Admission Peripheral Edema, Central Venous Pressure, and Survival in Critically Ill Patients

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Abstract

Rationale: The clinical significance of peripheral edema has not been well described in critical illness.

Objectives: To assess the clinical significance of peripheral edema detected on physical examination at the time of hospital admission for patients who were treated in an intensive care unit (ICU).

Methods: Using a large inception cohort of critically ill patients, we examined the association of peripheral edema, as documented on hospital admission physical examination, with hospital and 1-year survival.

Measurements and Main Results: Of 12,778 patients admitted to an ICU at a teaching hospital in Boston, Massachusetts, 2,338 (18%) had peripheral edema. Adjusting for severity of illness and comorbidities, including pulmonary edema, admission peripheral edema was associated with a 26% (95% confidence interval [CI] = 1.11–1.44, $P < 0.001$) higher risk of hospital mortality. In those patients whose peripheral edema could be graded, trace, 1+, 2+, and 3+ admission peripheral edema was associated with a 2% (95% CI = 0.80–1.31, $P = 0.89$), 17% (95% CI = 1.00–1.56, $P = 0.05$), 60% (95% CI = 1.26–2.04, $P < 0.001$), and 54% (95% CI = 1.04–2.29, $P = 0.03$) higher adjusted risk of hospital mortality, respectively, compared with patients without edema. The association was consistent across strata of patients with diabetes, congestive heart failure, sepsis, and premorbid diuretic or calcium channel blocker use. In a subset of patients with central venous pressures measurements obtained within 6 hours of ICU admission, the highest central venous pressure quartile (>13 cm H_2O) was similarly associated with a 35% (95% CI = 1.05–1.75, $P = 0.02$) higher adjusted risk of hospital mortality compared with the lowest quartile (≤7 cm H_2O).

Conclusions: Peripheral edema, as detected on physical examination at the time of hospital admission, is a poor prognostic indicator in critical illness. Whether peripheral edema simply reflects underlying pathophysiology, or has an independent pathogenic role, will require further interventional studies.

Keywords: peripheral edema; venous congestion; pulmonary edema; central venous pressure; mortality

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Sodium avidity occurs in a wide range of pathophysiologic settings, including left- and right-sided heart failure, kidney disease, and liver disease, and leads to isotonic fluid expansion. In some settings, such fluid overload leads to hypertension and pulmonary edema, but often results primarily in venous congestion. As the increasing outward venous hydrostatic pressure exceeds the inward oncotic pressure, fluid accumulates within the soft tissues, manifesting as peripheral edema or elevated central venous pressures (CVPs).

Table 1. Baseline characteristics stratified by peripheral edema

	With Peripheral Edema (*n* = 2,338)	Without Peripheral Edema (*n* = 10,440)	*P* Value
Demographics			
Age, mean (SD), yr	68.9 (15.1)	63.2 (17.8)	<0.001
Female, *n* (%)	1,101 (47.0)	4,416 (42.3)	0.12
White, *n* (%)	1,747 (74.7)	7,515 (71.9)	<0.001
Black, *n* (%)	176 (7.5)	787 (7.5)	<0.001
Hispanic, *n* (%)	52 (2.2)	330 (3.2)	<0.001
Asian, *n* (%)	34 (1.5)	262 (2.5)	<0.001
Other, *n* (%)	40 (1.7)	258 (2.5)	<0.001
Unknown, *n* (%)	289 (12.3)	1,288 (12.3)	<0.001
Cardiac care unit, *n* (%)	559 (23.9)	2,556 (24.5)	<0.001
Medical care unit, *n* (%)	921 (39.3)	3,755 (36.0)	<0.001
Surgical care unit, *n* (%)	858 (36.7)	4,129 (40.0)	<0.001
Past medical history, *n* (%)			
Diabetes	902 (38.6)	2,791 (26.7)	<0.001
Peripheral vascular disease	181 (7.8)	842 (8.5)	0.58
Hypertension	734 (31.4)	3,790 (36.3)	<0.001
Chronic pulmonary disease	518 (22.7)	1,726 (16.5)	<0.001
Congestive heart failure	963 (41.2)	2,113 (20.3)	<0.001
Prior medication use, *n* (%)			
Diuretic	1,126 (48.2)	2,694 (25.8)	<0.001
ACE-I	684 (29.0)	2,613 (25.1)	<0.001
ARB	234 (10.1)	707 (6.8)	<0.001
Calcium channel blocker	490 (20.9)	1,648 (15.7)	<0.001
Admission characteristics			
SOFA	3.4 (2.5)	2.4 (2.1)	<0.001
Systolic Bld Pres, mm Hg	121.3 (25.1)	125.7 (24.7)	<0.001
Diastolic Bld Pres, mm Hg	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

