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Right Ventricular Function, Peripheral Edema, and Acute Kidney Injury in Critical Illness



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Introduction: The cardiorenal syndrome generally focuses on left ventricular function, and the importance of the right ventricle as a determinant of renal function is described less frequently. In a cohort of critically ill patients with echocardiographic measurements obtained within 24 hours of admission to the intensive care unit, we examined the association of right ventricular function with acute kidney injury (AKI) and AKI-associated mortality. We also examined whether clinical measurement of volume overload modified the association between ventricular function and AKI in a subpopulation with documented admission physical examinations.

Methods: Among 1879 critically ill patients with echocardiographic ventricular measurements, 43% ($n = 807$) had ventricular dysfunction—21% ($n = 388$), 9% ($n = 167$), and 13% ($n = 252$) with isolated left ventricular dysfunction, isolated right ventricular dysfunction, and biventricular dysfunction, respectively. Overall, ventricular dysfunction was associated with a 43% higher adjusted risk of AKI (95% confidence interval [CI] 1.14–1.80; $P = 0.002$) compared with those with normal biventricular function, whereas isolated left ventricular dysfunction, isolated right ventricular dysfunction, and biventricular dysfunction were associated with a 1.34 (95% CI 1.00–1.77, $P = 0.05$), 1.35 (95% CI 0.90–2.10, $P = 0.14$) and 1.67 (95% CI 1.23–2.31, $P = 0.002$) higher adjusted risk. Although an episode of AKI was associated with an approximately 2-fold greater risk of hospital mortality in those with isolated left ventricular dysfunction and biventricular dysfunction, in those with isolated right ventricular dysfunction, AKI was associated with a 7.85-fold greater risk of death (95% CI 2.89–21.3, $P < 0.001$). Independent of ventricular function, peripheral edema was an important determinant of AKI.

Discussion: Like left ventricular function, right ventricular function is an important determinant of AKI and AKI-associated mortality. Volume overload, independently of ventricular function, is a risk factor for AKI. Whether establishment of euvolemia might mitigate AKI risk will require further study.

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KEYWORDS: acute kidney injury; congestion; edema; left ventricle; right ventricle; volume overload

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Renal dysfunction in the setting of heart failure, termed *the cardiorenal syndrome*, has traditionally been considered a hemodynamic consequence of left ventricular dysfunction, whereby decreasing cardiac output results in renal underperfusion and consequent decreased glomerular filtration.^{1–3} However, emerging data have highlighted the importance of the right ventricle. Morphologically distinct, with thinner walls less capable of pressure overload, the right ventricle similarly regulates sodium homeostasis, and right

ventricular dysfunction can lead to renin-angiotensin-aldosterone activation, sodium retention, and volume overload. Amidst the epidemiologic data linking cardiac and renal pathophysiology, the importance of the right ventricle has not been well described. Furthermore, the role of volume overload, both a consequence of heart failure and a potential mediator of renal dysfunction, as a potential confounder in the association between right ventricular function and acute kidney injury (AKI) has not been fully explored.⁴

Understanding the importance of the right ventricle is hindered by a lack of established criteria to quantify its function. Although a growing number of indexes have been explored, these have not gained widespread traction in clinical care. Nevertheless, standard clinical

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descriptors of right and left ventricular function are routinely documented in echocardiographic reports and are used to inform clinical decision-making. Using a large inception cohort of critically ill patients who underwent routine echocardiography within the first 24 hours of intensive care unit (ICU) admission, we examined the association of left, right, and biventricular dysfunction with the risk of AKI as defined by current guidelines, and we describe the risk of critical illness mortality associated with an episode of AKI according to ventricular function. In addition, in those patients with documented physical examinations, we explored the modifying effect of admission peripheral edema on the risk of AKI.

METHODS

Study Population

We used the Medical Information Mart in Intensive Care II database, a joint venture managed by the Laboratory for Computational Physiology at Massachusetts Institute of Technology and the Department of Medicine at the Beth Israel Deaconess Medical Center. The Medical Information Mart in Intensive Care II database contains data from 23,455 unique critical care admissions between 2001 and 2008 at Beth Israel Deaconess Medical Center, a 700-bed urban academic medical center with 77 adult ICU beds. The database contains high temporal resolution data from clinical systems, including laboratory results, provider electronic notes, and bedside monitor trends and waveforms. Use of the Medical Information Mart in Intensive Care II database has been approved by the institutional review boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. A total of 2451 patients had echocardiography performed within 24 hours of ICU admission. After 121 patients with end-stage renal disease were excluded, 1953 had recorded descriptions of both right and left ventricular function. Of these, 32 patients were missing measures of renal function, leaving a final sample size of 1879 individuals. In addition, we used a subsample of the larger cohort with documented admission physical examinations ($n = 1338$) to study the effect of peripheral edema on AKI risk.

