Original Article

Duplex Assessment Of Renal Perfusion After Fluid Administration In Critically-Ill Patients

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Abstract

Background: Circulatory shock is a life-threatening medical condition that characterized by a significant reduction of systemic tissue perfusion, resulting in decreased oxygen delivery to the tissues. Doppler ultrasound. Imaging of the kidneys can provide information about secondary damage to the kidneys from chronic poor blood-flow **Aim:** to evaluate changes in interlobar artery (ILA) resistivity index (RI) (ILA RI), using Doppler techniques, during volume expansion in critically ill patients and, in addition, to compare the performance of these changes with that of changes in systemic hemodynamics for the prediction of subsequent variations in urine output. We hypothesized that dynamic analysis of intrarenal hemodynamic using RIAD following a fluid challenge may help to identify responders to fluids better than systemic hemodynamics. **Subjects and Methods:** This study was a prospective cohort study conducted on 50 patients admitted to critical care department, Kasr El Aini Hospital. 40 patients were admitted with acute circulatory failure and 10 patients were served as control group. The control group included ICU patients with stable systemic hemodynamic receiving no specific intervention and has no problem to receive IV fluids. On the other hand, the interventional group consisted of patients with acute circulatory failure who required a fluid challenge. **Results:** This study showed that fluid challenge in critically ill patients with acute circulatory failure was associated with significantly decreased RI as assessed by RIAD. In addition, changes in RI were associated with improvement in MAP without significant correlation. However, these changes were not associated with UOP improvement. **Conclusion:** • The use of renal Doppler could help to predict the response to fluid challenge in patients with circulatory failure; however, the use of renal Doppler will be of limited value if the sonographer doesn't have the required experience.

Keywords: Duplex, Renal Perfusion, Fluid Administration, Critically-Ill Patients

INTRODUCTION

Circulatory shock is a life-threatening medical condition that characterized by a significant reduction of systemic tissue perfusion, resulting in decreased oxygen delivery to the tissues. This creates an imbalance between oxygen delivery DO_2 and oxygen consumption VO_2. Prolonged oxygen deprivation leads to cellular hypoxia and derangement of critical biochemical processes at the cellular level, which can progress to the systemic level. **[1,2]**

The effects of oxygen deprivation are initially reversible, but rapidly become irreversible. The result is sequential cell death, end-organ damage, multi-system organ failure, and death. This highlights the importance of prompt recognition and reversal of shock**.[3]** Circulatory shock is associated with high morbidity and mortality. Acute kidney injury (AKI) is a frequent complication of circulatory failure and associated with increased morbidity and mortality **[4,5]**

Fluid resuscitation is the first-line therapy used to restore oxygen delivery to the organs and prevent AKI **[4,5,6]** and yet the renal effects of fluid resuscitation are not easily assessed. Nowadays, several parameters are available to assess fluid responsiveness. Clinicians need to know all of them, with their limitations, without forgetting that the final aim of all therapies is to improve the microcirculation. **[7]**

Excessive fluid administration may have harmful effects, and mortality rates are increased in patients with AKI who develop a positive fluid balance **[8,9,10].** Hence, it could be important to identify those patients in whom renal hemodynamic improve in response to fluids. Although fluids are often given to patients with AKI with the aim of increasing renal perfusion, physicians generally evaluate the effectiveness of fluid therapy by looking at systemic hemodynamic variables, such as mean arterial pressure MAP or cardiac output CO, because the increase in urine output may be delayed or inconsistent and the decrease in serum creatinine may be even slower. A direct evaluation of renal hemodynamic would be valuable, but is not easily obtained at the bedside. **[11]**

Recently, interlobar artery (ILA) resistivity index (RI), a reliable surrogate of intrarenal vascular tone measured by renal interlobar artery Doppler (RIAD), has been proposed for bedside evaluation of intrarenal hemodynamic in critically ill

patients **[12,13,14].**

Doppler-based renal resistive index, which is a simple, rapid, non-invasive, and repeatable marker, could be a promising tool to prematurely detect the patients most at risk of developing AKI in the ICU and to distinguish transient from persistent AKI. Moreover, the resistive index could also be useful to adjust preventive or therapeutic modalities for the kidney perfusion at the bedside. **[15]**
This variable has been successfully used in critically ill patients to evaluate changes in renal hemodynamic following various therapeutic interventions, such as norepinephrine infusion, fluid challenge or paracentesis **[13,14,16,17,18,19].** However, limited studies compared the effectiveness of changes in systemic and in intrarenal hemodynamic to predict changes in urine output after a fluid challenge. **[20]**
Renal artery duplex scanning is accurate, non-invasive and cost-effective. Unlike angiography or CT scanning, no injection of X-ray contrast material is required, avoiding the risk of kidney damage from the contrast.
Blood-flow velocities and flow patterns in the aorta and renal arteries are evaluated with Doppler ultrasound. Imaging of the kidneys can provide information about secondary damage to the kidneys from chronic poor blood-flow. Flow patterns, resistance indices, in the small vessels within the kidneys can provide additional information about kidney damage and the potential for recovery of kidney function with therapy. **[21]**

This study aimed to evaluate changes in interlobar artery (ILA) resistivity index (RI) (ILA RI), using Doppler techniques, during volume expansion in critically ill patients and, in addition, to compare the performance of these changes with that of changes in systemic hemodynamics for the prediction of subsequent variations in urine output. We hypothesized that dynamic analysis of intrarenal hemodynamic using RIAD following a fluid challenge may help to identify responders to fluids better than systemic hemodynamics.