Definition of abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; Bld Pres = blood pressure; SOFA = sepsis-related organ failure.
Mean (SD) for continuous variables.
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Although examining hospitalized patients for peripheral edema is common practice, the clinical significance of peripheral edema is less well described (1). Current management guidelines suggest that peripheral edema is cosmetic and not life threatening. Treatment recommendations range from leg elevation and compression stockings, to dietary sodium restriction, to diuretic administration (2). Yet more recent data have suggested that venous congestion is an independent determinant of poor outcomes, including renal failure, hypertension, and heart failure (3–5).

To better understand the clinical importance of peripheral edema, we evaluated admission physical examinations from almost 13,000 critical illness hospitalizations. Herein, we describe the association of admission peripheral edema with the risk of hospital mortality and 1-year mortality in those who survived the critical illness hospitalization.

Table 2. Adjusted risk of admission characteristics and physical examination findings and subsequent hospital mortality

	Odds Ratio (95% CI)	*P* Value
Age (per year)	1.03 (1.02–1.03)	<0.001
SOFA (per 1 point)	1.27 (1.24–1.31)	<0.001
History of diabetes	1.02 (0.90–1.16)	0.70
History of congestive heart failure	1.28 (1.13–1.46)	0.002
Preillness diuretic use	1.11 (0.98–1.26)	0.10
Pulmonary edema on admission	1.13 (0.99–1.29)	0.07
Peripheral edema on admission	1.26 (1.11–1.44)	<0.001

Definition of abbreviation: CI = confidence interval; SOFA = sepsis-related organ failure.
Odds ratio, 95% CI, and *P* values provided. Adjusted for age, sex, 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 blood pressure, heart rate, temperature), admission creatinine, preillness medication usage (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, statin, calcium channel blocker, and diuretics), and pulmonary edema.

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 (Cambridge, MA) and the Department of Medicine at the Beth Israel Deaconess Medical Center (BIDMC; Boston, MA). 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 intensive care unit (ICU) beds. The database contains high temporal resolution data from clinical systems, including laboratory results, electronic documentation, and bedside monitor trends and waveforms. Use of the MIMIC II database for this project was approved by the institutional review boards of BIDMC and the Massachusetts Institute of Technology.

A total of 13,986 patients had complete admission history and physical examination as part of the hospital discharge summary. We excluded 270 patients with prevalent end-stage renal disease, and 848 were missing documentation of admission laboratory studies, leaving 12,778 unique individuals for primary analysis.

Primary Exposures

We developed a natural language processing (NLP) code based on standard clinical descriptors to identify peripheral and pulmonary edema as documented in the admission physical examination (*see* Table E1 in the online supplement). The developed code was "trained" by manual review of eight sequential sets of randomly selected discharge summaries, ranging

