venous pressure; (IVC) inferior vena cava; (eGFR) estimated Glomerular filtration rate; (Hb) Haemoglobin; (CVP) central venous pressure.

On post-operative D1 the hepatic vein flow ratio was significantly decreased in those who developed AKI vs those who did not (**Table 2**). There were no differences between groups on post-operative D4 (**Table 2**). Measurements of right ventricular (RV) base and tricuspid annular plane excursion (TAPSE) values were not different at all points.

Table 2. Comparative summary of ultrasound and haemodynamic data

		AKI (n=54)	No AKI (n=98)	P Value
Pre-operative Parameter		N (%), mean (SD), median (IQR)		
Hepatic vein flow (m/s)	S wave	0.21 (0.16-0.27)	0.19 (0.15-0.24)	0.04
	D wave	0.17 (0.13-0.26)	0.18 (0.12-0.22)	0.12
	Ratio	1.20 (0.71-1.61)	1.24 (0.73-1.50)	0.95
Hepatic vein flow pattern	Normal	7 (13.2)	17 (17.9)	
	Venous congestion	3 (5.7)	10 (10.5)	0.45
	Severe congestion	43 (81.1)	68 (71.6)	
IVC diameter (mm)	Minimum	15.5 (14-17)	11 (9-14)	0.07
	Maximum	17.5 (17-21)	13 (12-18)	0.10
	Variation (%)	16.0 (11.8-42.3)	28.6 (14-36.4)	0.57
TAPSE (mm)		21 (19 – 23)	22 (18 – 24)	0.33
RV Base (mm)		39 (34 – 45)	37 (33 – 41)	0.06
Day 1 Post-operative Parameter				
Hepatic vein flow (m/s)	S wave	0.19 (0.15-0.27)	0.20 (0.16-0.25)	0.73
	D wave	0.26 (0.17-0.35)	0.23 (0.16-0.31)	0.21
	Ratio	0.57 (0.45-0.91)	0.78 (0.56-1.04)	0.01
Hepatic vein flow pattern	Normal	1 (1.9)	2 (2.1)	
	Venous congestion	9 (17.0)	11 (11.4)	0.55
	Severe congestion	43 (81.1)	83 (86.5)	
IVC diameter (mm)	Minimum	18 (12-19)	14 (10-19)	0.67
	Maximum	23 (17-25)	16 (13-21)	0.14
	Variation (%)	24.4 (22.2-27.3)	13.3 (10-26.1)	0.25
CVP (mmHg)		12.5 (10 – 16)	11 (8 – 13)	<0.001
Day 4 Post-operative Parameter				
Hepatic vein flow (m/s)	S wave	0.21 (0.15-0.28)	0.20 (0.15-0.25)	0.44
	D wave	0.26 (0.12-0.36)	0.22 (0.12-0.31)	0.24
	Ratio	0.58 (0.46-0.85)	0.66 (0.40-0.90)	0.36
Hepatic vein flow pattern	Normal	1 (1.9)	5 (5.8)	
	Venous congestion	10 (19.2)	13 (14.9)	0.26
	Severe congestion	41 (78.9)	69 (79.3)	
IVC diameter (mm)	Minimum	15 (15-17)	12.5 (11.5-13.5)	0.19
	Maximum	20 (18-21)	20.5 (15.5-22)	0.77
	Variation (%)	21.1 (18.2-28.6)	39.7 (21.6-50.9)	0.31
TAPSE (mm)		11 (9 – 13)	12 (10 – 14)	0.34
RV Base (mm)		37 (33 – 43)	36 (33 – 41)	0.62

*(Pre-op) Pre-operatively; (RV) Right ventricular; (TAPSE) Tricuspid annular plane systolic excursion, (D1) Day 1; (CVP) central venous pressure; (IVC) inferior vena cava, (D4) Day 4; (TAPSE) Tricuspid annular plane systolic excursion; (IVC) inferior vena cava

Age and EuroSCORE II were predictive of AKI in a multivariable regression analysis (**Table 3**). Age, EuroSCORE II, pre-operative SCr and CVP levels were also independently associated with development of AKI in a model including day-1 parameters (**Table 4**).

Table 3. Factors associated with AKI pre-operatively

Parameter		UOR(95%CI)	P value	AOR(95%CI)	P value
Age		1.00 (0.98-1.03)	0.53	1.05 (1.00-1.10)	0.03
Gender	Male	0.90 (0.43-1.88)	0.79	0.76 (0.23-2.56)	0.66
Pre-operative eGFR		0.99 (0.98-1.01)	0.25	1.03 (0.99-1.06)	0.20
EuroSCORE II		1.36 (1.15-1.60)	<0.001	1.43 (1.14-1.80)	0.005
Pre-operative SCr (mmol/L)		1.02 (1.00-1.03)	0.03	1.02 (0.98-1.05)	0.31
Pre-operative hepatic vein flow (m/sec)	S wave	198 (2.20-17886.1)	0.02	5.48 (0.00-948864.7)	0.78
	D wave	37.81 (0.68-2090.01)	0.08	293.9 (0.00-0.81)	0.37
	Ratio	1.13 (0.87-1.47)	0.36	1.78 (0.21-14.82)	0.60
Pre-operative hepatic vein flow pattern	Normal	1 (base reference)		1 (base reference)	
	Venous congestion	0.73 (0.15-3.47)	0.69	0.23 (0.02-3.15)	0.27
	Severe congestion	1.54 (0.59-4.01)	0.38	1.18 (0.33-4.25)	0.80
Pre-operative IVC diameter (mm)	Minimum	1.04 (0.99-1.10)	0.12	1.34 (0.86-2.09)	0.20
	Maximum	1.04 (0.98-1.11)	0.18	0.80 (0.58-1.11)	0.41
	Variation (%)	0.50 (0.09-2.71)	0.42	162.85 (0.09-26.70)	0.18
RV Base (mm)		1.05 (0.998-1.097)	0.06	1.03 (0.96-1.10)	0.83
TAPSE (mm)		0.97 (0.90-1.05)	0.47	1.00 (0.902-1.100)	0.94

*(TAPSE) Tricuspid annular plane systolic excursion; (RV) Right ventricular; (IVC) inferior vena cava; (eGFR) estimated Glomerular filtration rate; (SCr) serum creatinine, (UOR) unadjusted odds ratio, (AOR) adjusted odds ratio

Table 4: Factors associated with AKI on D1 post-surgery

Parameter		UOR(95%CI)	P value	AOR(95%CI)	P value
Age		1.00 (0.98-1.03)	0.53	1.05 (1.00-1.10)	0.04
Gender	Male	0.90 (0.43-1.88)	0.79	0.46 (0.14-1.49)	0.20
Pre-operative eGFR		0.99 (0.98-1.01)	0.25	1.02 (0.99-1.05)	0.13
EuroSCORE II		1.36 (1.15-1.60)	<0.001	1.31 (1.05-1.65)	0.02
Pre-operative SCr (mmol/L)		1.02 (1.00-1.03)	0.03	1.04 (1.01-1.08)	0.01
	S wave	1.72 (0.03-107.50)	0.80		
D1 Hepatic vein flow (m/s)	D wave	33.69 (1.50-756.81)	0.03		
	Ratio	0.41 (0.16-1.09)	0.07	0.39 (0.12-1.28)	0.12
	Normal	1 (base)			
D1 Hepatic vein flow pattern	Venous congestion	1.64 (0.13-21.10)	0.71	0.22 (0.00-10.11)	0.44
	Severe congestion	1.04 (0.09-11.75)	0.98	0.20 (0.01-3.98)	0.29
	Minimum	1.04 (0.97-1.10)	0.28		
IVC diameter (mm)	Maximum	0.98 (0.92-1.05)	0.64		
	Variation (%)	1.20 (0.75-1.91)	0.44	1.32 (0.48-3.64)	0.60
D1 CVP (mmHg)		1.20 (1.08-1.33)	<0.001	1.31 (1.11-1.55)	0.001

*(RV) Right ventricular; (IVC) inferior vena cava; (eGFR) estimated Glomerular filtration rate; (SCr) serum creatinine, (UOR) unadjusted odds ratio, (AOR) adjusted odds ratio

Discussion

Patients who developed AKI presented with higher hepatic vein S waves pre-operatively, in this current study. Patients with AKI developed significantly reduced hepatic vein flow ratios on post-operative D1 reflected as biphasic/venous congestion with S<D waves. We postulate

that this is a function of perioperative events including the inflammatory response and fluid management. This was accompanied by elevated CVP values on D1 post-operatively. The association between venous congestion and fluid overload has been elucidated^{36,39,44,45} previously. The pathophysiology encompasses hepatic and renal venous profiles, and their relationship to AKI^{22,24,41,43,45,46}. Recent work on haemodynamic assessment in critically ill patients emphasizes that the primary determinants of cardiac output are encountered in the venous circulation due to preload⁴⁷, namely venous compliance, capacitance, resistance to venous return and right atrial pressure. As venous hypertension progresses, compliance decreases and the mean circulatory filling pressure increases⁴⁷. The value of hepatic vein Doppler interpretation is thought to lie in the assessment of flow and velocity, not as a static measurement, but in combination with clinical acumen and dynamic parameters importantly the ratios of S:D waves. This modality has a potential for use in this regard, as the sole use of CVP for haemodynamic assessment has shown its limitations.

The exploitation of this knowledge, coupled with the venous ultrasonographic profiles, as collective indicators of venous hypertension, may therefore afford clinicians a noninvasive modality of assessing volume status and inform management strategies aimed at mitigating the risk of AKI development. If used in combination with dynamic parameters, it could speak to the venous circulatory basis of GDT with specific haemodynamic goals including the avoidance of venous hypertension and undesirable recruitment of excessive stressed volume, which aligns with ERAS cardiac principles^{23,31,32,41,47–50}.

Beaubien-Souligny and colleagues²⁴, have suggested venous congestion as an important contributing factor associated with development of AKI and that association is further supported by data suggesting that deteriorating kidney function in patients with decompensated heart failure is associated with increased CVP. They, however, also highlighted various challenges with utilising CVP as a bedside clinical tool to evaluate venous congestion, such as interobserver variability and the fact that central venous catheters may be removed earlier to minimise the risk of infections²⁴. The directive in utilizing POCUS should not be to focus on the static measurement of CVP *per se*, however, but rather to consolidate the knowledge that venous hypertension, reduced venous compliance together with congestion, can be detected using Doppler, and that these factors have been associated with the development of AKI³². It therefore may be advantageous to use multimodality non-

invasive ultrasound parameters performed at bedside, in conjunction with other dynamic parameters and clinical acumen, to assess fluid status.

The development of AKI is thought to be mediated by central venous hypertension^{32,36,43}, where the notion of increased “afterload” or venous congestion is placed on the kidney, resulting in reduction in renal blood flow and ultimately tissue pressure and damage (19,38,43). In this study we find that this phenomenon is reflected in reduced hepatic vein ratios which are reflected as S< D waves indicative of venous congestion. A study by Spiegel and colleagues⁴⁶, showed that an S wave to D wave reversal in hepatic vein flow had an odds ratio of 4.15 (95% CI 1.54–11.23%) for an increase in the likelihood of a major adverse kidney event (MAKE-30) event in ICU patients, where the MAKE-30 event was described as an elevation of the creatinine level to ≥ 200 % of baseline, the need for renal replacement therapy or death⁴⁶.

There are several POCUS markers used to detect the high pressures associated with the congestive process^{23,32}, such as the assessment of large veins (IVC and internal jugular), as well as pressure changes in the hepatic and intra-renal veins^{32,43}. The clinical usefulness of POCUS in detecting significant venous congestion may be strengthened by combining the use of these markers³² and interpreting their clinical significance. In this study, we investigated utilisation of hepatic venous flow Doppler, CVP, IVC, RV base and TAPSE measurements to predict the development of AKI after cardiac surgery. However, we did not find any associations between AKI and IVC, RV base or TAPSE measurements.

The current study found an association between a higher EuroSCORE II and development of AKI. The EuroSCORE II is a well-established risk factor for development of AKI and has been reported in several studies^{50–53}. Furthermore, we found that the EuroSCORE II was independently predictive of development of AKI post cardiac surgery in two models, namely an adjusted and unadjusted odds ratio, including one pre-operative and another post-operative D1 parameters, $P=0.005$ and $P=0.02$ respectively. Similar to a previous study by Amini and colleagues⁵⁴, we found that increased age was predictive of development of AKI. It has been reported that the frequency of developing AKI in patients over 60 years of age may increase progressively in an age-dependant manner and could be three- to eightfold higher compared to younger patients⁵⁵.

A previous study conducted by the South African group of this study ⁵⁶ found raised pre-operative SCr to be a predictor of post-operative AKI. The current study yields similar results, albeit with the majority of patients enrolled in Denmark. SCr, together with age and ejection fraction, have been used in a risk stratification model, the ACEF criteria, to predict development of AKI ⁵⁷ and found to be significant contributors. Chen and colleagues ⁵⁸, compared the ACEF score with other risk scores (EuroSCORE II and Society of Thoracic Surgeons score) and found it to perform similarly. Patients who developed AKI had experienced significantly prolonged CPB times. CPB is known for inducing the stress response ^{1,10,31} which affects vascular integrity ^{3,8,11,19}. The inflammatory milieu accompanying the stress response can lead to tissue oedema and fluid retention ^{38,39,44}. This may be reflected as elevations in CVP levels ^{35,36}. Elevated CVP measurements have been associated with an increased risk of mortality and AKI, with the odds of developing AKI in critically ill adult patients increasing for every 1mmHg rise in CVP ³⁵. These intra-operative circumstances can be managed in line with guidelines that advocate for GDT and prevention of renal stress and injury.

Limitations

This was a two-center study with potential for inter-observer variability between study sites. Ultrasound parameters have a potential of being influenced by a multitude of factors and should be interpreted in the clinical context. CSA AKI has a complex aetiology, and this should be borne in mind.

Strengths

The study represents geographic and patient profile diversity, ensuring heterogeneous characteristics. The use of interdepartmental, inter-specialty, intercontinental investigators added expertise and wholistic review of the topic and data interpretation.

Conclusion

Hepatic venous ultrasound parameters pre-operatively and D1 were associated with AKI. Although these were not predictive of development of AKI in multivariable regression models, they could possibly be utilized in POCUS perioperatively to assist, in combination with clinical acumen and risk stratification, with early detection of AKI. D1 CVP values have indicated this progression in this study allowing for yet another point of possible mitigation when interpreted with the understanding of principles pertaining to venous compliance,

congestion, mean circulating filling pressure, not interpreted in isolation. ERAS Cardiac guidelines advocate for the use of GDT, to avoid deleterious effects of fluid overload and development of AKI. Hepatic venous ultrasound modality together with other ultrasound modalities aimed at evaluating fluid status, may add value towards the goal of preventing AKI development perioperatively.

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Declaration of interest

The authors declare no conflict of interest.

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Authors' contributions

GP: conceptualizing the study, designing the study, conducting the study, acquisition of data, interpretation of data, drafting article and partook in final approval of the manuscript.

PM: conceptualizing the study, designing the study, conducting the study, acquisition of data, interpretation of data, drafting article and partook in final approval of the manuscript.

HJM: designing the study, conducting the study, interpretation of data, drafting article and partook in final approval of the manuscript.

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JFP: conceptualizing the study, designing the study, conducting the study, acquisition of data, interpretation of data and partook in final approval of the manuscript.

PJO: conceptualizing the study, designing the study, conducting the study, acquisition of data, interpretation of data and partook in final approval of the manuscript

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NT: conducting the study, acquisition of data, interpretation of data and partook in final approval of the manuscript.

Appendix

Supplementary Table 1. Summary of pre-operative data

Parameter		Mean (SD)/ Median (IQR)/ N(%)
Age (years)		68 (55-73)
Weight (kg)		77 (68-90)
Height (cm)		171 (9.4)
Gender (M)		109 (72 %)
Hypertension		102 (67 %)
IDDM		38 (25 %)
Hypercholesterolaemia		74 (49 %)
Smoker		71 (47 %)
Pre-op SCr (mmol/L)		85 (70-102.5)
D1 SCr (mmol/L)		90 (75.5-102.5)
D2 SCr (mmol/L)		87.5 (72-123)
D3 SCr (mmol/L)		87 (69-113)
D4 SCr (mmol/L)		83 (66-107)
Pre-op K ⁺ (mmol/L)		3.9 (3.7-4.3)
D1 K ⁺ (mmol/L)		4.6 (4.3-4.9)
D4 K ⁺ (mmol/L)		4 (3.7-4.3)
Pre-op Na ⁺ (mmol/L)		138 (11.4)
D1 Na ⁺ (mmol/L)		139 (3.5)
D4 Na ⁺ (mmol/L)		138 (3.5)
Pre-op Hb (g/dL)		10 (2.7)
D1 Hb (g/dL)		7.8 (2.2)
D4 Hb (g/dL)		7.4 (1.9)
Pre-op eGFR		78.9 (25.9)
D1 eGFR		66.3 (21.4)
D4 eGFR		77.8 (33.3)
NO AKI		98 (65%)
AKI GRI		37 (24%)
AKI GRII		11 (7%)
AKI GRIII		6 (4%)
EuroSCORE II		1.84 (1.22-3.5)
Pre-op Hepatic vein systole (m/s)		0.2 (0.08)
D1 Hepatic vein systole (m/s)		0.2 (0.08)
D4 Hepatic vein systole (m/s)		0.21 (0.1)
Pre-op Hepatic vein diastole (m/s)		0.2 (0.1)
D1 Hepatic vein diastole (m/s)		0.25 (0.14)
D4 Hepatic vein diastole (m/s)		0.23 (0.12-0.33)
Pre-op Hepatic vein ratio		1.23 (0.7-1.56)
D1 Hepatic vein ratio		0.74 (0.52-1)
D4 Hepatic vein ratio		0.64 (0.4-0.89)
Pre-op Hepatic vein flow pattern	Normal	111 (75%)

	Venous congestion	24 (16%)
	Severe congestion	13 (9%)
D1 Hepatic vein flow pattern	Normal	126 (84%)
	Venous congestion	3 (2%)
	Severe congestion	20 (14%)
D4 Hepatic vein flow pattern	Normal	110 (79%)
	Venous congestion	6 (4%)
	Severe congestion	21 (15%)
Pre-op IVC min (mm)		12.8 (3.6)
D1 IVC min (mm)		15.4 (4.5)
D4 IVC min (mm)		13.8 (4.2)
Pre-op IVC max (mm)		16.5 (4)
D1 IVC max (mm)		19 (4.9)
D4 IVC max (mm)		18.8 (4)
Pre-op IVC Variation		24.9 (13.8)
D1 IVC Variation		21.7 (8.4)
D4 IVC Variation		32 (17)
D1 CVP (mmHg)		11.3 (3.7)
Pre-operative TAPSE (mm)		21.1 (4.4)
Pre-operative RV Base (mm)		38.2 (7.5)
D4 TAPSE (mm)		11.7 (3.3)
D4 RV Base (mm)		37.7 (6.9)

(Preop) Pre-operatively; (D1) Day 1; (D2) Day 2; (D3) Day 3; (D4) Day 4; (TAPSE) Tricuspid annular plane systolic excursion; (RV) Right ventricular; (CVP) central venous pressure; (IVC) inferior vena cava; (SCr) Serum creatinine; (Hb) Haemoglobin; (Na⁺) Sodium; (K⁺) Potassium; (eGFR) estimated Glomerular filtration rate(D1) Day 1; (CVP) central venous pressure; (IVC) inferior vena cava; (eGFR) estimated Glomerular filtration rate

Supplementary Table 2. Summary of ultrasound data for both AKI and No AKI groups

Parameter		AKI		
		Pre-op	D1	D4
Hepatic vein flow Median (IQR) (m/s)	S Wave	0.21 (0.16-0.27)	0.19 (0.15-0.27)	0.21 (0.15-0.28)
	D wave	0.17 (0.13-0.26)	0.26 (0.17-0.35)	0.26 (0.12-0.36)
	Ratio	1.20 (0.71-1.61)	0.57 (0.45-0.91)	0.58 (0.46-0.85)
Hepatic vein Flow pattern n (%)	Normal	7 (13.2)	1 (1.9)	1 (1.9)
	Venous congestion	3 (5.7)	9 (17.0)	10 (19.2)
	Severe congestion	43 (81.1)	43 (81.1)	41 (78.9)
IVC diameter (mm)	Minimum	15.5 (14-17)	18 (12-19)	15 (15-17)
	Maximum	17.5 (17-21)	23 (17-25)	20 (18-21)
	Variation	16.0 (11.8-42.3)	24.4 (22.2-27.3)	21.1 (18.2-28.6)
TAPSE (mm)		21 (19 – 23)	11.5 (10 – 13)	11 (9 – 13)
RV Base (mm)		39 (34 – 45)	38 (34.5 – 44.5)	37 (33 – 43)

CVP (mmHg)			12.5 (10 – 16)	12 (6 – 13)
		No AKI		
		Pre-op	D1	D4
Hepatic vein flow Median (IQR) (m/s)	S wave	0.19 (0.15-0.24)	0.20 (0.16-0.25)	0.20 (0.15-0.25)
	D wave	0.18 (0.12-0.22)	0.23 (0.16-0.31)	0.22 (0.12-0.31)
	Ratio	1.24 (0.73-1.50)	0.78 (0.56-1.04)	0.66 (0.40-0.90)
Hepatic vein Flow pattern n (%)	Normal	17 (17.9)	2 (2.1)	5 (5.8)
	Venous congestion	10 (10.5)	11 (11.4)	13 (14.9)
	Severe congestion	68 (71.6)	83 (86.5)	69 (79.3)
IVC diameter (mm)	Minimum	11 (9-14)	14 (10-19)	12.5 (11.5-13.5)
	Maximum	13 (12-18)	16 (13-21)	20.5 (15.5-22)
	Variation	28.6 (14-36.4)	13.3 (10-26.1)	39.7 (21.6-50.9)
TAPSE (mm)		22 (18 – 24)	9 (7 – 12)	12 (10 – 14)
RV Base (mm)		37 (33 – 41)	34 (31 – 38)	36 (33 – 41)
CVP (mmHg)			11 (8 – 13)	8 (6 – 12)

*(Preop) Pre-operatively; (D1) Day 1; (D4) Day 4; (TAPSE) Tricuspid annular plane systolic excursion; (RV) Right ventricular; (CVP) central venous pressure; (IVC) inferior vena cava.