Patients and Methods

This is a prospective cohort study conducted on 50 patients admitted to critical care department, Kasr El Aini hospital. 40 patients were admitted with acute circulatory failure and 10 patients were served as control group. The study population divided into two groups: control group (10 patients) and an interventional group (40 patients). The control group included ICU patients with stable systemic hemodynamics receiving no specific intervention and has no problem to receive IV fluids.
The interventional group consisted of patients with acute circulatory failure who required a fluid challenge.
Acute circulatory failure defined as the association of arterial hypotension (systolic arterial pressure <90 mmHg or MAP <65 mmHg) or need for vasopressor to correct hypotension, with at least one of the following criteria: oliguria defined as urine output <0.5 ml/kg/hour , impaired mentation, mottled extremities, arterial lactate >2 mmol/l, and superior vena cava ($ScvO_2$) or mixed (SvO_2) venous oxygen saturations <70 % or <65 %, respectively.
AKI was defined as an increase in serum creatinine ≥0.3 mg/dl over 24 h and/or a 1.5-fold increase in baseline serum creatinine over 7 days, and/or oliguria with a reduction in urine output <0.5 ml/kg/hour over 6 h. **[20]**

Exclusion criteria

1. Age <18 years.
2. Atrial fibrillation or frequent ventricular arrhythmias.
3. History of renal transplantation or stenosis of renal arteries.
4. End-stage renal disease.
5. Known unilateral kidney.
6. Pregnancy.
7. Body mass index BMI >40 kg/m 2.
8. Administration of diuretics or any changes in vasopressor during the study period.

All patients were subjected to all of the following:

- Detailed and full history taking and thorough clinical examination.
- Acute Physiology and Chronic Health Evaluation (APACHE II) scoring on admission.
- Daily SOFA scoring assessment.
- 12 leads ECG, abdominal ultrasound & chest x-ray.
- Full routine laboratory tests, including renal functions & electrolytes.
- Echocardiographic assessment for LV function.
- Monitoring including continuous electrocardiogram and heart rate recording and invasive measurement of MAP and pulse pressure (PP) (if feasible) through a radial or femoral catheter.
- Daily follow up of hemodynamics & dosage of vasopressors.
- measurement of arterial lactate and $ScvO_2$ / SvO_2
- Daily follow up of arterial blood gases ABG, blood urea, serum creatinine, sodium, potassium & hemoglobin.

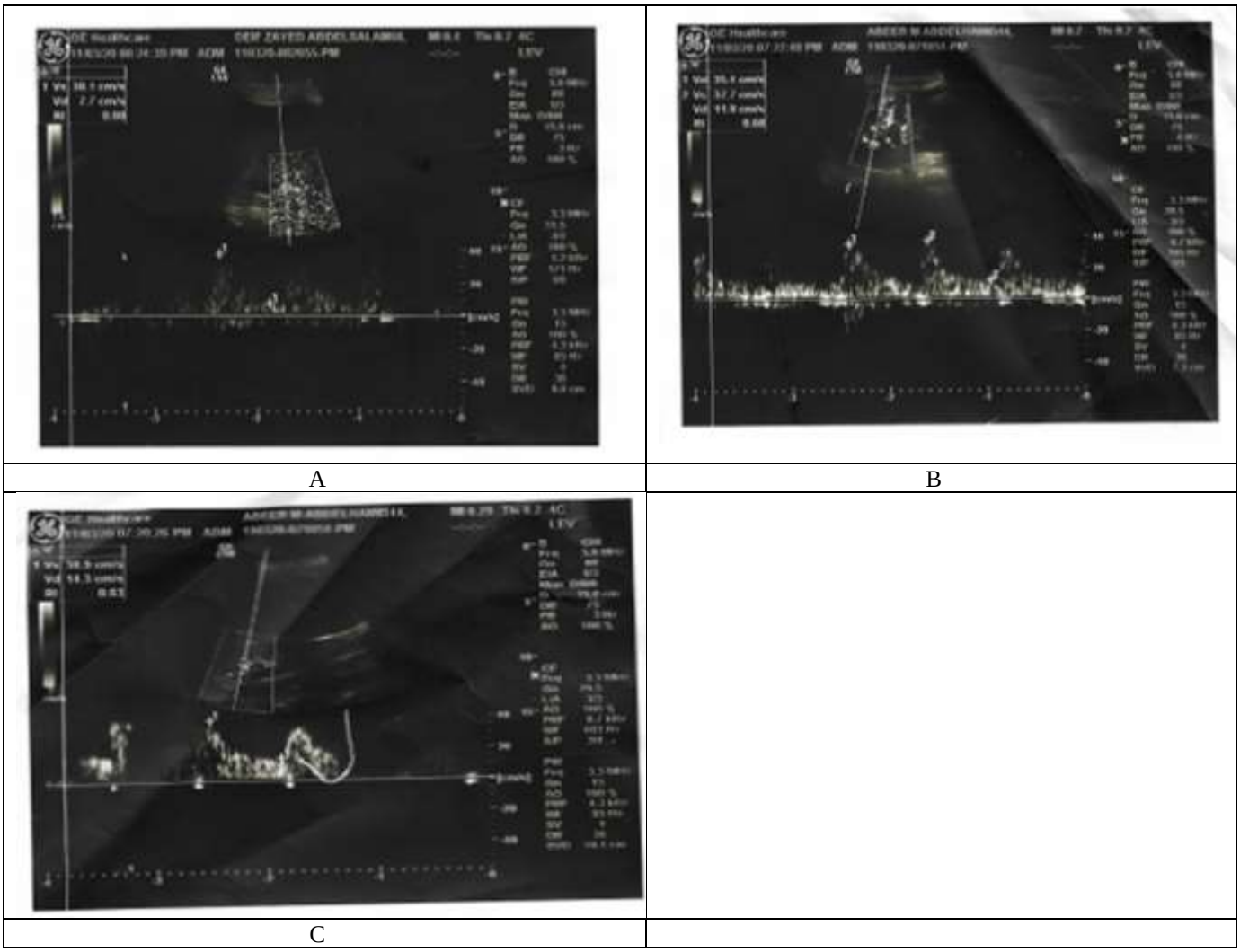
- Renal Doppler.
- Follow up of the clinical & hemodynamic parameters during ICU stay.