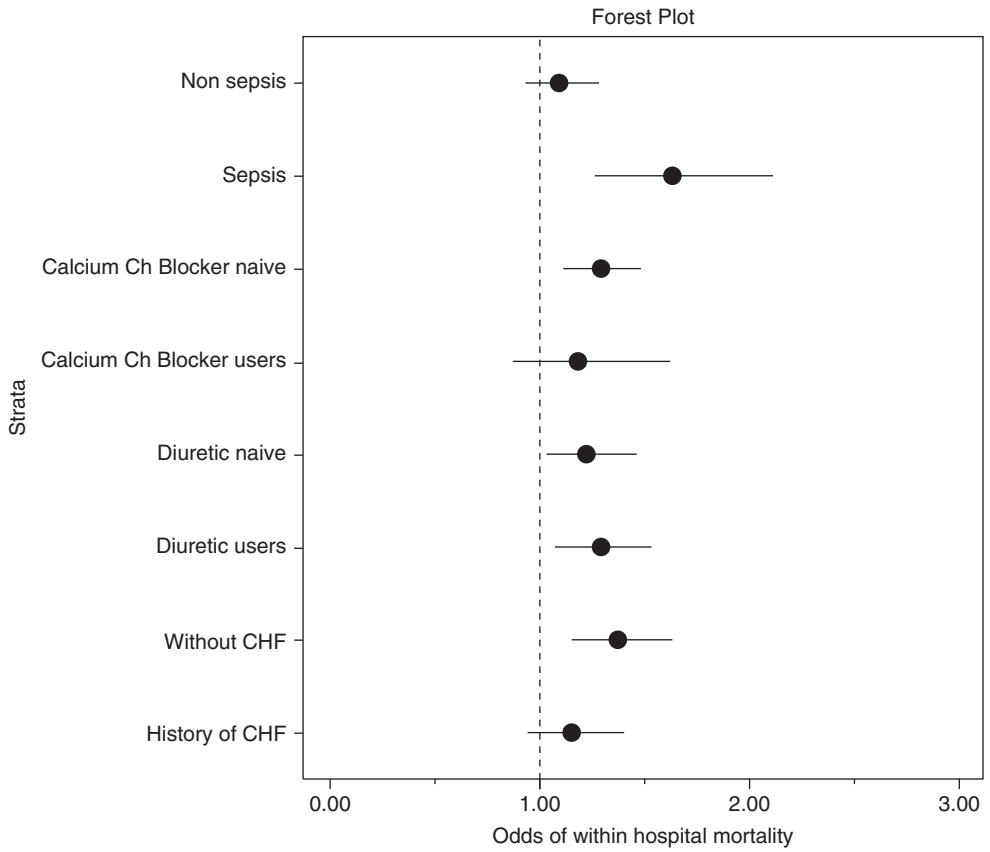

Figure 1. Risk of mortality for patients with admission peripheral edema compared with patients without edema. Adjusted for age, sex, race, intensive care unit (ICU) type, sepsis-related organ failure (SOFA), history of diabetes, congestive heart failure, hypertension, chronic pulmonary disease, peripheral vascular disease and 24 additional Elixhauser comorbidities, admission vitals (systolic and diastolic blood pressure, heart rate, temperature), admission creatinine, preillness medication usage (angiotensin-converting enzyme inhibitor [ACE-I], angiotensin receptor blocker [ARB], statin, calcium channel blocker, and diuretics), and pulmonary edema. Ch = channel; CHF = congestive heart failure.

from 50 to 100 in number. Once the code consistently achieved an accuracy rate of over 90% (Figure E1), all reviewed discharge summaries were combined, and the code was tested on 10,000 random samples with replacement of 100 discharge summaries. The histogram of "bootstrap" accuracy is provided in Figure E2. 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.

Outcome Measures

To evaluate risk of death during hospitalization and within 1 year from hospital discharge, we linked medical records to the Social Security Death Index.

Demographic information included age, sex, and race. Subjects were coded as white, African American, Asian, Hispanic, other, or unknown. Peripheral edema from the admission examination was defined as a binary term. We identified a diagnosis of patients with congestive heart failure through NLP searching of the past medical history section of the admission examination or Elixhauser discharge coding. We also used oral diabetes medication or insulin usage, along with Elixhauser discharge coding, to identify patients with diabetes. All additional Elixhauser discharge coding comorbidities were included as separate variables.

