

Original Article

Intrarenal Doppler Ultrasound Renal Venous Stasis Index Correlates With Acute Cardiorenal Syndrome in Patients With Acute Decompensated Heart Failure

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ABSTRACT

Background: Acute cardiorenal syndrome (ACRS) is associated with adverse outcomes in patients with acute decompensated heart failure (ADHF). Intrarenal venous blood flow can be assessed using Doppler ultrasound and has prognostic significance in ADHF. Although intrarenal Doppler (IRD) may be sensitive to renal congestion, an association between IRD parameters and ACRS has not been demonstrated in an ADHF population.

Methods: Hospitalized patients with ADHF ($n = 21$) or acute coronary syndrome (ACS; $n = 21$) were prospectively enrolled. Patients underwent echocardiography, including IRD, using a standard cardiac

RÉSUMÉ

Introduction : Le syndrome cardiorenal aigu (SCRA) est associé à des résultats défavorables chez les patients atteints d'une insuffisance cardiaque en décompensation aiguë (ICDA). Le flux veineux intrarénal qui peut être évalué à l'aide de l'échographie Doppler a une importance pronostique lors d'ICDA. Bien que la Doppler intrarénale (DIR) puisse être sensible à la congestion rénale, l'association entre les paramètres de la DIR et le SCRA n'a pas été démontrée au sein d'une population atteinte d'ICDA.

Méthodes : Nous avons inscrit de façon prospective les patients hospitalisés atteints d'une ICDA ($n = 1$) ou d'un syndrome coronarien aigu

Acute kidney injury (AKI) occurs frequently in patients with acute decompensated heart failure (ADHF) and is associated with adverse outcomes.¹ Acute cardiorenal syndrome (ACRS), also known as type I cardiorenal syndrome, is defined as AKI caused by ADHF, but the diagnostic criteria and treatment strategies for ACRS are not well defined.¹ AKI due to ADHF is often related to hemodynamic perturbations, namely reduced cardiac output and/or systemic venous congestion, but it also may be due to other factors such as urinary tract obstruction, acute tubular necrosis, and intravascular volume depletion. Consequently, evaluation of AKI in patients with ADHF can be challenging. Concerns about vascular underfilling may lead to unnecessary reduction in diuretic therapy among ADHF patients with AKI, leading to inadequate decongestion, an important risk factor for hospital readmission and mortality among such patients.²

The classic pathophysiology of ACRS implicates inadequate renal arterial perfusion. Recent data challenge this belief and instead suggest that renal venous congestion is a key hemodynamic factor associated with renal dysfunction in ADHF.^{3–5} Blood flow velocity in the renal interlobar vessels can be noninvasively assessed using Doppler ultrasound, and a perturbed venous flow pattern is strongly correlated with mortality and hospital readmission in ADHF patients.⁶ Furthermore, intrarenal Doppler (IRD) flow assessment may be a more sensitive marker of congestion than other clinical or ultrasound measures such as jugular venous distension, inferior vena cava distension, or hepatic vein flow.⁷ Given that renal congestion is a key pathophysiological mechanism underlying ACRS, IRD may represent a promising tool for its assessment. Despite this, IRD findings have not been correlated previously with AKI in ADHF patients. The identification of novel, noninvasive biomarkers for ACRS is urgently needed.¹

The primary objective of this study was to characterize IRD patterns in ADHF and evaluate associations between IRD-derived parameters and AKI attributable to ACRS among ADHF patients. A secondary objective was to compare IRD patterns of ADHF patients with those of patients hospitalized with acute coronary syndrome (ACS) without heart failure (HF). We hypothesized that IRD would reveal abnormal venous flow patterns in ADHF patients, compared

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Ethics Statement: All patients provided written informed consent, and the study was approved by the University of Calgary Research Ethics Board.

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ultrasound transducer. Intrarenal venous flow was quantified with the renal venous stasis index (RVS_I), defined as the duration of absent venous flow time divided by cardiac cycle duration. The primary outcome was acute kidney injury (AKI) as assessed using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Results: ADHF patients had a similar cardiac index (2.0 ± 0.6 vs 2.1 ± 0.4 L/min per m^2 , $P = 0.91$) but higher estimated central venous pressure (13.0 ± 3.2 vs 4.6 ± 2.4 mm Hg, $P < 0.001$) measured using echocardiography, compared with ACS patients. IRD was abnormal in all ADHF patients and normal in all ACS patients (RVS_I 0.62 ± 0.20 vs 0.0 ± 0.0 , $P < 0.001$). AKI stage II/III occurred in 10 of 21 ADHF patients (48%) vs 0 of 21 ACS patients ($P < 0.001$), with a mean rise in serum creatinine of 97.7 ± 79.3 vs 16.8 ± 10.9 $\mu\text{mol/L}$ ($P < 0.001$), respectively. RVS_I was correlated with AKI severity in ADHF patients ($r = 0.57$; $P = 0.004$).

Conclusions: RVS_I is associated with AKI among ADHF patients and may be a useful diagnostic biomarker for ACRS in this setting. Further studies are needed to validate this finding and evaluate the potential efficacy of IRD-guided decongestive therapy in this setting.

with ACS patients, and that IRD findings would correlate with AKI and its severity during hospitalization for ADHF.