Study protocol

All the patients were received a fluid challenge as resuscitative treatment while they were hemodynamically unstable. Fluid challenge consisted of a minimum volume of 500 ml crystalloid. Fluid administration was stopped when MAP reached a predetermined goal (generally MAP >65 mmHg, and/or MAP and/or stroke volume increase >10–15 % compared to baseline) and/or central venous pressure increased >15 mmHg. Systemic hemodynamic variables were recorded and renal Doppler measurements were performed before and at the end of the fluid challenge.

The urine output volume over the 3 h preceding and following the fluid challenge were recorded.

Doppler measurements using a convex 2–5.5 MHz probe, with the transducer applied in the lateral or postero-lateral view used to visualize the kidneys. Intrarenal vessels observed using color Doppler, then a pulsed Doppler signal obtained on the interlobar artery ILA. Three consecutive measurements displaying at least three ILA Doppler waves each (corresponding to three cardiac beats) were performed in the upper, middle and lower poles of both kidneys and averaged. Failure to meet these criteria or a difference of more than 5 % in RI between the kidneys was considered as a failure in measurement. Systolic (SV) and diastolic (DV) velocities were measured on each wave. Interlobar RI was calculated using the formula: RI = (SV – DV)/SV.



A | B

C

Figure 1(A, B&C): RI Measurement in Critical Cases

Scoring Systems used in the study:

1. Admission scores
2. Severity of illness scores

1. Admission scores:

Acute Physiology and Chronic Health Evaluation (APACHE)

- APACHE is an admission score and is based upon the most abnormal variables within the first 24 hours of ICU admission.
- Four versions of APACHE are currently available.
- We used APACHE II in our study.
- The APACHE II model, published in 1985, was developed to simplify the original APACHE model and has become the most frequently used general mortality prediction model. APACHE II has been extensively validated, and despite being the oldest system, it still performs well. More recent versions (APACHE III and IV) have not been widely adopted. All the APACHE models are based on the most abnormal values registered during the first 24 h after ICU admission.
- The parameters that make up the APACHE II are outlined in **next table** Maximum score is 71.

The APACHE II Severity of Disease Classification System

Physiologic Variable		+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature - rectal (°C)		≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mm Hg)		≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate		≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory Rate (nonventilated or ventilated)		≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation (mmHg) a. $FiO_2 > 0,5$ use $A\text{-}aDO_2$ b. $FiO_2 < 0,5$ use PaO_2	a	≥500	350-499	200-349		<200				
	b					> 70	61-70		55-60	<55
Arterial pH		≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum Sodium (mmol/l)		≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum Potassium (mmol/l)		≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum Creatinine (mg/dl, Double point score for acute renal failure)		≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)		≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White Blood Count (in 1000/mm³)		≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow-Coma-Scale (GCS)		Score = 15 minus actual GCS								
Serum HCO_3 (venous, mmol/l, use if no ABGs)		≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
A = Total Acute Physiology Score APS		Sum of the 12 individual variable points								
B = Age Points		**C = Chronic Health Points**								
≤44 years 0 points 45-54 years 2 points 55-64 years 3 points 65-74 years 5 points ≥75 years 6 points		If the patient has a history of severe organ system insufficiency or is immunocompromised assign points as follows: a. For nonoperative or emergency postoperative patients – 5 points b. For elective postoperative patients – 2 points								
APACHE II Score = Sum of A (APS points) + B (Age points) + C (Chronic Health points)										

(From: Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(10):818-29)

2. Severity of Illness Scores

Sequential Organ Failure Assessment (SOFA) score

- Evolved as the consequence of a consensus conference in 1994.
- Six organ systems, score of 0–4 dependent upon degree of organ dysfunction or support required for each organ:
  1. 0: no dysfunction
  2. 1–2: organ dysfunction

3. 3–4: organ failure

- Organ systems are assessed on the following criteria:

1. Respiratory: PaO2:FiO2 ratio
2. Cardiovascular: a composite score that includes both the mean arterial blood pressure and the degree of pharmacological support (dobutamine, dopamine, adrenaline, or noradrenaline)
3. Neurological: GCS
4. Renal: either plasma creatinine or daily urine output
5. Liver: plasma bilirubin
6. Coagulation: platelet count

- Allows for longitudinal evaluation of both individual organs and whole patient physiology.
- The worst value of the day is the recorded value.
- Was not designed to predict mortality; however, increasing SOFA score over the first 48 hours of ICU admission is associated with a higher risk of death.

SOFA score	0	1	2	3	4
Respiration					
PaO_2/FIO_2 (mmHg)	> 400	301–400	201–300	101–200	≤ 100
(kPa)	> 5.3)	(4.1–5.3)	(2.8–4.0)	(1.4–2.7)	≤ 1.3)
Coagulation					
Platelets ($x10^3/mm^3$)	> 150	101–150	51–100	21–50	≤ 20
Liver					
Bilirubin (mg/dl)	< 1.2	1.2–1.9	2.0–5.9	6.0–11.9	≥ 12.0
(μmol/l)	< 20)	(20–32)	(33–101)	(102–204)	≥ 204)
Cardiovascular					
Hypotension	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine > 5	Dopamine > 15
Central nervous system					
Glasgow coma score	15	13–14	10–12	6–9	< 6
Renal					
Creatinine (mg/dl)	< 1.2	1.2–1.9	2.0–3.4	3.5–4.9	> 5.0
(μmol/l)	< 110)	(110–170)	(171–299)	(300–440)	> 440)
or urine output				< 500 ml/day	< 200 ml/day

* adrenergic agents administered for at least 1 h (doses given are in μg/kg/min)

Statistical methods:

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. For comparison of serial measurements within each patient the non-parametric Wilcoxon signed rank test was used**.** For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 **.** Correlations between quantitative variables were done using Spearman correlation coefficient-values less than 0.05 were considered as statistically significant.