ICU types included cardiac, surgical, cardiothoracic, and medical units. Sepsis-related organ failure scores were used to indicate severity of illness. We included admission systolic and diastolic blood pressure, heart rate, and temperature as independent continuous variables, and admission creatinine, defined as the first available creatinine 24 hours before, or 6 hours after, ICU admission. We used NLP searches of prehospital medication lists to identify diuretic, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker (ARB), and statin usage.

Statistical Analyses

We present descriptive baseline characteristics stratified by peripheral edema. We used logistic regression to examine the association between admission peripheral edema and the risk of within-hospital mortality. We adjusted for age, sex, race, ICU type, sepsis-related organ failure score, history of diabetes, congestive heart failure, hypertension, chronic pulmonary disease, peripheral vascular disease and 24 additional Elixhauser comorbidities, admission systolic and diastolic blood pressure, heart rate, temperature, admission creatinine, and preillness medication usage, including diuretic, angiotensin-converting enzyme inhibitor, ARB, calcium channel blocker, or statin

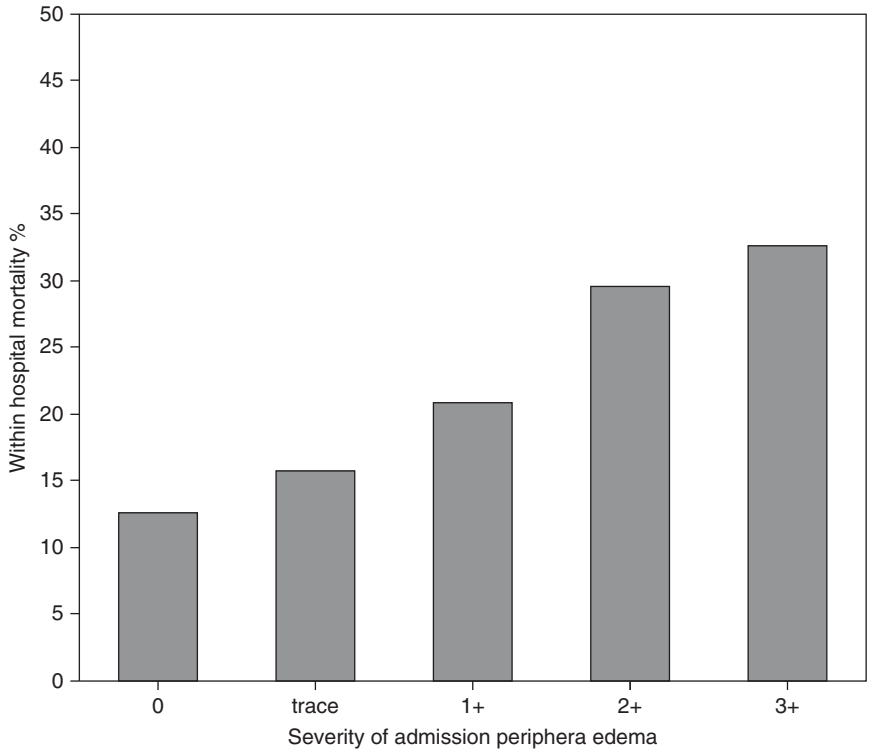

Figure 2. Rates of within-hospital death according to admission peripheral edema.

use, and the presence of pulmonary edema on admission examination. We explored interaction terms between peripheral edema and diabetes, congestive heart failure, sepsis, and diuretic and calcium channel blocker exposure.

In those patients with quantifiable edema, we created indicator variables for trace, 1+, 2+, and 3+ peripheral edema. A total of 462 patients had peripheral edema that could not be quantified, and were excluded. We describe the incidence of within-hospital mortality according to edema severity. We used logistic regression to describe the adjusted risk of peripheral edema severity within hospital mortality, adjusted for the covariates listed previously here. To describe the adjusted risk of edema severity with 1-year mortality in those who survived the critical illness hospitalization, we used Cox regression analyses, censoring those who survived 365 days or more, adjusting for the same variables as described previously here.