Methods

Study design and patients

Patients were prospectively enrolled at a single centre (Libin Cardiovascular Institute, University of Calgary, Calgary, Alberta, Canada) between December 2018 and June 2020. Inclusion criteria were patients admitted to hospital with a diagnosis of either ADHF, or ACS without HF as a comparator group. ADHF was diagnosed clinically and all patients had elevated N-terminal pro-B-type natriuretic peptide (NTproBNP).⁸ These ADHF patients were recruited < 72 hours after hospital admission, exhibited clinical signs of congestion (orthopnea, rales, edema, jugular venous distension, interstitial edema on radiograph), and had ongoing treatment with intravenous loop diuretic therapy. The group of hospitalized ACS patients without symptoms or signs of ADHF were recruited from the cardiac intensive care unit. ACS patients represent a relevant comparator group for several reasons: (i) ACS patients have structural heart disease but no symptoms or signs of HF (American College of Cardiology/American Heart Association stage B); (ii) ACS patients have a similar prevalence of diabetes and hypertension that are known to affect renal hemodynamics and progression of renal disease; (iii) ACS patients often have reduced cardiac output due to post-infarction left ventricular (LV) systolic dysfunction and treatment with B-blockers. Patients were excluded if they were unable to comply with the IRD scan protocol, could not provide written informed consent, were on mechanical ventilation, or had end-stage renal disease, prior renal transplant, or solitary kidney. Six patients with ADHF and

(SCA; $n = 21$). Les patients ont subi une échocardiographie, à savoir la DIR, à l'aide d'un transducteur d'échographie cardiaque standard. Le flux veineux intrarénal a été quantifié à l'aide de l'indice de stase veineuse rénale (ISVR), défini par la durée de l'absence du débit veineux divisée par la durée du cycle cardiaque. Le critère d'évaluation principal était l'insuffisance rénale aiguë (IRA) selon les critères de KDIGO (Kidney Disease: Improving Global Outcomes).

Résultats : Les patients atteints d'ICDA avaient un indice cardiaque similaire ($2,0 \pm 0,6$ vs $2,1 \pm 0,4$ l/min par m^2 , $P = 0,91$), mais une estimation plus élevée de la pression veineuse centrale ($13,0 \pm 3,2$ vs $4,6 \pm 2,4$ mmHg, $P < 0,001$) selon les mesures obtenues à l'échocardiographie, comparativement aux patients atteints d'un SCA. La DIR était anormale chez les patients atteints d'une ICDA et normale chez les patients atteints d'un SCA (ISVR $0,62 \pm 0,20$ vs $0,0 \pm 0,0$, $P < 0,001$). L'IRA de stade II/III est apparue chez 10 des 21 patients atteints d'une ICDA (48 %) vs 0 des 21 patients atteints d'un SCA ($P < 0,001$), selon une augmentation moyenne respective des concentrations sériques de la créatinine de $97,7 \pm 79,3$ vs $16,8 \pm 10,9$ $\mu\text{mol/l}$ ($P < 0,001$). L'ISVR corrélait à la gravité de l'IRA chez les patients atteints d'une ICDA ($r = 0,57$; $P = 0,004$).

Conclusions : L'ISVR est associé à l'IRA chez les patients atteints d'une ICDA et peut être un biomarqueur diagnostique utile du SCRA dans ce contexte. Des études plus approfondies sont nécessaires pour valider ces conclusions et évaluer l'efficacité potentielle du traitement de décongestion guidé par DIR dans ce contexte.

none with ACS were excluded due to an inadequate IRD signal. Medical history, outpatient medications, hospital medications, clinical findings, and laboratory values were abstracted from clinical records. All patients provided written informed consent, and the study was approved by the University of Calgary Research Ethics Board.

IRD

Patients underwent IRD ultrasound assessment as previously described.^{6,7} A standard echocardiography system with a 4-5 MHz cardiac transducer was used (S5, iE33, Philips Medical Systems, Andover, MD). Renal Doppler imaging was performed with patients in the supine or left lateral decubitus position, and typically only the right kidney was assessed. Interlobar renal vessels were identified using colour Doppler with aliasing velocity set to 15 cm/s (Fig. 1). Blood flow was interrogated using pulsed-wave Doppler during held respiration, with care to ensure parallel alignment between the direction of interlobar vessel flow and the ultrasound beam sample volume. The pulsed-wave Doppler velocity scale was set to 15-30 cm/s, and wall filter to minimum. Arterial and venous flow signals were recorded simultaneously. The intrarenal arterial resistance index (RI) was calculated as the maximum arterial flow velocity minus the nadir flow velocity divided by the maximum flow velocity. The intrarenal venous impedance index (VII) was calculated as the maximum venous flow velocity minus the minimum flow velocity divided by the maximum. The venous flow pattern was also graded as continuous, biphasic, or monophasic.⁶ Normal patients exhibit continuous intrarenal venous flow, whereas discontinuous flow patterns have been associated with HF and adverse prognosis, with monophasic flow representing more-advanced congestion than a biphasic flow pattern.⁶ The

renal venous stasis index (RVSI), a newly described measurement based on IRD, was calculated by dividing the time with absent venous flow over the total cardiac cycle time (Fig. 1).⁹ For patients with irregular cardiac rhythm, measurements were performed using an index cardiac cycle, defined as the cardiac cycle that followed a preceding and prepreceding R-R interval of similar duration.¹⁰