Primary Exposures

Ventricular function was determined by categorization as a binary variable according to standard clinical echocardiographic descriptors ([Supplementary Table S1](#)). Ventricular function was primarily determined by description of regional systolic function, but for those whose systolic function findings were absent, ventricular function was determined by descriptive terms of the ventricular cavity and wall. In those for

whom descriptors of both regional systolic and cavity/wall function were available, misclassification was minimal. Five percent and 6% of individuals were classified as having normal left and right regional systolic function, respectively, but had abnormal descriptors of regional wall cavity size. We classified patients as having normal biventricular function, isolated left ventricular dysfunction (iLVD), isolated right ventricular function (iRVD), or biventricular dysfunction (BiVD). The relatively small number of patients with iRVD prevented further characterization according to severity of ventricular dysfunction. In a sensitivity analysis, we restricted our analysis to those patients who had descriptions of both left and right ventricular systolic function ($n = 1498$) and examined the association of isolated left ventricular systolic dysfunction, isolated right ventricular systolic dysfunction, and biventricular systolic dysfunction with AKI and AKI-associated mortality. The reason for obtaining the echocardiogram was not documented.

Primary Outcomes

The primary outcome was AKI during the first 7 days of ICU care, as defined by an increase of ≥ 0.3 mg/dl in serum creatinine within 48 hours of ICU admission, an increase of $\geq 50\%$ within 7 days of ICU admission, or acute dialysis, in keeping with the Kidney Disease Improving Global Outcomes guidelines.⁵ Stage I AKI was defined as an increase of 50% to 100%, Stage II as an increase of $> 100\%$ to 200% increase, and Stage III as an increase of $> 200\%$ or the immediate initiation of dialysis. Following best practice guidelines, we used the admission creatinine value to define “baseline.”⁶

Covariates

Demographic information included age, sex, and race (coded as white, African-American, Asian, Hispanic, other, or unknown). We used treatment with oral diabetes medication or insulin and International Classification of Diagnoses, 9th revision diagnostic coding to identify patients with diabetes. The presence of hypertension and liver disease was obtained from Elixhauser discharge coding comorbidities.^{7,8} ICU types included cardiac, surgical, cardiothoracic, and medical. International Classification of Diagnoses, 9th revision coding was used to identify admission for acute myocardial infarction and pulmonary embolus, and patients with sepsis were identified using previously defined methodology involving both Current Procedural Terminology and International Classification of Diagnoses, 9th revision codes.⁹ We included hemoglobin and white blood cell count, defined as the first available value 24 hours before or 6 hours after

ICU admission. The time (in hours) from ICU admission to echocardiogram testing was also included.

Statistical Analysis

We present baseline characteristics stratified by ventricular function. Differences between continuous and categorical variables were evaluated using *t* and chi-squared tests, respectively, and *P* values for differences across categories were provided. We used logistic regression to examine the association between admission ventricular function and the subsequent risk of AKI, adjusting for the covariates described previously and including separate indicator variables for iLVD, iRVD, and BiVD. Normal biventricular function was considered the referent category.

We then describe the rate and risk of hospital mortality in those with and without AKI, according to ventricular function at the time of admission. We explored separate multiplicative interaction terms between AKI and iRVD, iLVD, and BiVD in the adjusted analyses described previously and then provide the stratified adjusted risk, considering patients who did not have AKI within each ventricular category as reference.

In a sensitivity analysis, we explored alternative definitions of the primary exposures, restricting to those with right, left, and biventricular systolic dysfunction, rather than the broader term that allowed description of ventricular cavity function. We used the same statistical approach described previously to examine the adjusted association of isolated left ventricular systolic dysfunction, isolated right ventricular systolic dysfunction, and biventricular systolic dysfunction with AKI and

AKI-associated mortality. In addition, in those individuals with documented home medication lists ($n = 1680$), we included pre-morbid exposure to diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers as additional covariates in the adjusted analyses described previously.