As a secondary exposure, we examined the association of CVP measurements obtained within 6 hours of ICU admission with mortality. In addition, in patients with documented body mass index (BMI) measurements, we examined whether the association between peripheral edema and hospital mortality was modified by BMI.

For all analyses, absent peripheral edema was considered the reference category. All analyses were performed using JMP 12 Pro (SAS Institute, Cary, NC).

Results

Of 12,778 critically ill patients, 2,338 (18%) had documented peripheral edema on admission physical examination. As seen in Table 1, patients with peripheral edema tended to be older, with a greater prevalence of heart failure, diabetes, and pulmonary disease, than those without peripheral edema. In addition, almost 50% of patients with peripheral edema were prescribed diuretics before admission, compared with 26% in patients without peripheral edema. Pulmonary edema was described in 2,244 patients (18%), and 729 patients (6%) had concurrent pulmonary and peripheral edema.

There were 1,835 (14%) deaths within the critical illness hospitalization, 518 (22.2%) versus 1,317 (12.6%) in those with and without peripheral edema, respectively. As seen in Table 2, peripheral edema was

Table 3. Peripheral edema severity on admission and subsequent risk of hospital and 1-year mortality

	No Edema	Trace Edema	1+ Edema	2+ Edema	3+ Edema
Within hospital mortality					
Deaths, *n* (%)	1,317 (12.6)	95 (15.8)	139 (20.1)	137 (29.6)	47 (32.6)
Odds ratio (95% CI)	Ref	1.02 (0.80–1.31)	1.17 (1.00–1.56)	1.60 (1.26–2.04)	1.54 (1.04–2.29)
P value	—	0.89	0.05	<0.001	0.03
1-year mortality in hospital survivors					
Deaths, *n* (%)	1,256 (13.8)	86 (16.9)	112 (21.3)	91 (27.9)	32 (32.9)
Odds ratio (95% CI)	Ref	0.95 (0.75–1.17)	1.00 (0.82–1.21)	1.30 (1.04–1.61)	1.48 (1.02–2.09)
P value	—	0.62	0.97	0.02	0.04

Definition of abbreviation: CI = confidence interval.
Hospital deaths and deaths within 1 year of discharge in hospital survivors provided, stratified by edema severity. Adjusted for age, sex, race, intensive care unit type, sepsis-related organ failure, history of diabetes, congestive heart failure, hypertension, chronic pulmonary disease, peripheral vascular disease and 24 additional Elixhauser comorbidities, admission vitals (systolic and diastolic blood pressure, heart rate, temperature), admission creatinine, preillness medication usage (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, statin, calcium channel blocker, and diuretics), and pulmonary edema.