Echocardiography

Comprehensive transthoracic echocardiography was performed according to published guidelines.^{11,12} LV ejection fraction (EF) was assessed by Simpson's biplane method. Estimated LV stroke volume was determined by calculating the LV outflow tract (LVOT) area and multiplying by the LVOT velocity time integral. Estimated cardiac output was calculated using the LVOT stroke volume multiplied by heart rate, and the cardiac index was calculated as the cardiac output indexed to body surface area. Left atrial volume index was assessed by Simpson's biplane method. Right ventricular function was assessed by tricuspid annular plane systolic excursion (TAPSE). Tricuspid regurgitation (TR) was graded according to current guideline-recommended criteria.¹³ Inferior vena cava ultrasound was performed to estimate central venous pressure (CVP). Estimated CVP was 3 mm Hg with inferior vena cava diameter < 2.1 cm with > 50% inspiratory collapse, 15 mm Hg with inferior vena cava > 2.1 cm and < 50% inspiratory collapse, or 8 mm Hg when findings were discordant.¹⁴ Estimated right ventricular systolic pressure was calculated using the TR maximum Doppler systolic velocity plus the estimated CVP. Transthoracic

echocardiography hemodynamic measurements were assessed on the same day as IRD.

Acute kidney injury assessment

AKI was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.¹⁵ The baseline creatinine level was defined as the nadir serum creatinine level within 1 year of admission during a period of clinical stability. Stage I AKI occurred when the creatinine level rose by 26.5 µmol/L within 48 hours or to 1.5-1.9 times the baseline level within 7 days. Stage II AKI was a creatinine level rise of 2-2.9 times the baseline level, and stage III AKI was a creatinine level rise ≥ 3 times the baseline level, to a value > 353.6 µmol/L, or the need for renal replacement therapy.¹⁵ All patients underwent assessment for alternate causes of AKI at the discretion of the treating physician. Patients with stage II or III AKI routinely had a comprehensive nephrology consultation, and renin-angiotensin-aldosterone system inhibitors and other renal toxic medications used at baseline were discontinued. No documented AKI episodes occurred that were clearly explained by a factor other than ACRS, such as urinary tract obstruction, sepsis, or adverse drug reaction.

Statistics

Statistical analysis was performed using SPSS, version 26. (IBM Corp., Armonk, NY). Continuous variables were compared using Student *t* tests, and categorical variables were assessed using Fisher's exact test. The correlation between IRD and echocardiographic parameters and creatinine level rise during AKI episodes was assessed using linear regression and Pearson's correlation coefficient. To test reproducibility, RVSI measurements were repeated in a blinded manner by the same observer (C.T.) after 3 months. Reproducibility was assessed as the mean percentage of error (absolute difference divided by the mean of the 2 observations). The mean percentage of error for intra-observer measurements was 9.2%. Adverse outcomes examined were 6-month all-cause mortality and hospital readmission.

Results

Patient characteristics

Characteristics of patients with ADHF and ACS are shown in Table 1. A total of 10 ADHF patients (48%) had underlying coronary artery disease, and 11 (52%) had nonischemic cardiomyopathy. Among ACS patients, 10 had ST-segment-elevation myocardial infarction, 10 had non-ST-segment-elevation myocardial infarction, and 1 had unstable angina. Patients with ADHF were older than those with ACS, and a minority of patients in each group were female. Body mass index and comorbidities were similar, but the prevalence of atrial fibrillation was significantly greater among ADHF patients (57% vs 0%, $P < 0.001$). Outpatient use of angiotensin-converting enzyme inhibitor or angiotensin receptor blockers was similar in ADHF and ACS patients, whereas a greater proportion of ADHF patients were treated with beta-blockers (71% vs 24%, $P = 0.005$) and loop diuretics (76% vs 0%, $P < 0.001$).

There were significant differences in hemodynamics, laboratory values, and transthoracic echocardiography findings

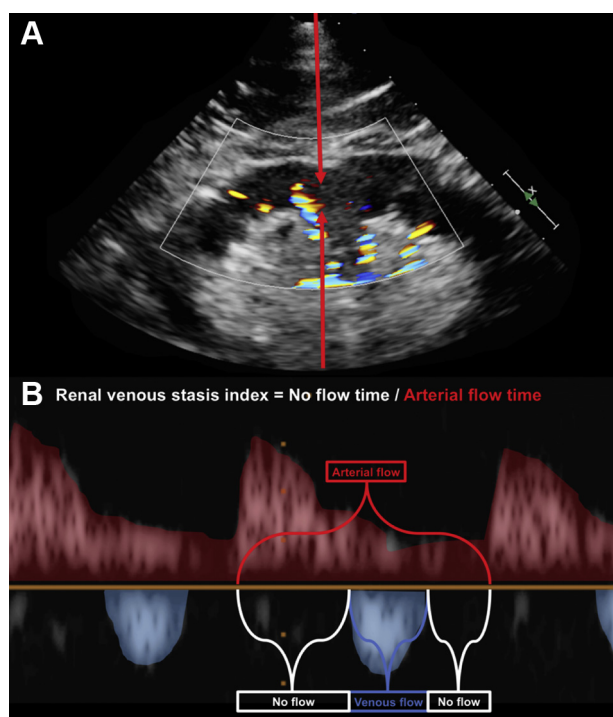


Figure 1. (A) Colour Doppler demonstrates parenchymal lobar vessels in the renal cortex. (B) Intrarenal Doppler signal demonstrates monophasic flow and illustrates calculation of the renal venous stasis index: venous no flow time divided by the arterial flow time.

