Ultrasonic evaluation of systemic and renal perfusion in sepsis patients before and after fluid resuscitation

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Abstract. – OBJECTIVE: This study aimed to explore the significance of renal Doppler ultrasound in evaluating systemic and renal perfusion in sepsis patients before and after fluid resuscitation.

PATIENTS AND METHODS: Forty sepsis patients admitted to the Department of Intensive Medicine and intensive care unit (ICU) of the Fourth Hospital of Hebei Medical University from June 2014 to December 2014 were enrolled in this study, and 35 patients were included in the final analysis. These patients were divided into positive and negative fluid responsiveness groups. They were also divided into an acute kidney injury (AKI) group and a non-AKI group according to changes in creatinine and urine volume. The correlations of the changes in hemodynamics before and after fluid resuscitation in each group with the changes in renal resistance index (RRI) and renal blood flow (RBF) grades were evaluated.

RESULTS: Before and after fluid resuscitation, the heart rate (HR), blood creatinine (Cre), and lactate (Lac) levels of all patients, including the patients in the positive fluid responsiveness group decreased, and the stroke volume (SV) and central venous pressure (CVP) increased. Only HR decreased in the negative fluid responsiveness group. In the AKI group, HR, Cre, and Lac decreased, while in the non-AKI group, HR decreased, but CVP and SV increased. There were differences between HR, Lac, and change rate of Lac (Lac%) after fluid resuscitation for the positive and negative fluid responsiveness groups. There was no statistical difference between the RRI values of each group before and after fluid resuscitation. The RRI values of the AKI group were higher than those of the non-AKI group, while the AKI group's RBF grades were lower than those of the non-AKI group. The change rate of RRI (RRI%) was higher in the AKI group than in the non-AKI group. Except for the negative fluid responsiveness group, the RBF grade of each group increased.

CONCLUSIONS: The approach of RBF classification based on Doppler ultrasound can be used to evaluate the systemic and renal perfusion of patients with severe sepsis before and after fluid resuscitation, while the RRI value cannot be used for evaluation. However, the RRI value can be used as a dynamic index for the evaluation of renal perfusion in patients with AKI.

Key Words:
Sepsis, Doppler ultrasound, Volume responsiveness, AKI, RRI, RBF.

Introduction

Sepsis is an imbalance in the host's response to infection, and it can cause life-threatening organ dysfunction[1-3]. Sepsis remains the most common cause of emergency in intensive care units (ICUs) worldwide. In high-income countries, patients with sepsis can account for up to 10% of the total number of patients in ICU[4]. Acute kidney injury (AKI) is a common complication of critically ill patients[5], and sepsis is the most common cause of AKI in these patients, accounting for approximately 40%-50% of cases[6]. Most importantly, the progression of AKI in the context of sepsis increases the risk of in-hospital death six- to eightfold[6,7]. Therefore, effective monitoring of systemic and renal perfusion and early diagnosis of AKI is crucial.

The diagnosis of AKI is usually based on changes in a patient's serum creatinine (Cre)

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value and urine volume[8,9]. However, changes in Cre are not sensitive to AKI because these changes can be detected only when the glomerular filtration rate is reduced by approximately 50%[10,11]. Moreover, oliguria is not a specific index of AKI.

As a simple tool, ultrasound is playing an increasingly important role in the field of critical care with its rapid, non-invasive, and repeatable characteristics. Several studies have observed that the renal resistance index (RRI) based on Doppler ultrasound can be used to effectively predict the occurrence of AKI[12-14]. In addition, renal Doppler ultrasound may help to determine the best mean arterial pressure (MAP), which may be a related endpoint in the process of hemodynamic titration in patients with septic shock[15]. Schnell et al[16] has also revealed that the systemic hemodynamic changes caused by volume-loading tests cannot be converted into changes in RRI. However, the MAP, lactate (Lac) levels, age, and AKI type of severe patients may affect RRI[17].

In addition, increasing attention is being directed toward the classification of renal blood flow (RBF) based on Doppler ultrasound. The method of semi-quantitative evaluation of renal perfusion based on RBF grading has been considered for a long time[18,19]; however, there remains a lack of validation in clinical practice.

The purpose of this study is to investigate the influence of hemodynamic changes on RRI and RBF grading in patients with sepsis before and after fluid resuscitation and to evaluate the feasibility of Doppler ultrasound in assessing systemic and renal perfusion in patients with sepsis.

Patients and Methods

Patients

Forty patients who met Sepsis 3.0 criteria and were admitted to the Department of Intensive Medicine and intensive care unit (ICU) of the Fourth Hospital of Hebei Medical University from June 2014 to December 2014 were enrolled in this study. The inclusion criteria were as follows: (1) patients who were diagnosed with sepsis according to the diagnostic criteria of sepsis in the 2012 SSC guidelines; (2) patients who met Sepsis 3.0 diagnostic criteria; (3) patients who received ventilator-assisted respiratory therapy; (4) patients on whom the physician in charge decided to implement fluid resuscitation; and (5) patients aged over 18. The exclusion criteria were as follows: (1) patients who were under 18 years or pregnant; (2) patients who were in their AKI recovery period; (3) patients with any condition that may have affected the measurement of RRI, including suspected or confirmed obstructive renal failure, intra-abdominal hypertension, arrhythmia, and renal artery stenosis; (4) patients with suspected chronic renal dysfunction; (5) patients for whom all the relevant data for this study could not be obtained; and (6) patients who were mortally ill or had undergone cardiopulmonary resuscitation.

