Peripheral Edema, Central Venous Pressure, and Risk of AKI in Critical Illness

Kenneth P. Chen, Susan Cavender,† Joon Lee,†‡ Mengling Feng,†§ Roger G. Mark,† Leo Anthony Celi,*† Kenneth J. Mukamal,* and John Danziger**

Abstract

Background and objectives Although venous congestion has been linked to renal dysfunction in heart failure, its significance in a broader context has not been investigated.

Design, setting, participants, & measurements Using an inception cohort of 12,778 critically ill adult patients admitted to an urban tertiary medical center between 2001 and 2008, we examined whether the presence of peripheral edema on admission physical examination was associated with an increased risk of AKI within the first 7 days of critical illness. In addition, in those with admission central venous pressure (CVP) measurements, we examined the association of CVPs with subsequent AKI. AKI was defined using the Kidney Disease Improving Global Outcomes criteria.

Results Of the 18% (n=2338) of patients with peripheral edema on admission, 27% (n=631) developed AKI, compared with 16% (n=1713) of those without peripheral edema. In a model that included adjustment for comorbidities, severity of illness, and the presence of pulmonary edema, peripheral edema was associated with a 30% higher risk of AKI (95% confidence interval [95% CI], 1.15 to 1.46; $P<0.001$), whereas pulmonary edema was not significantly related to risk. Peripheral edema was also associated with a 13% higher adjusted risk of a higher AKI stage (95% CI, 1.07 to 1.20; $P<0.001$). Furthermore, levels of trace, 1+, 2+, and 3+ edema were associated with 34% (95% CI, 1.10 to 1.65), 17% (95% CI, 0.96 to 1.14), 47% (95% CI, 1.18 to 1.83), and 57% (95% CI, 1.07 to 2.31) higher adjusted risk of AKI, respectively, compared with edema-free patients. In the 4761 patients with admission CVP measurements, each 1 cm H_2O higher CVP was associated with a 2% higher adjusted risk of AKI (95% CI, 1.00 to 1.03; P=0.02).

Conclusions Venous congestion, as manifested as either peripheral edema or increased CVP, is directly associated with AKI in critically ill patients. Whether treatment of venous congestion with diuretics can modify this risk will require further study.

Clin J Am Soc Nephrol 11: 602–608, 2016. doi: 10.2215/CJN.08080715

*Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts; †Division of Health Sciences and Technology, Harvard-Massachusetts Institute of Technology, Cambridge, Massachusetts; ‡School of Public Health and Health Systems, University of Waterloo, Waterloo, Ontario, Canada; and §Data Analytics Department, Institute for Infocomm Research, Agency for Science, Technology And Research, Singapore

Correspondence: Dr. John Danziger, 185 Pilgrim Road, Farr 8, Boston, MA 02215. Email: jdanzige@bidmc.harvard.edu

Introduction

The role of venous congestion as a determinant of renal function was first described almost 85 years ago. In early physiology experiments on dogs, F. R. Winton showed that increasing renal venous pressure decreased both urine and renal arterial flow (1), highlighting the importance of the "trans-renal pressure gradient," a balance between mean arterial and venous pressures (2). More recent clinical data have focused on venous congestion in heart failure (3), where central venous pressures (CVP), but not cardiac output or pulmonary capillary wedge pressures, are associated with renal dysfunction (4). Consequently, the current concept of the cardiorenal syndrome, typically used to describe renal injury in the setting of poor arterial flow due to left ventricular dysfunction, is being modified to include venous congestion (5–9) and right ventricular function (10). Whether venous congestion is similarly associated with poor renal outcomes in other populations is not known.

Venous congestion manifests as peripheral edema on physical examination and by increased CVP. Although peripheral edema can also be seen in the setting of mechanical obstruction, it usually reflects an outward hydrostatic pressure that exceeds the inward oncotic force, resulting in extravasation of intravascular fluid into the interstitial compartments. The clinical importance of peripheral edema is not well described, and is typically considered cosmetic and non-life threatening (11). Given the emerging importance of venous congestion in renal function, we hypothesized that peripheral edema and increased CVP would be associated with a higher risk of AKI.

Using a large cohort of critically ill patients admitted to a tertiary medical center, we examined whether the presence and severity of peripheral edema on the hospital admission physical examination was associated with AKI during the first 7 days of critical illness. We also examined whether CVP measurements taken on intensive care unit (ICU) admission were associated with AKI.