Table 1. Comparison of ADHF and ACS patient clinical characteristics, intrarenal Doppler, echocardiography, and AKI findings

Characteristic	ADHF (n = 21)	ACS (n = 21)	P
Demographics			
Age, y	68.7 (14.6)	61.1 (8.9)	0.048
Body mass index, kg/m ²	27.8 (5.1)	27.3 (3.9)	0.691
Female	6 (29)	3 (14)	0.454
Past medical history			
Diabetes	8 (38)	5 (24)	0.505
Hypertension	9 (43)	15 (71)	0.118
COPD	5 (24)	0 (0)	0.048
Atrial fibrillation	12 (57)	0 (0)	< 0.001
Obstructive sleep apnea	3 (14)	3 (14)	1.0
Outpatient medications			
β-blocker	15 (71)	5 (24)	0.005
ACEI/ARB	12 (57)	10 (48)	0.758
MRA	6 (29)	1 (5)	0.093
Loop diuretic	16 (76)	0 (0)	< 0.001
Pressure, mm Hg			
Mean arterial	80.1 (11.5)	91.4 (12.9)	0.005
Systolic	111.8 (19.3)	124.3 (17.4)	0.033
Diastolic	64.2 (9.0)	75.0 (12.4)	0.003
Heart rate, beats/min	77.6 (16.3)	66.5 (8.0)	0.01
Laboratory values			
Baseline GFR, mL/min/1.73 m ²	68.8 (25.0)	87.8 (14.5)	0.005
Baseline creatinine, μmol/L	98.9 (42.3)	77.6 (19.4)	0.043
Hemoglobin, g/L	115.6 (26.4)	145.0 (12.7)	< 0.001
Serum sodium, μmol/L	133.7 (5.2)	137.2 (3.4)	0.017
Intrarenal Doppler			
Venous stasis index	0.62 (0.2)	0.00 (0)	< 0.001
Arterial resistance index	0.76 (0.08)	0.68 (0.07)	0.002
Venous impedance index	1.00	0.37	< 0.001
Echocardiography			
LVEF, %	38.0 (17.6)	51.8 (9.0)	0.003
LAVI, mL/m ²	50.2 (10.1)	27.4 (6.7)	< 0.001
VTI cardiac output, L/min	3.91 (1.55)	4.02 (0.53)	0.997
VTI cardiac index, L/min/m ²	1.99 (0.64)	2.05 (0.37)	0.906
Central venous pressure, mm Hg	13.00 (3.2)	4.58 (2.4)	< 0.001
TAPSE, cm	1.42 (0.46)	2.00 (0.35)	< 0.001
Tricuspid regurgitation ≥ 2+	17 (81)	0 (0)	< 0.001
AKI			
AKI episode during admission	17 (81)	2 (10)	< 0.001
AKI – baseline creatinine, μmol/L	97.7 (79.3)	16.8 (10.9)	< 0.001
AKI creatinine / baseline	2.00 (0.76)	1.22 (0.16)	< 0.001

Continuous values are reported as mean (SD); proportions are reported as n (%).

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; AKI, acute kidney injury; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; TAPSE, tricuspid annular plane systolic excursion; VTI, velocity time integral.

between ADHF and ACS patients. ADHF patients had significantly lower mean arterial blood pressure and higher heart rate. The baseline estimated glomerular filtration rate,

hemoglobin level, and serum sodium level were significantly lower in ADHF patients. Mean LVEF was 38.0% ± 17.6% in ADHF patients, and 51.8% ± 9.0% in ACS patients (*P* = 0.003). Reflecting elevated left-sided filling pressures, ADHF patients had a significantly larger left atrial volume index (50.2 ± 10.1 vs 27.4 ± 6.7 mL/m², *P* < 0.001). Right heart function was worse in the ADHF patients, evidenced by lower TAPSE, greater incidence of at least moderate TR, and higher estimated CVP. Despite these differences in cardiac function, the estimated cardiac index was similar between ADHF and ACS patients (2.0 ± 0.6 vs 2.1 ± 0.4 L/min per m², *P* = 0.91).

IRD characteristics

IRD assessment demonstrated a normal continuous venous flow pattern in all ACS patients but no ADHF patients. ADHF patients all exhibited abnormal biphasic (7 of 21) or monophasic (14 of 21) discontinuous venous flow patterns. The intrarenal arterial RI was modestly but significantly higher in ADHF compared to ACS patients (0.76 ± 0.08 vs 0.68 ± 0.07, *P* = 0.02). The VII was significantly higher in ADHF patients (1.00 ± 0 vs 0.37 ± 0.10, *P* < 0.001), as was the RVSI (0.62 ± 0.18 vs 0 ± 0, *P* < 0.001). The estimated renal perfusion pressure was lower in ADHF than in ACS patients (67.0 ± 11.7 vs 87.4 ± 13.3 mm Hg, *P* < 0.001).

AKI occurred in 17 of 21 ADHF patients (81%), and in 2 of 21 ACS patients (10%; *P* < 0.001). The mean rise in serum creatinine level was 97.7 ± 79.3 vs 16.8 ± 10.9 μmol/L (*P* < 0.001) in ADHF and ACS patients, respectively. Stage II/III AKI occurred in 10 ADHF patients (48%) and no ACS patients (*P* < 0.001).