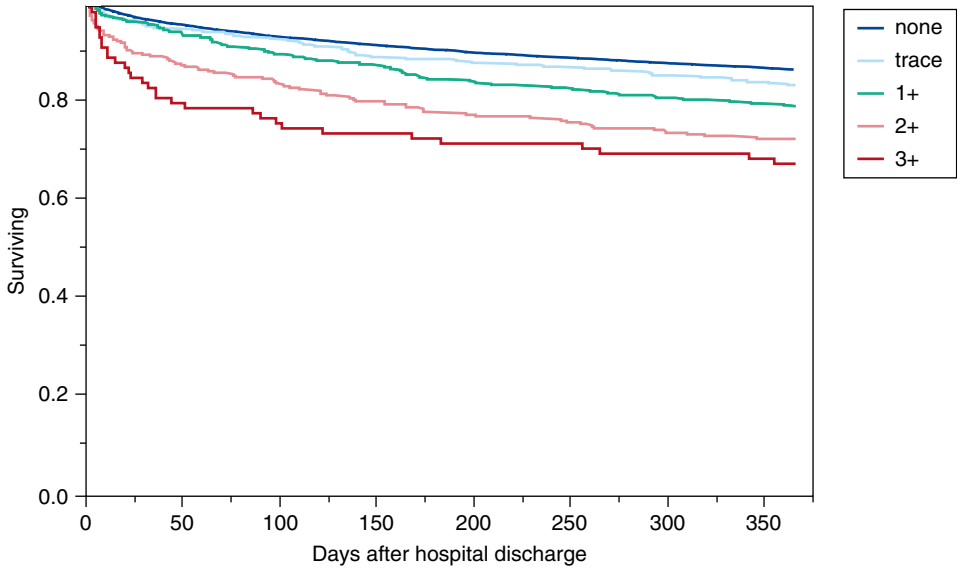

Figure 3. Unadjusted 1-year survival in hospital survivors according to admission peripheral edema severity (*P* value across groups < 0.001).

independently associated with hospital mortality in adjusted analysis. Multiplicative interaction terms between peripheral edema and diabetes, congestive heart failure, sepsis, and preillness diuretic and calcium channel blocker use were not significant ($P > 0.05$). Stratified risks according to comorbidities are illustrated in Figure 1.

To explore a dose–response effect, we examined the association of increasing peripheral edema severity with mortality in 12,316 patients. Hospital mortality increased with greater admission peripheral edema severity (Figure 2). Compared with patients without peripheral edema, trace, 1+, 2+, and 3+ admission peripheral edema had a 1.29 (95% confidence interval [CI] = 1.03–1.61, $P = 0.03$), 1.82 (95% CI = 1.49–2.21, $P < 0.001$), 2.91 (95% CI = 2.35–3.57, $P < 0.001$), and 3.35(95% CI = 2.34–4.74, $P < 0.001$) higher unadjusted risk of within hospital mortality, respectively, which remained robust in adjusted analyses (Table 3).

Among those who survived the critical illness hospitalization ($n = 10,573$), 1,577 (15%) died within 1 year of discharge. Increasing severity of admission peripheral edema was associated with a higher unadjusted risk of 1-year mortality in hospital survivors (Figure 3). Similarly, increasing admission peripheral edema was associated with a higher adjusted risk of 1-year mortality in hospital survivors (Table 3).

A total of 4,761 patients had a documented CVP measurement within 6 hours of ICU admission. Fluid balance before the CVP measurement was not available. Patients in the highest CVP quartile (CVP > 13 cm H_2O) had a 35% (95% CI = 1.05–1.75, $P = 0.02$) higher risk of hospital death compared with those with a CVP of 7 cm H_2O or less (Table 4). Finally, in 7,251 patients with a documented BMI, admission peripheral edema remained associated with hospital mortality (odds ratio = 1.31, 95% CI = 1.09–1.57, $P = 0.004$), and a multiplicative interaction term between peripheral edema and BMI was not significant ($P = 0.70$).

Discussion

Although the prevention of fluid overload through the use of dietary sodium restriction and diuretics is the mainstay of therapy in many disease states, the clinical importance of venous congestion has received surprisingly little attention. In our single-center analysis of almost 13,000 patients in the ICU, admission venous congestion, as evidenced by either peripheral edema or a markedly elevated CVP, was associated with a higher hospital and posthospitalization mortality.

Our findings add to the growing awareness of the importance of venous congestion. In a study of almost 2,600 patients undergoing right heart cauterization, increasing CVP was associated with reduced survival (6). Likewise, increased jugular venous pressures (7), radiolabeled blood volume (8), and bioimpedance measures of body hydration (9) have all been associated with higher mortality. In septic shock, a 5 mm Hg higher CVP was associated with an almost threefold increased odds of acute kidney injury (10). In addition, positive fluid balance has been associated with

Table 4. Admission central venous pressure and subsequent risk of hospital mortality

CVP (cm H_2O)	Odds Ratio (95% CI)	*P* Value
9–7	Ref.	—
>7–910	1.14 (0.87–1.48)	0.33
>10–913	0.94 (0.70–1.26)	0.71
>13	1.35 (1.05–1.75)	0.02

Definition of abbreviations: CI = confidence interval; CVP = central venous pressure. Adjusted for age, sex, race, intensive care unit type, sepsis-related organ failure, history of diabetes, congestive heart failure, hypertension, chronic pulmonary disease, peripheral vascular disease and 24 additional Elixhauser comorbidities, admission vitals (systolic and diastolic blood pressure, heart rate, temperature), admission creatinine, preillness medication usage (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, statin, calcium channel blocker, and diuretics), and pulmonary edema.

increased mortality in those patients at risk for sodium retention (11–13).