To explore the independent effects of volume overload and ventricular function on AKI risk, we used Natural Language Processing of admission physical examinations to describe the presence of peripheral edema in those patients with documented admission physical examinations ($n = 1338$), as previously described.^{10,11} We describe the incidence of AKI in patients with and without peripheral edema on admission according to ventricular function. We then added a binary variable for peripheral edema to the adjusted analysis, including measures of ventricular function, explored multiplicative interaction terms between peripheral edema and ventricular dysfunction, and provided the adjusted risk of developing AKI for patients with peripheral edema, compared with those without peripheral edema, according to ventricular function.¹²

RESULTS

Baseline Characteristics

Of the 1879 critically ill patients who underwent echocardiography within 24 hours of ICU admission, 21% ($n = 388$), 9% ($n = 167$), and 13% ($n = 252$) had iLVD, iRVD, and BiVD, respectively (Table 1). As expected, pulmonary embolism was more common in patients with iRVD (16%) than in those with other

Table 1. Baseline characteristics according to ventricular function

Characteristics	Whole cohort ($n = 1879$)	Normal biventricular function ($n = 1072$)	Left ventricular dysfunction ($n = 388$)	Right ventricular dysfunction ($n = 167$)	Biventricular dysfunction ($n = 252$)	<i>P</i> value
Age (yr)	66.8 (16.5)	65.3 (16.9)	69.7 (15.4)	66.5 (16.8)	68.8 (16.0)	<0.001
Female (n, %)	877 (47.0)	545 (50.1)	171 (44.1)	74 (44.3)	87 (34.5)	<0.001
ICU type						
Cardiac	749 (39.9)	337 (31.4)	212 (54.6)	54 (32.3)	146 (58.0)	<0.001
Medical	737 (39.2)	465 (43.4)	109 (28.1)	88 (52.7)	75 (29.8)	
Surgical	253 (13.4)	169 (15.8)	48 (12.4)	18 (10.8)	18 (7.1)	
Cardiothoracic	140 (7.4)	101 (9.42)	19 (4.9)	7 (4.2)	13 (5.2)	
Admission diagnoses						
Sepsis	318 (16.9)	196 (18.2)	55 (14.2)	25 (15.0)	42 (16.7)	0.26
Myocardial infarction	332 (17.6)	121 (11.3)	138 (35.6)	19 (11.4)	54 (21.4)	<0.001
Pulmonary embolism	46 (2.4)	14 (1.3)	3 (0.8)	26 (15.6)	3 (1.2)	<0.001
Admission characteristics						
Diabetes (n, %)	639 (34.0)	345 (32.2)	150 (38.7)	48 (28.7)	96 (38.1)	<0.001
Hyperfension (n, %)	541 (28.7)	339 (31.6)	103 (26.6)	48 (28.7)	51 (20.2)	0.002
SOFA score (SD)	3.2 (2.3)	3.1 (2.3)	3.2 (2.2)	3.3 (2.4)	3.7 (2.4)	<0.001
Creatinine (mg/dl)	1.6 (1.6)	1.5 (1.6)	1.6 (1.5)	1.5 (1.1)	1.9 (2.1)	0.02
Hemoglobin (g/dl)	11.6 (2.2)	11.4 (2.2)	11.8 (2.1)	11.8 (2.1)	12.1 (2.3)	<0.001
Systolic blood pressure (mm Hg)	123.3 (27.7)	125.8 (29.1)	123.1 (26.0)	119.7 (25.8)	115.7 (23.6)	<0.001

Values are expressed as mean with SDs in parentheses for continuous variables unless otherwise indicated. ICU, intensive care unit; SOFA, sequential organ failure assessment.

forms of ventricular dysfunction, whereas a diagnosis of myocardial infarction was seen in almost 36% of patients with iLVD. Blood pressure was lowest and admission serum creatinine level was highest in those with BiVD.

Risk of AKI

The overall incidence of AKI was 26% ($n = 485$). Of the patients with ventricular dysfunction, 29% ($n = 235$) developed AKI, compared with 23% ($n = 250$) of patients with normal biventricular function. Of those with iLVD, iRVD, and BiVD, 29% ($n = 112$), 26% ($n = 44$), and 31% ($n = 79$) developed AKI, respectively (Figure 1). Ventricular dysfunction was associated with a significantly higher adjusted risk of AKI, particularly among patients with BiVD (Table 2). When present, AKI tended to be more severe with both iRVD and BiVD (Figure 1). Stage III AKI occurred in 9% ($n = 15$) and 10% ($n = 26$) of patients with iRVD and BiVD, compared with 5% ($n = 20$) and 7% ($n = 78$) of patients with iLVD and normal biventricular function, respectively.