AKI in ADHF patients

Findings among ADHF patients stratified by AKI stages 0/I or II/III are shown in Table 2. There was nonsignificantly lower RVSI in patients with AKI stage 0/I vs AKI stage II/III (0.56 ± 0.21 vs 0.70 ± 0.09, *P* = 0.06), but RVSI was significantly lower in ADHF patients without AKI than in patients with AKI stage I or higher (0.35 ± 0.13 vs 0.69 ± 0.11, *P* < 0.001). Patients with AKI stage II/III had a significantly lower serum sodium level than did patients with stage 0/I AKI (130.5 ± 4.9 vs 136.6 ± 3.8, *P* = 0.005). Age, baseline comorbidities, and medication use were similar across AKI stages (Table 1; Supplemental Table S1). There were no significant differences in mean arterial pressure, baseline estimated glomerular filtration rate, hemoglobin, N-terminal pro-B-type natriuretic peptide, LVEF, left atrial volume index, CVP, arterial RI, or prevalence of grade 3-4 tricuspid regurgitation between the AKI stage 0/I vs II/III groups. The estimated renal perfusion pressure in the AKI 0/I group was 70.6 ± 12.7 mm Hg, and in the AKI II/III group, it was 63.2 ± 9.7 mm Hg (*P* = 0.154).

Figure 2 shows the creatinine change from baseline during AKI episodes plotted vs RVSI, cardiac index, TAPSE, and mean arterial pressure. There was a positive and significant correlation between increasing RVSI and creatinine level rise (*r* = 0.57, *P* = 0.004), but not with the other parameters (cardiac index, *r* = 0.05, *P* = 0.41; TAPSE, *r* = 0.08, *P* =

Table 2. Comparison of clinical characteristics, echocardiography, intrarenal Doppler, AKI, and outcomes among ADHF patients, stratified by AKI stages 0-I vs II-III

AKI stage	0-I	II-III	<i>P</i>
Number of ADHF patients	11	10	
Age, y	70.3 (16.4)	66.9 (13.0)	0.610
Past medical history			
Diabetes	3 (27)	5 (50)	0.387
Hypertension	3 (27)	6 (60)	0.198
Atrial fibrillation	6 (55)	6 (60)	1.000
Outpatient medications			
β-blocker	8 (73)	7 (70)	1.000
ACEI/ARB	7 (64)	5 (50)	0.670
MRA	2 (18)	4 (40)	0.361
Loop diuretic	6 (55)	9 (90)	0.149
MAP, mm Hg	83.0 (12.0)	76.8 (10.4)	0.220
Heart rate	76.7 (13.2)	78.6 (19.9)	0.800
Laboratory values			
Baseline GFR, mL/min/1.73 m ²	74.6 (27.4)	62.3 (21.5)	0.269
Hemoglobin, g/L	119.9 (32.2)	110.8 (18.6)	0.444
Serum sodium, mmol/L	136.6 (3.8)	130.5 (4.9)	0.005
NtproBNP, pg/mL	6096.0 (4704.9)	12,033.0 (13411.9)	0.203
Echocardiography			
LVEF, %	36.3 (18.2)	40.0 (17.7)	0.641
LAVI, mL/m ²	51.6 (9.2)	48.5 (11.4)	0.512
TR grade 3 or 4	5 (45)	4 (40)	1.000
Estimated CVP, mm Hg	12.5 (3.5)	13.6 (3.0)	0.433
RVSP, mm Hg	59.5 (18.5)	52.0 (20.0)	0.382
TAPSE, cm	1.53 (0.40)	1.31 (0.51)	0.281
VTI CO, L/min	4.14 (1.87)	3.65 (1.14)	0.481
VTI CI, L/min/m ²	2.07 (0.69)	1.91 (0.59)	0.592
Intrarenal Doppler			
Venous stasis index	0.556 (0.209)	0.701 (0.092)	0.055
Arterial resistance index	0.738 (0.104)	0.777 (0.038)	0.257
Acute kidney injury			
AKI – baseline creatinine, μmol/L	41.9 (15.5)	159.1 (75.5)	0.001
AKI creatinine / baseline	1.52 (0.24)	2.54 (0.79)	0.003
Outcomes			
Weight loss, kg	5.03 (4.02)	5.53 (5.00)	0.803
Length of stay, d	10.1 (6.2)	25.9 (31.9)	0.155
Heart failure readmission	2 (18)	5 (50)	0.183
Death	1 (9)	3 (30)	0.311

Continuous values are reported as mean (SD); proportions are reported as n (%).

ACEI, angiotensin-converting enzyme inhibitor; ADHF, acute decompensated heart failure; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CO, cardiac output; CI, cardiac index; CVP, central venous pressure; GFR, glomerular filtration rate; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NtproBNP, N-terminal pro b-type natriuretic peptide; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VTI, velocity time integral.

0.367; mean arterial pressure, $r = 0.162$, $P = 0.24$). Representative IRD profiles are shown in Figure 3 from a patient with ACS, an ADHF patient without AKI, and an ADHF patient with AKI. The IRD from the ACS patient exhibits continuous venous flow, with an RVSI of 0. The ADHF patients (Fig. 3B-D) all show discontinuous venous flow patterns with progressively increasing durations of venous no-flow time per cardiac cycle, which correspond to an increasing

RVSI value. Changes in IRD venous flow in an ADHF patient after 48 hours of decongestive therapy are shown in Figure 4. During a median follow-up of 119 days, 7 ADHF patients had readmission with ADHF, and 4 died. These patients had a mean RVSI of 0.73, compared to 0.55 in the ADHF patients who did not experience these endpoints ($P = 0.018$).