Although aggressive fluid resuscitation is an important component of ICU care, there remains scant data as to whether this excess fluid is diuresed, either spontaneously or pharmacologically, after illness resolution (14). Given that the most common cause of 90-day rehospitalization for patients on Medicare is decompensated congestive heart failure, further study on the importance of iatrogenic fluid overload during hospitalization is warranted (15).

There are several emerging pathophysiologic explanations for the association between venous congestion and poor outcomes. Unlike the thick-walled left ventricle, the right ventricle's thin-walled, conical wall morphology increases its susceptibility to changes in pressure. Increased pulmonary pressures, as might occur with a range of pulmonary disease, including pulmonary congestion, lead to pulmonary hypertension, right ventricular dilation, and right ventricular dysfunction. In turn, these responses to pulmonary vascular hypertension stimulate further sodium retention, thereby further exacerbating peripheral edema.

Our data cannot resolve whether the venous congestion *per se*, or underlying right ventricular dysfunction, is primarily associated with increased mortality, but does further support an awareness of the right ventricle as a determinant of outcomes (3). Early physiology studies suggested that the right ventricle may be less fluid responsive than the left (16), and more recent clinical studies have questioned the use of fluid expansion in acute right ventricular dysfunction (17), suggesting that right ventricular stretch may cause a paradoxical septal motion that impairs left ventricular compliance (18). A larger clinical study is ongoing (19).

In addition to the possibility of increased venous congestion impairing cardiac hemodynamics, there is a growing awareness of a potential nephrotoxic effect. Almost 90 years ago, early physiology experiments highlighted the importance of renal vein pressure—where increasing pressure on the renal vein to 20 mm Hg decreased urine formation, which was abolished at pressures greater than 25 mm Hg (20). Extrinsic compression of the renal veins and increased intra-abdominal pressure have also been found to decrease renal function (21–23).

In the abdominal compartment syndrome, which presumably impairs renal function through direct compression on the renal vein, reduction of pressure improves outcomes (24, 25). In hospitalized patients with heart failure with hemodynamic measures of both left and right heart pressures, venous filling pressures were the strongest determinant of worsening renal function (4). Consequently, the cardiorenal syndrome, once thought to be simply a consequence of ineffective arterial flow, has been redefined to include recognition of venous congestion as a determinant of renal function.

Limitations

There are several important limitations of this analysis. Our data cannot resolve whether the venous congestion *per se*, or the underlying pathophysiology that leads to venous congestion, accounts for the increased risk. Given the complexity and often subclinical nature of sodium-retaining disease processes, including systolic and diastolic left heart failure, cor pulmonale due to pulmonary disease, hepatic dysfunction, and renal disease, it is not possible to identify the cause of peripheral edema, as is often the case with clinical medicine.

In addition, we were unable to distinguish lymphedema that might occur with mechanical obstruction from peripheral edema. However, in a sensitivity analysis of those with documented BMI, peripheral edema remained associated with mortality and was not modified by BMI. We also had no knowledge about the patients' nutritional status. In addition, we did not know the cause of death, either within hospital or at follow up, further limiting potential mechanistic explanations. Finally, CVP measurements were likely affected by within-ICU care.

Conclusions

Our findings should raise awareness of the importance of peripheral edema in hospitalized patients, as detected on physical examination. At the very least, peripheral edema is a clinically valuable indicator of underlying pathophysiology, and is associated with an increased risk of mortality. Whether dietary or pharmacologic interventions to lessen venous congestion might improve outcomes will require further study. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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