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APPENDICES

APPENDIX 1: Publication in SAJAA

NOVEL MODALITIES FOR THE DIAGNOSIS OF CARDIAC SURGERY ASSOCIATED ACUTE KIDNEY INJURY: A NARRATIVE REVIEW OF THE LITERATURE

Abstract

Acute Kidney Injury (AKI) is a common complication post cardiac surgery and increases mortality during hospitalisation five-fold. If present, it is an independent risk factor for progression to chronic kidney disease. When renal replacement therapy (RRT) is required, it carries a 50 % mortality rate for cardiac surgery associated (CSA) AKI. Given the dynamic nature of CSA AKI, it is imperative to implement preventative and management strategies to: prevent or limit ischaemia; reduce systemic inflammation; modify amenable pre- and peri-operative risk factors; and address nutritional and fluid status at the pre- intra- and post-operative stages. Conventional modalities in the diagnosis of AKI have proven ineffectual in the timely diagnosis, and rely mostly on non-specific biometric parameters, namely a rise in serum creatinine, and a decrease in urine output. Novel biomarkers have promoted new ideas in the search for more effective, precise and reproducible tools to aid diagnosis. In addition, ultrasonic tools for renal, hepatic and portal vascular flow patterns using Duplex Doppler for venous flow parameters, together with renal arterial resistive index, have been used as novel predictors of peri-operative AKI. Although these parameters require further investigation, Duplex Doppler of the renal, hepatic, portal and cardiac systems appear to have promising results in the early detection of AKI.

Keywords: Acute kidney injury, Cardiac surgery, Renal ultrasound, Portal ultrasound, Hepatic ultrasound, Duplex Doppler, NGAL, TIMP-2, IGFBP7, Venous congestion, Venous flow patterns, Resistive Index (RI), Intrarenal venous flow patterns, Portal pulsatility, NephroCheck®

Introduction

The aetiology of AKI is multifactorial, however patients undergoing cardiac surgery are said to have a 40 % probability of developing AKI.¹ It is a pervasive disease, whose diagnosis evades practitioners until significant functional reserve has been lost. The current diagnostic modalities are not time-sensitive in detecting potentially irreversible injury.^{1–12} Given the magnitude of this condition, as well as the considerable complications that can occur, such as: the requirement of renal replacement therapy (RRT); long-term renal dysfunction or chronic renal disease; and mortality, it is imperative to establish preventative measures and early diagnosis.^{2,3,13–15} Current common practice makes use of the Kidney Development Improving Global Outcomes (KDIGO) group classification system for diagnosis of AKI, however, these parameters have proven ineffectual for timely diagnosis. New modalities are constantly being investigated, including conventional testing, urinary and blood biomarkers, as well as the use of ultrasound.^{1–3,5,13,16–18}

Physiology Of AKI

AKI is a well-recognized complication post cardiac surgery,^{1,3,13,14} which progresses to kidney dysfunction requiring RRT in 2-5 % of patients,¹⁵ chronic kidney disease (CKD) and mortality if not treated timeously and judiciously.^{1,3,13,16,19} Although AKI is multi-factorial in origin, its aetiology post cardiac surgery is compounded by unique considerations.

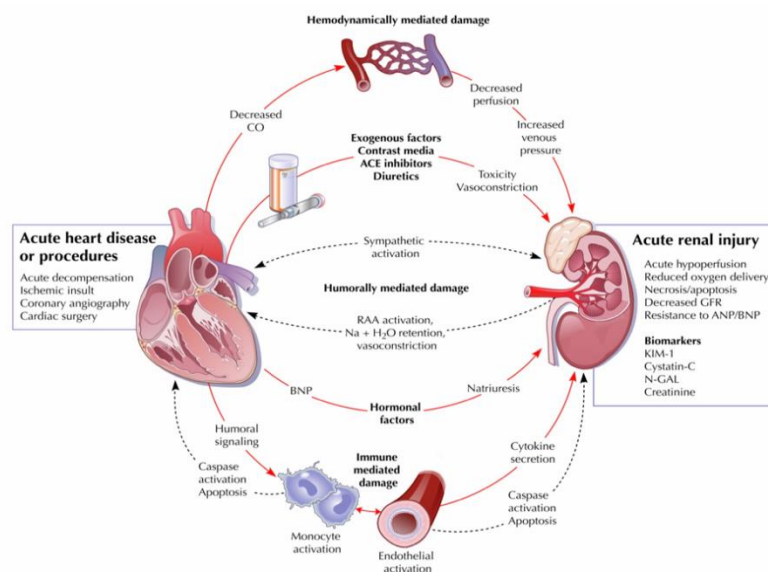


Figure 1 Pathophysiological interactions of Acute Cardiorenal Syndrome.⁶⁰

The physiological profile of many patients presenting for cardiac surgery includes multiple co-morbidities, such as hypertension, diabetes, hypercholesterolaemia, chronic illness

(cardiac, hepatic, renal, peripheral vascular) and advanced age, all of which increase the likelihood of CSA AKI occurring.^{3,5,16}

Surgical factors also pose additional risk: the nature of the surgery (valvular, CABG, congenital deformity), complexity of the surgery, use and duration of CPB, CPB perfusion pressure, use of blood products, haemodynamic instability, ischaemia-reperfusion injury, aortic cross-clamping, intraoperative thrombo-embolic phenomena, arrhythmias, and myocardial infarction. All these increase the probability of CSA AKI occurring perioperatively.^{1,5,13,16,19–21}

The pathophysiology of CSA AKI is presumed to originate predominantly intra-operatively, mostly due to acute tubular necrosis.^{2,3,5,22,23} Some of the factors at play are CPB-associated systemic inflammatory response, CPB pump pressure, damage to the endothelial glycocalyx, hypovolaemia and hypoperfusion, haemolysis, oxidative damage, sympathetic nervous system activation and the use of nephrotoxic agents (angiotensin converting enzyme inhibitors, contrast dyes).^{1,2,4,5,16,20,21}

Whilst kidney arterial perfusion parameters have previously enjoyed attention with regards to intra- and post-operative anticipation and prediction of the onset of AKI,^{1,5,13,15,16,24–28} recent focus has turned to the venous system, particularly looking at venous congestion of the renal, portal and hepatic systems as possible predictors of AKI.^{26,29–38}

Conventional Biomarkers Of AKI

Serum creatinine (SCr) levels and urine production are the conventional biometric parameters used to stage AKI, but these are non-specific, delayed-response parameters that result in late diagnosis.^{3,4,22} These parameters have been used extensively in defining criteria, scores and classifications in the diagnoses of AKI. Previously, AKI was defined using the Risk/Injury/Failure/Loss/End-stage (RIFLE) criteria, which categorizes the exposure (risk/injury/failure), and the outcome (loss/end-stage).³⁹

The Acute Kidney Injury Network (AKIN) criteria, was developed to follow the RIFLE criteria, which modified certain aspects of the RIFLE criteria, notably additions were to: the time period which was shortened from seven days to 48 hours; the initiation of RRT regardless of SCr levels; the removal of glomerular filtration rate from the classification system; lower SCr level threshold for diagnosis of AKI; and removal of the assumption of normal SCr levels in the absence of this information.³⁹ In a retrospective analysis conducted

by Bastin et al³⁹ it was noted that AKI diagnosis using the AKIN criteria was associated with a significantly increased incidence of hospital mortality when compared to the RIFLE criteria (0.86 vs 0.78, $P = 0.0009$).

Currently, the most widely used criteria for AKI is that proposed by the KDIGO group³ (Table I):

Table I. KDIGO Staging Classification system AKI³

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥ 0.3 mg/dl (≥ 26.5 μ mol/l) increase	< 0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dl (≥ 353.6 μ mol/l) OR Initiation of renal replacement therapy OR, In patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m ²	< 0.3 ml/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

Central to the contemporary management of AKI is early detection and institution of preventative measures. Preventative strategies, such as appropriate use of fluids including avoidance of positive fluid balance and renal venous congestion, nutritional optimization, avoidance of nephrotoxic agents, limiting CPB exposure, and use of experimental agents (calcium channel blockers, dexmedetomidine, high-dose steroids, fenoldopam), have been described.^{1,3,13–19} However, the current diagnostic criteria fail to assist in providing a timely diagnosis for some of these measures to be effective.^{1,3,4,6,13,16–19,24,39}

The need for a more sensitive, specific and real-time test/ biomarker of AKI is because SCr levels and urine production are not time-sensitive markers of AKI, as they may take up to 48 hours to change after an insult has occurred.^{1,3,10,13,16,19,24} When trying to predict the onset of a disease, the use of a retrospective marker is not logical, especially one that can be as delayed as the rise in SCr. The change in SCr used in the KDIGO criteria to detect the occurrence of AKI, cannot be used to predict the occurrence of AKI before the insult occurs.³

SCr alone may not assist with the evaluation of potentially damaged or at-risk renal cellular tissue.^{4,7–12} Its use, therefore, is significant in established disease, and cannot be used to preempt or anticipate the onset of AKI. There is therefore a need for methods to predict or preempt AKI, to ensure that the KDIGO preventative and supportive managements strategies can be implemented early.

Novel Biomarkers Of AKI

Novel biomarkers for diagnosis of AKI have been the focus of ongoing interest.^{6-9,11,12,40}

Biomarkers that have provoked discussion are Cystatin C, Neutrophil gelatinase-associated lipocalin (NGAL), Tissue inhibitor of metalloproteinase 2 (TIMP-2), Insulin-like growth factor binding protein 7 (IGFBP7), kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18) and liver fatty acid-binding protein (L-FABP).^{6-9,11,12,25,40} Biomarkers that have gained the most attention as potentially useful from current practice are NGAL, TIMP-2 and IGFBP7.^{6-9,11,12,40}

NGAL is a marker produced by the renal tubules and released into the bloodstream after an insult has occurred, and increased levels can be detected within two hours of the injury.^{6,7} NGAL is a component of the innate immune system but has multiple functions in the human body.^{6,7} It is bacteriostatic, is involved in cellular pathway signalling and is embryologically important for the development of renal tissue.^{6,7} It is upregulated shortly after an insult to the kidney has occurred, and is thought to appear when structural damage has occurred to the renal tubular cells, but prior to established dysfunction.^{6,7} It is, therefore, present in urine and blood tests shortly after injury has occurred, however it is also produced by injured epithelial cells of liver, colon and lung.^{6,7}

Its use for CSA AKI in adults appears to have promising results, however when tested in the paediatric population it appeared disappointing.⁷ Given that it is a biomarker of cellular stress or injury, it is tested when AKI is suspected, and therefore not as surveillance pre-operatively.^{6,7,12}

TIMP-2 and IGFBP7 are two biomarkers that are indicators of cell cycle arrest.^{8,9,11,12,40} They are produced when the cell enters but fails to exit cell cycling, and their production results in G₁ cell arrest, a known consequence of AKI, which results in inhibition of angiogenesis and endothelial cell proliferation.^{8,9,11,12,40} The combination of these two biomarkers, were shown to detect an increase in the risk of AKI seven-fold compared to NGAL ($P < 0.002$).^{8,11,12,40} A laboratory test kit, the NephroCheck® (Figure 2), which has been approved for use by the FDA, makes use of this combination (TIMP-2 and IGFBP7).^{8,12} It has been used to identify patients at risk of developing AKI following cardiac surgery, which could assist with the timely institution of preventative measures. Currently, the largest obstacle to its implementation in routine clinical practice is cost and availability.



Figure 2. The NephroCheck®, an FDA-approved laboratory test. It is used to measure urinary levels of serum biomarkers present in patients who have, or develop, AKI.^{41,42}

Novel Use Of Vascular Ultrasound In The Diagnosis Of AKI

The use of ultrasound has gained popularity due to its inherent properties.^{15,25–27,29,30,43–46} It is non-invasive, portable, well-tolerated by patients and produces real-time results.^{46–48}

Specifically, Duplex Doppler, a combination of Colour Doppler (CD) and Brightness mode ultrasonography, which gives descriptive information on flow patterns using hue and colour, has recently shown promising results as a novel technique to assist with early identification and prognostication of AKI.^{26–32,36,43–46,49–54} It has been used successfully to define venous and arterial renal parameters in the peri-operative period, such as the renal resistive index, renal venous flow patterns, portal pulsatility and portal venous flow.^{15,26,28–30,43–45,49,53,55} These parameters are described individually below.

ARTERIAL PROFILE: THE RENAL RESISTIVE INDEX

The renal arterial resistive index (RI), as defined by Pourcelot's formula^{53,56,57} has recently been used as a predictor of ensuing and persistent AKI.^{27,28,32,45,49,53} Resistive index is a measure of pulsatile blood flow that reflects the resistance to blood flow caused by the microvascular bed distal to the site of measurement.^{15,24,25,27,28,44,45,49,53} The formula^{53,56,57} used to calculate resistive index is as follows:

$$RI = \frac{v \text{ (systole)} - v \text{ (diastole)}}{v \text{ (systole)}}$$

where v describes the velocity of blood flow. It is calculated using the intra-lobar/arcuate artery, where an average is taken using the cranial, central and caudal arteries.^{27,28,43,49,53} It can be performed pre- and post-operatively, to assist with clinical judgement and decision making.

Table II. Classification of resistive index^{26,29,30,57}

<i>Resistive index (value)</i>	<i>Description of flow</i>
0	Continuous
1	Systolic present, diastolic absent
>1	Reversed diastolic flow

It is performed through the translumbar ultrasound windows with the patient lying supine, using a curvilinear probe (Figure 3,4). The probe is aligned to the eleventh and twelfth ribs on each side, along the anterior axillary line.^{46,47,55} A sagittal view of the kidneys can be obtained by rotating the probe from 0° to 45°. ^{46,47,55} Using CD, vessels can be delineated and pulsed wave doppler (PWD) applied, the RI can be calculated using the arterial waveform pattern.^{15,26,47,54,55} It can also be performed intra-operatively, with the use of a transoesophageal (TEE) probe as described by Bandyopadhyay et al⁵⁸ through the trans-gastric view using the corkscrew method. The method is only described for the left kidney as images of the right kidney are more difficult to obtain due to its anatomical position (Figure 5).



Figure 3. Illustration of probe position for renal vascular image acquisition (consent obtained from patient)

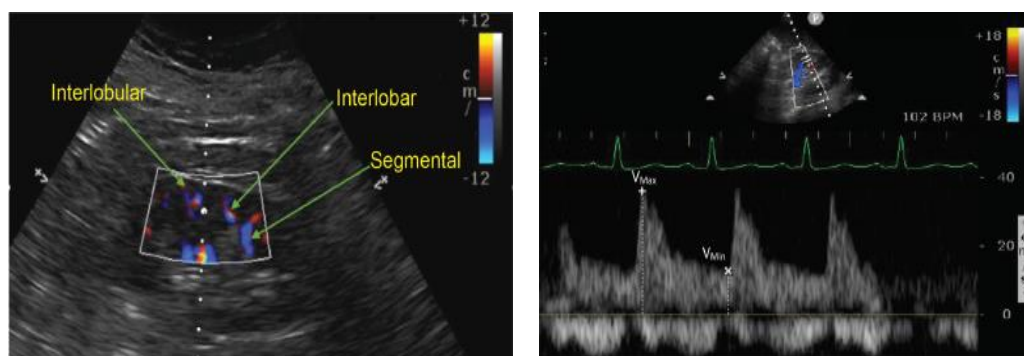


Figure 4. Colour Doppler of the right kidney and its vessels (*left*) and Normal Doppler of interlobar artery with tracing depicting below (*right*)⁵⁵

The classification of flow patterns, in relation to RI, is tabulated (Table II). Using a cut-off value of > 0.70 , the RI has been independently used to risk stratify morbidity, namely the development of sepsis, prolonged ventilation and the progression of heart failure.^{28,44}

In a systematic review by Ninet et al⁵³, of 154 studies over 28 years, Doppler-based RI and prediction of reversibility of renal dysfunction were assessed. They found that RI could be used as a predictor of persistent AKI.^{26,30,55} Use of this modality in cardiac surgery is still new.

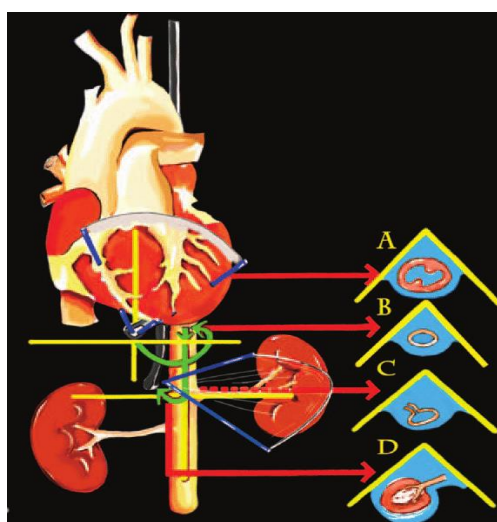


Figure 5. Illustration of the Corkscrew Technique using TEE to visualize renal vessels.⁵⁸

Bedside RI allows estimation of the renal vascular resistance, and a value > 0.70 has been found to be associated with an increased likelihood of major post-operative adverse outcomes.⁴⁴ RI can be influenced by parenchymal and vascular abnormalities such as: variations in vascular compliance; heart rate and rhythm; increased intra-abdominal pressure;

and ureteric obstruction.^{17,28,49} More studies in this area are necessary.

VENOUS PROFILE: RENAL, PORTAL AND HEPATIC FLOW PATTERNS

In the venous system, Duplex Doppler and waveform analysis have been used to identify surrogates of renal venous congestion.^{26,30–32,36,55} Central venous pressure (CVP) is a component of right atrial pressure, and inferior vena cava (IVC) pressures are a component of CVP.^{31,36,50–52} An elevated CVP can, therefore, be indicative of venous congestion provided supradiaphragmatic causes of obstruction such as pneumothorax, cardiac tamponade and excessive positive end expiratory pressure are ruled out, or it can be a function of diastolic dysfunction.^{36,50–52}

Given the intimate relationship between the cardiac and renal axes, Doppler assessment of the cardiac system must be considered when investigating the renal system.^{50,51,59–61} Systolic and diastolic function of the heart can be calculated using Doppler, and can be used to stratify patients based on their echocardiographic features, as described by Choi et al⁶¹. Patients with more severe cardiac dysfunction (systolic or diastolic) had an increased risk of developing AKI as well as long term renal impairment.⁶¹

Assessment of diastolic function can assist in differentiating between true diastolic dysfunction and volume overload, which results in elevated pressures in the abdominal venous system.^{50–52,61,62} A high CVP, secondary to venous congestion, has been shown to be associated with increased post-operative mortality.^{31,33–36,38,39,63} With these increased venous pressures, the IVC becomes non-compliant and right atrial pressures are transmitted throughout the cardiac cycle into the abdominal venous vasculature.^{28–31,48,55,57} Importantly, absolute values of IVC measurements do not accurately predict CVP measurements, but rather the IVC collapsibility and inspiratory-expiratory variations, which can discriminate between low/normal CVP and high CVP readings.^{26,30,31,36}

Under physiological conditions, renal venous flow is uninterrupted. In the face of venous congestion, it becomes biphasic, then monophasic, and finally completely discontinuous with severe congestion.²⁶ Intrarenal venous flow (IRVF) patterns (see Figure 6) have been found to be strongly correlated with adverse clinical outcomes, and to independently predict increased risk of peri-operative AKI and mortality.^{26,30,55} The venous flow patterns are categorized based on the data captured from analysing the arcuate/intralobar veins cranially, centrally and caudally.^{26,30,47,55}

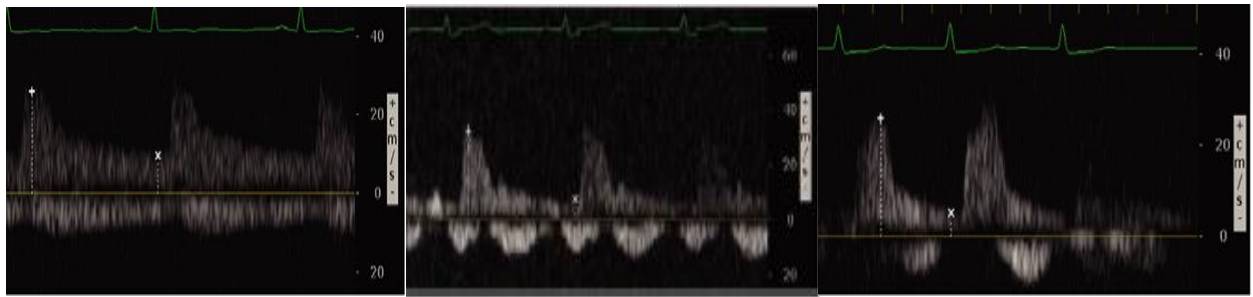


Figure 6. Intrarenal venous flow patterns of the right interlobar veins using Colour Doppler. Normal wave form pattern (*left*) showing continuous flow throughout the cardiac cycle vs Discontinuous biphasic venous flow with systolic and diastolic component (*middle*) vs Discontinuous wave form pattern (*right*) with flow only present during diastole.³⁰

The ideal positioning is with the patient supine, or in the left/right lateral decubitus positions, with the probe aligned with the eleventh and twelfth ribs, in the anterior axillary line.^{30,36,43,46,47} These measurements can also be obtained pre- and post-operatively as comparatives so as to detect the change in ultrasonographic data. These parameters can be obtained through standard translumbar renal ultrasound or TEE, with the use of PWD to categorize the flow patterns.^{30,47,48}

Portal venous flow (Figure 7) tends to be protected from backward venous pressure due to its anatomy, therefore, when differences between systolic and diastolic velocities exist, it is

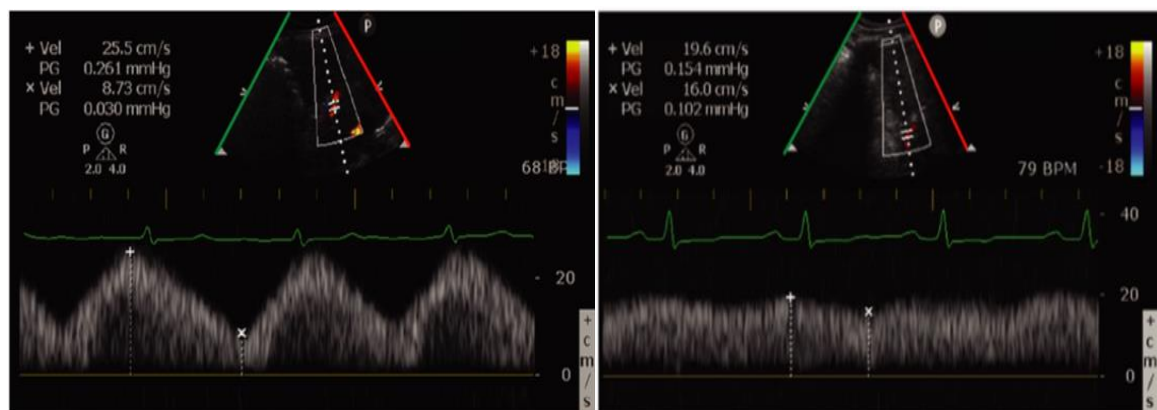


Figure 7. Duplex Doppler of Portal venous waveform patterns and pulsatility fraction³⁰ Normal portal flow (*right*) showing minimal differences between Vmax and Vmin, with lower pulsatility fraction vs abnormal variations (*left*) of flow velocities during the cardiac cycle (values of >50 % considered abnormal) where significant changes noted between Vmax and Vmin, resulting in higher pulsatility fraction (pulsatility fraction 18.4 % vs 66%).