Discussion

Doppler ultrasound enables noninvasive bedside evaluation of intrarenal hemodynamics but has not previously been evaluated in the setting of ACRS. The principal novel finding of this study is that abnormal IRD patterns at admission, as assessed using the RVSI, correlated with the incidence and severity of AKI in ADHF patients. IRD assessment demonstrated abnormal blood flow in the interlobar renal veins of ADHF patients, whereas patients with ACS exhibited normal, continuous flow. There was also a statistically significant but numerically small difference in the renal arterial RI between ACS and ADHF patients. Unlike venous flow patterns, however, renal arterial RI was not predictive of AKI among ADHF patients. The RVSI was normal in ACS patients and revealed various degrees of renal congestion among ADHF patients. Increasing RVSI was correlated with AKI among the ADHF patients, and RVSI was significantly lower among the ADHF patients without AKI. All ADHF patients had a VII of 1.0, which indicates the presence of a discontinuous venous flow pattern. The VII may be a useful measure to detect early abnormalities in patients with continuous venous flow, but in the ADHF population, it was not a differentiating factor for mild vs severe cases. ACS and ADHF patients had similar estimated cardiac index, but ADHF patients had lower mean arterial pressure and higher CVP, suggesting a reduced renal perfusion pressure. Additionally, ADHF patients had higher a higher prevalence of significant TR, which likely influenced intrarenal venous hemodynamics. Severe AKI episodes (stage II or III) occurred in nearly half of the ADHF patients but in none of the ACS patients.

Venous flow in the normal kidney is continuous with a VII < 0.53.⁶ IRD was first used to describe alterations of venous flow in the setting of ureteric obstruction.¹⁶ Acute ureteric obstruction causes increased interstitial pressure and a reduction of blood flow within the encapsulated kidney. In this setting, IRD reveals more phasic or sometimes discontinuous venous flow patterns. Mild intravenous volume loading results in similar changes in compensated HF patients.⁷ Increased VII or discontinuous flow becomes evident in such patients before alterations of more standard clinical or echocardiographic markers of congestion are apparent. Diuretic therapy can normalize venous flow pattern, but HF patients with more abnormal baseline venous flow may have a blunted diuretic response.⁷

Multiple studies have shown that elevated CVP is a key determinate of AKI in HF patients.^{1,3-5} The kidneys are the most highly perfused organs in the body and are exquisitely sensitive to hemodynamic perturbation.¹⁷ Arterial autoregulation stabilizes renal perfusion across a wide range of systemic blood pressures. In contrast, increased CVP results in a reduction of renal perfusion pressure without a direct