Materials and Methods

Study Population

We used the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC-II) database, a joint venture managed by the Laboratory for Computational Physiology at Massachusetts Institute of Technology (MIT) and the Department of Medicine at the Beth Israel Deaconess Medical Center (BIDMC). MIMIC-II contains data from 23,455 unique critical care admissions between 2001 and 2008 at BIDMC, a 700-bed urban academic medical center with 77 adult ICU beds. The database contains high temporal resolution data from clinical systems, including lab results, electronic documentation, and bedside monitor trends and waveforms. Use of the MIMIC-II database has been approved by the institutional review boards of BIDMC and MIT. A total of 13,986 patients had complete admission history and physical examination as part of the hospital discharge summary. We excluded 270 prevalent ESRD patients. Another 930 were missing documentation of admission laboratory studies, leaving 12,778 unique individuals for primary analysis.

Primary Exposures

In order to describe the effect of venous congestion independently of pulmonary congestion, we developed a Natural Language Processing (NLP) code based on standard clinical descriptors to identify both peripheral edema and pulmonary edema as documented in the admission physical examination (Supplemental Table 1). The developed code was "trained" by manual review of eight sequential sets of randomly selected discharge summaries, ranging from 50 to 100 in number. Once the code consistently achieved an accuracy rate of >90% (Supplemental Figure 1), all reviewed discharge summaries were combined, and the code was tested on 10,000 random resamples (with replacement) of 100 discharge summaries. The histogram of bootstrap accuracy is provided (Supplemental Figure 2). We also examined severity of peripheral edema, categorizing patients as having trace, 1+, 2+, and 3+ peripheral edema. We used CVP measurements obtained within 6 hours of ICU admission as a secondary primary exposure.

Primary Outcomes

The primary outcome was AKI during the first 7 days of ICU care, as defined by either a ≥0.3 mg/dl increase within 48 hours of admission or a ≥50% increase within 7 days of admission, or acute dialysis, in keeping with the Kidney Disease Improving Global Outcomes (KDOQI) guidelines (12). We also explored the association of peripheral edema with AKI severity, using defined measures of creatinine increase within 7 days of ICU admission. Stage I AKI was defined as a 50% to 100% increase, stage II as a >100% to 200% increase, and stage III as >200% increase, or the initiation of acute dialysis. Following best practice guidelines, we used the admission creatinine to define "baseline" (13). In addition, we explored the association of peripheral edema with AKI, as defined by changes in creatinine or urine output, and urine output alone, in keeping with alternative KDOQI definitions.

Covariates

Demographic information included age, sex, and race, coded as white, black, Asian, Hispanic, other, or unknown. We identified congestive heart failure patients through NLP searching of the past medical history section of the admission examination or Elixhauser discharge coding (14). We also used oral diabetes medication or insulin usage, along with Elixhauser discharge coding, to identify diabetic patients. All additional 27 Elixhauser discharge coding comorbidities were included as separate variables. ICU types included cardiac, surgical, cardiothoracic, and medical units. Sequential Organ Failure Assessment scores were used to indicate severity of illness. Because of the effect of hemodynamics on renal function, we also included systolic and diastolic BP, heart rate, and temperature as independent continuous variables. Admission creatinine, defined as the first available creatinine 24 hours prior to, or 6 hours after, ICU admission was used as a determinant of "baseline" kidney function. We used NLP searches of prehospital medication lists to identify angiotensin-converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), statin (15), calcium channel blocker, and diuretic usage.

Analyses

We present descriptive baseline characteristics stratified by peripheral edema. We used logistic regression to examine the association between admission peripheral edema and the subsequent risk of AKI. We adjusted for age, gender, race, ICU type, Sequential Organ Failure Assessment score, history of diabetes, congestive heart failure, hypertension, chronic pulmonary disease, peripheral vascular disease, and 24 additional Elixhauser comorbidities, admission systolic and diastolic BP, heart rate, temperature, admission creatinine, and preillness medication usage, including diuretic, ACE-I, ARB, calcium channel blocker, or statin use. In order to determine the effect of peripheral edema independently of pulmonary congestion, pulmonary edema was included as a separate variable in all analyses. We describe the incidence of AKI severity according to admission peripheral edema, and used cumulative ordinal logistic regression to describe the adjusted risk of peripheral edema with a one-step higher AKI stage using the same variables as above.

In those patients with quantifiable edema, we created indicator variables for trace, 1+, 2+, and 3+ edema, and used logistic regression to describe the adjusted risk of peripheral edema severity with AKI. In these analyses, 462 patients had peripheral edema that could not be quantified, and were excluded. Patients without peripheral edema were considered the reference category. We also describe the incidence of AKI severity according to peripheral edema severity.