Results

Ten ICU patients without hemodynamic instability were served as control group. The mean age of the control group was 61.08 ± 7.05 years (range: 49 – 72 years), Out of the control group, 8 patients (80%) were diabetics, 8 patients (80%) were hypertensives, 4 patients (40%) were with ischemic heart disease, 2 patients (20%) had COPD, 5 patients (50%) had chronic kidney disease CKD and 2 patients (20%) had liver disease, All patients were subjected to assessment by APACHE II scoring system on admission & daily assessment with SOFA score. It was found that the mean APACHE II score on admission was 11.1 ± 3.18. The average of the mean SOFA scores in the first day (SOFA 1) were 4.9 ± 2.33 while average of the mean SOFA scores following fluid challenge, calculated in the 3rd day, (SOFA 2) were 1.9± 0.99.

For interventional group: Forty patients with hemodynamic instability were eligible for the study. The mean age of them was 63.73±11.14 years (range: 38 – 85 years). Out of the 40 patients included in the study, 25 patients were males (62.5 %) & 15 patients were females (37.5 %).Out of the study population, 28 patients (70%) were diabetics, 28 patients (70%) were hypertensives, 11 patients (27.5%) were with ischemic heart disease, 6 patients (15 %) had COPD, 17 patients (42.5%) had chronic kidney disease and 5 patients (12.5%) had liver disease. All patients were subjected to assessment by APACHE II scoring system on admission & daily assessment with SOFA score. It was found that the mean APACHE II score on admission was 17.53 ± 3.86.

The average of the mean SOFA scores in the first day (SOFA 1) were 6.23 ±1.58 while average of the mean SOFA scores following fluid challenge, calculated in the 3rd day, (SOFA 2) were 4.25± 2.43.

There was no statistically significant difference between control & interventional groups regarding the age (P= 0.409). There was no statistically significant difference between control & interventional groups regarding the sex distribution (P = 0.494).

Table 1: Comparison Between Control and Interventional Groups Regarding the Age and gender.

	interventional					control					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Age (years)	63.73	11.14	65.50	38.00	85.00	61.80	7.05	62.50	49.00	72.00	0.409

		interventional		control		P value
		Count	%	Count	%	
Gender	Male	25	62.5%	5	50.0%	0.494
	Female	15	37.5%	5	50.0%	

There was no significant difference between control & interventional groups in the co morbidities and the body mass index BMI of the patients as shown below**.**

Table 2: Comparison Between Interventional & Control Groups Regarding the Co-morbidities.

		interventional		control		P value
		Count	%	Count	%	
DM	Yes	28	70.0%	8	80.0%	0.704
	No	12	30.0%	2	20.0%	
HTN	Yes	28	70.0%	8	80.0%	0.704
	No	12	30.0%	2	20.0%	
IHD	Yes	11	27.5%	4	40.0%	0.462
	No	29	72.5%	6	60.0%	
CKD	Yes	17	42.5%	5	50.0%	0.732
	No	23	57.5%	5	50.0%	
Liver disease	Yes	5	12.5%	2	20.0%	0.616
	No	35	87.5%	8	80.0%	
COPD	Yes	6	15.0%	2	20.0%	0.653
	No	34	85.0%	8	80.0%	

	interventional					control					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
BMI	29.22	2.43	29.00	25.00	35.00	28.70	1.49	28.50	27.00	32.00	0.676

There was a statistically significant difference between both groups regarding the SOFA 1 score (P value 0.032) . It was noted also that the interventional group patients had higher APACHI II & SOFA 2 scores than the control group and they were statistically highly significant (P value < 0.001).

Table 3: Comparison Between Control & Interventional Groups Regarding the Scoring Systems.

	interventional					control					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
APACHI II	17.53	3.86	17.50	9.00	24.00	11.10	3.18	10.50	7.00	17.00	< 0.001
SOFA Day 0	6.23	1.58	6.00	4.00	10.00	4.90	2.33	4.50	2.00	10.00	0.032
SOFA Day 2	4.25	2.43	3.50	1.00	10.00	1.90	0.99	2.00	1.00	4.00	0.001

There was no significant difference between interventional & control groups regarding mechanical ventilation as 45% of the interventional group required MV compared to 60% of the control group (p = 0.49).

Table 4: Comparison Between Interventional & Control Groups Regarding MV

		interventional		control		P value
		Count	%	Count	%	
mechanical ventilation	Yes	18	45.0%	6	60.0%	0.490
	No	22	55.0%	4	40.0%	

There was no statistically significant difference between interventional & control groups regarding the haemoglobin and most of the electrolytes; however, the results showed statistically significant differences between both groups regarding the creatinine & GFR (P value 0.003 & 0.004 respectively). It showed also highly statistical significance between both groups regarding HCO3 and serum lactate (P value < 0.001).

Table 5: Comparison Between Interventional & Control Groups Regarding the Laboratory Tests

	interventional					control					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Hb	10.72	2.37	10.50	5.00	16.00	10.50	2.07	10.00	7.00	14.00	0.784
Na	141.27	5.10	140.50	132.00	154.00	139.80	2.39	139.50	136.00	144.00	0.451
K	4.01	0.46	3.95	3.20	5.20	3.81	0.37	3.85	3.20	4.30	0.356
Cl	101.40	3.65	101.00	96.00	110.00	100.80	2.66	100.50	97.00	105.00	0.821
GFR	41.97	15.68	39.00	17.00	80.00	71.80	32.22	73.00	36.00	126.00	0.004
creatinine	2.38	0.74	2.15	1.40	4.40	1.48	0.65	1.40	0.70	2.50	0.003
HCO3	17.03	2.81	18.00	10.00	21.00	22.30	5.60	22.50	10.00	33.00	< 0.001
Lactate	3.61	1.40	3.20	1.60	7.70	1.56	0.32	1.50	1.20	2.00	< 0.001
ScvO2	68.58	4.43	69.50	55.00	75.00	71.50	2.80	70.50	68.00	76.00	0.074

6. Echocardiography:

Trans-thoracic Echocardiography was done for all patients included in the study for the assessment of LV systolic function. There was no statistically significant difference between the interventional & control groups regarding the echocardiographic data.