Research Process

All patients were connected to an electrocardiographic (ECG) monitor after they were admitted to ICU. They then had a deep venous catheter inserted through the internal jugular vein or subclavian vein and received tracheal intubation and ventilator-assisted breathing treatments. Their temperature (T), heart rate (HR), MAP, central venous pressure (CVP), and ventilator parameters were monitored.

Before fluid resuscitation, fluid challenge (FC) tests were conducted. Patients were injected with 200-500 ml of compound sodium chloride over 5-20 minutes, and the changes in the left ventricular outflow tract velocity time integral (VTI) before and after the test were determined. The method was as follows: a 2-Hz cardiac ultrasound probe was used to obtain a clear image of the five-chamber heart section, the left ventricular outflow tract was exposed, and the probe indicator was placed at the left ventricular outflow tract. VTI was measured by pulse-Doppler ultrasound. Data collection was performed repeatedly (at least three times), and the average value was calculated and regarded as VTI1. After the FC test, VTI2 was obtained by the same method, and finally, the VTI change (VTI%) was calculated: VTI% = (VTI2–VTI1) / VTI2%. In this study, VTI% of $\geq$12% obtained by ultrasound was regarded as the criterion to judge whether there was fluid responsiveness, and the results were blinded to the doctors in charge.

After confirming patients' fluid responsiveness, an ultrasound examination was performed before fluid resuscitation, i.e., at T0, measurements for RRI, RBF grade, stroke volume (SV), and cardiac output (CO) were obtained. The RRI and RBF grade values were obtained by measuring the right kidney using a 5-Hz abdominal ultrasound probe. First, RBF grades were evaluated by color Doppler ultrasound. Then, the interlobar artery or the arcuate artery was selected to obtain the renal artery blood flow waveform by pulse-Doppler ultrasound. The best Doppler spectrum was obtained after collecting at least three similar continuous intuitive waveforms. Most of the RRI and RBF was measured by the principal researcher certified by the Chinese Critical Ultrasound Study Group. Litter was measured by other doctors certified in the World Interactive Network Focused On Critical UltraSound (WINFOCUS). Between three and five RRI values were measured and averaged for each patient. The left ventricular outflow tract diameter (D) was measured on the long-axis section of the heart, and VTI was measured by pulse-Doppler ultrasound. At least three sets of measurements were obtained, and the average values were calculated. Then, SV was calculated, and CO was calculated based on HR. Patients were treated with sepsis cluster therapy, and ultrasound examination was performed repeatedly six hours after fluid resuscitation, i.e., at T1, RRI, RBF grade, SV, and CO values were obtained.

Experimental Grouping

Based on the FC test results, the patients were divided into two groups: a positive fluid responsiveness (FC [+]) group and a negative fluid responsiveness (FC [−]) group. In addition, according to Cre and urine volume, the patients were divided into an AKI (AKI [+]) group and a non-AKI (AKI [−]) group. The AKI groupings were determined according to the KDIGO standard[20]. The lowest Cre level in the previous three months was regarded as the base Cre value. If there was no previous data on Cre levels, the minimum Cre level during the patient's stay in ICU within the study period was used to assess potential renal function. When these Cre levels were not available, they were estimated using the MDRD formula. Transient AKI was defined as recovery of renal function within three days after patients were enrolled in the study. Renal recovery was defined as a return of urine volume to normal level or a >50% decrease in Cre, or a return to a normal Cre level without diuretics. Persistent AKI was defined as persistent oliguria or an increase of Cre for more than three days.

Index Selection

The indexes were as follows: patients' general information, including gender, age, body temperature, HR, CVP, and MAP; Cre; pulse pressure index; relevant ventilator support parameters such as positive end-expiratory pressure (PEEP), fraction of inspiration O_2 (FiO_2), and acute physiology and chronic health (APACHE) II score on the first day of ICU; sequential organ failure assessment (SOFA) score on the first day of ICU[18]; Ramsay score[21]; dosage of vasoactive drugs; RRI, RBF grade, Lac, and central venous blood oxygen saturation at T0 and T1; fluid balance before and after fluid resuscitation; and intra-abdominal pressure (IAP) of patients at T0 and T1.

Renal Blood Flow Grading

The grading criteria were as follows. (1) Grade 0: no blood flow signal was detected. (2) Grade 1: a small amount of blood flow signal was detected near the renal hilus. (3) Grade 2: obvious blood flow in the renal portal artery, a small amount of blood flow signal in the interlobar artery, and blood flow signal in most renal parenchyma were observed. (4) Grade 3: the RBF reached the arcuate artery, and blood flow signals could be seen in the whole kidney (Figure 1).