indicative of abnormal flow.^{29,30,36,55} With the patient in the supine position, or the left/right lateral decubitus position, the probe in the eight to eleventh intercostal spaces, midaxillary line, CD can be used to identify the Portal vein coronally, and PWD to determine the maximal systolic and diastolic flow velocities.^{36,47,48,55}

When portal flow pulsatility $[(\text{systolic velocity} - \text{diastolic velocity}) / \text{systolic velocity}]$ is $> 50\%$ it is considered a marker of venous congestion.^{29,30,36,55} It has been found to be an independent factor in predicting CSA-AKI, together with intrarenal venous flow patterns.^{29,30,55} When evaluated peri-operatively, it could provide information on the presence of congestion, if compared to pre-operative values.^{29,30,32} When used in conjunction with IRVF patterns, it assists in differentiating between supradiaphragmatic causes of venous obstruction, portal hypertension and true venous congestion, which can prove invaluable in the real-time setting of intra-operative decision making.^{15,29,30,32,55}

Hepatic venous flow pattern (see Figure 8), can also assist with the diagnosis and identification of venous congestion.^{29,30,36,55} With the patient in the supine position, the probe aligned from the seventh to tenth intercostal space, lateral to the midclavicular line, the hepatic vein can be identified using CD, and PWD used to categorize the flow

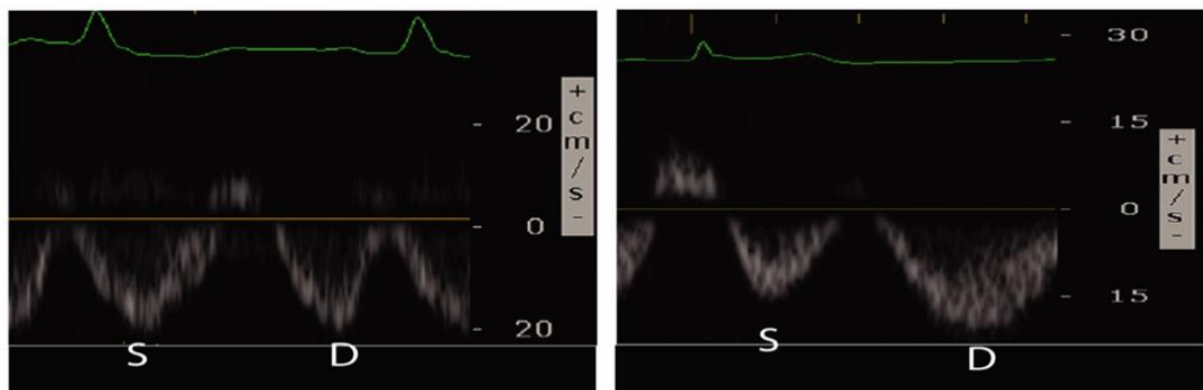


Figure 8. Duplex Doppler of Hepatic venous waveform patterns.³⁰ Normal hepatic venous waveform (*left*) with systolic (S) component $\geq$ diastolic component (D) vs abnormal (*right*) with systolic component (S) $<$ (D).

pattern.^{29,30,36,47,55} Under physiological conditions, the hepatic vein has a systolic:diastolic ratio of > 1 , which is reversed when venous congestion is present.^{29,30,55} When flow is significantly affected, the diastolic component of the cardiac cycle exceeds the systolic component, with attenuation of the systolic flow and eventually reversal of normal atrial flow.^{29,30,36,55}

These peri-operative ultrasonographic parameters, in varying combinations have been reviewed and shown interesting results, given the benefits of real-time changes and clear demarcations of indices, as outlined by the various formulae. The use of these ultrasonographic features to diagnose and predict ensuing AKI has recently been reviewed by Beaubien-Souligny et al⁵⁵, in cardiac surgical patients, and have shown that the peri-operative comparative change within an individual, with the use of sound clinical judgement and

understanding of the interpretation of ultrasonographic detail, can be invaluable.

Management Of AKI

The fundamental principle underlying the treatment of AKI is to treat the cause, and therefore, the importance of identifying and risk stratifying patients according to their predisposing and precipitating factors is imperative.^{2-5,13,16,64} Important directives to achieve in minimizing CSA AKI are to prevent or limit ischaemia, decrease inflammation, modify amenable risk factors, address nutritional status and manage fluid status appropriately.^{2-5,13,16,64} The goal of early initiation of therapy is to limit the severity of the complications; it has been found, however, that initiation of RRT early in the treatment plan results in better outcomes for both CSA AKI and non-CSA AKI.^{1,14,33}

The notion of fluid therapy is central to the prevention and treatment of AKI, yet, there is no standardised fluid management strategy.^{3,33,34} Positive fluid balance in critically ill patients results in worse outcomes, such as prolonged hospital stay, increased risk of respiratory failure requiring ventilation, and risk of long-term progression to renal dysfunction.^{33-35,63} Fluid overload in patients with AKI has been shown to be an independent risk factor for mortality, regardless of the need for RRT, and cardiac surgery complicates the considerations, as it poses multiple risk factors that too can damage the endothelial glycocalyx, leading to “leaky” capillaries and rapid accumulation of fluid in the interstitium.^{5,33-36,63}

The clinical conundrum, therefore, arises with patients who develop CSA AKI, and yet are fluid-replete, as nutritional requirements will still demand an intake of approximately 1 Litre per day, which cannot be counteracted by insensible losses alone, directing therapy to initiate RRT earlier, so as to avoid fluid overload.^{2-4,22,33-36,63} The lack of unanimity regarding specific fluid management strategies for patients with CSA AKI remains problematic.

Conclusion

Novel techniques to diagnose AKI timeously are clinically relevant and important. Duplex Doppler appears to be showing promising results in RI, IRVF patterns, portal and hepatic venous flow, and cardiac profiles. Further investigations into these parameters, and possible use of biomarkers to correlate with the degree of AKI could prove to assist with earlier detection of CSA AKI.

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APPENDIX 2: LITERATURE REVIEW

Introduction

This literature review will outline the relationship between cardiac surgery and Acute Kidney Injury (AKI). It will discuss risk factors, pathophysiology, prevention, diagnostic tools, treatment and fluid management in the face of AKI. It will explore arterial and venous ultrasound of the cardiac, hepatic, portal and renal systems, and discuss its' utility in the peri-operative period.

1. Cardiac surgery and AKI

1.1 Background

Patients presenting for cardiac surgery are at an increased risk of developing AKI (1–6). Advanced age (> 65 years old), co-morbidities such as hypertension, diabetes and hyperlipidaemia are often the cause (1–4). Cardiac surgery on its own presents a unique spectrum of risk factors that predispose patients to develop AKI: the type of surgery, ischaemia-reperfusion, cardiopulmonary bypass (CPB), haemodynamic instability, the use of nephrotoxins, and oxidative stress (1–4). AKI is a common adverse event post cardiac surgery occurring in 30 – 40 % of patients (1,2). AKI post cardiac surgery has been found to increase mortality during hospitalisation five-fold (1), and as an independent risk factor for progression to chronic kidney disease (3). Renal replacement therapy (RRT) is necessary for 2 – 5 % (1,2) of patients who develop cardiac surgery associated AKI (CSA AKI), and amongst these patients there is a 50 % mortality rate (6).

The incidence of AKI is influenced by the type of cardiac surgery: coronary artery bypass graft (CABG) has the lowest incidence, 2 – 5 % in a review (2), and up to 30 % in valvular surgery, depending on race and gender (5). This can be attributed to the technical difficulty of the procedure, length of time spent in the operating room, exposure to, and duration of CPB, use of blood products, and degree and duration of haemodynamic instability (1–3,6). CABG itself also has different risk profiles, as off-pump versus on-pump surgery present distinct differences in probabilities of developing AKI (7,8). Complex surgery, septal defect repair, redo surgery, combined surgery, focal arrhythmic ablation, emergency surgery and many other procedures all carry varying risks of developing AKI (1,6,7,9). Importantly, the other complications associated with cardiac surgery, such as myocardial infarction, bleeding and coagulopathy, emboli and arrhythmias can also increase the risk of CSA AKI (8,9). CSA

AKI is thought to originate intra-operatively, and progress to acute tubular necrosis. There may, however, be pre- and intra-operative risk factors that can be addressed (1–4).

CPB induces systemic inflammation, for a number of reasons that will be detailed below, which can damage the endothelial glycocalyx, leading to vascular permeability and fluid accumulation in the interstitium, ultimately resulting in fluid overload (1,2,6,10,11). This increases the complexity of managing fluid status in these patients, and can precipitously lead to AKI warranting RRT, as even small positive fluid balances can be harmful enough to necessitate initiation of RRT (2,10,12,13).

Due to the complex nature of cardiac surgery, and the inherent risks, complications occur fairly frequently, and AKI associated mortality is in the range of 50 – 80 % (5). CSA AKI also increases the risk of infection, prolongs hospital stay and prolongs intensive care unit (ICU) stay (14,15). Clinical trials suggest that early institution of RRT in cardiac surgery patients with severe AKI may lower mortality and shorten ICU stay (1,16).

1.2 Cardiorenal syndromes

The cardiac and renal systems are intimately related in disease, despite the independence of organ function under normal physiological states (17,18). The term cardiorenal syndrome (CRS) was developed to better describe the cluster of symptoms and clinical disease that presents when these two organ systems adversely interact (17). The CRS is defined as “disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other” (17). There are five forms of cardiorenal syndrome (17) :

- I. Acute cardiorenal syndrome (Type 1)
- II. Chronic cardiorenal syndrome (Type 2)
- III. Acute renocardiac syndrome (Type 3)
- IV. Chronic renocardiac syndrome (Type 4) and
- V. Secondary cardiorenal syndrome (Type 5)

Patients treated for acute or chronic heart failure have a 30 % chance of developing AKI (1,2), with the highest mortality occurring in patients undergoing cardiac surgery (17).

The aetiology of the CRS can be divided into four mechanisms: increased renal venous pressure, reduced renal perfusion, right ventricular dilatation and dysfunction, and lastly neurohormonal- activation of the renin angiotensin aldosterone system (RAAS) (17).

However, the exact pathophysiology of the interactions between the cardiac and renal systems is not yet fully understood (19,20).

Interestingly, renal venous congestion is a well-known concept, dating back to the 1930s, where Winton (21) found that an increase in renal venous pressure (regardless of cardiac output (CO) and renal blood flow) directly led to impaired renal function. Not only did the author discover this, but he also concluded that the renal impairment improved when the renal venous pressure was subsequently reduced (21). This highlights the importance of renal venous pressures on renal function.

Traditionally, renal hypoperfusion has been thought to be secondary to sub-optimal CO (19,20), amongst other things. A study by Mullens et al. (19) found that the strongest haemodynamic determinant of worsening renal function was the presence of venous congestion. Moreover, the cardiac index (CI), which is the cardiac output (CO) divided by the body surface area, was found to have limited effect on renal function (19). The traditional assumption that impaired CO is the single most important factor leading to renal dysfunction, therefore should be reconsidered. This study also showed that in patients with persistent venous congestion, there was an increased risk of deteriorating renal function when compared to baseline function (19).

2. Acute kidney injury

2.1 Background

AKI is a heterogeneous syndrome with multiple aetiologies, and devastating long-term consequences if not managed timeously (1–4,14,17,22,23). It is a dynamic condition that evolves from early reversible prerenal azotaemia, to established disease which requires intervention, and may result in long-term consequences such as chronic kidney disease and the need for RRT (4,24). AKI is associated with increased number of therapeutic interventions, morbidity, mortality, prolonged hospitalisation, and increased hospital costs (2,4).

Due to the complex nature and origin of AKI, as well as the long-term ramifications of untreated AKI, the Kidney Disease Improving Global Outcomes (KDIGO) group (4)

recommend risk stratifying patients according to their susceptibilities and exposures, so that they may be managed accordingly, and therefore reduce the risk of AKI occurring. The KDIGO group also recommend further studies to validate scoring systems, namely in special situations such as cardiac surgery (4). There are limitations to the current diagnosis of AKI, as the standard parameters used (reduced urine output and increased serum creatinine (SCr)) are nonspecific and not always highly sensitive (3,4,6,14,15).

AKI can occur due to changes in renal perfusion (1–4,14,22); accordingly, the use of ultrasound to define renal blood flow and identify venous congestion and arterial restrictive index have a potential for useful predictive value. Early detection of renal dysfunction, prior to progression to chronic renal disease, is a research priority, as the cost to patient, hospitals and society can be exorbitant (1–4,15,22,23). The accurate prediction of the development of AKI, as well as the early recognition and treatment of AKI, is therefore a matter of urgency (4,16).

2.2 Risk factors associated with CSA AKI

The risk factors for CSA AKI can be divided into three main categories, however, it must be noted that they are not separate entities, and there is significant overlap in some areas. Importantly, the presence of some of the risk factors pre-operatively greatly increase the likelihood of development of AKI post cardiac surgery (18).

The non-modifiable patient risk factors are advanced age (> 65 years), ethnicity, female gender, features of metabolic syndrome (hypertension, diabetes, hyperlipidaemia), presence of chronic disease (cardiac, renal, hepatic, peripheral vascular), cardiogenic shock, critical illness and trauma (with regards to the development of crush syndrome) (1,3,4).

The modifiable patient risk factors are anaemia (as defined by haemoglobin < 10g/dL), hypovolaemia, low haematocrit during CPB, venous congestion and sepsis (1,4,9,10,19).

The non-modifiable surgical risk factors are the type of cardiac surgery, especially cardiac surgery warranting CPB, the duration of CPB, duration of aortic cross-clamping, complex cardiac surgery involving more than one region, hypoperfusion as a surgical and or anaesthetic technique, presence and duration of vasopressor and diuretic use, blood

transfusion requirements, the number of cycles of reperfusion and ischaemia, the extent of the systemic inflammatory response and oxidative damage (1,3,8,9,15)

2.3 Pathophysiology of CSA AKI

The aetiology of AKI is abundant in origin, therefore only the relevant aetiologies and their origins will be briefly described. CSA AKI itself has a multitude of causal factors that interact with each other and can exacerbate pre-existing renal dysfunction, or precipitate AKI in previously healthy patients (2,18,25). The major pathophysiological factors attributed to AKI post cardiac surgery are peri-operative renal ischaemia resulting in prerenal azotaemia, reperfusion injury or prolonged aortic cross-clamping, sympathetic nervous system activation (resulting in activation of RAAS), CPB-induced haemolysis and inflammation, oxidative stress and coagulopathy with increasing blood product requirements (1,18,25). The use of peri-operative nephrotoxic agents, such as angiotensin-converting enzyme inhibitors, aminoglycosides, loop diuretics and contrast dyes may also increase the likelihood of developing CSA AKI (18).

Peri-operative renal ischaemia occurs secondary to hypoxic injury or hypovolaemia which result in cellular dysfunction and if not remedied timeously, to cell lysis and death (18,25). Sympathetic nervous system activation leads to activation of RAAS, and renal arterial vasoconstriction in an effort to maintain perfusion, which ultimately worsens the injury (9,18,25). Activation of RAAS also increases renal oxygen demand, and can lead to supply-demand imbalance (1,6,9).

Intra-operative renal blood flow is significantly influenced by CPB, as CPB induces non-pulsatile blood flow (1,2). In normal physiological states, 20 % of CO is directed to the kidneys, with the majority of the blood flow going to the cortical glomeruli and hence being shunted away from the vasa recta (1). This occurs to maintain the solute balance that exists between the cortex and the medulla, but also predisposes this area to hypoxia (1,2,9). The resultant increased cortical perfusion that occurs during CPB may paradoxically precipitate ischaemia in the medulla, due to imbalance of the normal physiological flow (1). As the medulla normally functions at low oxygen tension, small alterations in renal blood flow may result in supply-demand imbalance, leading to ischaemia and cellular injury (1,2,9).

CPB can also cause AKI due to exposure of the red blood cell (RBC) to non-physiological surfaces resulting in haemolysis, and as a result of the shear forces applied to the RBC, mechanical breakdown occurs, leading to cell lysis and death (2,26). The free haemoglobin that results from mechanical breakdown during CPB causes injury to the kidney by inducing free-radical production, which leads to oxidative stress and damage, and the by-products lodge in the glomeruli and tubules, resulting in AKI (1,26).

Aortic cross-clamping can cause reperfusion injury, as well as athero-emboli (2,18). The cross-clamping results in up to 50 % decrease in renal blood flow, regardless of the position of the clamps, and results in reduced capability of solute handling for > 24 hours (9). After the cross-clamp is released, the renal blood flow increases above normal values (reflex hyperaemia), however glomerular filtration rate (GFR) remains below 30 % of baseline for up to two hours (9). The athero-emboli stimulate an inflammatory response which can damage the glomeruli and tubular cells, resulting in activation of local cytokines and vasoconstriction, ultimately causing cellular damage (1,2,25). Once immune cells have been activated in the renal parenchyma, the inflammatory process ensues and eventually results in AKI and fibrosis (1,25).

2.4 Prevention of CSA AKI

The CSA AKI syndrome is complex and has multiple factors, therefore, focus must be placed on prevention and early treatment to improve clinical outcomes. To date, the preventative strategies for AKI are basic measures aimed at modification of the patient factors within the clinicians realm; namely judicious use of fluids, improvement of nutritional status, avoidance of venous congestion, limited CPB duration and avoidance of exposure to nephrotoxic agents (2–4,15). Of note, where possible and feasible, off-pump cardiac surgery, especially CABG, should be performed (4,6).

Despite the importance of fluid management in patients with AKI, as well as post-operative cardiac surgery patients, there is still no universally proven and accepted fluid management strategy (4,10–13). The KDIGO group (4) recommend judicious use of crystalloid administration in the face of haemodynamic stability to prevent prerenal azotaemia and AKI. Studies have been conducted to elucidate the requirements of fluid management, and most advocate that a positive fluid balance should be avoided, as it is an independent risk factor for mortality (12,13,27).

Ultrasound is increasingly being utilised in the peri-operative period to delineate those at risk of developing AKI (23,24,28–32). Research is aimed at assessing fluid status using Doppler, and how the cardiac, hepatic, renal and portal venous systems transform in the face of congestion and fluid overload (10,27,31–35). In detecting venous congestion, preventative measures can be placed and an attempt to reduce CSA AKI instituted. Duplex Doppler has also been used to assess the renal arterial system and has been used to stratify those at risk of developing AKI, as well as to predict those who will have persistent AKI (36). Ultrasound is a useful tool when used in combination with clinical acumen and investigations to predict those at risk of developing AKI and can therefore be implemented as a preventative strategy for those undergoing high-risk surgery (1,24,29,31–33,36)

Alternative forms of preventative strategies have looked at calcium channel blockers, Fenoldopam, sodium bicarbonate, dexmedetomidine, high-dose steroids and remote ischaemic pre-conditioning; however, none have shown conclusive evidence of protective capability (1,18).

2.5 Diagnosis of CSA AKI

AKI is an elusive disease that has no defining clinical characteristics and is relatively asymptomatic until the extremes of disease occur (18). CSA AKI presents a uniquely difficult set of circumstances as clinicians cannot rely on clinical signs or symptoms alone: there is a high risk of AKI occurring and yet there are limited diagnostic tests available to detect it (6,7,15,22). The contemporary consensus for classifying and diagnosing AKI is that defined by KDIGO (4) which uses SCr values and urine output production. Previously, the Risk of renal failure, Injury to the kidneys, Failure of kidney function, Loss of kidney function, and End-stage renal failure (RIFLE) and Acute Kidney Injury Network (AKIN) criteria were used to classify patients with AKI, and to date may still be used in combination with the KDIGO AKI guidelines(4), nonetheless, KDIGO recommend the use of their classification system, partly to add uniformity to the diagnosis of AKI.

The KDIGO group classification of AKI is as follows (4).

- **Stage 1:** Increase in SCr $> 26.5\mu\text{mol/L}$; or 1.5 – 1.9 times baseline SCr level; or $< 0.5\text{ml/kg/hour}$ urine production for 6 – 12 hours.

- **Stage 2:** Increase in SCr of 2.0 – 2.9 times baseline level; or < 0.5ml/kg/hour for > 12 hours.
- **Stage 3:** Increase in SCr of > 3.0 times baseline level; or SCr level of > 354µmol/L; or initiation of RRT; or < 0.3ml/kg/hour urine production for > 24 hours; or anuria for > 12 hours.

Neither urine output nor SCr provide the ideal diagnostic test for AKI, as urine flow rate is a poor measure of kidney function; decreased urine output is a nonspecific marker that can occur in multiple disease states, as well as in some states of normality (1–4,22,23). However, oliguria generally reflects a decreased GFR and so reduced urine output together with increased blood urea nitrogen (BUN) have been used as surrogates for decreased estimated glomerular filtration rate (eGFR) (3). In theory, oliguria can occur without a decrease in GFR (4). Nonetheless, it is a non-specific marker of AKI, especially post cardiac surgery, where reduced urine output is a common finding (1–4). SCr values are better validated than oliguria in the diagnosis of AKI, but it can take up to 24 hours after an insult for the levels to change (1,4,6,15). It is also found to be elevated in other clinical conditions such as liver disease and is dependent on body habitus (4,25).

Whilst eGFR is the most used test in clinical practice, it is problematic for a number of reasons: it is an estimation of the clearance of a biomarker, not a measurement; it tends to overestimate renal function when creatinine is used (until the eGFR < 60mls/min); no ideal biomarker has yet been found and it cannot be truly measured in humans (4,37). Measured GFR is not cost effective as the biomarkers used for the test (inulin, para-aminohippurate, iothexal, iothalamate) are expensive, and the test is labour-intensive for patient and the clinician, which makes it unsuitable for use in daily practice (38). It is an important test to assist in the diagnosis of AKI, but KDIGO guidelines (4) recommend the use of SCr and urine output in conjunction with eGFR, alternatively just SCr and urine output, as these variables can be measured as opposed to estimated.

Multiple prediction formulae have been developed to estimate serum creatinine clearance: Modified Diet in Renal Disease (MDRD), Cockcroft-Gault and Chronic Kidney Disease Epidemiology Collaboration. These formulae were developed for stable patients with chronic renal insufficiency and thus are inappropriate to use in the diagnosis of AKI (3,38).

Furthermore, the prediction formulae have been shown to overestimate renal function at lower levels, and there is relatively little standardisation of laboratory technique used to estimate creatinine, leaving room for error (38).

A urinary 24-hour creatinine clearance test is also a good measure of renal function, but again there are concerns with this investigation. Creatinine is filtered at the glomerulus freely and subsequently not reabsorbed but it is secreted at the tubules and thus tends to overestimate true filtration rate (9,38). Urinary creatinine clearance requires a 24-hour urine sample which has proven to be impractical as it is inconvenient to patients and therefore often inaccurate (38).