Table 6: Comparison Between Interventional & Control Groups Regarding Echocardiographic Data

	interventional					control					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
LVEF %	55.57	5.20	55.00	50.00	70.00	53.00	3.50	52.50	50.00	60.00	0.181

In comparison between the interventional & control groups regarding the hemodynamic parameters (MAP, HR, CVP and UOP), the results showed a statistically highly significant difference between both groups (P value <0.001 , 0.001, <0.001&<0.001 respectively).

Table 7: Comparison Between Control & Interventional Groups Regarding Haemodynamic Parameters Pre-Fluid Challenge.

	interventional					control					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
MAP (pre)	54.70	4.61	55.00	45.00	60.00	72.50	7.17	70.00	65.00	85.00	< 0.001
HR (pre)	97.23	10.23	98.00	78.00	120.00	78.20	8.97	78.00	66.00	92.00	< 0.001
CVP (pre)	5.23	3.87	4.00	0.00	16.00	11.40	2.67	11.50	8.00	15.00	< 0.001
Pre UOP (cc/h)	16.75	11.52	20.00	0.00	40.00	73.00	17.67	70.00	50.00	100.00	< 0.001

a) Post-fluid challenge:

There were also statistical highly significant difference between both groups regarding the hemodynamic parameters (MAP, HR, CVP and UOP) post-fluid challenge (P value <0.001 , 0.001, <0.001&<0.001 respectively).

Table 8: Comparison Between Control & Interventional Groups Regarding Haemodynamic Parameters Post-Fluid Challenge.

	interventional					control					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	P value
MAP (post)	63.93	10.26	65.00	40.00	82.00	76.20	5.03	75.00	70.00	85.00	< 0.001
HR (post)	93.45	12.94	90.00	74.00	132.00	77.50	6.49	77.00	68.00	90.00	< 0.001
CVP (post)	7.00	3.50	7.00	2.00	15.00	12.10	2.08	12.00	9.00	15.00	< 0.001
Post UOP (cc/h)	19.88	14.65	20.00	0.00	45.00	75.00	14.91	72.50	55.00	100.00	< 0.001

Renal Duplex assessment parameters:

a) Pre-fluid challenge:

All patients were subjected to renal Duplex for assessment of the interlobar artery resistivity index (ILA RI) on both right and left sides. The assessment was performed in the upper, middle and lower poles of both kidneys and averaged.

In comparison between the interventional & control groups regarding the Renal Duplex assessment parameters (ILA RI) on both kidneys, the results showed a statistically highly significant difference between both groups (P value <0.001 & <0.001, respectively).

Table 9: Comparison Between Control & Interventional Groups Regarding Right & Left ILA Average RI Pre-Fluid Challenge.

	interventional					control					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Rt ILA average RI (pre)	0.78	0.06	0.78	0.65	0.88	0.60	0.05	0.59	0.55	0.69	< 0.001
Lt ILA average RI (pre)	0.78	0.06	0.79	0.64	0.89	0.61	0.05	0.59	0.55	0.68	< 0.001

b) Post-fluid challenge:

There was also statistical highly significant difference between both groups regarding the Renal Duplex assessment parameters (ILA RI) on both kidneys post-fluid challenge (P value <0.001 & <0.001, respectively).

Table 10: Comparison Between Control & Interventional Groups Regarding Right & Left ILA Average RI Post-Fluid Challenge.

	interventional					control					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	P value
Rt ILA average RI (post)	0.76	0.06	0.76	0.61	0.88	0.59	0.04	0.57	0.55	0.66	< 0.001
Lt ILA average RI (post)	0.76	0.06	0.76	0.60	0.88	0.59	0.04	0.58	0.55	0.66	< 0.001

Changes in Hemodynamic & Renal Duplex Assessment Parameters:
There was a statistically significant difference between the interventional & control groups regarding the change in MAP and the percentages of the change pre and post-fluid challenge (P value 0.034 and 0.02, respectively). However, there was no significant difference between both groups regarding the change in the other hemodynamic parameters and the change in ILA RI pre and post-fluid challenge.

Table 11: Comparison Between Control & Interventional Groups Regarding the Change in Hemodynamic Parameters

	interventional					control					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	P value
MAP change	9.23	8.22	10.00	-10.00	27.00	3.70	4.95	4.50	-5.00	11.00	0.034
HR change	-3.78	11.99	-1.00	-28.00	18.00	-0.70	3.77	-2.00	-6.00	6.00	0.641
CVP change	1.78	4.31	0.00	-4.00	11.00	0.70	1.06	0.50	-1.00	2.00	0.526
UOP (cc/h) change	3.12	10.96	0.00	-20.00	30.00	2.00	5.87	0.00	-10.00	10.00	0.858
Rt ILA average RI change	-0.02-	0.03	-0.04-	-0.05-	0.02	-0.02-	0.02	-0.02-	-0.03-	0.01	0.285
Lt ILA average RI change	-0.02-	0.03	-0.04-	-0.05-	0.02	-0.02-	0.02	-0.01-	-0.04-	0.01	0.526