In addition, in those patients with uninterrupted urine void measurements, we describe the association of peripheral edema with AKI as defined by KDOQI urine guidelines. Because we could not ascertain bladder catherization, and to avoid misclassification due to lack of recorded urine output in noncatherized patients, we required patients to have two or more urine output recordings within 9 hours (the length of a typical nursing shift.) Patients with adjacent urine output recordings >9 hours apart were considered interrupted, and were not included.

In a sensitivity analyses, in those patients with available creatinine measurements >7 days prior to admission, we used premorbid creatinine values rather than admission creatinine to account for "baseline" function in our

adjusted model. The correlation between premorbid and admission creatinine values was 0.73 ($P<0.001$). Given that we could not distinguish peripheral edema from lymphedema, a common occurrence with obesity, we also examined the association of peripheral edema with AKI in patients with documented admission body mass indexes (BMI). To explore the association between CVP and AKI, we examined the association of CVPs obtained within 6 hours of ICU admission and subsequent AKI. We used logistic regression, using the same variables as above except for the substation of CVP for peripheral edema, to define the association of CVP with AKI. CVP was defined continuously and in quartiles. Furthermore, to account for the effect of hydration status, we included serum sodium concentrations in adjusted analysis.

We examined whether peripheral edema remained associated with AKI in patients with and without sepsis, pulmonary edema, baseline diuretic use, baseline calcium channel blocker use, and CKD, as defined by an estimated glomerular filtration rate of ≤60 ml/min per 1.73 m^2 upon ICU admission, as determined by the Modified Diet in Renal Disease Study Equation. We individually tested multiplicative interaction terms between peripheral edema and these variables in adjusted analysis, and provide graphical representation of the stratified risks.

Results

Baseline Characteristics

Of 12,778 critically ill patients, 18% (n=2338) had documented peripheral edema on admission. As seen in Table 1, these patients tended to be older, with a higher prevalence of diabetes, heart failure, and pulmonary disease, but less hypertension, than those without peripheral edema, and tended to have a greater premorbid use of diuretics, ACE-Is, ARBs, and calcium channel blockers.

Peripheral Edema and AKI

The overall incidence of AKI within 7 days of ICU admission was 18.3% (n=2344), 27.0% (n=631) in those with peripheral edema, and 16.4% (n=1713) in those without peripheral edema. In adjusted analysis accounting for severity of illness (Table 2), comorbidities, premorbid medication exposure, and admission serum creatinine, peripheral edema was associated with a 30% higher risk of AKI occurring within the first 7 days of critical

Table 1. Baseline characteristics stratified by peripheral edema

Characteristics	With Peripheral Edema n=2338	Without Peripheral Edema n=10,440	P value
Demographics			
Age, mean (SD), years	68.9 (15.1)	63.2 (17.8)	<0.001
Female, n (%)	1101 (47.0)	4416 (42.3)	0.12
White	1747 (74.7)	7515 (71.9)	<0.001
Black	176 (7.5)	787 (7.5)	
Hispanic	52 (2.2)	330 (3.2)	
Asian	34 (1.5)	262 (2.5)	
Other	40 (1.7)	258 (2.5)	
Unknown	289 (12.3)	1288 (12.3)	
Cardiac care unit	559 (23.9)	2556 (24.5)	<0.01
Medical care unit	921 (39.3)	3755 (36.0)	
Surgical care unit	858 (36.7)	4129 (40.0)	
Past medical history, n (%)			
Diabetes	902 (38.6)	2791 (26.7)	<0.001
Peripheral vascular disease	181 (7.8)	842 (8.5)	0.58
Hypertension	734 (31.4)	3790 (36.3)	<0.001
Chronic pulmonary disease	518 (22.7)	1726 (16.5)	<0.001
Congestive heart failure	963 (41.2)	2113 (20.3)	<0.001
Prior medication use, n (%)			
Diuretic	1126 (48.2)	2694 (25.8)	<0.001
ACE-I	684 (29.0)	2613 (25.1)	<0.001
ARB	234 (10.1)	707 (6.8)	<0.001
Calcium channel blocker	490 (20.9)	1648 (15.7)	<0.001
Admission characteristics			
SOFA	3.4 (2.5)	2.4 (2.1)	<0.001
Systolic BP (mmHg)	121.3 (25.1)	125.7 (24.7)	<0.001
Diastolic BP (mmHg)	61.1 (16.3)	64.2 (15.9)	<0.001
Temperature (°C)	36.5 (1.7)	36.5 (1.6)	0.76
Creatinine (mg/dl)	1.6 (1.4)	1.3 (1.3)	<0.001
eGFR<60 ml/min/1.73 m^2	1300 (55.6)	3604 (34.5)	<0.001