Another urinary biomarker that has received attention recently is Cystatin C. It is produced by all nucleated cells in the human body, and is structurally defined as a low molecular weight protein (28). It too, like creatinine, is freely filtered by the glomeruli but it then should be totally reabsorbed by the proximal tubule (28). Any Cystatin C that is detected in the urine is thus an indicator of a tubulopathy (28). Studies to corroborate its use as a proxy for GFR are ongoing, but in a study conducted by Schnell et al (28), it was found that renal resistive index (RI) was a better predictive parameter for the development of AKI on Day 3 post polytrauma and or severe sepsis, than urinary or serum Cystatin C. Further investigation of the validity of Cystatin C is being explored.

Novel biomarkers have been investigated recently, one being the urinary and plasma neutrophil gelatinase-associated lipocalin (NGAL). NGAL belongs to the lipocalin superfamily, and is produced in the kidney tubules after an insult has occurred (26,39). Both urinary and plasma NGAL levels have been shown to be accurate predictors of early kidney damage (3,26,39). Levels are clinically detectable up to two hours post kidney injury, which in comparison to SCr, is much earlier in the disease process (1,26,39). The prompt rise in NGAL levels makes it a promising biomarker for the early detection of AKI, and several studies have also looked into using it as a predictor of clinical severity and outcomes in patients who develop AKI (26,39).

Newer biomarkers of AKI include tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) (39–41). These two urinary biomarkers were combined in a single urinary test kit called the NephroCheck, approved by the Federal

Drug Administration, for use in critically ill patients at risk of developing AKI (40). The theory behind the use of these two biomarkers is that they are indicators of cell-cycle arrest (40,41). A known consequence of AKI is G₁ cell-cycle arrest, which results in inhibition of endothelial cell proliferation and angiogenesis (40,41). The renal tubular cells secrete both TIMP-2 and IGFBP7 during phases of cellular damage (39,40). Therefore, when TIMP-2 is expressed in quantities great enough to be detected in urine sampling, it serves as a warning that AKI has possibly occurred (40,41).

IGFBP7 is a cell-cycle arrest protein, that induces p21, leading to G₁ cycle arrest (40,41). The effects of both these bio-proteins are pleiotropic and not confined to the kidney. It is important to note that the Federal Drug Administration approved the use of the NephroCheck only as an adjunct to other tests in critically ill patients at risk of developing AKI (40). It cannot be used as a single marker of AKI; in the Discovery (41,42), Sapphire (41,42) and Topaz (41,43) clinical trials the validity of the Nephrocheck was assessed. The Discovery trial (42) conducted three cohorts in patients with sepsis, shock and major trauma or surgery. This multicentre prospective cohort looked at which biomarkers, novel and standard, could best predict the development of AKI (42). It was found that above all current biomarkers, TIMP-2 and IGFBP7 were superior in detecting AKI, including current standards SCr and urine output (42).

The follow-on trial, the Sapphire trial (41,42), was conducted in 35 sites, scattered throughout North America and Europe. The Sapphire trial included patients over the age of 21, who were critically ill but did not have AKI and who had been admitted to ICU within 24 hours (42,43). The objective was to ascertain if the results from the Discovery trial were indeed accurate; it looked at other novel biomarkers, such as kidney injury molecule 1 (KIM-1), NGAL, interleukin 18 (IL-18) and liver fatty acid-binding protein (L-FABP) (42). In comparison to the other biomarkers mentioned, the TIMP-2 and IGFBP7 combination outperformed the other markers, with an area under the curve of 0.80 (42).

The Topaz trial (41,43), again looked to validate the use of these two biomarker. This trial used similar inclusion criteria as the Sapphire trial, however, it was conducted in 23 different American sites (43). The NephroCheck was noted to have a sensitivity of 89 % and a specificity of 46 % (40,43). The Topaz trial differed from the Sapphire trial in that the urine was sampled three times, instead of once, and was used on patients from a different centre, to try and increase the heterogeneity of the study sample (43). In a multicentre study, Bihorac et

al (41) found the sensitivity of the NephroCheck to be 92 %, but the specificity ranged from 37 – 42 %, depending on the cut-off values applied. It is, therefore, necessary to use this test in the appropriate setting, in patients at moderate-high risk of AKI, so as to minimise the number of false positive tests.

Multiple strategies or scoring systems have been proposed to predict the development of CSA AKI. The most validated scoring systems are the Cleveland Clinic Score (15), the Mehta score (44) and the EuroSCORE II (45). The Cleveland Clinic Score comprises 10 variables and has a score range from 0 – 17 (15). It is categorised as follows: low risk (0 – 2), intermediate risk (3 – 5), moderate risk (6 – 8), high risk (> 9) (14,15,22). The Cleveland Clinic Score was developed from the study conducted by Thakar et al. (15) where more than 33 000 patients were enrolled; approximately half of the study group was used to develop the criteria for the scoring system, and the other half was then used to validate it.

Although the Cleveland Clinic scoring system (15) has proven beneficial, there are some limitations to its use (7,14,22). Firstly, the Cleveland Clinic Score (15) was based on patients requiring open-heart surgery, therefore no percutaneous or minimally-invasive procedures were considered (14,22). Secondly, patients undergoing off-pump CABG were included in the study which may have added to confounding factors, as these patients are known to have a lower risk of developing AKI (14,22). Thirdly, it has not been validated in non-Western societies, although its use has been validated in one South Asian cohort by Rao et al. (14). Finally, a fundamental limitation of the Cleveland Clinic Score is that it does not predict milder forms of AKI (6,7,22).

The Mehta Score also comprises 10 variables, however, it has a score range of 0 – 83 (44). This is troublesome, as it can be perceived as cumbersome and therefore, simpler methods have been proposed (22). Another limitation of the Mehta score is that it can only be used for patients undergoing CABG alone, mitral/aortic surgery alone, or the combination of the aforementioned alone, which restricts the patient population (7,22).

Birnie et al. (7) set out in 2014 to develop a predictive scoring system for any stage of AKI, because as previously mentioned, the Cleveland Clinic Score (15) is not a good predictor of milder forms of AKI (6). The “any-stage” AKI score showed more favourable acumen than the Cleveland Clinic Score, and it was also found to be better calibrated (7). Despite this, the

Cleveland Clinic score (15), which was developed in the 2000s, and the Mehta score (44), which was developed in 2006, are used more often to predict clinical outcomes post cardiac surgery (7,15,22).

The EuroSCORE II (45), which was published in 2012, is a revision of the original EuroSCORE (46), which was published in 1999, as a risk prediction model for cardiac surgery. The revised score has 18 variables, some of which were added due to criticism of the original EuroSCORE undervaluing the influence of the intervention, and others (such as the definition of unstable angina requiring IV nitrates for diagnosis) were retracted due to advances in the medical field since 1999 (45).

A comparative study was published which commended the EuroSCORE II on the addition of number of previous procedures performed, as well as the current procedure, ultimately resulting in a more robust scoring model (45,47). One of the limitations of the EuroSCORE II is that it is not procedure-specific, and may underestimate the risk in patients with rarer disease profiles due to its generalisability (45). It may also be inaccurate in the African setting, as only two of the 43 participating countries were African (South Africa and Sudan) where 25 were European, three were South American, three were North American and the remaining nine were Asian (45).

2.6 Treatment of CSA AKI

The treatment of AKI is dependent on its causal mechanism to a degree, although the end-point in severe cases is RRT. It has been found in both population groups (CSA AKI as well as non-CSA AKI), that the initiation of RRT has better outcomes when initiated earlier in the course of AKI (1,12,16). The fundamental principle that the origin of the AKI must be treated is the reason why it is important to identify and risk stratify patients according to their predisposing factors, and treat the precipitating factors (4,18,25). Important directives are to prevent or limit ischaemia, decrease inflammation, modify amenable risk factors, and address both the nutritional and fluid status of the patient at the pre-, intra- and post-operative stages (1,4). To address the general well-being of the patient, KDIGO recommends avoiding hyperglycaemia and protein-calorie malnutrition (4).

The notion of fluid therapy is central to the prevention and treatment of AKI. There is, however, no standardised fluid management strategy as yet (4,12,13). The recommended

fluid type for initial intravascular volume expansion in patients who have no evidence of haemorrhagic shock, is an isotonic crystalloid (4). Zarbock and Kellum (18), it was again noted that there is a lack of consensus regarding the amount of fluid administration necessary to maintain normal nutritional status but to avoid overload, as many patients will benefit from fluid restrictive regimens (12,13). The argument has been made, and proven, that fluid restrictive regimens result in better outcomes for critically ill patients, but, this poses a clinical conundrum for patients who have AKI, and yet are fluid-replete, as they are at high risk of developing fluid overload (12,27).

In these unique circumstances, it is recommended that patients with severe oliguria or anuria begin RRT early, because if they are volume-replete, they will still require a nutritional intake of approximately 1 L/day and drug intake of approximately 500 mls/day (18). The fluid input in this circumstance, (severe oliguria or anuria) cannot be counteracted by insensible losses alone and therefore without RRT to assist with fluid reduction, these patients may become overloaded relatively quickly (12,48).

2.7 Fluid management

The principle of a positive fluid balance being detrimental to overall outcome in patients with AKI is well recognised, and importantly as little as 10 % (12) fluid overload has been shown to be sufficient to precipitate adverse outcomes (13,25). A positive fluid balance is defined as an increase of > 10 % baseline body weight (13). This can be calculated as follows:

$$[(\text{Sum of daily fluid intake} - \text{total output}) / \text{body weight}] \times 100 \text{ (13).}$$

A positive fluid balance results not only in an increased risk of mortality, but also an increased risk of adverse events, such as prolonged hospital stay, respiratory failure requiring ventilation, and a risk of progression to long-term renal dysfunction (13).

It has been shown that restrictive fluid management strategies are valuable in the post-operative patient by reducing the need for mechanical ventilation and cardiovascular complications (13,27). Cardiac surgery possesses multiple risk factors that can damage the endothelial glycocalyx, leading to “leaky” capillaries and rapid accumulation of fluid in the interstitium, resulting in fluid overload (10–12). Fluid overload in patients with AKI has been shown to be an independent risk factor for mortality, regardless of the need for RRT (11,12).

In an American study conducted by Bouchard et al. (13) that included patients from five different centres, fluid overload was found to be associated with an increased number of patients with multi-organ system failure, increased ventilator requirements and sepsis. Importantly, this study noted that percentage fluid accumulation in patients with AKI at the time of diagnosis was lower in the survivor group versus the non-survivor group (13). This data was corroborated by Payen et al. (12) in a European cohort which reviewed 198 ICU from 24 European countries, who found that the mean fluid balance in patients with AKI was significantly more positive than in patients without AKI. The same study found higher mortality rates in the patients with AKI than those without (60-day mortality 35.7 % versus 16.4 %) ($P < 0.01$) (12).

This information is significant, as it adds to the magnitude of the relationship between fluid accumulation and AKI specifically, not just in critically ill patients. The lack of unanimity regarding specific therapeutic fluid management strategies for patients with CSA AKI remains an issue, however, RRT should be instituted as early as possible in patients who require it (12,13,16).

3. Ultrasound

3.1 Background

Ultrasound has been used in innovative ways to visualize the renal vasculature and try to predict which patients are at risk of developing AKI (23,24,28,33). Research is focusing on finding a link between renal vascular ultrasound parameters and renal function (33,49). Ultrasound has the ability to assess blood flow by using the Doppler principle, which can determine the shift of frequency that occurs when sound strikes moving RBC compared to stationary tissue (48,50). Stationary tissue returns echoes unchanged, however, echoes from the moving RBC return to the probe with small differences in frequency. The probe processes these differences (the shift) and then generates an image (48,51). Using the Doppler effect equation, the velocity of blood flow can be calculated if the parameters are rearranged (51).

Ultrasound has gained popularity as it is non-invasive, portable, well tolerated by patients and produces results in real-time (48,51). The two types of vascular ultrasound wave propagation are continuous or pulsed wave Doppler; the names are attributed to the way in which the waves are transmitted (50). In continuous wave Doppler, the waves are transmitted

uninterruptedly from a segment of the probe while a separate segment is responsible for receiving signals; pulsed wave Doppler transmits waves in predetermined bursts, and then waits for the signal to return and be captured, so transmission and reception of the signal occur at different time intervals (50). Three types of Doppler imaging are used in cardiovascular ultrasound: Colour, Power and Spectral Doppler (48).

Colour Doppler qualitatively indicates flow velocity; importantly, it cannot measure actual velocity, as corrections need to be made within the processor for angulation to allow accurate measurement of quantitative velocity (51). A pixel is assigned to the direction of movement, and therefore the colour represents the direction of movement, whereas the hue indicates the velocity (48,50).

Power Doppler is related to the signal strength, which in turn is related to the number of moving RBC at a particular point (50,51). The intensity of the signal is proportional to the volume of movement, which is portrayed by colour and hue, rather than the velocity or direction of flow (50). Therefore power Doppler cannot be used to quantitatively measure the velocity of blood flow (48,50,51).

Spectral Doppler allows waveform analysis and can give quantitative information regarding velocity (48). The resistance inherent to a vascular bed can be measured using systolic and diastolic velocities (48,50). This principle is used in continuous and pulsed wave Doppler.

Duplex doppler, a sub-parameter used in cardiovascular imaging, is a combination of Colour Doppler and Brightness mode (B-mode) ultrasonography; hence the name Duplex (52).

Colour Doppler is highly influenced by the angle of the beam with regards to the interrogated territory, and therefore duplex Doppler is prone to the same errors (50,52). Duplex Doppler has an additional parameter of B-mode which anatomically delineates the vessel or territory in question using ultrasound, and combines it with the information gathered on flow, using colour Doppler (52). Duplex Doppler, therefore, affords a more intricately defined structural image with information regarding flow, that can be used for more precise diagnostic information when interpreted correctly (50,52).

When visualising the vasculature with Doppler, the arterial system can be explored, mainly using Duplex, Power and Spectral Doppler, and the venous system can be explored, mainly using Duplex and Colour Doppler (36,49,51,52).

3.2 Arterial Doppler

Spectral Doppler allows for an image to be created that is portrayed as a graph (velocity versus time), from which multiple parameters can be calculated (pulsatility index (PI), resistance index (RI) and systolic/diastolic (S/D) ratio) (51). Doppler-based renal RI is a parameter that has gained much attention recently, and it has favourable characteristics; it is quick, non-invasive and easily repeatable (23).

The RI is an arterial parameter that is calculated by Pourcelot's formula (53), and it reflects arterial compliance and resistance of the vascular bed in question. It is defined as $(S - D)/S$, where S represents the peak systolic value and D represents the peak diastolic trough (54). In the human vasculature, the interaction of arterial compliance and vascular resistance results in the natural amelioration of pulsatility, where total resistance to flow through the arteries down to the capillaries and veins, may be considered in series (53,54). The majority of the resistance is found within the arterioles and arteries, followed by the capillaries and then the veins (53). Due to this fact, the RI measurement from the main renal artery should be equitable to that of the interlobar or interlobular renal arteries (53).

Studies show that RI may carry prognostic information incremental to GFR estimation (55). A study conducted by Lerolle et al. (29) showed that a high RI in patients with septic shock was predictive of AKI ensuing in future. Bedside RI allows estimation of the renal vascular resistance (24). In a study conducted by Dewitte et al. (24), they confirmed the notion proposed by Darmon et al. (56), that Doppler RI can be used to delineate patients in whom AKI will be persistent, as defined by an RI of > 0.795 .

In a study conducted by Giustiniano et al. (30) the RI was used as a marker for prediction of morbidity, including development of AKI, prolonged ventilation and sepsis. The study looked at complications post major surgery, using RI of > 0.70 as the cut-off value, and found that in patients with RI values above this, the likelihood of adverse outcomes was greatly increased (30).

It is essential to be aware that the RI can be influenced by parenchymal and vascular abnormalities (55,56). It can be altered by vascular compliance, heart rate and rhythm, external compression by the probe or increased intra-abdominal pressure (55,57). Ureteric obstruction also affects the RI (57). Therefore, when interpreting RI, the above-mentioned factors must be taken into account before conclusions can be drawn.

3.3 Cardiac Doppler

Ultrasonography has been used to assess venous system flow (33,57,58). It has been used for monitoring and evaluation of the central venous (CVP) and right atrial pressures (RAP). CVP is a parameter that is often used in critically ill patients for haemodynamic observation. CVP provides a good estimation of RAP which translates to right ventricular preload, unless extenuating circumstances (such as severe tricuspid regurgitation, constrictive pericarditis, cardiac tamponade or inferior vena cava (IVC) obstruction) are present (10,58).

Venous congestion from the right atrium, transmits high pressures to the IVC, the hepatic system, the renal system, and finally the portal system (10). The higher the IVC pressures, the less compliant the IVC becomes (10,58). Elevated CVP can be indicative of right ventricular diastolic dysfunction, and the transmitted pressure to the IVC can be measured using Doppler (10,31,32).

Diastolic dysfunction can be graded, using pulsed wave Doppler, into three grades: delayed relaxation, pseudonormal filling and restrictive filling (59). This classification is based on the ratio between the early (E) ventricular filling wave and the atrial (A) contraction wave (59). Initially, delayed relaxation results in an E/A of < 1 , which progresses to pseudonormal filling with an E/A 1– 2, finally followed by the restrictive filling pattern with an E/A > 2 (59). The associated flow measurement is known as the early ventricular filling deceleration time (DT), and is measured with Colour Doppler (59). Delayed relaxation is characterized by a DT > 200 milliseconds, pseudonormal filling by a DT 150 – 200 milliseconds, and restrictive filling by a DT < 150 milliseconds (59). The ventricular filling wave ratios and deceleration time can be significantly influenced by volume status (34,35,59).

Therefore, the information gathered from Doppler assessment of diastolic function can help to differentiate between patients with true diastolic dysfunction, and those who have volume overload, which can be transmitted to the venous system and result in venous organ congestion (34,35,59).

In a study conducted Choi et al. (60) the systolic and diastolic dysfunction parameters were used in combination to review the odds ratio of developing AKI. This study found that patients with worse echocardiographic parameters had increased risk of AKI as well as developing long-term renal dysfunction (60). The poorer echocardiographic parameters also appeared to predict the outcome of long term renal dysfunction (60).

3.4 Venous Doppler

A high CVP ($> 10\text{mmHg}$) is often associated with overload status (12,19,58). Ilyas et al. (58) conducted a cross-sectional study from 100 medical ICU patients and found that there was a positive relationship between CVP and IVC diameters at minimum and maximum values, and an inverse relationship between CVP and IVC collapsibility. IVC collapsibility has been used to measure patients' response to therapy in acute heart failure, and provides insight into the fluid status when used in combination with the range of CVP measurements, the IVC diameter, clinical picture and haemodynamic parameters (10,31,58).

A non-compliant IVC can be indicative of venous congestion, where factors such as supra-diaphragmatic obstruction (pneumothorax, cardiac tamponade), positive pressure ventilation, high positive end expiratory pressure and hyperinflation of the lung, have been excluded (10,31,58). It is also important to note that absolute values of IVC measurements do not accurately predict CVP measurements, but rather, IVC collapsibility and inspiratory-expiratory variations can discriminate between low or normal CVP and high CVP (10,32,58).

With increased venous pressure, and therefore a non-compliant IVC, the right atrial pressures throughout the cardiac cycle are conducted into the abdominal venous vasculature; namely the hepatic venous system, the portal venous system and the renal venous system (31,32). Hepatic venous flow patterns under physiological conditions have a systolic:diastolic of > 1 , with a period of atrial flow reversal (10). In critically ill patients, the reversal of the

systolic:diastolic with enhanced atrial reversal should be interpreted, cautiously, as possible venous congestion (10).

This occurs as the hepatic venous flow patterns with systolic:diastolic < 1 are seen in decompensated cardiac failure, which is known to cause venous congestion that transmits backward pressures from the right atrium, through the IVC and into the hepatic venous system (10,31,58). Unless the aforementioned extenuating circumstances co-exist in the critically ill patient, the use of the systolic:diastolic < 1 as a possible marker of venous congestion is reasonable, if interpreted holistically.

The portal venous system is usually precluded from the backward pressures of venous congestion due to its anatomy; the liver sinusoids and splanchnic capillary bed are separate from the systemic circulation (10). Consequently, when a detectable difference in velocities between systolic and diastolic flows occur, it is abnormal and indicative of portal hypertension (10,31,32). Portal hypertension can be cardiogenic in origin, however, the other causes of portal hypertension, such as cirrhosis and portal thrombosis, must be excluded first (10,31).

The portal pulsatility fraction $[(\text{Systolic velocity} - \text{Diastolic velocity} / \text{Systolic velocity}) \times 100]$ value of $> 50\%$ represents abnormal flow; this parameter was noted to be independently associated with AKI post cardiac surgery (31,32). In a prospective study by Beaubien-Souligny et al. (32), the portal flow pulsatility was noted to be a marker of venous congestion and independently associated with occurrence of AKI post cardiac surgery.

The concept of renal venous congestion as a consequence of fluid overload has been explored (10). Renal venous congestion occurs as a result of the “back pressure” that occurs when there is raised RAP, which translates to raised CVP, raised IVC pressure, and therefore, raised renal venous pressure (19,58). Blood flow in the interlobar veins, under physiological conditions, is uninterrupted (10). New evidence shows that when the CVP is elevated, or when there is renal venous congestion, flow becomes biphasic, then monophasic, and if left untreated, totally discontinuous (10).

In a study conducted by Iida et al. (33), they found that “intrarenal venous flow patterns (IRVF) patterns strongly correlated with clinical outcomes independent of right atrial pressure (RAP)”. The flow patterns were grouped into three categories using spectral Doppler analysis: continuous, biphasic and monophasic. In this heart failure study, Cox Proportional Hazard Model showed biphasic and monophasic IRVF patterns to be independent predictors of death from cardiac causes or unplanned hospitalisations from heart failure (HR 6.85 CI 95 % 2.82 – 16.6 P < 0.001) (HR 17.8 CI 95 % 7.62 – 41.9 P < 0.001), biphasic and monophasic respectively (33).

This was found to be independent of CVP, haemodynamic status, echocardiographic indices and RI (10,33). IRVF patterns appear to have promising results for predicting clinical outcomes, and thus require further studies to be conducted to better define the relationship. Another study looked at the relationship between power Doppler vascular indices and renal function, and found a significant correlation between eGFR and all three vascular indices-vascularisation index, flow index and vascularisation-flow index (49). The use of power Doppler reliably predicted renal function based on the vascular indices described (49).

Doppler has limitations in that it is operator dependent and requires training (48,50,57). A pilot study by Schnell et al. (61) showed that there was good correlation between RI values obtained by senior operators when compared to those obtained by junior operators ($r^2 = 0.64$; 95 % CI, 0.48 – 0.76; P < 0.0001). The junior participants in the study were given a half day training program, which included lectures on Doppler and its limitations, as well as a practical session to gain the skill (61).