In-Hospital Mortality

Of the patients with normal ventricular function, iLVD, iRVD, and BiVD, 23% ($n = 241$), 23% ($n = 84$), 27% ($n = 45$), and 33% ($n = 84$), respectively, died during hospitalization for treatment of critical illness. Although AKI was associated with higher hospital mortality rates across all cardiac categories (Figure 2), the association was strongest in those with iRVD (multiplicative interaction between iRVD and AKI, $P = 0.01$). Although an episode of AKI was associated with an approximately 2-fold greater risk of hospital mortality in patients with iLVD and BiVD, in those with iRVD, AKI was associated with a 7.85-fold greater risk of death (95% confidence interval [CI] 2.89–21.3, $P < 0.001$) (Table 3).

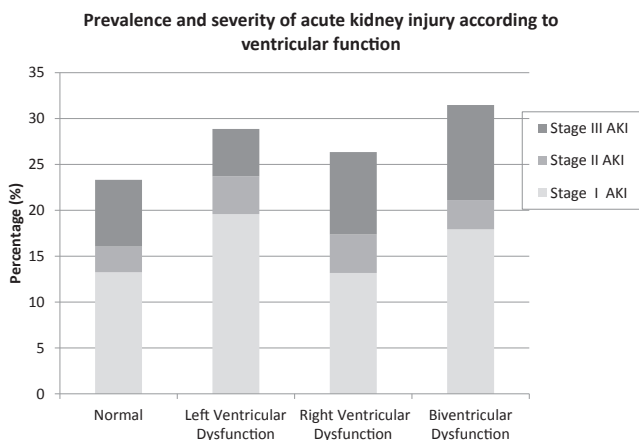


Figure 1. Incidence and severity of acute kidney injury (AKI) according to ventricular function.

Table 2. Ventricular function and risk of acute kidney injury

Normal biventricular function (reference category)	Ventricular dysfunction		
		1.43 (1.14–1.80) $P = 0.002$	
	Left ventricular dysfunction	Right ventricular dysfunction	Biventricular dysfunction
	1.34 (1.00–1.77) $P = 0.05$	1.35 (0.90–2.01) $P = 0.14$	1.67 (1.23–2.31) $P = 0.002$

Values are expressed as odds ratios with 95% confidence intervals in parentheses and P values provided below. Adjustments were made for age, gender, race, intensive care unit type, admission diagnosis (myocardial infarction, sepsis, pulmonary embolism, or other), history of diabetes, hypertension or liver disease, white blood cell count, hemoglobin, and hours from admission to echocardiogram. Reference category is patients with normal biventricular function.

AKI and AKI-associated Mortality in Those With Ventricular Systolic Dysfunction

Of 1498 patients with a description of systolic function available, 20% ($n = 295$), 7% ($n = 104$), and 15% ($n = 225$) had isolated left ventricular systolic dysfunction, isolated right ventricular systolic dysfunction, and biventricular systolic dysfunction, respectively. The adjusted risks of AKI and AKI mortality are provided in Table 4.

Home Medication Use

Of the patients with recorded home medication use, 38% ($n = 636$), 27% ($n = 458$), and 9% ($n = 146$) were prescribed diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, respectively. Inclusion of these 3 classes of medication did not meaningfully alter the findings described previously.

Peripheral Edema, Ventricular Function, and AKI

Among 1338 patients with documented admission physical examinations, peripheral edema was observed in 24% ($n = 188$), 23% ($n = 64$), 26% ($n = 29$), and 30% ($n = 51$) with normal biventricular function, iLVD, iRVD, and BiVD, respectively. Peripheral edema was associated with higher AKI incidence in patients with all forms of ventricular dysfunction (Figure 3). In a model that included adjustment for ventricular

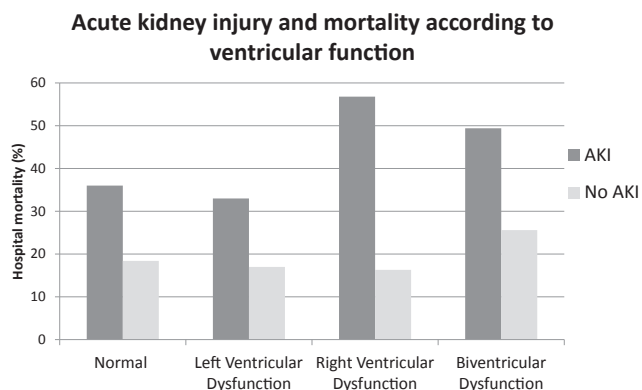


Figure 2. Hospital mortality associated with an acute kidney injury (AKI) episode according to ventricular function.