Mean (SD) for continuous variables, and within column number (%) provided. ACE-I, angiotensin inhibitor converting enzyme-inhibitor; ARB, angiotensin receptor blocker; SOFA, Sequential Organ Failure Assessment. eGFR determined using the Modified Diet Renal Disease equation.

illness (95% confidence interval [95% CI], 1.15 to 1.46; $P<0.001$), whereas pulmonary edema was not associated with AKI.

Peripheral edema was also associated with AKI severity. In those with peripheral edema, 16.4% (n=308), 3.3% (n=62), and 7.6% (n=143) developed stage I, II, and III AKI, respectively, compared with 10.6% (n=1107), 2.4% (n=250), and 3.4% (n=356) in those without peripheral edema. In adjusted analysis, peripheral edema was associated with a 1.13-fold (95% CI, 1.07 to 1.20; $P<0.001$) higher risk of a higher stage of AKI.

Severity of Peripheral Edema and AKI

Of the 2338 individuals with documented peripheral edema, 1876 had descriptors that allowed quantification of peripheral edema; 32% (n=603), 36% (n=666), 25% (n=463), and 8% (n=144) had trace, 1+, 2+, and 3+ peripheral edema respectively, with a 25.0% (n=151), 25.1% (n=167), 31.5% (n=146), and 34.1% (n=49) incidence of AKI per increasing edema category, respectively. As seen in Table 3, compared with those without peripheral edema, the risk of AKI was higher among patients with more severe peripheral edema. The incidence of AKI severity according to peripheral edema severity is illustrated in Figure 1.

Sensitivity Analyses

We identified 5813 patients with a serum creatinine measured >7 days prior to ICU admission. Substitution of this premorbid creatinine rather than admission creatinine to establish "baseline" renal function did not meaningfully change the association between admission peripheral edema and AKI (Odds Ratio [OR] 1.29; 95% CI, 1.10 to 1.51; P=0.002). Of 8924 patients with uninterrupted urine measurements, AKI by urine output criteria occurred in 47% (n=4208), with 26% (n=2332) stage I, 18% (n=1647) stage II, and 3% (n=229) stage III AKI. In adjusted analysis, peripheral edema was associated with an OR of 1.61 (95% CI, 1.43 to 1.82; $P<0.001$) for AKI by urine criteria. Defining AKI by either creatinine or urine parameters, peripheral edema was associated with an OR of 1.50 (95% CI, 1.35 to 1.66; $P<0.001$). In 5971 patients with documented admission BMIs, peripheral edema remained associated with AKI risk (OR 1.48; 95% CI, 1.29 to 1.72; $P<0.001$) and a multiplicative interaction term between BMI and peripheral edema was not significant ($P>0.05$). Inclusion of admission serum sodium concentrations did not meaningfully change the results.

To examine whether the peripheral edema remained associated with AKI across a range of patients, we explored multiplicative interaction terms between peripheral edema and sepsis, pulmonary edema, baseline diuretic use, baseline

Table 2. Unadjusted and adjusted determinants of AKI

Characteristics	Unadjusted Odds Ratio 95% CI *P* value	Adjusted Odds Ratio[a] 95% CI *P* value
Age (per 5 years)	1.07 1.06 to 1.09 <0.001	1.03 1.02 to 1.05 <0.001
Diabetes	1.49 1.35 to 1.66 <0.001	1.20 1.07 to 1.33 0.002
Hypertension	1.32 1.20 to 1.45 <0.001	1.33 1.19–1.48 <0.001
SOFA (1 point)	1.29 1.27 to 1.32 <0.001	1.33 1.29 to 1.36 0.001
Baseline ACE-I	1.27 1.14 to 1.40 <0.001	1.09 0.96 to 1.21 0.19
Baseline diuretic use	1.60 1.45 to 1.70 <0.001	1.07 0.95 to 1.18 0.40
Pulmonary edema	1.54 1.34 to 1.68 <0.001	1.08 0.95 to 1.23 0.22
Peripheral edema	1.88 1.69 to 2.09 <0.001	1.30 1.15 to 1.46 <0.001

95% CI, 95% confidence interval; SOFA, Sequential Organ Failure Assessment; ACE-I, angiotensin inhibitor converting enzyme-inhibitor.