Table 12: Comparison Between Control & Interventional Groups Regarding the Percentage of Change in Hemodynamic Parameters

	interventional					control					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	P value
MAP % change	16.69	15.18	20.00	-20.00-	49.09	5.58	7.24	6.07	-6.25-	16.92	0.020
HR % change	-3.50-	11.73	-1.11-	-24.11-	20.00	-0.51-	5.00	-2.31-	-6.67-	9.09	0.607
CVP % change	121.59	280.68	0.00	-30.00	1,100.00	7.91	11.20	4.55	-6.67	25.00	0.608
UOP (cc/h) % change	15.71	79.25	0.00	-100.00-	300.00	3.96	8.50	0.00	-10.00-	20.00	0.810
Rt ILA average RI % change	-2.44-	3.29	-4.55-	-6.49-	3.03	-2.54-	2.65	-3.93-	-5.17-	1.75	0.591
Lt ILA average RI % change	-2.53-	3.38	-4.55-	-6.67-	2.99	-2.50-	2.80	-2.36-	-6.45-	1.82	0.802

Outcome:
There was no statistical significant difference between the interventional & control groups regarding the days of mechanical ventilation (P value 0.729) and there was no statistical significant difference between both groups regarding the final outcome (P value 0.184); however, the results showed a statistically high significant difference between both groups regarding the ICU stay period (P value < 0.001).

Table 13: Comparison Between Interventional & Control Groups Regarding the Days of MV and ICU Stay.

	interventional					control					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Days of MV	4.63	5.74	0.00	0.00	18.00	2.50	2.68	2.00	0.00	7.00	0.729
ICU stay	11.87	4.26	11.00	6.00	24.00	6.80	2.82	6.50	3.00	12.00	< 0.001

Table 14: Comparison Between Interventional & Control Groups Regarding the Final Outcome.

		interventional		control		P value
		Count	%	Count	%	
Outcome	mortality	8	20.0%	0	0.0%	0.184
	survival	32	80.0%	10	100.0%	

There was no statistically significant difference between pre and post-fluid challenge in control group regarding the hemodynamic parameters.

The comparison between pre& post-fluid challenge regarding the ILA average RI in control group showed statistically significant difference on the right ILA (P value 0.023) with no significant difference on the left side.

Table 15: Comparison of Pre and Post-Fluid Challenge Regarding Hemodynamic & Duplex Assessment Parameters in Control Group.

control	Pre					post					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
MAP	72.50	7.17	70.00	65.00	85.00	76.20	5.03	75.00	70.00	85.00	0.061
HR	78.20	8.97	78.00	66.00	92.00	77.50	6.49	77.00	68.00	90.00	0.535
CVP	11.40	2.67	11.50	8.00	15.00	12.10	2.08	12.00	9.00	15.00	0.068
UOP (cc/h)	73.00	17.67	70.00	50.00	100.00	75.00	14.91	72.50	55.00	100.00	0.334
Rt ILA average RI	0.60	0.05	0.59	0.55	0.69	0.59	0.04	0.58	0.55	0.66	0.023
Lt ILA average RI	0.61	0.05	0.59	0.55	0.68	0.60	0.04	0.59	0.56	0.67	0.056

In comparison of pre and post-fluid challenge hemodynamic parameters in interventional group, there was a highly statistically significant difference regarding the mean arterial pressure MAP (P value < 0.001); however, there was no statistically significant difference regarding the HR and CVP. Furthermore, there was no statistically significant difference regarding the UOP. Regarding the pre and post-fluid challenge right and left averages ILA RI, there were statistically significant differences (P value 0.003).

Table 16: Comparison of Pre and Post-Fluid Challenge Regarding Hemodynamic & Duplex Assessment Parameters in Interventional Group.

interventional	Pre					post					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
MAP	54.70	4.61	55.00	45.00	60.00	63.93	10.26	65.00	40.00	82.00	<0.001
HR	97.23	10.23	98.00	78.00	120.00	93.45	12.94	90.00	74.00	132.00	0.063
CVP	5.23	3.87	4.00	0.00	16.00	7.00	3.50	7.00	2.00	15.00	0.076
UOP (cc/h)	16.75	11.52	20.00	0.00	40.00	19.88	14.65	20.00	0.00	45.00	0.064
Rt ILA average RI	0.78	0.06	0.78	0.65	0.88	0.76	0.06	0.76	0.61	0.88	0.003
Lt ILA average RI	0.78	0.06	0.79	0.64	0.89	0.76	0.06	0.76	0.60	0.88	0.003

Correlation in cases:

Although the comparison between pre and post-fluid challenge showed that there was a highly statistically significant difference regarding the mean arterial pressure MAP and statistically significant differences regarding the pre and post-fluid challenge right and left averages ILA RI, there was no statistically significant difference regarding the correlation between right & left ILA RI and MAP in the interventional group.

Table 17: Correlation Between ILA RI and MAP in Interventional Group

interventional		Rt ILA average RI change	Lt ILA average RI change
MAP change	**Correlation Coefficient**	-0.109-	-0.082-
	P value	0.503	0.616
	N	40	40

Discussion

This study showed that fluid challenge in critically ill patients with acute circulatory failure was associated with significantly decreased RI as assessed by RIAD. In addition, changes in RI were associated with improvement in MAP without significant correlation. However, these changes were not associated with UOP improvement. Moreover, there was no improvement in the heart rate nor the CVP in association to the improved MAP.

These data provide interesting insights into the mechanisms of the renal response to fluids. First, the decrease in RI suggests that renal perfusion increased in these patients. The association of changes in MAP with changes in RI suggests that the improvement in the systemic hemodynamic is associated with improvement in renal hemodynamic and this association can be detected by the assessment of the changes in RI using the renal Duplex. Second, the effects of fluids may depend on basal renal hemodynamic conditions.