Calculation Formulas

The calculation formula for RRI was as follows: (systolic peak flow velocity − diastolic minimum flow velocity)/systolic peak flow velocity

SV (ml) = VTI × π(D/2)2
CO (L/min) = VTI × π(D/2)2 × HR
Pulse pressure index = (systolic blood pressure − diastolic blood pressure/systolic blood pressure)

Data Processing

The data were statistically analyzed using statistical software SPSS 19.0 (IBM, Armonk, NY, USA). Normally distributed measurement data were expressed as mean ± standard deviation (x ± SD). Non-normally distributed parameters and ranked data were expressed in terms of median values (or interquartile range). Count data were compared using a Chi-square test. Paired analysis of non-normally distributed data and ranked data was carried out using rank-sum testing. Inter-group and intra-group comparison of normally distributed measurement data were conducted using paired *t*-tests. Correlation analysis of RRI% and the corresponding SV% and Lac% values among all patients and patients in different subgroups were conducted, with $p < 0.05$ considered statistically significant.

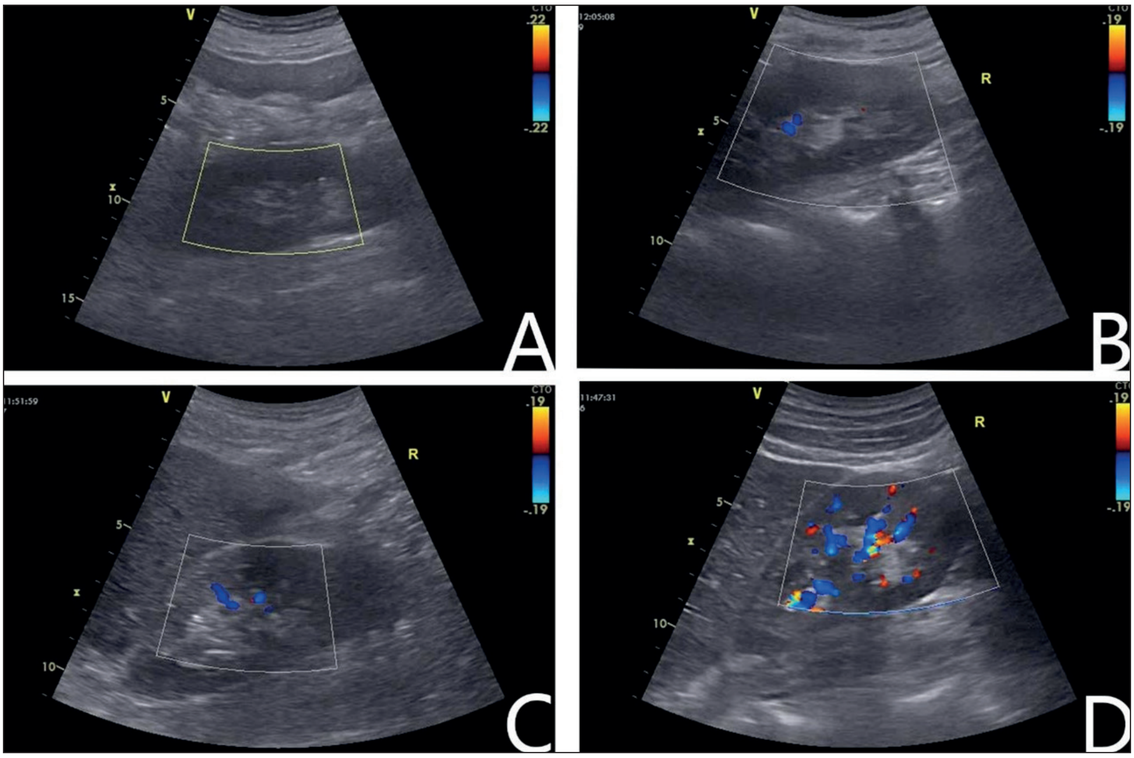

Figure 1. RBF classification. **A,** Grade 0. **B,** Grade 1. **C,** Grade 2. **D,** Grade 3.

Results

General Clinical Data

A total of 40 patients were included in this study. Two of these patients were excluded because they did not undergo an ultrasound examination in time. Two were excluded because of persistent arrhythmia at T1, and one was excluded due to a rejection of ultrasonography at T1. Therefore, 35 patients were included in the final analysis. All these patients were treated with intravenous analgesia and sedative drugs after a definite diagnosis of sepsis.

The age range of these patients was 61 ± 15 years, 26 (75.3%) were males, and nine (25.7%) were females. APACHE II scores were ranged from 17 ± 5, and SOFA scores ranged from 5.6 ± 3.8. The types of infection included pulmonary infection in 12 patients (34.3%), thoracic infection in six patients (17.1%), abdominal infection in 12 patients (34.3%), bloodstream infection in two patients (5.7%), biliary tract infection in two patients (5.7%), and urinary tract infection in one patient (2.9%).

In this study, the RRI values of patients with and without vasopressor drug use were similar (0.65 ± 0.08 and 0.66 ± 0.07, respectively, at T0; $p = 0.863$). For all patients, HR ($p < 0.001$), Cre ($p = 0.004$), and Lac ($p = 0.09$) decreased after resuscitation, while SV ($p = 0.006$) and CVP ($p = 0.013$) increased. Based on this, all patients demonstrated significant improvement of RBF grading ($p < 0.001$) (Table I). However, RRI did not change significantly ($p = 0.133$), and the impacts of intra-abdominal pressure ($p = 0.122$) and pulse pressure index ($p = 0.25$) were excluded.

Based on the FC tests, 20 patients (57.1%) were classed in the positive fluid responsiveness group, and the other 15 patients (42.9%) were classed in the negative fluid responsiveness group. Meanwhile, 17 patients (48.6%) were placed in the AKI group and 18 (51.4%) in the non-AKI group.