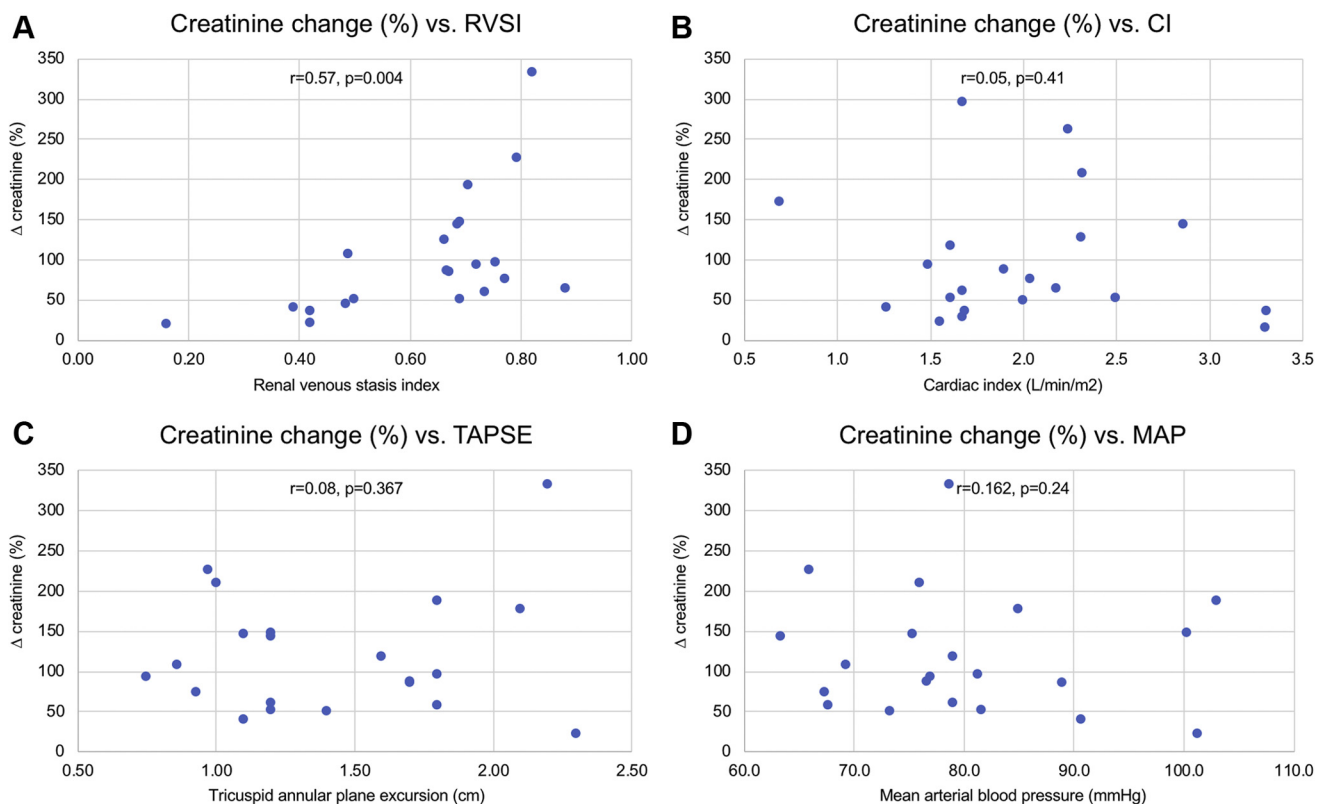


Figure 2. Shown is a comparison of percent change in serum creatinine level during acute kidney injury episode relative to baseline creatinine level vs (A) renal venous stasis index (RVSI); (B) cardiac index (CI; L/min per m²); (C) tricuspid annulus plane systolic excursion (TAPSE; cm); and (D) mean arterial blood pressure (MAP; mm Hg).

physiological compensatory mechanism. In patients with HF, increased CVP results in reductions of renal plasma flow and glomerular filtration rate, and pharmacologic interventions that reduce CVP improve renal plasma flow and glomerular filtration rate.¹⁸ Elevated CVP can also increase

intra-abdominal pressure, which is also transmitted to the kidneys.¹⁹ Glomerular filtration is driven by the pressure difference between the glomerular capillary and Bowman's space and is opposed by the plasma oncotic pressure.¹⁷ Elevated renal interstitial pressure caused by venous

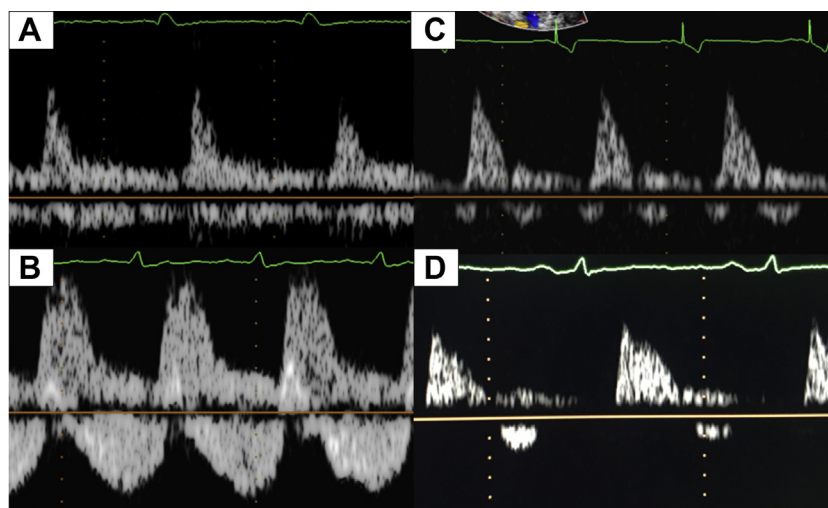


Figure 3. Examples of intrarenal Doppler venous flow patterns: Arterial flow is above the baseline, and venous flow is below the baseline. (A) Continuous venous flow (renal venous stasis index = 0) in an acute coronary syndrome patient without acute kidney injury (AKI). (B) Mildly discontinuous venous flow in a patient with acute decompensated heart failure (ADHF) without AKI. (C) Biphasic flow in a patient with ADHF with stage II AKI. (D) Monophasic flow (renal venous stasis index = 0.82) in an ADHF patient with stage III AKI.

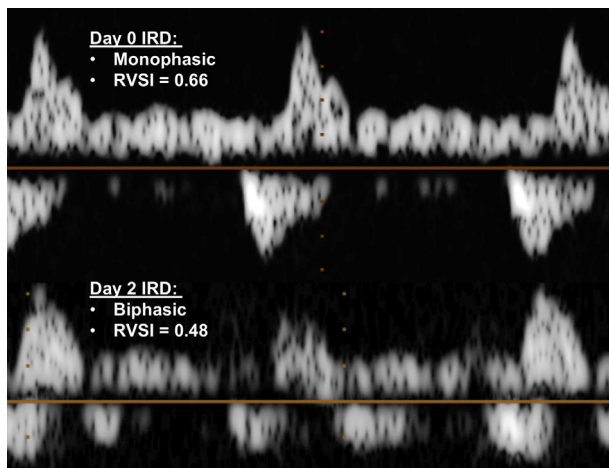


Figure 4. Shown is the intrarenal Doppler (IRD) flow in a patient with acute decompensated heart failure at the time of admission (day 0) and after 48 hours of decongestive therapy (day 2). Day 0 IRD shows discontinuous monophasic venous flow indicative of severe congestion. Day 2 IRD shows an improved IRD venous pattern with biphasic flow. The renal venous stasis index (RVS) decreased from 0.66 to 0.48. This patient had stage I acute kidney injury with a creatinine level rise by 85% over baseline. Weight loss of 4.7 kg was achieved with decongestive therapy, and renal function recovered.