The absence of significant improvement in the UOP despite the improvement in the ILA RI and consequently the renal perfusion was surprising and suggesting that the systemic hemodynamic improvement especially the MAP plays very important role in the renal hemodynamic improvement. Furthermore, co-morbidities, regional factors, duration of shock state or the severity of AKI may explain why the decreased RI was not associated with improved UOP.

Direct assessment of intrarenal vasoreactivity may, therefore, better reflect changes in MAP and improvement in the systemic hemodynamic than the prediction of UOP improvement which means that the intrarenal pathophysiological features are not correlated with the assessment of the intrarenal vasoreactivity changes.

Moussa, Scolletta, S., Fagnoul, D. et al. studied the effects of fluid administration on renal perfusion in critically ill patients and found that fluid loading in critically ill patients with acute circulatory failure was associated with significantly decreased RI as assessed by RIAD which is similar to our result; however, they found that changes in RI were correlated with changes in urine output and better predicted the increase in urine output after fluid administration than changes in MAP and PP which is different than our results. **[11]**

The poor ability of systemic hemodynamic variables to predict an increase in urine output following fluid challenge was studied in many studies. Moussa, Scolletta, S., Fagnoul, D. et al. found that changes in MAP and PP were not associated with renal response to fluids. This observation was consistent with previous investigations by Bourgoin et al. **[22]** and LeDoux et al. **[23],** which showed the lack of correlation between changes in MAP and response in urine output **[22,23]** or serum creatinine concentrations **[22]** using norepinephrine to increase MAP from 65 to 85 mmHg. However, Deruddre et al. **[13]** observed an increase in urine output when MAP was increased from 65 to 75 mmHg using norepinephrine infusion but not when it was increased further from 75 to 85 mmHg. A possible deleterious effect of norepinephrine was considered to explain the observations in the high MAP range. In the study of Moussa, Scolletta, S., Fagnoul, D. et al, the norepinephrine infusion rate was not correlated with changes in urine output or in RI. **[11]** The impact of MAP may be affected by individual factors and, although a minimal MAP is required, further increases in MAP are often not associated with improved urine output, creatinine level **[24]** or renal hemodynamic.

In apparent contrast to our observations, Schnell et al. **[14]** did not observe significant changes in RI in septic patients who responded to a fluid challenge. However, these authors defined the response to fluid challenge as an increase in descending aortic blood flow evaluated by oesophageal Doppler, which is thus a systemic response to fluid challenge, while we preferred to stop the fluid administration when the MAP reached a predetermined goal (generally MAP >65 mmHg, and/or MAP and/or stroke volume increase >10–15 % compared to baseline and/or central venous pressure increased >15 mmHg). Hence, their study and ours studied the correlation between the systemic and the renal response to fluid challenge. Our study further emphasizes that an improvement in systemic hemodynamic, mainly MAP, is associated with improved renal hemodynamic as evidenced by RI decrease and this was ineffective at predicting an increase in urine output.

Of note, the changes in renal Doppler variables, although statistically significant, were relatively limited. Thus, clinical applicability of the observed differences is questionable, especially if multiple and potentially less experienced investigators are performing the examinations **[25].**

Nevertheless, we showed that, in experienced hands, RI measurements had excellent reproducibility, precision and stability over time. To eliminate any impact of inter-observer variability, one single investigator performed all measurements and we suggest that the same sonographer should obtain the measurements. Furthermore, we used strict criteria to define failure in measurement, resulting in more patients being excluded than commonly described. Because of these precautions, the changes observed during fluid challenge were well above the spontaneous variability of measurements

The technique has some limitations. First, changes in RI may not reflect changes in renal perfusion gradient, as several other confounding factors may be present, including changes in intrarenal compliance, renal interstitial pressure, heart rate, and intra-abdominal pressure; therefore, we excluded all known cases with these medical problems. Second, pulsed Doppler techniques provide focal measurements that may not reflect heterogeneous changes in the vascular tone of the entire kidney. In addition, RI measured at the ILA level may not indicate afferent arteriolar or interlobular tone, and these vessels are known to be the most important site of renal myogenic tone regulation **[26].** Third, we included patients with AKI and with different stages of AKI. A study on septic patients showed that MAP was correlated with RI in patients with normal renal function but not in those with AKI **[27].** In other trial, included septic patients as well as patients with hypovolemic and cardiogenic shock, the response to fluids did not differ according to the presence of AKI.; this heterogeneity may limit the external validity of our results. Fourth, the volume and the type of fluid used may also be confounding factors. We used crystalloid as a choice for fluid challenge. Moussa, Scolletta, S., Fagnoul, D. et al. noted that the use of colloids in some patients may have affected the oncotic gradient between the two sides of the glomerular filtration barrier and, thereby, reduced the glomerular filtration rate, but the changes in oncotic pressure are likely to have been small. They also noted that the use of hydroxyethyl starch, even though limited, may also have biased their observations. **[11]** Finally, we did not measure urinary chemical content variations, because changes in these variables are slower than urine output, and may be influenced by other factors over time **[28,29]**

The association between acute kidney injury and renal RI suggests a pathophysiological reasoning, reflecting the renal structural alterations in the tubular, interstitial and vascular compartments and consequent increases in renal impedance values **[30,31].** On the other hand, the positive association between age and renal RI, observed in the model, potentially reflects vascular changes due to aging, with loss of large vessel compliance and increased aortic impedance **[32,33,34].** However, in our study there was no relation between the age and the RI.