Grouping Based on Fluid Responsiveness

There were no significant differences in age ($p = 0.07$), Ramsay score ($p = 0.58$), norepinephrine dosage ($p = 0.98$), PEEP value ($p = 0.97$), or HR at T0 ($p = 0.11$) between the positive and negative fluid responsiveness groups. There was no significant difference in fluid balance between the two groups before and after fluid resuscita-

Table I. Grouping based on fluid responsiveness.

	All Patients N = 35	FC (+) N = 20 (57.1%)	FC (-) N = 15 (42.9%)	*p*
Male gender	26 (74%)	16 (80%)	10 (67%)	0.45
Age (y)	61 ± 15	65 ± 13	55 ± 17	0.07
Ramsay score	4 ± 1	3 ± 1	4 ± 1	0.58
SOFA score	5.6 ± 3.8	5.9 ± 3.7	5.3 ± 4.1	0.63
APACHE II	17 ± 5	18 ± 5	16 ± 5	0.35
SaO_2 (%)	95.23 ± 3.57	94.85 ± 3.72	95.73 ± 3.43	0.48
Temperature	37.5 ± 1.1	37.2 ± 1.0	37.9 ± 1.0	0.04
AKI	17 (48.6%)	11 (55%)	6 (40%)	0.30
NE dose	0.19 ± 0.38	0.19 ± 0.45	0.20 ± 0.26	0.99
PEEP (cm H_2O)	5.5 ± 1.4	5.5 ± 1.3	5.5 ± 1.5	0.97
FiO_2	0.55 ± 0.21	0.56 ± 0.21	0.53 ± 0.23	0.71
T0				
HR (beats/min)	124 ± 21	119 ± 19	131 ± 24	0.11
MAP (mmHg)	92 ± 22	94 ± 22	89 ± 23	0.52
Pulse pressure index	0.40 ± 0.09	0.40 ± 0.87	0.40 ± 0.11	0.93
IAP (mmHg)	9(8-11)	10(7-11)	9(8-11)	0.84
CVP (mmHg)	9 ± 4	8 ± 9	10 ± 4	0.15
CO (L/min)	8.35 ± 3.49	8.47 ± 3.66	8.19 ± 3.16	0.81
SV (ml)	68 ± 27	70 ± 26	64 ± 30	0.55
Cre (µmol/L)	125.27 ± 107.24	104.30 ± 49.74	153.24 ± 152.01	0.19
Lac (µmol/L)	2.3 (1.5-5.5)	2.2 (1.6-5.25)	3.0 (1.0-5.5)	0.75
RRI	0.66 ± 0.07	0.67 ± 0.06	0.64 ± 0.09	0.21
RBF (level)	2 (2-3)	2 (2-3)	2 (2-3)	0.96
T1				
HR (beats/min)	106 ± 20#	99 ± 21#	115 ± 15#	0.02
MAP (mmHg)	96 ± 15	96 ± 12	96 ± 18	0.90
Pulse pressure index	0.44 ± 0.08	0.43 ± 0.07	0.45 ± 0.09	0.60
IAP (mmHg)	8 (7-11)	8 (7-11)	8 (7-11)	0.81
CVP (mmHg)	10 ± 4#	10 ± 3#	11 ± 4	0.17
CO (L/min)	8.33 ± 3.02	8.76 ± 3.45	7.76 ± 2.32	0.34
SV (ml)	79 ± 25#	87 ± 25#	68 ± 20	0.02
Cre (µmol/L)	106.20 ± 92.49#	87.84 ± 46.12#	130.67 ± 129.30	0.18
Lac (µmol/L)	1.7 (1.1-2.7)#	1.7 (1.1-2.5)#	2.0 (1.1-3.5)	0.40
RRI	0.65 ± 0.06	0.66 ± 0.05	0.63 ± 0.07	0.26
RBF (level)	3 (3-3)#	3 (3-3)#	3 (3-3)	0.85
Liquid balance amount (ml)	+2675 ± 2173	+2627 ± 2093	+2739 ± 2349	0.88
RR I%	-1.2 ± 6.5	-1.8 ± 6.8	-0.4 ± 1.2	0.54
SV %	25.5 ± 38.4	32.7 ± 39.4	15.8 ± 36.3	0.20
Lac %	-18.0 ± 37.4	-28.3 ± 26.8	-4.5 ± 45.4	0.04

Note: Compared with that T0 before fluid resuscitation, #$p < 0.05$.

tion ($p = 0.88$). The reason for this may be that the fluid responsiveness results were blinded to the physician in charge. However, there was a significant difference in body temperature ($p = 0.04$) between the two groups. Furthermore, the difference in RRI value at T0 was not statistically significant ($p = 0.21$). In the positive fluid responsiveness group, HR ($p < 0.001$), Cre ($p = 0.033$), and Lac ($p = 0.04$) decreased, while SV ($p = 0.003$) and CVP ($p = 0.04$) increased, after liquid resuscitation. Based on this, RBF grade improved significantly, ($p = 0.003$) (Table I); however, there was no significant difference in RRI ($p = 0.570$) or in MAP ($p = 0.71$). In the negative fluid responsiveness group, HR also decreased significantly ($p = 0.019$). There was no significant difference in the change of Cre ($p = 0.055$), Lac ($p = 0.561$), SV ($p = 0.551$), or MAP ($p = 0.059$). There was no improvement in RBF grade ($p = 0.05$) (Table I) or in RRI ($p = 0.157$) before and after fluid resuscitation ($p = 0.05$). There was also no significant improvement in the tissue perfusion index (Figure 2).