[a]Adjusted for age, gender, race, intensive care unit type, SOFA, history of diabetes, congestive heart failure, hypertension, chronic pulmonary disease, peripheral vascular disease, and 24 additional Elixhauser comorbidities, admission vitals (systolic and diastolic BP, heart rate, temperature), admission creatinine, preillness medication usage (ACE-I, angiotensin receptor blocker, statin, calcium channel blocker, and diuretics), and pulmonary edema.

Table 3. Peripheral edema severity and subsequent risk of AKI

Risk	No Edema	Trace Edema	1+ Edema	2+ Edema	3+ Edema
Odds ratio	Ref	1.34	1.17	1.47	1.57
95% CI		1.10 to 1.65	0.96 to 1.14	1.18 to 1.8)	1.07 to 2.31
P value		<0.01	0.13	<0.001	0.02

Odds ratio adjusted for age, gender, race, intensive care unit type, sequential organ failure assessment, history of diabetes, congestive heart failure, hypertension, chronic pulmonary disease, peripheral vascular disease, and 24 additional Elixhauser comorbidities, admission vitals (systolic and diastolic BP, heart rate, temperature), admission creatinine, preillness medication usage (angiotensin inhibitor converting enzyme-inhibitor, angiotensin receptor blocker, statin, calcium channel blocker, and diuretics), and pulmonary edema. 95% CI, 95% confidence interval.

calcium channel blocker use, and chronic kidney disease, as defined by an estimated glomerular filtration rate of ≤60 ml/min per 1.73 m^2 upon ICU admission. No multiplicative term was statistically significant (all *P* values >0.05). Stratified adjusted analyses are presented in Figure 2. Across all strata, admission peripheral edema was associated with an increased risk of AKI.

Association Between CVP and AKI

A total of 4761 patients had a CVP measurement within 6 hours of ICU admission. The incidence of AKI was higher in those with CVP measurements (23%) compared with those who did not have CVP measured (12%). As seen in Table 4, the incidence and risk of AKI was higher across increasing CVP quartiles. In adjusted analysis, each 1 cm H_2O higher CVP was associated with a 1.02 (95% CI, 1.00 to 1.03, *P*=0.02) risk of AKI. The mean (SD) CVP in patients with and without peripheral edema was 11.1 (6.1) and 10.8 (5.0) cm H_2O, respectively (*P*=0.01). In patients with quantifiable peripheral edema who also had a measured CVP (*n*=4566), the mean (SD) CVP was 10.7 (5.4), 11.5 (5.3), 11.8 (6.2), 11.9 (6.4) and 12.7 (7.3) cm H_2O in those with 0, trace, 1+, 2+, and 3+ peripheral edema respectively (*P* value for trend 0.01).

Discussion

Our data extend the association of venous congestion and renal dysfunction to a significantly broader pool of patients. In critically ill patients, the presence and severity of peripheral edema on admission physical examination is associated with AKI and AKI severity during the first 7 days of critical illness. Increasing admission CVP is likewise associated with AKI risk.

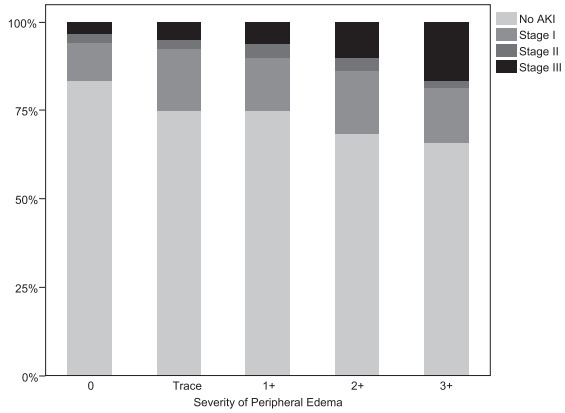

Figure 1. | Incidence of AKI severity according to peripheral edema severity.

Our findings add to a growing literature regarding the importance of venous congestion on renal outcomes (16). Renal perfusion depends on the balance between arterial pressure and venous drainage, and early studies highlighted the importance of renal congestion. In one such early experiment, urine production was reduced upon raising renal venous pressure to 20 mmHg, and abolished at pressures >25 mmHg (17). Similarly, extrinsic compression of the renal veins (18) and increased intra-abdominal pressure impair renal function (19,20), and the abdominal compartment syndrome is a well-described cause of renal failure (21), which improves with decompression in some (22) but not all studies (23).