3.5 Renal and portal venous ultrasound in the peri-operative period

In a peri-operative study conducted by Beaubien-Souligny et al. (32), intrarenal venous flow was found to be an independent predictor of increased risk of AKI (HR 2.81 CI 95 % 1.42 – 5.56 P = 0.003). The risk prediction improved with the addition of pre-operative risk factors and CVP at intensive care admission (32). The presence of portal flow pulsatility fraction post cardiac surgery was associated with the development of AKI (31). In a prospective perioperative study conducted by Beaubien-Souligny et al. (32) it was found that the addition

of portal flow pulsatility lead to a better assessment of CVP and venous congestion, and was found to have an association with intrarenal venous flow patterns.

Bossard et al. (36) found that RI could predict the development of CSA AKI early after cardiac surgery, with a high sensitivity and specificity (94 % and 89 % respectively). An RI value of > 0.74 was noted to be superior to SCr and urine output in predicting AKI, and importantly, RI also correlated with the severity of the renal impairment (36). Stratification of patients requiring post-operative dialysis was also possible, using an RI value > 0.83 (36). Clinically, this is significant, as the raised RI value antedates the onset of AKI by 1 – 2 days (36). In summary, the timeous correction of AKI is of the utmost importance, prior to the development of established dysfunction.

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APPENDIX 3: JOURNAL GUIDELINES TO AUTHORS (SAJAA [SOUTH AFRICAN JOURNAL OF ANAESTHESIA AND ANALGESIA])

“CATEGORIES OF SUBMISSIONS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles

Original articles on research relevant to anaesthesia and analgesia should not exceed 3 200 words, no more than 30 references, with up to 6 tables or figures. A structured abstract under the following headings, Background, Methods, Results, and Conclusions is a requirement and should not exceed 300 words.

Clinical Review articles

Review articles relevant to anaesthesia and analgesia should not exceed 2 400 words, with a maximum of 20 references and no more than 6 tables or figures. A summary of 300 words or less is required.

Case reports

Case reports should not exceed 1 800 words with no more than 10 references. Figures are limited to 2 figures and may include images or photographs. The case report should have three headings: Summary (not exceeding 100 words), Case report (with no introduction) and Discussion. Case reports will be published online only. The summary and the URL will appear in the printed version.

Scientific Letters

Scientific Letters should not exceed 2 400 words with a maximum of 10 references. Only one table or illustration is permissible. A structured abstract under the following headings,

Background, Methods, Results, and Conclusions, is a requirement and should not exceed 250 words.

Letters to the editor

Letters to the editor should be 800 words or less with only one image or table.

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - www.icmje.org. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details

This information must be provided for ALL authors and must be submitted as a supplementary file.

Email addresses of all author must be provided.

ORCID number of **ALL** authors must be provided – if authors do not have ORCID, please register at <https://orcid.org/>

Abbreviations

All abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements

Scientific measurements must be expressed in SI units except blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age) should also be preceded by a space e.g. > 20 years. No spaces should precede ± and °, i.e. '35±6' and '19°C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting

The manuscript must be in Microsoft Word or RTF document format. Text must be 1,5-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, except for Tables). *The manuscript must be free of track changes.*

Disclaimers should follow the Conclusion and it should be in the following order: Acknowledgements, Declaration conflict of interest, Funding source, Ethics declaration and ORCID.

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file **and** provided as '**supplementary files**'. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes, tabs or enters) and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Figure 1)'. Figure legends: Figure 1: 'Title...'. All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft PowerPoint or Excel must be accompanied by the original workbook.

REFERENCES

Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists may be generated with the use of reference manager software, but the final document must be delinked from the reference database or otherwise generated manually. Citations should be inserted in the text as superscript, e.g. These regulations are endorsed by the World Health Organization,² and others.^{3,4-6} The superscript reference number should come after the punctuation mark and should not be in brackets.

All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first four names should be given followed by et al. First and last page, volume and issue numbers should be given. **Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID).** Authors are encouraged to use the DOI lookup service offered by [CrossRef](#). Crossref DOIs should always be displayed as a full URL link in the form <https://doi.org/10.xxxx/xxxxx>

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<http://www.who.int/whr/2002> (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

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A covering letter to the editor is mandatory and must include statements that the manuscript has not been published previously and is not under review elsewhere. It should state details of any prior publication of the research in abstract form or in Congress proceedings. The letter must declare if any of the authors have a conflict of interest and that the requirements for submission, including ethics approval and patient permission for case reports have been fulfilled. All authors must sign the covering letter.

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APPENDIX 4: PROPOSAL

4. Introduction

Acute Kidney Injury (AKI) is a well-described complication post cardiac surgery (1–4), occurring in up to 40 % of patients (1). AKI can lead to the requirement of renal replacement therapy (RRT), and could result in chronic kidney disease (CKD) or death if not treated judiciously and timeously(1–7). RRT is needed in 2 — 5 % (8) of patients, and has been found to be an independent risk factor for mortality if present (3). The mortality associated with AKI post cardiac surgery ranges from 50 — 80 % (9). Patients presenting for cardiac surgery often have co-morbidities, such as hypertension, diabetes, hyperlipidaemia, chronic disease (cardiac, renal, hepatic, peripheral vascular) and are of advanced age, which all increase the likelihood of cardiac surgery associated (CSA) AKI developing (3–5). The recent focus has been on detecting venous congestion and perfusion, using ultrasound, to try and predict those at risk of ensuing CSA AKI.

AKI is multi-factorial in aetiology; however, CSA AKI poses a unique set of additional considerations. These include type of cardiac surgery, the complexity of surgery, the use of cardiopulmonary bypass (CPB), the use of blood products, haemodynamic instability, coagulopathy, emboli, arrhythmias and myocardial infarction, which all contribute to the pathophysiology of CSA AKI (1–3,5,6,8,10). Intra-operative factors that contribute to the aetiology of CSA AKI are secondary to acute tubular necrosis, which may occur as a result of CPB-induced systemic inflammation, endothelial glycocalyx damage, hypovolaemia and hypoperfusion, oxidative damage, haemolysis, sympathetic nervous system activation, and the use of nephrotoxic agents such as angiotensin converting enzyme inhibitors and contrast dyes (1,3,5,10–13). Cardiac surgery induces systemic inflammation, which affects the renal system and can result in diminished perfusion from venous congestion, and ensuing AKI when this is complicated by hypovolaemia, emboli, aortic cross-clamping, the use and duration of CPB, cardiogenic shock and the need for vasopressor exposure (1,3,5,6,8,10–13).

The complex interactions of the cardio-renal axes are well-recognized, which makes for challenging circumstances in preventing, diagnosing and managing CSA AKI (2,4,5,11,12,14). Until recently, the criteria required to diagnose this dynamic condition has been changing (4,13). Strategies aimed at managing AKI focus on preventative measures,

risk classification, early detection and treatment. Early and timeous diagnosis enables prepared management. Successful prediction of CSA AKI allows for proper optimization, vigilant monitoring and mitigation of risk factors, as well as early initiation of preventative and therapeutic interventions. This calls for ongoing trials in pursuit of therapeutic strategies. The current consensus on diagnostic criteria for AKI was proposed by the Kidney Disease Improving Global Outcomes (KDIGO) group (4), outlined below:

KDIGO classification of AKI

- **Stage 1:** increase in serum creatinine (SCr) $> 26.5\text{mmol/L}$; or 1.5 — 1.9 times baseline SCr level; or $< 0.5\text{ml/kg/hour}$ urine production for 6 — 12 hours
- **Stage 2:** increase in SCr of 2.0 — 2.9 times baseline level; or $< 0.5\text{ml/kg/hour}$ urine production for more 12 hours
- **Stage 3:** increase in SCr of > 3.0 times baseline level; or SCr level $> 354\text{mmol/L}$; or initiation of RRT; or $< 0.3\text{ml/kg/hour}$ urine production for more than 24 hours; or anuria for more than 12 hours

Despite wide use of this classification system, research continues to focus on novel approaches to diagnose AKI, as these criteria use markers that are often non-specific, and can take up to 24 hours to reflect changes in renal function (1–4,8,11,15,16). Early detection of CSA AKI is central to contemporary management, and the current diagnostic criteria lags behind the cellular injury.

Treatment strategies have looked at attenuation of ischaemia, reduction of intrarenal inflammation and supportive care, which includes the management of fluids, nutritional optimization, avoidance of exposure to nephrotoxic agents, limiting exposure to CPB, and the use of a pharmacological agents postulated to be renoprotective (calcium channel blockers, dexmedetomidine, fenoldopam, high-dose steroids) (1,4,11,12). Importantly, avoiding a positive fluid balance and renal venous congestion are key strategies in protecting renal function and long term outcome, because as little as a 10 % (17) positive fluid balance has been seen to result in adverse outcomes, such as prolonged hospital stay, prolonged mechanical ventilation and progression to chronic renal dysfunction (13,17–19). Although preventative measures have ranged from remote ischaemic pre-conditioning to drugs, such as

steroids, and fluid management, all have been met with controversial outcomes (1,4,11–13,17–19).

Stratification scores for AKI such as EuroSCORE II (20), the Cleveland Clinic Score (11) and the Mehta score (21) all aim to risk stratify patients, using clinical risk factors, and therefore may highlight those who will benefit from preventative strategies and earlier implementation of treatment if necessary (11,15,20,22,23). All of the classification systems have limitations, and are intended for use as a guide and aid to clinical acumen (11,15,20,22,23). Limitations include poor generalisability of procedure, outdated definitions, validation in Western societies with little validation in other societies and failure to predict mild early forms of AKI (11,15,20,22,23).

Novel biomarkers used in diagnosing AKI include blood and urinary tests, such as Cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinase 2 (TIMP-2), insulin-like growth factor binding protein 7 (IGFBP7), kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18) and liver fatty acid-binding protein (L-FABP) (24–29). Of the aforementioned, NGAL, TIMP-2 and IGFBP7 have gained the most attention as potential replacements for current biomarkers (24–27,29). NGAL is produced in the renal tubules after an insult has occurred, and levels are detectable within two hours (1,24,25). TIMP-2 and IGFBP7 are markers of cell cycle arrest; a known consequence of AKI, resulting in the inhibition of angiogenesis and endothelial cell proliferation (26,28,29). They have been combined for use in a single urinary test, NephroCheck, and have been found to have a sensitivity of 92 % (26). However, biomarkers have yet to be incorporated in preventative strategies.

The focus of novel techniques to diagnose AKI has recently turned towards renal Doppler ultrasound (30–37). Vascular assessment by ultrasound is a novel, non-invasive measure of diagnosing AKI which is still under investigation. The recent peri-operative research has focused on venous congestion and perfusion as the predictive measure of ensuing AKI, mostly in the renal venous, hepatic system, portal system, as well as the arterial renal system (35,37,38). Ultrasound based flow assessment can be beneficial in timeous diagnosis of venous flow congestion or reduced perfusion, providing real-time insight into renal perfusion which could allow for optimization of perfusion and directed management (30–33,35–39).

Ultrasound uses the Doppler principle to assess flow, by determining the shift that occurs when sound strikes a moving red blood cell (RBC) compared to stationary tissue (40,41). By processing the information gathered by the probe, velocity of blood flow can be calculated, direction of flow established and waveform analysis of the vascular bed in question can be determined (41,42). Duplex Doppler, a combination of colour Doppler and Brightness mode (B-mode) ultrasonography, is able to anatomically delineate vasculature and combine it with information regarding flow and velocity (41).

Duplex Doppler, together with spectral analysis, has been successfully used to define venous and arterial renal parameters in the perioperative period (31,34,35,37,41). The arterial resistive index (RI), as defined by Pourcelot's formula (43), has recently been used as a predictor of ensuing and persistent AKI (33,36,44,45). Using a cut-off value of > 0.70 , the RI has also been used as a predictor of morbidity, including the development of sepsis and prolonged ventilation (34).

In the venous system, Duplex Doppler and waveform analysis have been used to identify renal venous congestion. Renal venous congestion occurs due to "back pressure", which translates to raised venous pressures in the inferior vena cava (IVC) and right atrium (RAP) (46,47). An elevated central venous pressure (CVP) can be indicative of venous congestion or diastolic dysfunction, if supra-diaphragmatic causes of obstruction (pneumothorax, cardiac tamponade, excessive positive end expiratory pressure) have been ruled out (35,38,39,47,48).

A high CVP has been associated with increased mortality post-operatively (17–19,39,47,49). With increasing CVP, the IVC becomes non-compliant, and the right atrial pressures are transmitted through the vasculature to the IVC, hepatic, renal and finally portal venous systems (31,31,35,38,39,47).

The hepatic venous flow pattern, under physiological conditions, has a systolic:diastolic > 1 (35,38,39). This pattern is reversed when venous congestion is present (39). There is also usually a period of atrial flow reversal, which enhances with venous congestion (39).

Portal venous flow tends to be precluded from backward venous pressure due to its anatomy (39). Therefore, when a detectable difference between systolic and diastolic velocities exists, it is indicative of abnormal flow, that can be classified as cardiogenic or non-cardiogenic

portal hypertension (35,38,39). When the portal flow pulsatility is > 50 % it is considered abnormal and a marker of venous congestion (35,38). It has been noted to be an independent predictor of AKI post cardiac surgery, inclusive of intrarenal venous flow (IRVF) patterns (35,38,39).

Under physiological conditions, renal venous flow is uninterrupted, however, when venous congestion is present, it becomes biphasic, then monophasic and finally, discontinuous if not corrected (31). New evidence shows that IRVF patterns strongly correlate with clinical outcome, and have been found to be an independent predictor of mortality (31), and an independent predictor of an increased risk of perioperative AKI occurring (35).

5. Problem Statement

The aetiology of AKI is multifactorial, however, patients undergoing cardiac surgery have a 40 % chance of developing AKI (1). Given the magnitude of this problem, as well as the considerable complications that may occur, such as RRT or progression to chronic renal disease, it is a priority to establish preventative measures, identify patients at risk and assist with early diagnosis (2,4,7,13,37).

Current consensus makes use of SCr values and urine output to diagnose AKI according to the KDIGO group classification system; these parameters have proven ineffectual for timely diagnosis, and are non-specific (1–5,50,51). A major contributing factor to renal injury during cardiac surgery is venous congestion and poor arterial perfusion (31,33,33,35,37,39,45,46,52,53).

Biomarkers have also been looked at with promising results, but none have been incorporated in predictive scores yet (24,26–29). Duplex Doppler has recently shown promising results in arterial RI, renal venous flow patterns, portal flow pulsatility and hepatic venous flow pattern, to assist with early identification of those at risk of developing AKI. Early diagnosis would allow for early optimization, increased vigilance in monitoring, early mitigation of risk factors and treatment (30,31,34,35,35,36,39,44–48,54,55). Investigating risk of development of CSA-AKI in cardiac patients at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) by any modality, including renal and hepatic ultrasound profiles has not been investigated.

6. Aim

To investigate the risk of development of CSA AKI in adult patients presenting to Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) using renal and hepatic ultrasound profiles. To determine the relationship between current KDIGO AKI criteria and ultrasound profiles in patients at risk of developing CSA AKI.

7. Objectives

- To determine the occurrence of AKI in patients undergoing cardiac surgery at CMJAH, over a four-day peri-operative period, using SCr levels and urine output as per KDIGO AKI criteria
- To determine the renal venous flow pattern category pre-operatively, on the first day post-operatively and on the fourth day post-operatively
- To calculate the renal arterial resistive index pre-operatively, on the first and fourth day post-operatively for the development of acute kidney injury
- To determine the hepatic venous flow pattern pre-operatively, on the first day post-operatively and the fourth day post-operatively
- To determine the portal flow pulsatility pre-operatively, on the first day post-operatively and the fourth day post-operatively
- To determine the relationship between the hepatic and renal ultrasound parameters and renal outcomes, namely the occurrence of AKI and change in SCr values

8. Research Assumptions

The following definitions will be used in this study.

Adult: a person 18 years and older

Acute Kidney Injury: the KDIGO group definition will be used. AKI will be defined as an increase in the serum creatinine of equal to or greater than $26,5\mu\text{mol/L}$ from baseline for a

period of 48 hours or more, or a reduction in urine output of $> 0.5\text{ml/kg/hour}$ for $> 6 - 12$ hours (4)

Resistive index: as per Pourcelot's formula, the resistive index is defined as the peak systolic value (S) minus the peak diastolic trough value (D), divided by the peak systolic value (S) $(S - D / S)$ (56)

Portal flow pulsatility: defined by the equation $[(\text{Systolic velocity} - \text{diastolic velocity}) / \text{systolic velocity}]$ (35,38,39)

Duplex Doppler: the combination of pulsed Doppler spectral analysis and brightness mode ultrasonography (41)

9. Demarcation of study field

This study will be conducted at CMJAH in Johannesburg, Gauteng, South Africa. CMJAH is affiliated with the University of the Witwatersrand. The study will be conducted on patients presenting to CMJAH for cardiac surgery that satisfy the inclusion criteria, from August 2019, until the sample size has been obtained, and that agree to participate in the study, after informed consent has been obtained. A counterpart study will be conducted at Aarhus University, Denmark, which will collect data from 100 patients. The studies will run concurrently, but independently. The data will be anonymised and then analyzed.

10. Ethical considerations

The Human Research Ethics Committee (HREC), the Graduate Studies Committee of the University of the Witwatersrand, as well as the National Health Research Committee will be approached and approval obtained prior to commencement of the study (see Appendix A). Permission will be requested from the Heads of Department of Anaesthesiology and CMJAH CEO (see Appendix B).

This is a prospective study. Patient details will be collected and kept separately from the raw data once a study number has been assigned. The ultrasound analysis will be performed offline, the images will be numbered and no identifying patient details will be found on the images; they will not be used for distribution, and will only be used to extract data.

Patients presenting to CMJAH for cardiac surgery, that satisfy the inclusion criteria, will be invited to participate in the study. They will be given a patient information sheet (see Appendix E) that explains in appropriate terms, without the use of medical jargon, what the study hopes to accomplish and what data will be captured and used, and for what purpose. The patient information sheet also details that patients will receive no form of remuneration for participation, but will also not be disadvantaged in any way if they choose not to participate in the study. The patient information sheet also explains how the ultrasound examinations will be performed, where they will be performed and that they should not cause any harm to the patient. The Danish study have obtained their own consent, from Denmark Ethical Committee (identifier: 1-10-72-267-18), and the pooled anonymized data for analysis has been approved by HREC using the Material Transfer Agreement (MTA) document.

The information sheet details the request for permission to access the results of the blood tests taken on a daily basis as routine in the CTICU, as well as the use of the clinical information captured by daily medical and nursing care charts. The information sheet provides the names and contact details of the principal investigator, the primary supervisor, and the chairperson of HREC. These are made available in case the participant feels anxious about the study process, the conduction of the study, or requires further clarification on the study details.

If the patient agrees to participate in the study, they will be given an informed consent sheet, in the form of a tick sheet, that reiterates important points regarding consent and being a participant in the study. It is also clearly stated, and will be reiterated, that should the patient want to recuse themselves from the study at any point in time, they reserve that right. They will be appointed a participant number and raw data will be captured under the participant number only, with no identifiable patient details.

No identifying details will be placed on data collection sheets, and to ensure confidentiality, only the supervisors and the researcher will have access to the raw data. The data will be stored in a password protected database for a period of six years. This study will satisfy the regulations set out by the Declaration of Helsinki (57) and the South African Guidelines for Good Practice (58).

11. Data Collection

11.1 Research design

The research design used for this study will be prospective, contextual and descriptive.

A study design is the systematic planning and strategy formulated to conduct research (59).

A prospective study is one in which research commences prior to the outcome occurring (59).

This study is prospective as ultrasound images will be measured and then analysed later.

A contextual study concentrates on a specific group/population/location (59). This study will focus on adults presenting for cardiac surgery to CMJAH that satisfy the inclusion criteria.

A descriptive study aims information is described (59). Descriptive studies aim to define associations or relationships between variables being studied (59).

11.2 Study population

The study population will include adult patients presenting for cardiac surgery to CMJAH during the time period in which the study is being conducted, that satisfy the inclusion criteria and agree to participate in the study.

11.3 Inclusion and Exclusion criteria

Inclusion criteria for this study will be patients with ≥ 1 of the following risk factors:

- age > 18 years
- Surgery
 - Coronary artery bypass graft and/or valve surgery
 - Any valve surgery except isolated aortic-valve surgery
 - Redo surgery
 - Endocarditis

Exclusion criteria for this study will be:

- Insufficient ultrasonographic imaging of the kidneys

- Use of aortic balloon pumps intra-operatively
- Known morphological kidney disease
- Pre-operative dialysis
- Patients with known end-stage renal disease
- Prior participation in the study
- Refusal to participate

11.4 Study sample

Sample Method

The method of sampling in this study will be consecutive convenience sampling. Patients will be included in the study consecutively as they are presented for surgery (59). The study will include those patients that are available during the data collection period.

Sample size

The sample size calculation was performed with the assistance of a biostatistician. Based on a previous study showing an incidence of AKI of 33.8%, and assuming that patients with pulsatile intrarenal venous flow are at high risk to develop AKI (hazard ratio: 2.81, confidence interval, 1.42–5.56) it was determined that a sample size of 139 patients would have a statistical power of 80% to detect the expected difference in the risk of postsurgical AKI with a significance level of 95%. The number of adult cardiac patients operated on at CMJAH annually is approximately 240. We anticipate that prospective data collection for the whole study would take 10-15 months. Therefore, this study is fashioned to be an exploratory pilot study and aims to collect data on 50 patients for the purposes of a Masters in Medicine, with the aim of continuing the full study subsequently. A post-hoc power calculation of the study will be performed. The data will be anonymized, pooled and analysed, and separate projects will outline and write up objectives, answering different research questions.

11.5 Collection of data

Data collection sheet

The data collection sheet (see Appendix C) will contain the following information for the pre-operative, first day post-operatively and fourth day post-operatively:

- Patient demographics
 - Age
 - Weight
 - Height
 - Gender
 - Race
 - Co-morbidities
 - Hypertension
 - Insulin dependent diabetes
 - Hypercholestromia
 - Smoking exposure
 - Other
- Type of surgery
 - Valvular (excluding isolated aortic valve surgery)
 - Coronary artery bypass grafting (CABG)
 - Other
- Patient information
 - Daily fluid balance
 - Daily urine output
 - Central venous pressure (range)
 - Blood results (routinely taken in CTICU)
 - Serum creatinine (SCr)
 - Potassium (K⁺)
 - Sodium (Na⁺)
 - Pre-operative haemoglobin (Hb)
- Ultrasound information
 - Renal – pre-operative, day-1 and day-4
 - Arterial
 - Resistive index measured in arcuate/intralobar arteries at the cranial, middle and caudal part of the kidney
 - Venous

- Flow pattern category measured in arcuate/intralobar arteries at the cranial, middle and caudal part of the kidney
 - Continuous
 - Biphasic discontinuous
 - Monophasic discontinuous
 - Maximal velocities measured in arcuate/intralobar arteries at the cranial, middle and caudal part of the kidney
 - systole (S)
 - diastole (D)
 - the ratio (S/D)
- Hepatic – pre-operative, day-1 and day-4
 - Venous measured in the hepatic vein
 - Maximal systolic velocity (S)
 - Maximal diastolic velocity (D)
 - Systolic:diastolic ratio (S/D)
 - Portal measured in the portal vein
 - Flow pattern classification based on pulsatility (> 50 % abnormal)

Data capturing

The researcher/principal investigator, Dr Pettey, will capture the raw data on a Microsoft Excel[®] and REDCap[®] (affiliated with the University of the Witwatersrand) spreadsheet after relevant authorities have granted permission, and the data will be kept confidential under a password encoded device (see Appendix D). The raw data will not contain patient identifying information, and will be assigned a participant number. The participant number and patient details will not be simultaneously accessible.