There was no significant difference in the change rate of RRI between the two groups ($p = 0.54$). There was no correlation between SV% and RRI% before and after fluid resuscitation among all patients ($p = 0.079$), patients in the positive fluid responsiveness group (p = 0.171), or patients in the negative fluid responsiveness group (p = 0.185). Similarly, there was no correlation between Lac% and RRI% before and after fluid resuscitation among all patients (p = 0.536), patients in the positive fluid responsiveness group (p = 0.250), or patients in the negative fluid responsiveness group (p = 0.828) (Figure 3).

In the positive fluid responsiveness group, there were no significant differences between IAP (p = 0.158) and pulse pressure index (p = 0.11), which can affect RRI changes before and after fluid resuscitation. In the negative fluid responsiveness group, there were no significant differences in IAP (p = 0.561) or pulse pressure index (p = 0.144) values before and after resuscitation. In the positive fluid responsiveness group, SV% and Lac% were 32.7% ± 39.4% and −28.3% ± 26.8% before and after fluid resuscitation, respectively. The corresponding values in the negative fluid responsiveness group were 15.8% ± 36.3% and −4.5% ± 45.4%, respectively. The difference in Lac% between the two groups was statistically significant (p < 0.05). The results are shown in detail in Table I.

Grouping Based on Renal Function Status

There were no significant differences in general physiological characteristics between the AKI group and the non-AKI group before fluid resuscitation. In the AKI group, the differences in reduction of HR (p < 0.001), Cre (p = 0.016), and Lac (p = 0.048) before and after fluid resuscitation were statistically significant. Based on this, the RBF grade also improved significantly (p = 0.007) (Table II), and there was a significant difference in RRI (p = 0.004) (Figure 4). There was no correlation between the changes of SV% (p = 0.902) and Lac% (p = 0.880) before and after fluid resuscitation with RRI% in the AKI group (Figure 5). In the non-AKI group, there was a statistically significant difference only in HR (p < 0.003), SV (p < 0.05), and CVP (p < 0.05). There was a significant difference in RBF grade (p = 0.008) (Table II); however, there was no significant change in RRI (p = 0.449) (Figure 4). Our results also revealed that before fluid resuscitation, the RRI was higher in the AKI group than in the non-AKI group (p < 0.001), and the RBF grade was lower in the AKI group than in the non-AKI group (p = 0.003). Similar findings were observed after fluid resuscitation. There was no significant difference between the two groups for other vital characteristics before and after fluid resuscitation, including liquid balance (p = 0.29). Here, we must point out that for the definition of persistent AKI and transient AKI according to the experimental grouping, most patients in the AKI group (n = 15, 88%) recovered their renal function within three days (patients with transient AKI), while some had renal dysfunction (n = 2, 12%) (persistent AKI). The specific results are shown in Table II.

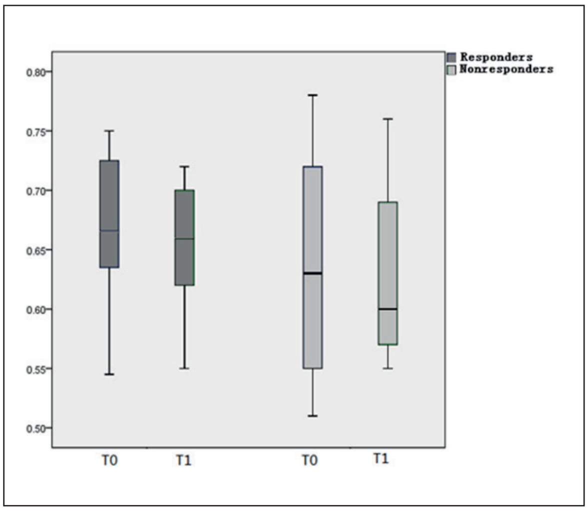

Figure 2. RRI during fluid resuscitation in FC(+) and FC(−).

Discussion

The findings of the present study reveal that for all patients, including patients in the positive fluid responsiveness group, fluid resuscitation significantly optimized systemic hemodynamics and improved tissue perfusion (including a decrease of HR, Cre, and Lac, and an increase of SV and CVP), but these changes did not present as a significant change of RRI. Factors that may affect RRI, such as age, oxygenation status, vasoactive drugs, changes in PEEP value, intra-abdominal pressure, pulse pressure index, and fluid balance before and after resuscitation, were excluded. However, the results obtained were still negative. RRI only changed significantly before and after fluid resuscitation for patients with higher basal Cre levels in the AKI group. However, the correlation analysis did not show a correlation between SV% and Lac%.