congestion may reduce the pressure gradient necessary for glomerular filtration. Elevated interstitial pressure may also compress renal parenchymal blood vessels and increase resistance to flow. Discontinuous venous IRD patterns likely emerge when flow is transiently insufficient to overcome transmitted right atrial pressure changes during the cardiac cycle. Seo et al. showed that IRD flow patterns correlated with right atrial hemodynamics among 73 patients who underwent right heart catheterization.²⁰ Right ventricular dysfunction, atrial fibrillation, and TR were important determinates of the RA pressure waveforms as well as the IRD flow patterns. The IRD flow patterns were sensitive to changes in specific RA pressure waveforms rather than the mean right atrial pressure.²⁰ ACRS pathophysiology may be similar to cardiac derangements occurring in cardiac tamponade, in which congestion of the encapsulated kidneys abolishes pressure gradients necessary for normal organ function, resulting in reduced blood flow and glomerular filtration. An abnormal venous flow pattern detected through IRD may reflect decreased renal perfusion pressure, increased abdominal compartment pressure, and abnormal transmitted pressure waves from the right heart.²¹

Iida et al. first showed the strong prognostic value of IRD in 217 patients with HF.⁶ HF patients with a discontinuous venous flow pattern (biphasic or monophasic) had a significantly increased risk of death or HF hospitalization, compared with patients with continuous flow. The venous flow pattern was influenced by right atrial pressure and tricuspid TR but was independent of cardiac index. IRD was the strongest independent predictor of outcomes on multivariable assessment. An association between IRD venous flow pattern and AKI was not systematically assessed. Additionally, over half of the HF patients had a continuous venous flow

pattern, in contrast to our finding of discontinuous flow in all ADHF patients, perhaps owing to inclusion of HF patients after effective decongestion, as well as compensated outpatients, in the Iida study. Subsequent studies have also confirmed a strong prognostic value of IRD in outpatients with stable HF and patients with pulmonary hypertension.^{9,22} Recently, a small case series demonstrated the presence of discontinuous IRD venous flow patterns in 13 of 15 ADHF patients (87%) at the time of hospital admission. After decongestive treatment, the venous flow pattern normalized in approximately half of these patients at 48 hours.²³ Yamamoto et al. have also shown that the changes in IRD pattern at follow-up are prognostically important, and that a persistently discontinuous pattern is associated with deteriorating renal function.²⁴ Beaubien-Souligny demonstrated that abnormal IRD and portal venous Doppler flow patterns predicted AKI among post-cardiac surgery patients.²⁵ These authors also developed a multiparameter point-of-care venous excess ultrasound score (VEXUS) for grading systemic venous congestion severity.²⁶ Given that IRD may not be feasible in all patients, other systemic markers of venous congestion, such as inferior vena cava dimension and portal vein flow, may be useful. Increasing evidence supports the diagnostic and prognostic relevance of IRD in acute and chronic HF. IRD patterns are dynamic and are influenced by volume loading as well as decongestive therapy. Future larger and ideally multicentre prospective clinical trials are needed to assess the utility of IRD-guided therapy in patients with HF, compared with standard clinical assessment.

Limitations

Our study has several limitations to consider. This was a single-centre observational pilot study that included a small number of patients, and so the presence of bias cannot be excluded, and larger studies are needed to confirm the findings. This study used the need for intravenous diuretic therapy as a surrogate indicator of clinical congestion for ADHF patients, among other parameters. Use of intravenous diuretic was not standardized for the observational pilot study and was subject to variability based upon the clinical judgement of the treating clinician. Only ADHF patients with persistent congestion following early initiation of diuretic therapy were included, because the IRD pattern likely changes during therapy. Although there is no gold-standard test for ACRS, alternative causes of AKI were excluded by thorough clinical assessment, and our sample reflected ACRS as encountered during clinical practice. IRD can be technically challenging, likely due to the required short breath hold needed to optimize image quality, and the higher body mass index of some patients in our study. The use of a dedicated abdominal ultrasound imaging system may result in improved technical success. ACS patients were used as a comparator group in this analysis because they represent a population with vascular disease and reduced cardiac index but without increased central venous pressure. However, use of a different patient population comparator group, such as compensated HF patients, may have yielded different results, and further studies are needed to better define differences in IRD patterns in other patient populations. Patients did not

routinely undergo right heart catheterization, and hemodynamics were estimated using echocardiography at the time of IRD. Lastly, the influence of other potential determinants of IRD-based assessment of renal congestion in HF patients that warrant further study but are beyond the scope of this analysis include the presence of severe TR, breath hold and Valsalva maneuvers, and the use of renin-angiotensin-aldosterone system inhibitors.

Conclusions

We found that ADHF patients have abnormal, discontinuous intrarenal venous blood flow on Doppler ultrasound assessment. Quantified through the RVSI, renal congestion was correlated with ACRS and may represent a novel diagnostic biomarker for this clinically challenging condition. Future studies are needed to validate these findings in a larger population of HF patients, and to assess the value of IRD-guided therapy. Additionally, establishment of a correlation between IRD and other ACRS biomarkers, as well as further study into ACRS pathophysiology, are needed. IRD could be integrated into routine clinical ultrasound assessment as an initial step in the diagnostic algorithm for AKI when ACRS is suspected.

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Disclosures

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjcopen.ca/> and at <https://doi.org/10.1016/j.cjco.2021.07.010>.