Table 3. Risk of hospital mortality associated with acute kidney injury according to ventricular function

Normal biventricular function (reference category)		Ventricular dysfunction		
		2.73 (1.90–3.92) <i>P</i> < 0.001		
	Left ventricular dysfunction	Right ventricular dysfunction	Biventricular dysfunction	
1.92 (1.37–2.71) <i>P</i> < 0.001	2.27 (1.27–4.04) <i>P</i> = 0.006	7.85 (2.89–21.3) <i>P</i> < 0.001	2.31 (1.24–4.30) <i>P</i> < 0.001	

Values are expressed as odds ratios with 95% confidence intervals in parentheses and *P* values provided below. Adjustments were made for age, gender, race, intensive care unit type, admission diagnosis (myocardial infarction, sepsis, pulmonary embolism, or other), history of diabetes, hypertension or liver disease, white blood cell count, hemoglobin, and hours from admission to echocardiogram. Reference category is patients without acute kidney injury within each ventricular category.

function, admission peripheral edema was associated with a 64% higher risk of AKI (95% CI 1.22–2.21, *P* < 0.001). Peripheral edema did not significantly modify the association between ventricular function and AKI risk (multiplicative interaction term *P* values all > 0.05), and even among those with normal biventricular function (*n* = 782), it was associated with a higher adjusted risk of AKI (odds ratio 1.52, 95% CI 1.07–2.45, *P* = 0.02). Among those with iLVD, iRVD, and BiVD, the adjusted odds ratio of peripheral edema with AKI was 0.85 (95% CI 0.42–1.74, *P* = 0.67), 5.90 (95% CI 1.45–24.1, *P* = 0.01), and 3.10 (95% CI 1.33–7.19, *P* = 0.008), respectively.

DISCUSSION

In critical illness, ventricular dysfunction is associated with higher risks of AKI and AKI-associated mortality. Although the risk of AKI is similar for patients with iLVD and iRVD, the severity of AKI and the associated risk of hospital mortality is highest among those with iRVD. Furthermore, peripheral edema, a manifestation of volume overload, is similarly associated with higher AKI risk, an effect that is independent of ventricular function.

Table 4. Ventricular systolic function and risk of acute kidney injury and mortality

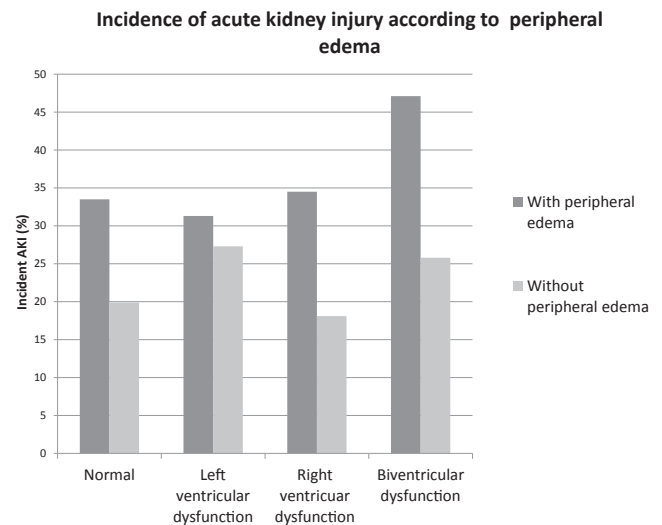
Outcome	Left ventricular systolic dysfunction	Right ventricular systolic dysfunction	Biventricular systolic dysfunction
AKI ^a	1.46 (1.05–2.03) <i>P</i> = 0.03	1.21 (0.71–2.00) <i>P</i> = 0.48	1.63 (1.13–2.32) <i>P</i> = 0.001
AKI-associated mortality ^b	1.96 (0.99–3.87) <i>P</i> = 0.05	9.02 (2.28–44.5) <i>P</i> = 0.001	2.16 (1.10–4.26) <i>P</i> = 0.02

Values are expressed as odds ratios with 95% confidence intervals in parentheses and *P* values provided below. Adjustments were made for age, gender, race, intensive care unit type, admission diagnosis (myocardial infarction, sepsis, pulmonary embolism, or other), history of diabetes, hypertension or liver disease, white blood cell count, hemoglobin, and hours from admission to echocardiogram.