We have considered possible explanations for these findings. First, related studies have revealed

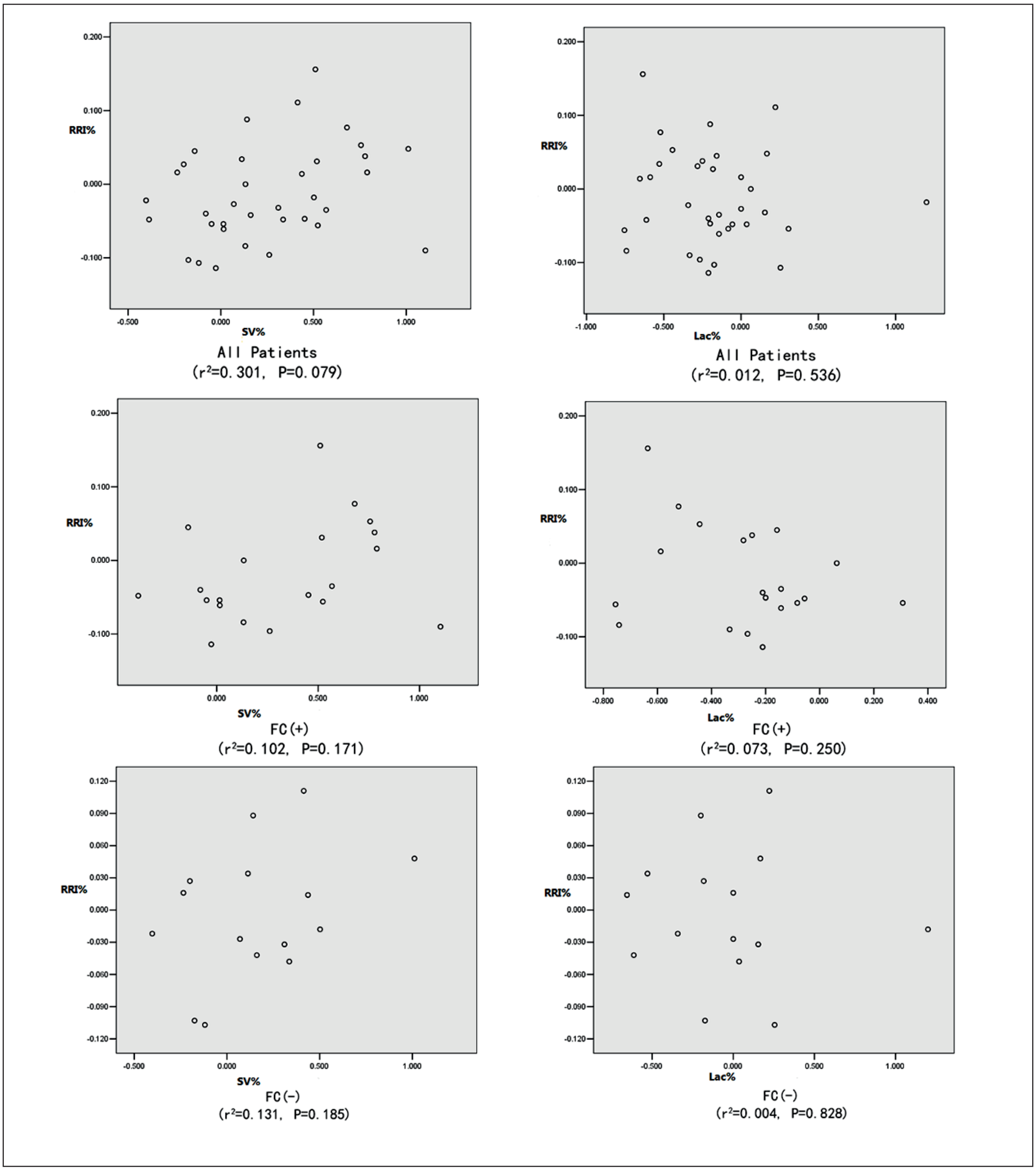

Figure 3. Relationship between RRI% and SV%, RRI% and Lac% in different responders.

that the most important factor in determining RRI value is vascular compliance rather than renal vascular resistance[22-24]. However, in the current study, except for using numerical values such as age and pulse pressure index for analysis, there was no effective way to verify whether there was a statistically significant difference between renal vascular compliance in each subgroup. Second, some previous studies have also revealed that an increase in renal interstitial pressure will lead to an increase in renal vascular resistance and, in turn, increase the RRI[25,26]. Changes in CVP can increase renal interstitial pressure, and in the current study, CVP in all patients changed before

Table II. Grouping based on fluid responsiveness.