The ultrasound examinations will be conducted by Ms Samantha Nel, a research cardiac ultrasound technician. Details of quality assurance for ultrasound parameters are contained in section 10 below.

The ultrasound images will be captured offline, with no discernible patient information, and will be obtained using a curvilinear probe in the supine and lateral decubitus positions. The

principal investigator will obtain consent, clinical data and patient information prior to commencement of clinical duties, during working breaks or in personal time.

11.6 Data analysis

An Excel spreadsheet will be used to capture data. The data analysis will be performed in consultation with a biostatistician using Stata version 15 (StataCorp®, USA). Averages will be represented in the form of means and standard deviation if normally distributed or medians and inter-quartile range if not normally distributed. The categorical data will be represented using categories and percentages.

For continuous variables, results will be presented by means/standard deviations or medians and interquartile ranges, whereas for dichotomous variables, results will be presented in number. For continuous independent variables, comparisons between the two groups will be performed using the *t* test or the Mann-Whitney *U* test. Categorical variables will be compared using the X^2 test. For comparison between more than three variables, will be performed using ANOVA or Kruskal-Wallis tests.

12. Significance of the study

The study will assist in providing information regarding detection of AKI early to allow for optimization of modifiable risk factors, vigilant monitoring and early treatment (1–4,7,12,13). In a high risk population, such as those undergoing cardiac surgery, the probability of AKI ensuing is higher than the average population and early detection, and therefore management, has been associated with better prognosis and outcomes (1–4,6,8,13,15,34,37).

Novel techniques for diagnosing AKI early such as Duplex Doppler are needed as they may offer a speedy non-invasive contemporary way of diagnosis, allowing for optimization and perioperative vigilance in monitoring and treatment (1–4,7,12,13). The intention of this study is to investigate this novel way of diagnosing AKI in our population, which has not been investigated before. If a novel way to identify AKI earlier is identified or to prognosticate those at risk of developing AKI, it could considerably reduce morbidity, mortality, and cost to patient, hospital and public health in general.

13. Validity and reliability of the study

The validity of a study is defined as the accuracy with which the study methods and design define the research questions (59). The reliability of a study is defined as the reproducibility of the results when the study conditions are implemented in a different population/group (59).

The validity and reliability of this study will be safeguarded by:

- Selecting the appropriate study design
- Selecting the appropriate study sample and size, which will be deduced in consultation with a biostatistician, for the parameters being statistically compared
- The collection of data by the expert advisor will ensure standardisation, accuracy of data capture and quality control determining the inter/intra-observer variability, for 20 patients, calculated pre-operatively, within a 24 hour time period
- Checking data for input errors
- Data analysis in consultation with a biostatistician to minimize incorrect analyses

Reproducibility and validation of the method of renal and hepatic ultrasound assessment will be assured by training of Ms Samantha Nel, a research cardiac ultrasound technician in the Department of Cardiology, over a two week period (12 – 23 August) by Dr Johan Hermansen and Dr Peter Juhl-Olsen (from Denmark) who are experienced in renal and hepatic vascular ultrasound. Interobserver variability will be assessed by performance of 15 to 20 examinations on patients in the cardiac pre-operative ward by the Ms Samantha Nel, Dr Johan Hermansen and Dr Peter Juhl-Olsen and comparison of images to see any differences. Inter-observer agreement will be determined for renal RI, and renal and hepatic venous patterns between the investigators.

To assess the intra-observer reliability in the context of the study, Ms Samantha Nel, who will be the primary investigator of the ultrasound parameters will assess 15 to 20 patients twice each during this period in a blinded fashion and this data will be analysed independently by Dr Johan Hermansen to assess for reproducibility.

14. Potential limitations of the study

Ultrasound images will be captured offline and are at risk of being lost should the electronic system collapse. Difficulty in obtaining images in patients with unfavourable ultrasound windows could be a challenge.

The information obtained will be on patients at CMJAH only and therefore geographically dependent. The implication is that the information obtained may be contextual and therefore, not be extrapolated to other patients undergoing cardiac surgery

Ultrasound images will be captured by one operator however data from these images will remain user dependent.

Activity	Jan '19	Feb '19	March '19	April '19	May '19	June '19	July '19	Aug '19	Sept '19	Oct '19	Nov '19	Dec '19	Jan '20	Feb '20
Proposal														
Proposal submission														
Ethics approval														
Postgraduate approval														
Data collection														
Data analysis														
Draft article														
Submission														

15. Project outline

16. Financial plan

The University of the Witwatersrand Department of Anaesthesia will pay for the cost of printing and paper. The blood results will be from the National Health Laboratory Service, at no additional cost, as these are routine blood tests conducted on these patients in the CTICU,

used for monitoring. The ultrasound machine from the Department of Anaesthesia will be used, at no additional cost.

Item	Price per page	Quantity	Total
Paper and printing	R1	800	R800
Photocopying	R100	2	R200
Total			R1000

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APPENDIX 5: JOURNAL GUIDELINES TO AUTHORS

JOURNAL OF CARDIOTHORACIC AND VASCULAR ANESTHESIA (JCVA)

“Publication

The *Journal of Cardiothoracic and Vascular Anesthesia* will consider for publication suitable articles on all topics related to anesthesia for cardiac, vascular, and thoracic surgery. The scope of this *Journal* is broad and seeks to consolidate all material pertinent to cardiothoracic anesthesiology, including topics from critical care medicine, pharmacology, monitoring, perfusion technology, internal medicine, surgery, and transplantation.

Articles, editorials, letters to the Editor, and other text material in the *Journal of Cardiothoracic and Vascular Anesthesia* represent the opinion of the authors and do not necessarily reflect the opinion of the Editor, Editorial Board, or Publisher. The Editors and Publisher deny any responsibility or liability for statements and opinions expressed by the authors. Neither the Editor nor the Publisher guarantees, warrants, or endorses any product or service advertised in this publication, nor do they guarantee any claim made by the manufacturer of such product or service.

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All submissions must be directed to our web site: <http://ees.elsevier.com/jcva>. On the home page you will find links not only to this Guide, but also to a Tutorial for Authors, Artwork Guidelines, and general information on the *Journal*.

First-time authors can register from the home page by clicking on the register link. You will receive e-mails guiding you on the basic information for submitting a manuscript. Each page of the web site during the review process contains important information for that step. The Editorial Office will send by e-mail to the corresponding author all communications related to the status of a submission, including the final decision and the scheduled date of publication.

Detailed information on submissions is provided below. Further inquiries and information may be directed to the Editorial Office at: dwalk@louisville.edu.

Editorial Policies

Manuscripts are accepted for consideration on the condition that they are contributed solely to the *Journal of Cardiothoracic and Vascular Anesthesia*. No substantial part of a paper may have been published elsewhere, except for a scientific abstract.

Manuscripts will be reviewed by the Editor in Chief, Associate Editors, members of the Editorial Board, and appropriate independent referees. Acceptance of a paper for publication is based on the originality of the observation or investigation, the quality of the work described, and the clarity of the presentation. Clinically relevant material is especially desirable. Good English usage is an essential prerequisite for consideration of the paper.

In all cases the authors must accept the responsibility of conforming to the instructions in the sections below. Manuscripts must conform fully before reviewers will be assigned.

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Expedited Review. Our online submission and review process commonly results in editorial decisions within 1 month. The Journal will nevertheless consider reports of original investigations of uncommon scientific importance in the field of cardiothoracic and vascular anesthesia for expedited review, decision, and publication. The value to the readership of accelerated publication is a major criterion for accepting a manuscript for expedited review. The corresponding author of the manuscript may request an expedited review in his/her cover letter; the Editor in Chief may also initiate a rapid review process for any submission. The Editor in Chief will normally provide decisions on such manuscripts within 2 weeks of receipt at the Editorial Office. Authors of accepted expedited manuscripts may expect publication within 6 months.

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Article types. The following may be submitted: original research articles, case reports, review articles, articles on emerging technology, case conferences, pro and con articles, diagnostic dilemmas, special articles (those not easily suited to another type), and letters to the Editor. Potential authors are invited to e-mail the Editorial Office to establish a consultation with our Editor in Chief, Associate Editors, or a Section Editor in regard to interest in a proposed submission.

Article Types

For all manuscript types, see examples in any recent issue of the *Journal*.

Original Research Articles. This article type requires 4 items: Cover Letter, Title Page, Structured Abstract, and Manuscript (which includes only the *references* to tables or figures). The Manuscript document must have 4 identified sections: Introduction, Methods, Results, and Discussion.

Case Reports. This article type requires 4 items: Cover Letter, Title Page, Summary, and Manuscript (which includes only the *references* to tables or figures). The Manuscript document should begin with a short introduction and follow with 2 identified sections: Case Report and Discussion. A 1-paragraph summary should complete the article. In most situations the introduction and summary can be combined to form the Summary item.

Case Conferences. These articles are handled by a Section Editor for Case Conferences. Some offline communication between authors and editors is expected.

- There are 3 parts to each case conference: (1) case presentation, (2) case discussion, and (3) commentary(ies). The case presentation and discussion will originate from 1 institution. Their authors are invited to solicit expert commentators.
- The case presentation and case discussion should be set up as a case report. The discussion should focus on the perioperative management of the patient.
- The commentary provides input from related specialties and/or other viewpoint(s) on anesthetic or intensive care management of the case already presented and discussed. A

commentary should be submitted with its author's full name, degrees, and affiliation on its first page. The commentators may be from any appropriate medical or medically-related discipline within the same or another institution. The *Journal* reserves the right to solicit commentary(ies) appropriate to a submitted case conference and to make final determination of commentators.

- Each author of a commentary shall receive a galley proof of the case conference to provide copyediting of his or her contribution; this responsibility is not to be delegated to an author of the case presentation or case discussion.
- Figures, tables, and references for all three sections are desirable to expand the teaching value of the case. Follow the guidelines for preparing illustrations, tables, and references.
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Letters to the Editor. These should be double-spaced, brief, and concisely focused. They should have a title. Cited works must have full, accurate references. A cover letter should be provided with full information on the author(s), as in the cover page described above. Figures and tables may be included.

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- All manuscripts (except figure files) should be prepared in Microsoft Word for Windows.
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Online submission requires that the submitted material be uploaded in several separate files. For examples, an original science article or case report requires:

1. A cover letter addressed to the Editor in Chief is required as part of the online submission. The letter must include at the end a list of all authors as if for signature. Cover letters scanned from official letterhead with all signatures are strongly encouraged. The cover letter must state that the authors agree with and are responsible for the data presented. The letter should also acknowledge or deny any potential conflicts of interest including commercial relationships such as consultation and equity interests. The cover letter may not be sent as an "offline" item.
2. Title page with (a) title of paper; (b) authors' full names with advanced degrees; (c) name(s) of institution(s) in which work was done; (d) acknowledgment of research support, if

any; (e) information on the corresponding author: full name and advanced degrees, a reliable e-mail address, complete street address (not only P.O. box), telephone and fax numbers.

3. For an original science article, a structured abstract (see section below); but for a case report, a summary (max. 200 words to recapitulate the essential features of the case, its resolution, and likely consequences for further study or clinical practice). A structured abstract will be published; a summary is not published but is circulated to invited reviewers.

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1. *Objective(s)*: What scientific question was the study designed to answer?

2. *Design*: A phrase describing whether a study is prospective, randomized, blinded, etc.

3. *Setting*: Type of hospital or laboratory; university or community setting; single or multi-institutional.

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Following these 7 paragraphs, repeat the list of key words that are uploaded into the key word file. No references or abbreviations should be used in the abstract. Do not include a summary at the end of an original research paper.

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and letters to editors must be identified as such. Inclusive page numbers of references are required.

Sample References

Journal article, one to three authors

1. Beutler E: The effect of methemoglobin formation on sickle cell disease. *J Clin Invest* 40:1856-1858, 1961
2. Karpatkin S, Smith K, Charnatz A: Heterogeneity of human platelets. III. Glycogen metabolism in platelets of different sizes. *Br J Haematol* 19:135-137, 1970

Journal article, four or more authors

3. Golomb HM, Vardiman J, Sweet DL, et al: Hairy cell leukemia: Evidence for the existence of a spectrum of functional capabilities. *Br J Haematol* 38:161-162, 1968

Journal article in press

4. O'Malley JE, Eisenberg L: The hyperkinetic syndrome. *Semin Psychiatry* (in press)
(Note: A copy of the in-press article must be included as a separate Manuscript file, described as "In-press, Reference [#].")

Complete book

5. Lillie RD: *Histopathologic Technic and Practical Histochemistry* (ed 4). New York, NY, Blakiston, 1965, pp 39-41

Chapter of book

6. Moore G, Minowada J: Human hemopoietic cell lines: A progress report, in Farnes P (ed): *Hemic Cells in Vitro*, vol 4. Baltimore, MD, Williams & Wilkins, 1969, pp 100-105

Chapter of book that is part of published meeting

7. Hatvg JB, Kunkel HG, Gedde-Dahl T Jr: Genetic studies of the heavy chain sub-groups of gamma globulin, in Killander J (ed): *Gamma Globulins, Proceedings of the Third Nobel Symposium*. New York, NY, Wiley, 1967, pp 19-26

Chapter of book that is part of unpublished meeting

8. Polliak A: A morphologic study of the lymphoproliferative lesions induced by excess vitamin A. First Meeting, European Division, International Society of Hematology, Milan, Italy, 1971, p 181

Abstract

9. Curnutte JT, Karnovsky ML, Babior BM: Manganese-dependent NADPH oxidation by a particulate preparation from guinea pig granulocytes: An alternative interpretation. *Clin Res* 23:371A, 1975

Letter to Editor

10. Seeler RA: Sickle cell anemia monthly variations. *Blood* 47:879, 1976

Preparing Figures

Authors are responsible to meet the graphic standards in the Author Artwork

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Figures must be cited in order in the text using Arabic numerals, eg, Figure 1. Legends to figures should be double-spaced in a list at the end of the manuscript document. A legend must be provided for each illustration. Legends should not appear on the associated Figure document.

Color figures are acceptable for papers dealing with color imaging; however, as color printing is costly, it will be used at the discretion of the Editor. If color images are to be

reproduced in black and white, the contributor should submit the prints in black and white for best results.

The use of any figure or table that has been previously published must be supported by a letter of permission to reprint, signed by the publisher. The author will be expected to furnish the letter to the publisher shortly after the paper has been accepted for publication.”

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[Alexander H. Flannery, Katherine Bosler, Victor Ortiz-Soriano, Fabiola Gianella et al. "Kidney Biomarkers and Major Adverse Kidney Events in Critically Ill Patients", Cold Spring Harbor Laboratory, 2020](#)
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["7th World Congress of Pediatric Cardiology & Cardiac Surgery Abstracts", Cardiology in the Young, 2017](#)
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[Kevin R. Regner. "Epidemiology of acute kidney injury after cardiac surgery: an update", Journal of Organ Dysfunction, 2009](#)
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[Juanjuan Xu, Yan Chen, Shi Liu, Xiaohua Hou. " Electroacupuncture at \(ST-36\) Restores Impaired Interstitial Cells of Cajal and Regulates Stem Cell Factor Pathway in the Colon of Diabetic Rats ", Journal of Evidence-Based Complementary & Alternative Medicine, 2012](#)

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[R. Bellomo. "Changes in blood pressure before the development of nosocomial acute kidney injury", Nephrology Dialysis Transplantation, 09/03/2008](#)

Abnormalities In Hepatic Vein Flow Patterns Are [Associated With Development Of Acute Kidney Injury After Cardiac Surgery](#) Abstract The contemporary definition of [the diagnosis of acute kidney injury](#) (AKI) is neither time- sensitive, nor specific. AKI is notoriously multifactorial in origin and found to occur more commonly in cardiac surgery [patients when compared to non- cardiac surgery patients](#). [Cardiac surgery associated acute kidney injury \(CSA AKI\)](#) carries substantial morbidity [and](#) mortality. Pursuits to timeously diagnose CSA AKI have, to date, not been actualized. We investigated the use of hepatic venous and right heart ultrasound parameters in predicting CSA AKI. Methods The study was a prospective contextual and descriptive two-center study. The sites of the study were Johannesburg, South Africa, and Aarhus, Denmark. Adult patients that satisfied inclusion criteria, between August 2019 and January 2020 were included, with a total of 152 participants. Blood tests, clinical and ultrasound data were obtained pre-operatively, day-1 and day-4 post-operatively. hepatic vein, inferior vena cava and right heart Doppler ultrasound parameters were obtained and analysed. [Results The median \(IQR\) age of patients was 68 \(55-73\) years](#), predominantly male and the majority were hypertensive. Of 152 patients analysed, 54 (35 %) patients developed AKI. Among these, 37 (69 %) were classified as KDIGO stage I, 11 (20 %) in stage II, whilst 6 (11 %) were in stage III. [Age \[AOR 1.05, 95%CI 1.00-1.10 P=0.031\], EuroSCORE II \[AOR1.43, 95 %CI 1. 14 -1. 80, P=0.005\] and pre-operative serum creatinine \[AOR 1.04, 95%CI 1.01- 1. 08, P = 0. 013\]](#) were predictive of AKI. Those who developed AKI had experienced [longer cardiopulmonary bypass \(CPB\) times \(P<0. 001\)](#). Pre-operatively hepatic vein S wave measurements [were significantly higher in patients with AKI \(P<0.05\)](#). On post-operative day-1, hepatic vein flow ratios of patient with AKI were significantly decreased, driven by low S waves and high D waves, accompanied by significantly elevated central venous pressure (CVP) levels. CVP levels on day-1 (D1) post-operatively were predictive of AKI [\[AOR 1. 31, 95%CI 1. 11 -1. 55, P = 0.001\]](#). Measurements [of](#) right ventricular (RV) base, [tricuspid annular plane excursion \(TAPSE\) and](#) inferior vena cava were not [associated with the development of AKI \(P>0. 05\)](#). Conclusion Pre-operative hepatic vein S waves were higher in those who developed AKI. This phenomenon seemed to precede the decrease in D1

hepatic flow ratios driven by low S waves and high D waves. The element of venous congestion was reflected by significantly elevated CVP values which were independently associated with AKI on D1. RV base and TAPSE measurements were however not associated with AKI. These parameters may reflect peri-operative circumstances including prolonged CPB times, and potential fluid management aspects that can be modified peri-operatively.

Keywords: [Cardiac surgery associated acute kidney injury](#), ultrasound, [venous](#) hypertension, venous congestion, hepatic vascular ultrasound, goal directed fluid therapy, IVC Introduction [Cardiac surgery associated acute kidney injury \(CSA AKI\) is a well-recognised](#) post-operative [complication](#) 1–11. It [occurs in up to](#) 40 % [of](#) adults post [cardiac surgery](#) 1. CSA [AKI](#) may complicate into the need for renal replacement therapy (RRT) 1,10, develop into chronic kidney disease (CKD), and result in mortality if not managed effectively 3,4,6,7,12. CSA AKI has been shown to increase hospital mortality five-fold 1 with rates ranging from 50 – 80 % once RRT has been instituted 13. Given the magnitude of its complications, improved methods of predicting and diagnosing CSA AKI are essential. The current consensus for the diagnosis of AKI is by Kidney Disease Improving Global Outcome (KDIGO) group 4 classification, which combines serum creatinine (SCr) and urine output values 4. This has proven to be non-specific and ineffective in predicting early kidney stress 3–6,8,9,11,14 . The clinical use of novel biomarkers 15–18 and ultrasound assessment for vascular congestion have been areas of recent research focus 2,5,14,15,19–30. The cause of CSA AKI is multifactorial 2,19,31. It is associated with abnormalities in perfusion of the kidneys and imbalances between the arterial and venous pressures 24,32–36. Current evidence guiding the [enhanced recovery after cardiac surgery \(ERAS Cardiac\)](#) recommendations puts emphasis on protection against kidney stress and injury, and on goal directed fluid therapy (GDT) as part of an effort to improve postoperative outcomes 37. Fluid overload leads to venous congestion and increased right atrial pressure (RAP) 33,38,39. RAP is transmitted retrogradely into systemic veins including hepatic veins. Hepatic venous waveforms are characterised by four waves; two are retrograde (“A” and “V”) and two are antegrade (“S” and “D”) 40 (Figure 1A and 1B). They can be categorised as continuous/normal (S>D), biphasic/venous congestion (S

[In this study, we sought to describe the relationship between](#) hepatic venous flow patterns and the development of kidney. Methods This was a prospective, contextual, and descriptive two-centre study. The study was a multimodality study investigating association between several ultrasound vascular parameters and development of AKI. Consecutive convenience sampling was used. The study locations were [Charlotte Maxeke Johannesburg Academic Hospital \(CMJAH\), University of the Witwatersrand, South Africa](#) (55 participants) and Aarhus University Hospital, Denmark (100 participants). [Approval to conduct the study was obtained from the human research ethics committees of](#)

[the University of](#) the Witwatersrand (M190310) [and](#) the Region Central Denmark Ethical Committee (identifier: 1-10-72-267-18). Adults (age > 18 years) presenting for cardiac surgery were recruited. The exclusion criteria was: isolated aortic valve, reoperation surgery, insufficient ultrasonographic imaging, aortic balloon pump use intraoperatively, preoperative dialysis or known end-stage renal disease, prior participation in the study, refusal to partake in the study and inability to give informed consent. The data collection process is shown in flow diagram (Figure 2). Eligible adults approached (n=167) Included (n=152) Excluded (n=15) (52)#(100)* (3)#(12)* Pre-operative D1 post-operative D4 post-operative assessment and data assessment assessment Blood tests and clinical data n=(152) (52)#(100)* Ultrasound data n=(152) (52)#(100)* Blood tests and clinical data n=(152) (52)#(100)* Ultrasound data n=(152) (52)#(100)* Blood tests and clinical data (n=152) (52)#(100)* Ultrasound data (n=141) (52)# (89)* Figure 2. Flow chart depicting the process of data collection #South Africa, *Denmark. Reasons for exclusion: 3 poor ultrasonographic data, 8 patients refused participation, 4 were unable to provide consent. 11 participants not scanned D4 post-operatively due to: 6 declined further participation, 3 transferred to another facility, 2 no operators available to perform scan Ultrasound assessments were performed using a GE Healthcare S6 or S70 ultrasound system (Denmark) and Philips CX C50 (South Africa). Ultrasound data was collected by (SN) in South Africa and (JH) in Denmark. Hepatic venous ultrasound measurements were obtained with the patient lying supine, the curvilinear transducer aligned from the seventh to the tenth intercostal spaces on the right side, lateral to the midclavicular line. The hepatic vein was identified using Colour Doppler (CD), and Pulse-wave Doppler (PWD) applied to delineate flows. Hepatic venous flow waveforms were analysed, and flow classified into three patterns: normal, venous congestion and severe congestion. [eGFR was calculated using the Cockcroft- Gault equation.](#) Statistical analysis Using [a](#) previous study by Beaubien-Souligny and colleagues 24, it was determined that to obtain a power of 80 %, with an α of 0.05, a sample size of 152 patients would be adequate. Data was collected for 167 patients to allow for loss to follow up. Three patients were later excluded due to poor quality ultrasound data in South Africa and 12 in Denmark. Data analysis was performed with the assistance of a biostatistician, using Stata version 16 (StataCorp?, USA). [Normally distributed data were reported as means and standard deviations whilst non-normally distributed data was reported as medians and inter-quartile ranges.](#) Categorical data [were presented as counts and](#) proportions on a contingency table. A comparative summary of ultrasound and haemodynamic parameters was done between those who developed AKI and those who did not, at baseline, day-1 (D1) and day-4 (D4) post- operatively. Comparisons between continuous independent [variables were done using the Mann-Whitney test. Categorical variables were compared using Chi-square test.](#) Where relevant, [Fisher' s exact](#)

test was used to determine non-random associations between categorical variables. A univariable regression analysis was performed to determine association with AKI following which all parameters with a P value ≤ 0.1 and those deemed clinically relevant were included in a multivariable logistic regression analysis. Results Data for 152 patients were analysed. Their median (IQR) age was 68 (55- 73) years. They were predominantly male (72 %), and the majority were hypertensive (67 %). The median (IQR) EuroSCORE II was 1.84 (1.22-3.5). Baseline ultrasound and clinical data is tabled (Supplementary Table 1). A summary of ultrasound data for both groups over the 4-day period are shown (Supplementary Table 2). The majority of patients had normal hepatic vein flow patterns pre-operative (75 %), on D1 (84 %) and D4 post-operatively (79 %). Overall, 54 (35 %) participants developed AKI. Among those who developed AKI, 37 (69 %) were classified as KDIGO stage I, 11 (20 %) in stage II, whilst 6 (11 %) were in stage III. Patients who developed AKI had significantly lower pre-operative eGFR ($P=0.010$), higher pre-operative serum creatinine ($P=0.028$) and EuroSCORE II values ($P<0.001$) (Table 1). Pre-operative hepatic vein flow patterns were comparable (Table 1). Patients who developed AKI presented with significantly higher hepatic vein S wave flow measurement while all other ultrasound parameters were comparable (Table 2). Those who developed AKI had experienced longer cardiopulmonary bypass times $P<0.001$.