Because peripheral edema might be a direct consequence of right ventricular dysfunction, our findings similarly raise interest in the possibility of right ventricular function as an independent determinant of renal function (10). Animal models of right ventricular dysfunction through graded pulmonic stenosis show a decrease in renal blood flow and intense sodium retention (24). Disorders associated with right ventricular dysfunction, such as obesity, sleep apnea, and cor pulmonale, are associated with sodium retention and AKI (25–27). Unlike the thick-walled left ventricle, where higher filling volume leads to improved left ventricular function, as described by the Frank Starling mechanism, the thin-walled right ventricle dilates in response to increasing pulmonary pressure, as frequently occurs with chronic heart failure and primary pulmonary disease (28,29). Expanding into the pericardial sack and causing paradoxical septal movement, the failing right ventricle impinges on the left ventricle, decreasing its compliance and output. In an interesting preliminary study of patients with acute right ventricular dysfunction due to pulmonary embolus, diuretic therapy was associated with better renal function compared with those who received fluid (30), prompting the design of a larger study of the utility of diuretics in acute right ventricular dysfunction (31). Whether diuretic therapy might improve renal outcomes in those with more chronic right ventricular dysfunction has not been explored.

Clinical studies support the mechanistic association of venous congestion with poor renal outcomes. In a study of

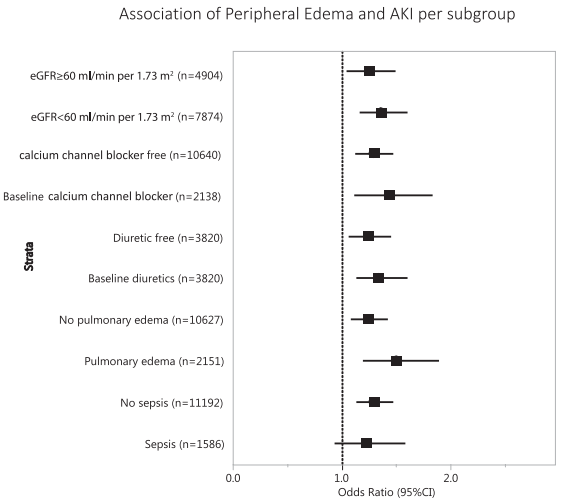

Figure 2. | Forest plot for risk of peripheral edema and AKI per subgroup. Adjusted for age, gender, race, intensive care unit type, Sequential Organ Failure Assessment, history of diabetes, congestive heart failure, hypertension, chronic pulmonary disease, peripheral vascular disease, and 24 additional Elixhauser comorbidities, admission vitals (systolic and diastolic BP, heart rate, temperature), admission creatinine, preillness medication usage (angiotensin inhibitor converting enzyme-inhibitor, angiotensin receptor blocker, statin, calcium channel blocker, and diuretics), and pulmonary edema (excluded in pulmonary edema stratification). eGFR calculated from admission serum creatinine concentration using the Modified Diet in Renal Disease equation.

almost 2600 patients undergoing right heart catherization, higher CVP was associated with significantly lower baseline renal function, as well as reduced survival (32). In hospitalized heart failure patients with hemodynamic measures of both left and right heart pressures, CVP was the strongest determinant of worsening renal function (4). Similarly, pulmonary edema was not associated with AKI in our analysis, although selection bias might account for this observation.

Our study is limited by the inability to characterize the directionality of association. It is plausible that peripheral edema reflects underlying renal dysfunction not fully accounted for using serum-based creatinine measurements. Furthermore, because worsening renal function often prompts cessation of diuretics or the administration of fluid, residual confounding by indication is possible, and peripheral edema and increased CVP might reflect previous therapeutic responses to renal deterioration. However, in analysis of those with available baseline creatinine measurements prior to critical illness admission, the association of peripheral edema with AKI remained robust.

In addition, we could not ascertain the cause of peripheral edema, which likely includes a range of pathophysiologies, including undiagnosed systolic and diastolic left heart failure and primary right-sided heart failure. Thus, residual confounding to the underlying pathophysiologic processes, rather than fluid accumulation *per se*, is possible. Given the difficulty in identifying subtle forms of cardiac and pulmonary disease, it is likely that the use of diagnostic codes to identify disease leads to significant misclassification. We therefore used preillness diuretic use to classify patients with sodium retentive pathophysiology, and found no significant effect modification. Furthermore, the severity of peripheral edema was likewise associated with AKI and AKI severity, supporting a dose–response association.