The association between mean arterial blood pressure and renal RI was intriguing. It might reflect the role of systemic blood pressure in renal vascular resistance. Increased mean blood pressure may lead to a reduction in renal vascular resistance due to flow-induced renal vasodilation or due to increasing the number of perfused renal vessels, leading to lower renal RI values **[11,13].** Although the mechanism of this association has not been completely elucidated, it has been described since 1988 **[293]** and observed by others **[11,13].**

Another prospective observational study included 96 patients by Dewitte A, Coquin J, Meyssignac B, et al. was designed to evaluate if mean arterial pressure (MAP) is determinant of renal RI in septic, critically ill patients suffering or not from AKI and found a poor correlation between renal RI and MAP, age, or PaO2/FiO2 ratio in septic and critically ill patients without AKI compared to patients with AKI. These findings suggested that determinants of RI were multiple. Dewitte A, Coquin J, Meyssignac B, et al. stated that renal circulatory response to sepsis estimated by Doppler ultrasonography cannot reliably be predicted simply from changes in systemic hemodynamic. As many factors influence its value, the interest in a single RI measurement at ICU admission to determine optimal MAP remains uncertain**.[27]**

Rozemeijer S, Haitsma Mulier JLG, Röttgering JG, et al. studied, in a prospective observational cohort study, whether renal RI is elevated in shock and to identify determinants of renal RI and found that overall, high age, APACHE III score, lactate, vasopressor support, pulse pressure index (PPI), central venous pressure (CVP), fluid balance, and low preadmission estimated glomerular filtration rate, mean arterial pressure (MAP) and creatinine clearance were associated with high renal RI at univariable regression. At multivariable regression, vasopressor support, CVP, PPI and MAP and preadmission eGFR were independent determinants of renal RI. They concluded that patients with shock have a higher renal RI than patients without shock. Independent determinants of high renal RI were pressure indices of the systemic circulation, low membrane capacitance and preadmission renal dysfunction. **[35]**

The intrarenal resistive index (RI), which is a function of the blood velocity waveform of the artery in the kidney, is an index of the kidney's peripheral arterial resistance. It has been reported that the RI value is related to the aggravation of renal function disorder, and a renal insufficiency above 0.8 is related to an increase in peripheral arterial resistance. **[36]**

Abe M, Akaishi T, Miki T, et al. studied the influence of renal function and demographic data on intrarenal Doppler ultrasonography. Overall, 162 patients with CKD without apparent renal arterial stenosis were included in this study, and the pulsed-wave Doppler ultrasonography findings were evaluated in terms of the following parameters: peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistive index (RI) at the renal arterial trunk, hilum, segmental, and interlobar regions. Age showed a significant positive correlation with RI in all 4 regions. Additionally, the eGFR showed a negative correlation with RI. Both age and eGFR were found to be independently associated with aortic blood flow. On the intrarenal ultrasound, EDV and RI showed stronger correlations with eGFR than PSV, suggesting that the former indices would be better markers of renal function. In particular, the interlobar EDV was found to be the best index that reflects renal function. Although the RI is also a good marker of renal function, it is confounded by age; thus, its utility would be weaker than that of the EDV. Abe M, Akaishi T, Miki T, et al. concluded that intrarenal pulsed-wave Doppler ultrasonography is a useful tool to estimate and evaluate the renal function; the interlobar EDV may be the best index to estimate the effective perfusion and filtration of the kidneys. **[37]**

Wu J, Xu Z, Zhang H, et al investigated the value of RRI as an early predictor and discriminator of severe acute pancreatitis (SAP)-related acute kidney injury (AKI) and concluded that high RRI on ICU admission was a significant predictor for development of severe AKI during the first week, and RRI can help predict the tendency of AKI in SAP. **[38]**

The RRI calculated by Doppler ultrasonography has been reported to be correlated with renal structural changes and outcomes in patients with essential hypertension or renal disease. **[39]** In a prospective study, Iwakura Y, Ito S, Morimoto R, et al. examined the utility of this index to predict blood pressure (BP) outcome after adrenalectomy in patients with primary aldosteronism. BP, eGFR, and urinary albumin excretion significantly decreased after adrenalectomy. The resistive indices of all compartment arteries were significantly reduced 1 month after adrenalectomy and remained stable for 12 months. Patients whose interlobar RI was high at baseline had higher systolic BP after adrenalectomy than those whose RI was low. Logistic regression analysis demonstrated that the RI of the interlobar and hilum arteries could be an independent predictive marker for intractable hypertension (systolic BP ≥140 mm Hg, increased BP, taking ≥3 antihypertensive agents, or increased number of agents) even after adrenalectomy. Therefore, in patients with aldosteronoma, the RRI indicates partially reversible renal hemodynamic and renal structural damages that would influence postoperative BP outcome**. [39]**

In designing this protocol, the aim was not to detect the hemodynamic response to fluid challenge but rather to evaluate the renal perfusion using the Doppler-based assessment of the RI. Moreover, to correlate with the improvement in systemic hemodynamic and urine output in order to assess the usefulness of the rapid and non-invasive renal Doppler in critically ill patients with acute circulatory failure. In this context, even though it is difficult to answer unequivocally whether the renal Doppler is highly valuable or not, this question does not invalidate the conclusion that the response of hemodynamic to the fluid challenge can be predicted with the assessment of the renal perfusion using the renal Doppler to detect the renal resistive index.

This study was limited by several factors. The most important one was the limited number of study population, a total of 50 patients with only 40 patients were involved in the interventional group. Moreover, the inability to use wide range of hemodynamic assessment tools such as pulmonary artery catheter and the inability to include more hemodynamic parameters were additional limitation factors to assess, in depth, the correlation between renal RI and the hemodynamic improvement.

Conclusion

Fluid challenge resulted in reduced intrarenal vasoconstriction in hemodynamically impaired ICU patients. In hemodynamically impaired patients, changes in MAP after the fluid challenge was associated with improved renal hemodynamic and reduced RI. However, changes in renal interlobar artery RI in these patients cannot predict an increase in urine output. The use of renal Doppler could help to predict the response to fluid challenge in patients with circulatory failure; however, the use of renal Doppler will be of limited value if the sonographer doesn't have the required experience

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