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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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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 Q4 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

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