Given that a reduction in CVP, as might occur with volume depletion or sepsis, is likely also associated with AKI risk, we could not distinguish between the competing associations of low and high CVP on AKI risk. In addition, we could not distinguish peripheral edema from lymphedema, but in analysis of those with documented BMI, the association of peripheral edema with AKI remained robust, and the association of peripheral edema and AKI was not modified by BMI. In addition, our analytic techniques did not account for on-study care, and it is plausible that peripheral edema patients were more likely to receive potentially nephrotoxic medications, such as diuretics. Finally, although our technique of using bootstrapping with replacement to validate the script identification could be affected by resubstitution bias, our accuracy in 88% of individual subsets was close to 90%, suggesting an acceptable approach.

Our data suggests that venous congestion, as indicated by peripheral edema on physical examination or increased admission CVP, is associated with an increased risk of AKI. We cannot conclude whether venous congestion *per se* causes AKI, or simply reflects an underlying pathophysiology that is responsible for AKI. Whether restoration of euvolemia

Table 4. Admission central venous pressure and subsequent risk of AKI

Risk	≤7 cm/H_2O	>7 to ≤10 cm/H_2O	>10 to ≤13 cm/H_2O	>13 cm/H_2O	Per 1 cm H_2O positive
N, % AKI	275 (21)	275 (22)	227 (23)	312 (26)	—
Odds ratio	Ref	1.06	1.08	1.18	1.02
95% CI		0.86 to 1.29	0.87 to 1.29	0.96 to 1.33	1.00 to 1.03
P value		0.57	0.46	0.09	0.02

Within quartile incidence (%) of AKI provided. Odds ratio adjusted for age, gender, race, intensive care unit type, sequential organ failure assessment, history of diabetes, congestive heart failure, hypertension, chronic pulmonary disease, peripheral vascular disease, and 24 additional Elixhauser comorbidities, admission vitals (systolic and diastolic BP, heart rate, temperature), admission creatinine, preillness medication usage (angiotensin inhibitor converting enzyme-inhibitor, angiotensin receptor blocker, statin, calcium channel blocker, and diuretics), and pulmonary edema. 95% CI, 95% confidence interval.

with aggressive diuretic use might mitigate the risk of AKI will require well-designed studies.

Acknowledgments

Dr. L.A.C's work in the Laboratory for Computational Physiology at MIT is funded by the National Institute of Biomedical Imaging and Bioengineering under NIBIB grant 2R01 EB001659. Dr. M.F. is supported by Agency for Science, Technology and Research (A*STAR) Graduate Scholarship. This work is supported by NIH grant R01 EB001659.

Disclosures

None.