AKI, acute kidney injury.

^aReference category is patients with normal biventricular function.

^bReference category is patients without acute kidney injury within each ventricular category.

**Figure 3.** Incidence of acute kidney injury (AKI) in patients with and without peripheral edema according to ventricular function.

Our data add to the physiologic complexity underlying the cardiorenal syndrome, suggesting right and left ventricular function might have different hemodynamic consequences. Whereas the left ventricle affects glomerular filtration through its changes in contractility, cardiac output, and consequent renal perfusion, the right ventricle seems to affect renal function through different mechanisms, including pulmonary hypertension, tricuspid regurgitation, and a potential inhibitory effect on left ventricular function.^{13–17} Perhaps most important is venous congestion, a manifestation of sodium avidity and fluid expansion, as supported by emerging evidence. Directly increasing renal venous pressure in animal models causes sodium retention, lowers urinary output, and decreases glomerular filtration^{18–21} and is widely thought to explain AKI in the setting of the abdominal compartment syndrome.^{22,23} In clinical studies, central venous pressure is directly associated with renal dysfunction, independently of ventricular function,^{13,24} and admission peripheral edema is associated with higher mortality¹⁰ and greater risk of AKI.¹¹ Such awareness of a primary role of renal venous congestion reshapes our understanding of renal function as not simply a reflection of arterial perfusion, but rather a balance between arterial supply and venous drainage.

In weighing the relative importance of right ventricular function *per se*, or the consequent volume overload that occurs as a result of ventricular dysfunction, our data suggest a primary role for both. In adjusted analysis, including measures of ventricular function, peripheral edema remained positively and independently associated with a higher AKI risk, even among patients with normal biventricular function.

Ultimately, our data raise important clinical questions. If peripheral edema, independently of cardiac function, is indeed associated with higher AKI risk, then more aggressive diuretic and fluid management strategies might improve outcomes. In multiple settings, volume overload—as manifested by positive fluid balance,¹² peripheral edema,¹⁰ pulmonary edema, bioimpedance, and central venous pressures—has been associated with worse outcomes, and although the mechanisms have not been clearly defined, worsening renal function might be one explanation. Currently, aggressive diuretic regimens to maintain euvolemia are generally accepted in the care of patients with left-sided heart failure. However, management of right ventricular dysfunction lacks consensus. The idea of a “preload”-dependent right ventricle requiring additional i.v. fluid primarily pertains to acute right ventricular dilatation or infarction²⁵ and has not been studied in patients with chronic right ventricular dysfunction. Fluid-restrictive strategies are now being clinically tested, and a small trial showing a benefit of fluid-restrictive strategies on renal function²⁶ is now being reproduced in a large, multicenter, randomized controlled study.²⁷

Our study has several important limitations. Although we attempted to tease out the independent roles of ventricular function and volume overload on AKI risk, given the complex physiologic interdependence of volume status and cardiac function, such distinctions are admittedly limited, particularly in epidemiologic data. Furthermore, clinical measurements of volume status are fraught with error. We chose not to use central venous pressure measurements, particularly because i.v. fluid administration is frequently a clinical response to AKI. Instead, we used physical examinations of volume status at the time of admission, which are unlikely to be affected by care provided in the study. Our observation that peripheral edema was paradoxically associated with a lower risk of AKI in patients with iLVD likely reflects a component of selection bias, since volume overload is an indication for ICU admission that is readily treatable and is in keeping with the complex epidemiology between left ventricular function and outcome.^{28–30} Because our study was limited to critically ill patients, the applicability of our findings to a broader context is uncertain. The indication for performing echocardiography was not known, potentially introducing selection bias into our analyses. We relied on standard clinical echocardiographic descriptions of ventricular function, which lack the sensitivity to reliably characterize diastolic dysfunction and likely introduce misclassification. Further studies with more accurately adjudicated exposures are needed. Finally,

we were unable to characterize baseline renal function before critical illness.

CONCLUSION

Both right and left ventricular function are important determinants of AKI and AKI outcomes. Well-designed studies to address whether stricter control of euvolemia might mitigate this risk are warranted.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIAL

Table S1. Standard clinical descriptors used to determine left and right ventricular function.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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