	AKI (+) N = 17 (48.6%)	AKI (-) N = 18 (51.4%)	*p*
Male gender	13 (80%)	13 (67%)	0.54
Age (y)	64 ± 11	58 ± 18	0.27
Ramsay score	5 ± 1	4 ± 1	0.59
SOFA score	6.0 ± 4.6	5.3 ± 3.0	0.59
APACHE II	17 ± 5	17 ± 6	0.76
SaO_2 (%)	95.0 ± 3.0	95.5 ± 4.0	0.65
Temperature	37.6 ± 0.7	37.4 ± 1.3	0.55
NE dose	0.16 ± 0.34	0.22 ± 0.40	0.65
PEEP (cm H_2O)	5.4 ± 1.4	5.5 ± 1.4	0.85
FiO_2	0.51 ± 0.17	0.58 ± 0.25	0.36
FC (+)	11 (64.7%)	9 (50%)	0.30
T0			
HR (beats/min)	128 ± 19	120 ± 23	0.28
MAP (mmHg)	87 ± 20	96 ± 24	0.25
Pulse pressure index	0.42 ± 0.09	0.38 ± 0.10	0.18
IAP (mmHg)	9.0(8.5-10.0)	9.5(8-12)	0.49
CVP (mmHg)	9.4 ± 4.2	8.7 ± 4.3	0.64
CO (L/min)	9.37 ± 3.64	7.39 ± 3.13	0.10
SV (ml)	74 ± 28	61 ± 25	0.16
Cre (μmol/L)	147.73 ± 135.79	104.07 ± 68.32	0.23
Lac (μmol/L)	3.3 (1.8-6.7)	2.0 (1.0-4.8)	0.21
RRI	0.72 ± 0.03	0.60 ± 0.05	< 0.001
RBF (level)	2 (1-2)	3 (2-3)	0.003
T1			
HR (beats/min)	109 ± 16$^{\#}$	103 ± 24$^{\#}$	0.34
MAP (mmHg)	94 ± 11	98 ± 18	0.47
Pulse pressure index	0.45 ± 0.08	0.43 ± 0.07	0.27
IAP (mmHg)	8.0 (7.0-11.0)	8.0(7.0-10.0)	0.41
CVP (mmHg)	10.3 ± 4.4	10.2 ± 3.2$^{\#}$	0.96
CO (L/min)	8.94 ± 3.44	7.75 ± 2.52	0.25
SV (ml)	82 ± 28	76 ± 22$^{\#}$	0.49
Cre (μmol/L)	118.95 ± 114.79$^{\#}$	94.16 ± 65.98	0.44
Lac (μmol/L)	2.0 (1.3-2.9)$^{\#}$	1.6 (1.1-2.7)	0.18
RRI	0.69 ± 0.04$^{\#}$	0.60 ± 0.04	< 0.001
RBF (level)	3 (2-3)$^{\#}$	3 (3-3)$^{\#}$	0.028
Liquid balance amount (ml)	+3078 ± 2223	+2294 ± 2116	0.29
RRI %	-4.1 ± 5.1	1.5 ± 6.7	0.01
SV %	16.7 ± 38.4	33.8 ± 37.7	0.19
Lac %	-29.8 ± 27.8	-6.95 ± 42.4	0.07

Note: Compared with that T0 before fluid resuscitation, $^{\#}p < 0.05$.

and after resuscitation. However, given that the CVP increase was limited in this study and the patients did not experience capacity overload, the renal perfusion disorder caused by fluid overload and its significant impact on the experimental results were not considered. Finally, because RRI is affected by the lowest end-diastolic flow velocity of the renal artery, it is also affected by HR[27]. In the present study, there were significant differences in HR before and after resuscitation. However, the impact of HR on RRI remains unclear. Compared with stable HR, the impact of cardiac arrhythmia may be more significant, and in this study, patients with arrhythmias were excluded. Therefore, the impact of HR changes on this study remains to be investigated. In addition, there may be many other interference factors that limit the potential response of RRI to systemic hemodynamics in critically ill patients.

Sepsis is a serious medical condition characterized by a maladaptive host response to infection, leading to organ dysfunction, including AKI. The ensuing reduction in RBF has long been regarded as the main pathophysiological mechanism leading to AKI. In the present study, the improvement of HR, Cre, SV, CVP, and Lac in all patients, including the patients in the positive fluid responsiveness group, was characterized by significant

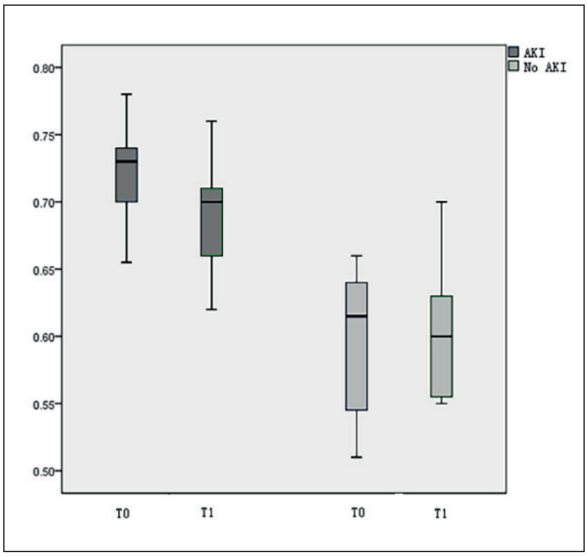

Figure 4. RRI during fluid resuscitation in AKI(+) and AKI(–).

improvement of the RBF grade. Furthermore, similar changes were observed in the AKI and non-AKI groups with improved tissue perfusion. However, no positive changes were observed in the patients in the negative fluid responsiveness group who did not exhibit adequate improvement of tissue perfusion. This indicates that RBF grading can be used to evaluate systemic and renal perfusion in sepsis patients before and after fluid resuscitation. Although the use of this method of semi-quantitative assessment of renal perfusion by Doppler ultrasound has been under consideration for a long time, it still requires further verification. However, the low RBF of critically ill patients may be an important factor that makes it difficult to promote standardization of renal ultrasound operations in clinical practice.

Similar to previous studies[14,28], our results showed higher RRI in the AKI group than in the non-AKI group at T0. Furthermore, there was no significant difference in Cre at T0 between the two groups. These findings confirm that RRI is helpful for the early identification of patients with AKI. In a previous study of sepsis patients, RRI at admission was generally significantly higher in patients who developed an AKI[12]. Although these results are of interest, both our findings and those of previous studies[14,28] in this regard have been obtained from samples of only a few selected patients; therefore, they need to be confirmed in a larger sample study.