References

1. Winton FR: The influence of venous pressure on the isolated mammalian kidney. *J Physiol* 72: 49–61, 1931
2. Winton FR: The glomerular pressure in the isolated mammalian kidney. *J Physiol* 72: 361–375, 1931
3. Testani JM, Khera AV, St John Sutton MG, Keane MG, Wiegers SE, Shannon RP, Kirkpatrick JN: Effect of right ventricular function and venous congestion on cardiorenal interactions during the treatment of decompensated heart failure. *Am J Cardiol* 105: 511–516, 2010
4. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB, Tang WH: Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol* 53: 589–596, 2009
5. House AA: Cardiorenal syndrome: new developments in the understanding and pharmacologic management. *Clin J Am Soc Nephrol* 8: 1808–1815, 2013
6. Whaley-Connell A, Sowers JR: Basic science: Pathophysiology: the cardiorenal metabolic syndrome. *J Am Soc Hypertens* 8: 604–606, 2014
7. Haddad F, Doyle R, Murphy DJ, Hunt SA: Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. *Circulation* 117: 1717–1731, 2008
8. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ: Right ventricular function in cardiovascular disease, part I: Anatomy, physiology, aging, and functional assessment of the right ventricle. *Circulation* 117: 1436–1448, 2008
9. Onuigbo MA: RAAS inhibition and cardiorenal syndrome. *Curr Hypertens Rev* 10: 107–111, 2014
10. Dini FL, Demmer RT, Simioniuc A, Morrone D, Donati F, Guarini G, Orsini E, Caravelli P, Marzilli M, Colombo PC: Right ventricular dysfunction is associated with chronic kidney disease and predicts survival in patients with chronic systolic heart failure. *Eur J Heart Fail* 14: 287–294, 2012
11. Sterns RH: Wolters Kluver. Available at: http://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-edema-in-adults. Accessed December 15, 2015
12. Palevsky PM, Liu KD, Brophy PD, Chawla LS, Parikh CR, Thakar CV, Tolwani AJ, Waikar SS, Weisbord SD: KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis* 61: 649–672, 2013
13. Ad-hoc Working Group of ERBPFliser D, Laville M, Covic A, Fouque D, Vanholder R, Juillard L, Van Biesen W. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant* 27: 4263–42722012
14. Elixhauser A, Steiner C, Harris DR, Coffey RM: Comorbidity measures for use with administrative data. *Med Care* 36: 8–27, 1998
15. Yagi S, Aihara K, Ikeda Y, Akaike M, Sata M, Matsumoto T. Effects of statins on cardiorenal syndrome. *Int J Vasc Med* 2012: 162545, 2012
16. F Gnanaraj J, von Haehling S, Anker SD, Raj DS, Radhakrishnan J: The relevance of congestion in the cardio-renal syndrome. *Kidney Int* 83: 384–391, 2013
17. Winton FR: The influence of increase of ureter pressure on the isolated mammalian kidney. *J Physiol* 71: 381–390, 1931
18. Blake WD, Wegria R, et al: Effect of increased renal venous pressure on renal function. *Am J Physiol* 157: 1–13, 1949
19. Bradley SE, Bradley GP: The effect of increased intra-abdominal pressure on renal function in man. *J Clin Invest* 26: 1010–1022, 1947
20. Dalfino L, Tullo L, Donadio I, Malcangi V, Brienza N: Intra-abdominal hypertension and acute renal failure in critically ill patients. *Intensive Care Med* 34: 707–713, 2008
21. Doty JM, Saggi BH, Sugerman HJ, Blocher CR, Pin R, Fakhry I, Gehr TW, Sica DA: Effect of increased renal venous pressure on renal function. *J Trauma* 47: 1000–1003, 1999
22. Mullens W, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, Paganini E, Tang WH: Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? *J Am Coll Cardiol* 51: 300–306, 2008
23. De Waele JJ, Hoste EA, Malbrain ML: Decompressive laparotomy for abdominal compartment syndrome–a critical analysis. *Crit Care* 10: R51, 2006
24. Barger AC, Yates FE, Rudolph AM: Renal hemodynamics and sodium excretion in dogs with graded valvular damage, and in congestive failure. *Am J Physiol* 200: 601–608, 1961
25. Danziger J, Chen KP, Lee J, Feng M, Mark RG, Celi LA, Mukamal KJ: Obesity, acute kidney injury, and mortality in critical illness. *Crit Care Med* 2011, in press
26. de Louw EJ, Sun PO, Lee J, Feng M, Mark RG, Celi LA, Mukamal KJ, Danziger J: Increased incidence of diuretic use in critically ill obese patients. *J Crit Care* 30: 619–623, 2015
27. Chen Y, Li Y, Jiang Q, Xu X, Zhang X, Simayi Z, Ye H: Analysis of early kidney injury-related factors in patients with hypertension and obstructive sleep apnea hypopnea syndrome (OSAHS). *Arch Iran Med* 18: 827–833, 2015
28. Sarnoff SJ, Berglund E: Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. *Circulation* 9: 706–718, 1954
29. Dell'Italia LJ, Pearce DJ, Blackwell GG, Singleton HR, Bishop SP, Pohost GM: Right and left ventricular volumes and function after acute pulmonary hypertension in intact dogs. *J Appl Physiol (1985)* 78: 2320–2327, 1995
30. Ternacle J, Gallet R, Mekontso-Dessap A, Meyer G, Maitre B, Bensaid A, Jurzak P, Gueret P, Dubois Randé JL, Lim P: Diuretics in normotensive patients with acute pulmonary embolism and right ventricular dilatation. *Circ J* 77: 2612–2618, 2013
31. Gallet R, Meyer G, Ternacle J, Biendel C, Brunet A, Meneveau N, Rosario R, Couturaud F, Sebbane M, Lamblin N, Bouvaist H, Coste P, Maitre B, Bastuji-Garin S, Dubois-Rande JL, Lim P: Diuretic versus placebo in normotensive acute pulmonary embolism with right ventricular enlargement and injury: a double-blind randomised placebo controlled study. Protocol of the DiPER study. *BMJ Open* 5: e007466, 2015
32. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL: Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol* 53: 582–588, 2009

Received: July 28, 2015 **Accepted:** December 16, 2015

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.08080715/-/DCSupplemental.