Table 1. Comparison of baseline characteristics between those with AKI and No AKI

Parameter	AKI (n= 54)	No AKI (n= 98)	P Value
Median Age (IQR) in years	68 (59-73)	67.5 (53-73)	0.67
Gender (Female)	16 (29.6)	27 (27.6)	0.79
IDDM	18 (33.3)	20 (20.4)	0.08
Smoker	25 (46.3)	46 (46.9)	0.94
Hypertension	37 (68.5)	65 (66.3)	0.78
Hypercholesterolaemia	n 27 (50.0)	47 (48.0)	0.81
Pre-operative eGFR	71 (56-84)	84 (70-90)	0.01
Euro SCORE II	3.06 (1.48-6.16)	1.675 (1.15-2.43)	<0.001
Pre-operative Hb (g/dL)	9.1 (7.90-12.50)	9.15 (8.5-11.9)	0.40
Pre-operative SCr (mmol/L)	90 (78-107)	81.5 (67-99)	0.03
CPB time (minutes)	151 (112 – 207)	114 (89 -143)	<0.001
Pre-operative Normal	7 (13.2)	17 (17.9)	
Hepatic flow Venous congestion	3 (5.7)	10 (10.5)	
Severe congestion	43 (81.1)	68 (71.6)	0.45
Pre-operative IVC Minimum	15.5 (14-17)	11 (9-14)	0.07
Maximum	17.5 (17-21)	13 (12-18)	0.10
Variation	16.0 (11.8-42.3)	28.6 (14-36.4)	0.57
Pre-operative TAPSE (mm)	21 (19 – 23)	22 (18- 24)	0.33
Pre-operative RV Base (mm)	39 (34 – 45)	37 (33 – 41)	0.06

*(Pre-op) Pre-operatively; (D1) Day 1; (D4) Day 4; (TAPSE) Tricuspid annular plane systolic excursion; (RV) Right ventricular; (CVP) central venous pressure; (IVC) inferior vena cava; (eGFR) estimated Glomerular filtration rate; (Hb) Haemoglobin; (CVP) central venous pressure. On postoperative D1 the hepatic vein flow ratio was significantly decreased in those who developed AKI (Table 2). There were no differences between groups on post-operative D4 (Table 2). Measurements of right ventricular (RV) base and tricuspid annular plane excursion (TAPSE) values were not different at all points. Table 2. Comparative

summary of ultrasound and haemodynamic data [AKI \(n=54\)](#) [No AKI \(n= 98\)](#) [P Value](#)

Parameter	AKI (n=54)	No AKI (n= 98)	P Value
Pre-operative			
eGFR	1.00 (0.98-1.03)	1.00 (0.98-1.03)	1.00
EuroSCORE II	1.00 (0.98-1.03)	1.00 (0.98-1.03)	1.00
Gender	Male 0.90 (0.43-1.88)	Female 0.99 (0.98-1.01)	1.36 (1.15-1.60)
Pre-operative SCr (mmol/L)	1.02 (1.00-1.03)	0.03 1.02 (0.98-1.05)	0.31
Pre-operative hepatic S wave	198 (2.20-17886.1)	0.02 5.48 (0.00-948864.7)	0.78
Pre-operative hepatic vein flow D wave	37.81 (0.68-2090.01)	0.08 293.9 (0.00-0.81)	0.37
Pre-operative hepatic vein flow Ratio	1.13 (0.87-1.47)	0.36 1.78 (0.21-14.82)	0.60
Pre-operative hepatic vein flow pattern	Normal 1 (base reference)	1 (base reference)	
Pre-operative hepatic vein flow Venous congestion	0.73 (0.15-3.47)	0.69 0.23 (0.02-3.15)	0.27
Pre-operative hepatic vein flow Severe congestion	1.54 (0.59-4.01)	0.38 1.18 (0.33-4.25)	0.80
Pre-operative IVC diameter (mm) Minimum	1.04 (0.99-1.10)	0.12 1.34 (0.86-2.09)	0.20
Pre-operative IVC diameter (mm) Maximum	1.04 (0.98-1.11)	0.18 0.80 (0.58-1.11)	0.41
Pre-operative IVC diameter (mm) Variation	0.50 (0.09-2.71)	0.42 162.85 (0.09-26.70)	0.18
Pre-operative RV Base (mm)	1.05 (0.998-		
Post-operative			
Hepatic vein flow S wave	0.19 (0.15-0.27)	0.20 (0.16-0.25)	0.73
Hepatic vein flow D wave	0.26 (0.17-0.35)	0.23 (0.16-0.31)	0.21
Hepatic vein flow Ratio	0.57 (0.45-0.91)	0.78 (0.56-1.04)	0.01
Hepatic vein flow pattern	Normal 1 (1.9)	2 (2.1)	
Hepatic vein flow Venous congestion	9 (17.0)	11 (11.4)	0.55
Hepatic vein flow Severe congestion	43 (81.1)	83 (86.5)	
IVC diameter Minimum	18 (12-19)	14 (10-19)	0.67
IVC diameter Maximum	23 (17-25)	16 (13-21)	0.14
IVC diameter Variation	24.4 (22.2-27.3)	13.3 (10-26.1)	0.25
CVP (mmHg)	12.5 (10 – 16)	11 (8 – 13)	<0.001
Day 1 Post-operative			
Hepatic vein flow S wave	0.19 (0.15-0.27)	0.20 (0.16-0.25)	0.73
Hepatic vein flow D wave	0.26 (0.17-0.35)	0.23 (0.16-0.31)	0.21
Hepatic vein flow Ratio	0.57 (0.45-0.91)	0.78 (0.56-1.04)	0.01
Hepatic vein flow pattern	Normal 1 (1.9)	2 (2.1)	
Hepatic vein flow Venous congestion	9 (17.0)	11 (11.4)	0.55
Hepatic vein flow Severe congestion	43 (81.1)	83 (86.5)	
IVC diameter Minimum	18 (12-19)	14 (10-19)	0.67
IVC diameter Maximum	23 (17-25)	16 (13-21)	0.14
IVC diameter Variation	24.4 (22.2-27.3)	13.3 (10-26.1)	0.25
CVP (mmHg)	12.5 (10 – 16)	11 (8 – 13)	<0.001
Day 4 Post-operative			
Hepatic vein flow S wave	0.19 (0.15-0.27)	0.20 (0.16-0.25)	0.73
Hepatic vein flow D wave	0.26 (0.17-0.35)	0.23 (0.16-0.31)	0.21
Hepatic vein flow Ratio	0.57 (0.45-0.91)	0.78 (0.56-1.04)	0.01
Hepatic vein flow pattern	Normal 1 (1.9)	2 (2.1)	
Hepatic vein flow Venous congestion	9 (17.0)	11 (11.4)	0.55
Hepatic vein flow Severe congestion	43 (81.1)	83 (86.5)	
IVC diameter Minimum	18 (12-19)	14 (10-19)	0.67
IVC diameter Maximum	23 (17-25)	16 (13-21)	0.14
IVC diameter Variation	24.4 (22.2-27.3)	13.3 (10-26.1)	0.25
CVP (mmHg)	12.5 (10 – 16)	11 (8 – 13)	<0.001

Age and EuroSCORE II were predictive of AKI in a multivariable regression analysis (Table 3). Age, EuroSCORE II, pre-operative SCr and CVP levels were also independently associated with development of AKI in a model including day-1 parameters (Table 4).

Table 3. Factors associated with AKI pre-operatively

Parameter	UOR(95%CI)	P value	AOR(95%CI)	P value
Gender				
Pre-operative eGFR	1.00 (0.98-1.03)	1.00	1.00 (0.98-1.03)	1.00
Pre-operative EuroSCORE II	1.00 (0.98-1.03)	1.00	1.00 (0.98-1.03)	1.00
Pre-operative SCr (mmol/L)	1.02 (1.00-1.03)	0.03	1.02 (0.98-1.05)	0.31
Pre-operative hepatic S wave	198 (2.20-17886.1)	0.02	5.48 (0.00-948864.7)	0.78
Pre-operative hepatic vein flow D wave	37.81 (0.68-2090.01)	0.08	293.9 (0.00-0.81)	0.37
Pre-operative hepatic vein flow Ratio	1.13 (0.87-1.47)	0.36	1.78 (0.21-14.82)	0.60
Pre-operative hepatic vein flow pattern	Normal 1 (base reference)	1 (base reference)		
Pre-operative hepatic vein flow Venous congestion	0.73 (0.15-3.47)	0.69	0.23 (0.02-3.15)	0.27
Pre-operative hepatic vein flow Severe congestion	1.54 (0.59-4.01)	0.38	1.18 (0.33-4.25)	0.80
Pre-operative IVC diameter (mm) Minimum	1.04 (0.99-1.10)	0.12	1.34 (0.86-2.09)	0.20
Pre-operative IVC diameter (mm) Maximum	1.04 (0.98-1.11)	0.18	0.80 (0.58-1.11)	0.41
Pre-operative IVC diameter (mm) Variation	0.50 (0.09-2.71)	0.42	162.85 (0.09-26.70)	0.18
Pre-operative RV Base (mm)	1.05 (0.998-			

1.097) 0.06 1.03 (0.96-1.10) 0.83 TAPSE (mm) 0.97 (0.90-1.05) 0.47 1.00 (0.902-1.100) 0.94 *(TAPSE) Tricuspid annular plane systolic excursion; (RV) Right ventricular; (IVC) inferior vena cava; (eGFR) estimated Glomerular filtration rate; (SCr) serum creatinine. Table 4: Factors associated with AKI on D1 post-surgery

Parameter	UOR(95%CI)	P value	AOR(95%CI)	P value
Age				
Gender				
Pre-operative eGFR				
EuroSCORE II				
Pre-operative SCr (mmol/L)				
Male	1.00 (0.98-1.03)	0.90 (0.43-1.88)	0.99 (0.98-1.01)	1.36 (1.15-1.60)
S wave	1.02 (1.00-1.03)	1.72 (0.03-107.50)	0.53 0.79	0.25 <0.001
D1 Hepatic vein flow D wave Ratio Normal	0.46 (0.14-1.49)	1.02 (0.99-1.05)	1.31 (1.05-1.65)	1.04 (1.01-1.08)
Hepatic vein flow pattern Venous congestion Severe congestion Minimum	0.03 0.07	0.39 (0.12-1.28)	33.69 (1.50-756.81)	0.41 (0.16-1.09)
Hepatic vein flow pattern Venous congestion Severe congestion Minimum	1.64 (0.13-21.10)	1.04 (0.09-11.75)	1.04 (0.97-1.10)	0.71 0.98
IVC diameter Maximum Variation	0.28 0.22 (0.00-10.11)	0.20 (0.01-3.98)	0.98 (0.92-1.05)	1.20 (0.75-1.91)
D1 CVP	0.64 0.44 1.32 (0.48-3.64)	1.20 (1.08-1.33)	<0.001	1.31 (1.11-1.55)
0.02 0.01 0.12 0.44 0.29 0.60	0.001	*(RV) Right ventricular; (IVC) inferior vena cava; (eGFR) estimated Glomerular filtration rate; (SCr) serum creatinine.		

Discussion Patient who developed AKI presented with higher hepatic vein S waves pre-operatively, in this current study. They developed significantly reduced hepatic vein flow ratios on post-operative D1 reflected as biphasic/venous congestion with Sin patients with decompensated heart failure is associated with increased CVP. They, however, also highlighted various challenges with utilising CVP as a bedside clinical tool to evaluate venous congestion, such as interobserver variability and the fact that central venous catheters may be removed earlier to minimise the risk of infections 24. It therefore may be advantageous to use multimodality non-invasive ultrasound parameters performed at bedside to assess fluid status. The development of AKI is thought to be mediated by central venous hypertension 32,36,43, where the notion of increased “afterload” or venous congestion is placed on the kidney, resulting in reduction in renal blood flow and ultimately tissue pressure and damage (19,38,43). In this study we find that this phenomenon is reflected in reduced hepatic vein ratios which are reflected as S < D waves indicative of venous congestion. A study by Spiegel and colleagues 46, showed that an S wave to D wave reversal in hepatic vein flow had an odds ratio of 4.15 (95% CI 1.54–11.23%) for an increase in the likelihood of a major adverse kidney event (MAKE-30) event in ICU patients, where the MAKE-30 event was described as an elevation of the creatinine level to $\geq 200\%$ of baseline, the need for renal replacement therapy or death 46. There are several POCUS markers used to detect the high pressures associated with the congestive process 23,32, such as the assessment of large veins (IVC and internal jugular), as well as pressure changes in the hepatic and intra-renal veins 32,43. The clinical usefulness of POCUS in detecting significant venous congestion may be strengthened by combining the use of these markers 32 and interpreting their clinical

significance. In this study, we investigated utilisation of hepatic venous flow Doppler, CVP, IVC, RV base and TAPSE measurements to predict the development of AKI after cardiac surgery. However, we did not find any associations between AKI and IVC, RV base or TAPSE measurements. The current study found an association between a higher EuroSCORE II and development of AKI. The EuroSCORE II [is a well-established risk factor for](#) development of AKI [and](#) has been reported [in](#) several studies 50–53. Furthermore, we found that the EuroSCORE II was independently predictive of development of AKI post cardiac surgery in two models, one including pre-operative and another post-operative D1 parameters, [P=0.005 and P=0.02 respectively](#). Similar [to a](#) previous study by Amini and colleagues 54, we found that increased age was predictive of development of AKI. It has been reported that the frequency of developing AKI in patients over 60 years of age may increase progressively in an age- dependant manner and could be three- to eightfold higher compared to younger patients 55. A previous study conducted by the South African group of this study 56 found raised pre- operative SCr to be a predictor of post-operative AKI. The current study yields similar results, albeit with the majority of patients enrolled in Denmark. SCr, together with age and ejection fraction, have been used in a risk stratification model, the ACEF criteria, to predict development of AKI 57 and found to be significant contributors. Chen and colleagues 58, compared the ACEF score with other risk scores (EuroSCORE II and Society of Thoracic Surgeons score) and found it to perform similarly. Patients who developed AKI had experienced significantly prolonged CPB times. CPB is known for inducing the stress response 1,10,31 which affects vascular integrity 3,8,11,19. The inflammatory milieu accompanying the stress response can lead to tissue oedema and fluid retention 38,39,44. This may be reflected as elevations in CVP levels 35,36. Elevated CVP measurements [have been associated with an increased risk of](#) mortality and [AKI](#), with [the](#) odds [of](#) developing [AKI](#) in critically ill adult patients increasing for every 1mmHg rise in CVP 35. These intra-operative circumstances can be managed in line with guidelines that advocate for GDT and prevention of renal stress and injury. Limitations This was a two-center study with potential for inter-observer variability between study sites. Ultrasound parameters have a potential of being influenced by a multitude of factors and should be interpreted in the clinical context. CSA AKI has a complex aetiology, and this should be borne in mind. Strengths The study represents geographic and patient profile diversity, ensuring heterogeneous characteristics. The use of interdepartmental, inter-specialty, intercontinental investigators added expertise and wholistic review of the topic and data interpretation. Conclusion There were associations between pre-operative and D1 hepatic venous ultrasound parameters. Although these were not predictive of development of AKI in multivariable regression models, they present an additional non-invasive tool in an armamentarium of early detection of risk of

AKI. D1 CVP values have indicated this progression in this study allowing for yet another point of possible mitigation. ERAS Cardiac guidelines advocate for the use of GDT, to avoid deleterious effects of fluid overload and development of AKI. Hepatic venous ultrasound modality together with other ultrasound modalities aimed at evaluating fluid status, may add value towards the goal of preventing AKI development peri-operatively. Acknowledgments The authors would like to thank Drs N Antil and colleagues for use of the image from their article. Declaration of interest The authors declare no conflict of interest. Funding source None. Authors' contributions GP: conceptualizing the study, designing the study, conducting the study, acquisition of data, interpretation of data, drafting article and partook in final approval of the manuscript. PM: conceptualizing the study, designing the study, conducting the study, acquisition of data, interpretation of data, drafting article and partook in final approval of the manuscript. HJM: designing the study, conducting the study, interpretation of data, drafting article and partook in final approval of the manuscript. MM: interpretation of data, drafting article and partook in final approval of the manuscript. JFP: conceptualizing the study, designing the study, conducting the study, acquisition of data, interpretation of data and partook in final approval of the manuscript. PJO: conceptualizing the study, designing the study, conducting the study, acquisition of data, interpretation of data and partook in final approval of the manuscript SM: conducting the study, acquisition of data, interpretation of data and partook in final approval of the manuscript. NT: conducting the study, acquisition of data, interpretation of data and partook in final approval of the manuscript. Appendix Supplementary Table 1.