The present study aimed to investigate whether, after improving renal perfusion in septic patients with AKI by fluid resuscitation, a downward trend of RRI could be achieved. As expected, RRI was significantly higher at T0 in the AKI group, and it decreased significantly after fluid resuscitation. A possible reason for these positive results is that the majority of patients with AKI in our sample had transient AKI (15 patients, 88.2%), whereas only a few patients progressed to persistent AKI. Therefore, for most patients, renal function improved significantly after active fluid therapy, leading to a decrease in RRI. A previous study revealed that the average RRI of patients with persistent AKI was significantly higher than that of patients with transient AKI[29]. Furthermore, in our non-AKI group, no decrease

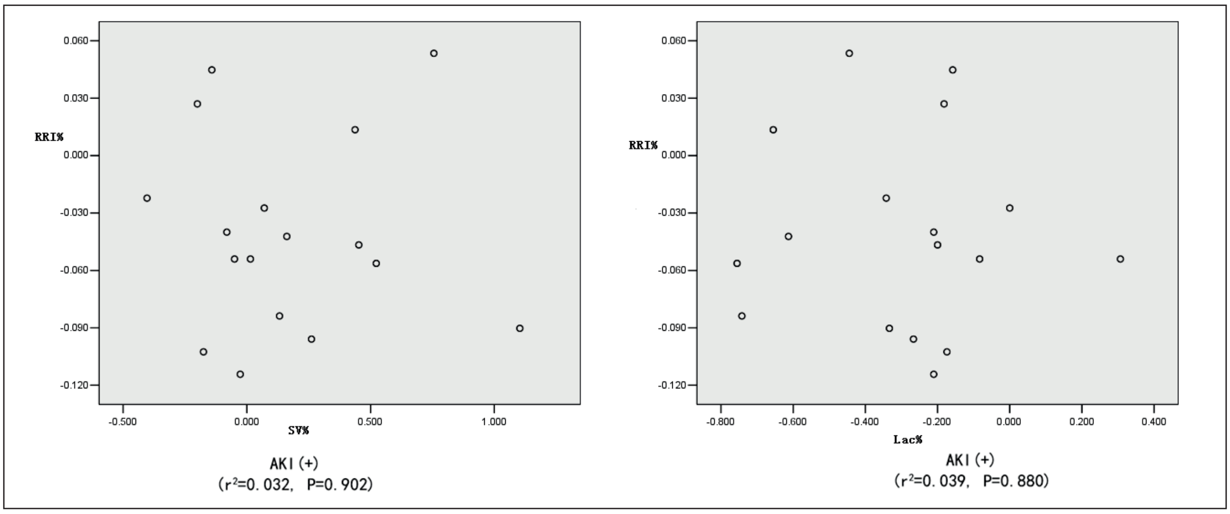

Figure 5. Relationship between RRI% and SV%, RRI% and Lac% in AKI(+).

in RRI was observed with fluid resuscitation. This may be related to the fact that there was no obvious change of renal function before and after the two time points. Therefore, the root cause of the RRI decrease in the AKI group seems to be that fluid resuscitation improved renal perfusion, thus, changed the state of renal function. However, the correlation analysis of RRI% with SV% and Lac% was not confirmed. Therefore, it needs to be investigated further in a larger sample study. However, at this stage, our findings suggest that RRI can be used as a dynamic index for the evaluation of renal perfusion in patients with AKI.

The present study has certain limitations. First, the repeatability of the data needs to be tested. Due to the limited resources, one principal researcher cannot complete the entire study, so it is inevitable that there is a deviation in data collection. In this study, most of the RRI and RBF was measured by the principal researcher certified in the Chinese Critical Ultrasound Study Group. Another doctor certified in WINFOCUS measured the litter. Second, it was difficult to ensure that the experimental data were blinded to the doctors in charge. In order to minimize deviations, the operators who performed the ultrasound examinations did not participate in the clinical treatment of the patients, and the most important assessment factors, including that of fluid responsiveness, were blinded to the physicians in charge. In addition, the sample size of this study limits the study. First, the smaller sample size may limit the major changes we expect in RRI. Second, the smaller sample size makes it difficult to carry out further analysis according to the AKIN classification. This needs to be further studied using larger samples. Finally, although we statistically analyzed relevant confounding factors and excluded changes of RRI caused by their differences, the assessment of these factors was not the primary objective of the present study; therefore, larger-scale studies are needed to adjust for these confounding factors.

Conclusions

In summary, RRI values based on renal color Doppler ultrasound cannot be used to evaluate the systemic and renal perfusion of patients with severe sepsis before and after fluid resuscitation. However, this approach can be helpful for identifying patients with early AKI. It can also be used as a dynamic index for the evaluation of renal perfusion in patients with AKI. Furthermore, RBF classification based on renal color Doppler ultrasound can be used to evaluate the systemic and renal perfusion of patients with severe sepsis before and after fluid resuscitation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics approval and consent to participate

I confirm that I have read the Editorial Policy pages. This study was conducted with approval from the Ethics Committee of The Fourth Hospital of Hebei Medical University (2019150). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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