Summary of pre-operative data Parameter Mean (SD)/ Median (IQR)/ N(%)

Age (years) 68 (55-73) Weight (kg) 77 (68-90) Height (cm) 171 (9.4) Gender (M) 109 (72 %) Hypertension 102 (67 %) IDDM 38 (25 %)

Hypercholesterolaemia 74 (49 %) Smoker 71 (47 %) Pre-op SCr (mmol/L) 85 (70-102.5) D1 SCr (mmol/L) 90 (75.5-102.5) D2 SCr (mmol/L) 87.5 (72-123) D3 SCr (mmol/L) 87 (69-113) D4 SCr (mmol/L) 83 (66-107) Pre-op K⁺ (mmol/L) 3.9 (3.7-4.3) D1 K⁺ (mmol/L) 4.6 (4.3-4.9) D4 K⁺ (mmol/L) 4 (3.7-4.3) Pre-op Na⁺ (mmol/L) 138 (11.4) D1 Na⁺ (mmol/L) 139 (3.5) D4 Na⁺ (mmol/L) 138 (3.5) Pre-op Hb (g/dL) 10 (2.7) D1 Hb (g/dL) 7.8 (2.2) D4 Hb (g/dL) 7.4 (1.9) Pre-op eGFR 78.9 (25.9) D1 eGFR 66.3 (21.4) D4 eGFR 77.8 (33.3) NO AKI 98 (65%) AKI GRI 37 (24%) AKI GRII 11 (7%) AKI GRIII 6 (4%) EuroSCORE II 1.84 (1.22-3.5) Pre-op Hepatic vein systole (m/s) 0.2 (0.08) D1 Hepatic vein systole (m/s) 0.2 (0.08) D4 Hepatic vein systole (m/s) 0.21 (0.1) Pre-op Hepatic vein diastole (m/s) 0.2 (0.1) D1 Hepatic vein diastole (m/s) 0.25 (0.14) D4 Hepatic vein diastole (m/s) 0.23 (0.12-0.33) Pre-op Hepatic vein ratio 1.23 (0.7-1.56) D1 Hepatic vein ratio 0.74 (0.52-1) D4 Hepatic vein ratio 0.64 (0.4-0.89) Pre-op Hepatic vein flow pattern Normal 111 (75%) Venous congestion 24 (16%) Severe congestion 13 (9%) D1 Hepatic

vein flow pattern Normal 126 (84%) Venous congestion 3 (2%) Severe congestion 20 (14%) D4 Hepatic vein flow pattern Normal 110 (79%) Venous congestion 6 (4%) Severe congestion 21 (15%) Pre-op IVC min (mm) 12.8 (3.6) D1 IVC min (mm) 15.4 (4.5) D4 IVC min (mm) 13.8 (4.2) Pre-op IVC max (mm) 16.5 (4) D1 IVC max (mm) 19 (4.9) D4 IVC max (mm) 18.8 (4) Pre-op IVC Variation 24.9 (13.8) D1 IVC Variation 21.7 (8.4) D4 IVC Variation 32 (17) D1 CVP (mmHg) 11.3 (3.7) Pre-operative TAPSE (mm) 21.1 (4.4) Pre-operative RV Base (mm) 38.2 (7.5) D4 TAPSE (mm) 11.7 (3.3) D4 RV Base (mm) 37.7 (6.9) *(Preop) Pre-operatively; [\(D1\) Day 1; \(D2\) Day 2; \(D3\) Day 3; \(D4\) Day 4;](#)(TAPSE) [Tricuspid annular](#) plane [systolic excursion;](#) (RV) [Right ventricular;](#) (CVP) central venous [pressure;](#) (IVC) inferior vena cava; (SCr) Serum creatinine; [\(Hb\) Haemoglobin; \(Na+\) Sodium; \(K+\) Potassium; \(eGFR\) estimated Glomerular filtration rate*](#)(D1) Day 1; [\(CVP\) central venous pressure; \(IVC\) inferior vena cava;](#) (eGFR) estimated Glomerular filtration rate

Supplementary Table 2. Summary of ultrasound data for both AKI and No AKI groups

Parameter	Pre-op	AKI	D1	D4	Hepatic vein flow S Wave
Median (IQR)	0.21 (0.16-0.27)	0.19 (0.15-0.27)	0.21 (0.15-0.28)	0.26 (0.17-0.35)	0.26 (0.12-0.36)
D wave	0.17 (0.13-0.26)	0.26 (0.17-0.35)	0.26 (0.12-0.36)	Ratio 1.20 (0.71-1.61)	0.57 (0.45-0.91)
Ratio	0.58 (0.46-0.85)	Hepatic vein Flow Normal 7 (13.2)	1 (1.9)	1 (1.9)	pattern n (%)
Hepatic vein Flow	Normal 7 (13.2)	1 (1.9)	1 (1.9)	pattern n (%)	Severe congestion 43 (81.1)
Severe congestion	43 (81.1)	41 (78.9)	IVC diameter Minimum 15.5 (14-17)	18 (12-19)	15 (15-17)
IVC diameter	Minimum 15.5 (14-17)	18 (12-19)	15 (15-17)	Maximum 17.5 (17-21)	23 (17-25)
Maximum	17.5 (17-21)	23 (17-25)	20 (18-21)	Variation 16.0 (11.8-42.3)	24.4 (22.2-27.3)
Variation	16.0 (11.8-42.3)	24.4 (22.2-27.3)	21.1 (18.2-28.6)	TAPSE (mm) 21 (19 – 23)	11.5 (10 – 13)
TAPSE (mm)	21 (19 – 23)	11.5 (10 – 13)	11 (9 – 13)	RV Base (mm) 39 (34 – 45)	38 (34.5 – 44.5)
RV Base (mm)	39 (34 – 45)	38 (34.5 – 44.5)	37 (33 – 43)	CVP (mmHg) 12.5 (10 – 16)	12 (6 – 13)
CVP (mmHg)	12.5 (10 – 16)	12 (6 – 13)	Pre-op No AKI	D1	D4
Pre-op No AKI	D1	D4	Hepatic vein flow S wave	0.19 (0.15-0.24)	0.20 (0.16-0.25)
Hepatic vein flow S wave	0.19 (0.15-0.24)	0.20 (0.16-0.25)	0.20 (0.15-0.25)	Median (IQR)	D wave 0.18 (0.12-0.22)
Median (IQR)	D wave 0.18 (0.12-0.22)	0.23 (0.16-0.31)	0.22 (0.12-0.31)	Ratio 1.24 (0.73-1.50)	0.78 (0.56-1.04)
Ratio	1.24 (0.73-1.50)	0.78 (0.56-1.04)	0.66 (0.40-0.90)	Normal 17 (17.9)	2 (2.1)
Normal	17 (17.9)	2 (2.1)	5 (5.8)	Hepatic vein Flow	Normal 17 (17.9)
Hepatic vein Flow	Normal 17 (17.9)	2 (2.1)	5 (5.8)	pattern n (%)	Severe congestion 68 (71.6)
Severe congestion	68 (71.6)	83 (86.5)	69 (79.3)	IVC diameter Minimum 11 (9-14)	14 (10-19)
IVC diameter	Minimum 11 (9-14)	14 (10-19)	12.5 (11.5-13.5)	Maximum 13 (12-18)	16 (13-21)
Maximum	13 (12-18)	16 (13-21)	20.5 (15.5-22)	Variation 28.6 (14-36.4)	13.3 (10-26.1)
Variation	28.6 (14-36.4)	13.3 (10-26.1)	39.7 (21.6-50.9)	TAPSE (mm) 22 (18 – 24)	9 (7 – 12)
TAPSE (mm)	22 (18 – 24)	9 (7 – 12)	12 (10 – 14)	RV Base (mm) 37 (33 – 41)	34 (33 – 41)
RV Base (mm)	37 (33 – 41)	34 (33 – 41)	36 (33 – 41)	CVP (mmHg) 11 (8 – 13)	8 (6 – 12)
CVP (mmHg)	11 (8 – 13)	8 (6 – 12)	*(Preop) Pre-operatively; (D1) Day 1; (D4) Day 4;	(TAPSE) Tricuspid annular plane systolic excursion; (RV) Right ventricular; (CVP) central venous pressure; (IVC) inferior vena cava.	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

APPENDIX 7

Appendix A HREC certificate



R14/49 Dr G Pettey

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE NO. M190310

NAME: Dr G Pettey
(Principal Investigator)
DEPARTMENT: School of Clinical Medicine
Department of Anaesthesiology
Charlotte Maxeke Johannesburg Academic Hospital

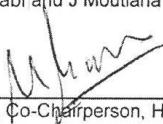
PROJECT TITLE: Evaluation of cardiac surgery associated acute kidney
injury using ultrasound
Change of study title noted on 2020/01/06

DATE CONSIDERED: 2019/03/29

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Drs P Motshabi and J Moutlana

APPROVED BY: 
Dr N Naran, Co-Chairperson, HREC (Medical)

DATE OF APPROVAL: 2019/04/26

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and ONE COPY returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in March and will therefore reports and re-certification will be due early in the month of March each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Gabriela Pettey
Principal Investigator Signature

2 June 2019
Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

Appendix B Permission letters

7 March 2019
Department of Anaesthesiology
Charlotte Maxeke Johannesburg Academic Hospital
Parktown
2196

Ms GM Bogoshi
Chief Executive Officer
Charlotte Maxeke Johannesburg Academic Hospital

Masters in Medicine for Anaesthesiology Research Data Collection: Dr Gabriela Pettey

Dear Ms Bogoshi,

My name is Gabriela Pettey, and I am a Registrar in the Department of Anaesthesiology at the University of the Witwatersrand. My intention is to conduct a prospective study of patients undergoing cardiac surgery between the months of April to September 2019, and obtain ultrasound profiles of the renal, portal and cardiac systems.

The aim of the study is to use Doppler in a novel approach to identify Acute Kidney Injury in post-cardiac surgery patients, by profiling their renal, portal and cardiac Doppler parameters pre-operatively and post-operatively. The intention is to review the Doppler profiles and attempt to anticipate a rise in serum creatinine.

I would, therefore, like to request your permission to conduct this study on patients that meet the inclusion criteria that are admitted to the Cardiothoracic Intensive Care Unit, so that I may meet the objectives defined by this study. This study will be a collaborative effort with international fellows, who will also seek permission to conduct their study.

Thank you in advance,
Dr Gabriela Pettey
+27 82 888 38 28

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

03 September 2019
Person No: 305177
PAG

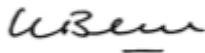
Dr G Pettey
34 Sandhurst Estate
101 Empire Place
Sandhurst
2196
South Africa

Dear Dr Gabriela Pettey

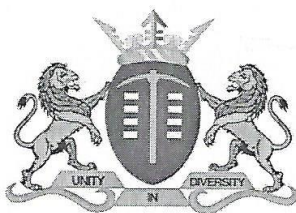
Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *Evaluation of cardiac surgery associated acute kidney injury using ultrasound* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely



Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences



GAUTENG PROVINCE

HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Tell: (011) 488-4812
Email: Nolwazi.Mzila@gauteng.gov.za
10th February 2020

GP_202001_013

Dear Dr. G. Petty

STUDY TITLE: Evaluation of cardiac surgery associated acute kidney injury using ultrasound

Permission is granted for you to conduct the above recruitment activities as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported / not supported

Dr. P. Africa
Acting Clinical Director

DATE: 26/01/2020

Approved/not approved

Ms. G. Bogoshi
Chief Executive Officer

Date: 26.02.2020

Appendix C Data collection sheet

The data collection sheet will contain the following information, or extracted variables, for the pre-operative day, first day post-operatively and fourth day post-operatively for 50 patients;

- Patient demographics
 - Age
 - Weight
 - Height
 - Gender
 - Race
 - Co-morbidities
 - Hypertension
 - Insulin dependent diabetes
 - Hypercholestromia
 - Smoking exposure
 - Other
- Type of surgery
 - Valvular (excluding isolated aortic valve surgery)
 - Coronary artery bypass grafting (CABG)
 - Other
- Patient information
 - Fluid balance
 - Urine output
 - Central venous pressure (range)
 - Blood results
 - Serum creatinine (SCr)
 - Potassium (K)
 - Sodium (Na)
 - Haemoglobin (Hb)
- Ultrasound information
 - Renal
 - Arterial

- Resistive index measured in arcuate/intralobar arteries at the cranial, middle and caudal part of the kidney
- Venous
 - Flow pattern category measured in arcuate/intralobar arteries at the cranial, middle and caudal part of the kidney
 - Continuous
 - Biphasic discontinuous
 - Monophasic discontinuous
 - Maximal velocities measured in arcuate/intralobar arteries at the cranial, middle and caudal part of the kidney
 - systole (S)
 - diastole (D)
 - the ratio (S/D)
- Hepatic
 - Venous measured in the hepatic vein
 - Maximal systolic velocity (S)
 - Maximal diastolic velocity (D)
 - Systolic:diastolic ratio (S/D)
 - Portal measured in the portal vein
 - Flow pattern classification based on pulsatility (>50% abnormal)

Appendix D Data collection

Patient Number: [12345]

Patient Demographics	Variables
Age (years)	
Weight (kg)	
Height (cm)	
Gender	
Race	
Co-morbidities	Hypertension
	Insulin dependent diabetes
	Hypercholestrolaemia
	Smoking exposure
	Other

Clinical information	Value
Fluid balance (mls)	
Urine output (mls)	
Central venous pressure (mmHg)	

Blood results	Value
SCr ($\mu\text{mol/L}$)	
K ⁺ (mmol/L)	
Na ⁺ (mmol/L)	
Hb (g/dL)	

Type of assessment

Pre-op / 1st day post-op / 4th day post op

Surgery information	Variables
Type of surgery	
	Valvular
	CABG
	Other
Date of surgery	
	Pre-operative
	1st day post-operatively
	4th day post-operatively

Ultrasound information

Renal Duplex (Arcuate, Intralobar)	Specification	Value/ pattern
Resistive index (RI)	Cranial	
	Middle	
	Caudal	
Intrarenal venous flow (IRVF) pattern classification	Cranial	
	Middle	
	Caudal	
Maximal velocities- cranial	Systole	
	Diastole	
	Ratio (S/D)	
Maximal velocities- middle	Systole	
	Diastole	
	Ratio (S/D)	
Maximal velocities- caudal	Systole	
	Diastole	
	Ratio (S/D)	

Hepatic Duplex	Specification	Value
Maximal velocities hepatic vein	Systole	
	Diastole	
	Ratio (S/D)	
Portal vein	Pulsatility ratio	

Appendix E Patient information sheet

Patient Information sheet

Dear Sir/Madam

My name is Gabriela Pettey. I am currently specializing in Anaesthesiology through the University of the Witwatersrand. Part of our training to become specialist doctors requires us to conduct a research project. My research topic is the use of ultrasound to detect acute kidney injury (kidney failure) after cardiac surgery (heart surgery).

I would like to invite you to participate in the study- it is a voluntary process and should you choose not to participate, it will not cause you harm. It involves an ultrasound being done, which is a device used to take pictures of different organs in your body. The organs we would like to look at are the kidneys, liver, liver veins and the heart. The ultrasound is not painful, and takes approximately 15 minutes to do. We would like to do the ultrasound before your operation, on the day after your operation and four days after your operation.

We will be conducting this study with a set of international doctors from Denmark. With your permission, we would like to anonymously share the information we gain from the ultrasound, your blood results and your hospital records with them, so that we have more information to compare. With this information, we will try to find specific features on the pictures of the organs that can help us to predict if acute kidney injury (kidney failure) could occur.

There may be no direct benefit to you immediately from participating in this study, however, the study enables us to test whether our ideas are correct or not. This is beneficial in the long term, as acute kidney injury (kidney failure) occurs quite often (about 40 % of the time) after cardiac surgery (heart surgery). If we could find a way to prevent it from happening, we could make a difference in the future to other people who would be at risk of having acute kidney injury (kidney failure).

During the ultrasound, pictures will be taken of your organs, but it will be anonymous, so there will be no information about you (name, ID number, telephone number, address) on the

pictures. Once we have the pictures, they will be kept in a safe location, and no one outside the study group will have access to them.

While you are in hospital, your blood will be taken on a daily basis by the ward (Cardio-Thoracic Intensive Care Unit) in which you will stay. The amount of blood that will be taken on each occasion should be no more than 4 teaspoons (20mls) and will usually only be taken once daily- unless it is taken for purposes outside of this study. With your permission, we would like to access this information to add information to our study about your kidney functions, your liver functions, your heart functions and your blood counts. This is the way that acute kidney injury (kidney failure) is currently diagnosed and so we need access to this information to add it to our ultrasound pictures. The results of your blood tests will again remain anonymous and only the results will be used in our study with no identifying information.

We would also like to request permission to use the information that will be recorded on your hospital charts on a daily basis: your vital signs, weight, urine output, intravenous fluids, if you require dialysis, if any complications arise from the operation.

If you feel uncomfortable during the ultrasound, or no longer want to participate in the study, you can decline to participate at any point. If you feel distressed or anxious about the study, we can put you in contact with a social worker or a psychologist at Charlotte Maxeke Johannesburg Academic Hospital.

If you would like the results of the study, please contact me directly on the details below and I will send it to you. If you would like to contact me during the study process to ask any questions or clarify something my details are below. If you are concerned about the ethics within this study, or feel that your rights were violated during this study, please contact Clement Penny at Human Resources Ethics Committee at the University of the Witwatersrand on 011-717-2301 or email on Clement.Penny@wits.ac.za.

Thank you for reading this information sheet.

Dr Gabriela Pettey
(Principal investigator)
0828883828
Gabi.Pettey@gmail.com

Dr Palesa Motshabi
(Clinical Supervisor)
011-488-4344
February 2019

Appendix F Consent form

Evaluation of cardiac surgery associated acute kidney injury using ultrasound

By Dr Gabriela Pettey

I, _____ (name of patient), give my permission to be included in this study. I understand that part of the study involves ultrasound being conducted prior to cardiac surgery, on the first day and fourth day post-operatively. I also understand that blood will be taken for examination daily.

I, _____ (name of patient), agree to participate in this study. I understand that there will be no compensation for my participation. I also understand that I am permitted to decline participation in this study at any point in time.

I agree to the following (please circle applicable):

Ultrasound to be conducted on the renal, hepatic, portal and cardiac systems pre-operatively

YES NO

Ultrasound to be conducted on the renal, hepatic, portal and cardiac systems post-operatively on the first and fourth days

YES NO

Blood tests being taken for evaluation pre-operatively, and on each day post-operatively

YES NO

The results of my ultrasound and blood tests being shared, anonymously, with other Doctors involved in this study

YES NO

The information from my hospital records and charts during admission can be used, anonymously, for this study

YES NO

The information I provide may be used, anonymously, in this study and future studies

YES NO

..... (signature)

..... (name of patient)

..... (date)

Appendix G Supplementary Table 1

Supplementary Table 1. Summary of pre-operative data

Parameter		Mean (SD)/ Median (IQR)/ N(%)
Age (years)		68 (55-73)
Weight (kg)		77 (68-90)
Height (cm)		171 (9.4)
Gender (M)		109 (72 %)
Hypertension		102 (67 %)
IDDM		38 (25 %)
Hypercholesterolaemia		74 (49 %)
Smoker		71 (47 %)
Pre-op SCr (mmol/L)		85 (70-102.5)
D1 SCr (mmol/L)		90 (75.5-102.5)
D2 SCr (mmol/L)		87.5 (72-123)
D3 SCr (mmol/L)		87 (69-113)
D4 SCr (mmol/L)		83 (66-107)
Pre-op K ⁺ (mmol/L)		3.9 (3.7-4.3)
D1 K ⁺ (mmol/L)		4.6 (4.3-4.9)
D4 K ⁺ (mmol/L)		4 (3.7-4.3)
Pre-op Na ⁺ (mmol/L)		138 (11.4)
D1 Na ⁺ (mmol/L)		139 (3.5)
D4 Na ⁺ (mmol/L)		138 (3.5)
Pre-op Hb (g/dL)		10 (2.7)
D1 Hb (g/dL)		7.8 (2.2)
D4 Hb (g/dL)		7.4 (1.9)
Pre-op eGFR		78.9 (25.9)
D1 eGFR		66.3 (21.4)
D4 eGFR		77.8 (33.3)
NO AKI		98 (65%)
AKI GRI		37 (24%)
AKI GRII		11 (7%)
AKI GRIII		6 (4%)
EuroSCORE II		1.84 (1.22-3.5)
Pre-op Hepatic vein systole (m/s)		0.2 (0.08)
D1 Hepatic vein systole (m/s)		0.2 (0.08)
D4 Hepatic vein systole (m/s)		0.21 (0.1)
Pre-op Hepatic vein diastole (m/s)		0.2 (0.1)
D1 Hepatic vein diastole (m/s)		0.25 (0.14)
D4 Hepatic vein diastole (m/s)		0.23 (0.12-0.33)
Pre-op Hepatic vein ratio		1.23 (0.7-1.56)
D1 Hepatic vein ratio		0.74 (0.52-1)
D4 Hepatic vein ratio		0.64 (0.4-0.89)
Pre-op Hepatic vein flow pattern	Normal	111 (75%)

	Venous congestion	24 (16%)
	Severe congestion	13 (9%)
D1 Hepatic vein flow pattern	Normal	126 (84%)
	Venous congestion	3 (2%)
	Severe congestion	20 (14%)
D4 Hepatic vein flow pattern	Normal	110 (79%)
	Venous congestion	6 (4%)
	Severe congestion	21 (15%)
Pre-op IVC min (mm)		12.8 (3.6)
D1 IVC min (mm)		15.4 (4.5)
D4 IVC min (mm)		13.8 (4.2)
Pre-op IVC max (mm)		16.5 (4)
D1 IVC max (mm)		19 (4.9)
D4 IVC max (mm)		18.8 (4)
Pre-op IVC Variation (%)		24.9 (13.8)
D1 IVC Variation (%)		21.7 (8.4)
D4 IVC Variation (%)		32 (17)
D1 CVP (mmHg)		11.3 (3.7)
Pre-operative TAPSE (mm)		21.1 (4.4)
Pre-operative RV Base (mm)		38.2 (7.5)
D4 TAPSE (mm)		11.7 (3.3)
D4 RV Base (mm)		37.7 (6.9)

*(Preop) Pre-operatively; (D1) Day 1; (D4) Day 4; (TAPSE) Tricuspid annular plane systolic excursion; (RV) Right ventricular; (CVP) central venous pressure; (IVC) inferior vena cava. *(Preop) Pre-operatively; (D1) Day 1; (D2) Day 2; (D3) Day 3; (D4) Day 4; (TAPSE) Tricuspid annular plane systolic excursion; (RV) Right ventricular; (CVP) central venous pressure; (IVC) inferior vena cava; (SCr) Serum creatinine; (Hb) Haemoglobin; (Na⁺) Sodium; (K⁺) Potassium; (eGFR) estimated Glomerular filtration rate*(D1) Day 1; (CVP) central venous pressure; (IVC) inferior vena cava; (eGFR) estimated Glomerular filtration rate; (SCr) serum creatinine.

Appendix H Supplementary Table 2

Supplementary Table 2. Summary of ultrasound data for both AKI and No AKI groups

Parameter		AKI		
		Pre-op	D1	D4
Hepatic vein flow Median (IQR) (m/s)	S Wave	0.21 (0.16-0.27)	0.19 (0.15-0.27)	0.21 (0.15-0.28)
	D wave	0.17 (0.13-0.26)	0.26 (0.17-0.35)	0.26 (0.12-0.36)
	Ratio	1.20 (0.71-1.61)	0.57 (0.45-0.91)	0.58 (0.46-0.85)
Hepatic vein Flow pattern n (%)	Normal	7 (13.2)	1 (1.9)	1 (1.9)
	Venous congestion	3 (5.7)	9 (17.0)	10 (19.2)
	Severe congestion	43 (81.1)	43 (81.1)	41 (78.9)
IVC diameter (mm)	Minimum	15.5 (14-17)	18 (12-19)	15 (15-17)
	Maximum	17.5 (17-21)	23 (17-25)	20 (18-21)
	Variation	16.0 (11.8-42.3)	24.4 (22.2-27.3)	21.1 (18.2-28.6)
TAPSE (mm)		21 (19 – 23)	11.5 (10 – 13)	11 (9 – 13)
RV Base (mm)		39 (34 – 45)	38 (34.5 – 44.5)	37 (33 – 43)
CVP (mmHg)			12.5 (10 – 16)	12 (6 – 13)
		No AKI		
		Pre-op	D1	D4
Hepatic vein flow Median (IQR) (m/s)	S wave	0.19 (0.15-0.24)	0.20 (0.16-0.25)	0.20 (0.15-0.25)
	D wave	0.18 (0.12-0.22)	0.23 (0.16-0.31)	0.22 (0.12-0.31)
	Ratio	1.24 (0.73-1.50)	0.78 (0.56-1.04)	0.66 (0.40-0.90)
Hepatic vein Flow pattern n (%)	Normal	17 (17.9)	2 (2.1)	5 (5.8)
	Venous congestion	10 (10.5)	11 (11.4)	13 (14.9)
	Severe congestion	68 (71.6)	83 (86.5)	69 (79.3)
IVC diameter (mm)	Minimum	11 (9-14)	14 (10-19)	12.5 (11.5-13.5)
	Maximum	13 (12-18)	16 (13-21)	20.5 (15.5-22)
	Variation (%)	28.6 (14-36.4)	13.3 (10-26.1)	39.7 (21.6-50.9)
TAPSE (mm)		22 (18 – 24)	9 (7 – 12)	12 (10 – 14)
RV Base (mm)		37 (33 – 41)	34 (31 – 38)	36 (33 – 41)
CVP (mmHg)			11 (8 – 13)	8 (6 – 12)

*(Preop) Pre-operatively; (D1) Day 1; (D4) Day 4; (TAPSE) Tricuspid annular plane systolic excursion; (RV) Right ventricular; (CVP) central venous pressure; (IVC) inferior vena cava.