Acute worsening of renal function is common in hospitalized patients with acute decompensated heart failure and is associated with increased risk of hospital readmission and both in-hospital and postdischarge mortality. The pathogenesis of worsening of renal function in hospitalized heart failure patients is thought to be attributable to 2 interdependent multifactorial mechanisms: (1) a short-term and in most cases reversible decrease in glomerular filtration due to decreased renal blood flow, pharmacological inhibition of angiotensin-II signaling, sympathetic activation, and tubuloglomerular feedback mechanisms and (2) a longer-term and in some cases irreversible ischemic renal tubular injury triggered by decreased renal oxygen supply (due to decreased arterial perfusion pressure, increased renal vein pressure, and anemia) and/or increased renal oxygen demand (caused by increased tubular sodium and water reabsorption mediated by activation of vasoconstrictor hormones and tubuloglomerular feedback mechanisms). Clinical observation of the time course for return to predmission serum creatinine levels is most often used to retrospectively determine the principal underlying mechanism in individual patients. Because there is no definitive diagnostic test to uncover the mechanism of worsening renal function, it is uncertain how these underlying causes relate to increased risk of in-hospital and postdischarge adverse outcomes.

Loop diuretics, the most commonly prescribed class of drugs in patients with acute decompensated heart failure, have been implicated in the pathogenesis of worsening renal function. Loop diuretics immediately reduce glomerular filtration by activation of neurohormonal and tubuloglomerular feedback mechanisms but are also known to increase renal medullary oxygen tension and reduce tubular injury in experimental models of acute ischemic kidney injury through inhibition of the Na-K-2Cl pump with consequent reduction of renal oxygen consumption in the ascending loop of Henle. The net effect of loop diuretics on serum creatinine in individual patients is likely determined by the interaction of these pharmacological actions with other clinical factors such as intravascular volume status, concomitant medications, and intrinsic chronic kidney disease. Concern about the safety of loop diuretics has engendered clinical trials to identify alternative therapies for reducing congestion in acute decompensated heart failure (ultrafiltration, natriuretic peptides, vasopressin receptor antagonists, and adenosine type-1 receptor antagonists). Meanwhile, clinicians are faced with the quandary as to whether guideline-recommended use of loop diuretics in the treatment of acute decompensated heart failure is a “necessary evil” that may potentially be doing harm.

The retrospective analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial database reported in this issue of Circulation by Testani and colleagues introduces a new level of complexity to the understanding of the links between diuretic use, renal function, and mortality. The subgroup of subjects with the greatest degree of hemoconcentration (as evidenced by an increase in serum levels of albumin and total protein and/or increase in hematocrit in response to treatment during hospitalization) received higher doses of loop diuretics, had increased risk of worsening renal function (defined in this study as a ≥20% decrease in estimated glomerular filtration rate) but also had markedly reduced posthospitalization mortality when compared with subjects who did not show evidence of hemoconcentration. Because hemoconcentration is most likely attributable to reduction of plasma volume in the intravascular space by loop diuretics, these findings provide some reassurance about the safety of this therapeutic class in patients with heart failure. These findings are in accord with previous observational studies, which have consistently demonstrated that volume overload in heart failure, as evidenced by hemodynamic measurements, physical findings of congestion (S3 gallop and elevation of jugular venous pressures), or directly measured increased blood volume, is associated with greater risk of worsening renal function and adverse clinical outcomes.

Although the retrospective nature of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness subgroup analysis does not permit inference of causal relationships, these findings support the hypothesis that more aggressive decongestion therapy (as evidenced by intravascular volume reduction sufficient to cause hemoconcentration) may be associated with increased survival in patients with decompensated heart failure despite transient worsening of renal function. Potential mechanisms linking decongestion with improved outcomes include reduction in preload-dependent functional mitral regurgitation and ventricular remodeling, reduced inflammation due to relief of congestion-induced changes in vascular endothelial cell phenotype, improved renal perfusion associated with reduced renal...
vein pressures, and reduced peripheral vascular resistance due to relief of tissue congestion in skeletal muscle.\textsuperscript{15}–\textsuperscript{17} Clinical trials of strategies to optimize decongestion therapy with indirect measures of intravascular volume (hemodynamic measurements and brain natriuretic peptide levels) have failed to consistently demonstrate superiority over standard care.\textsuperscript{18}–\textsuperscript{20} Whether these findings reflect the diagnostic limitations of these surrogate measures of intravascular volume, or other clinical and pharmacological factors related to reduction of vascular congestion remains unknown.

There are several caveats to consider in the interpretation and clinical implementation of the presented findings. Since the population of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial had severe but not necessarily acutely decompensated heart failure, further work is needed to determine the relationship between hemoconcentration, renal function, and clinical outcomes in other retrospective or prospective studies of patients with acute decompensated heart failure. Hematocrit monitoring for detection of hemoconcentration during dialysis and ultrafiltration procedures was developed to assess minute-by-minute changes of the plasma volume in settings of rapid mechanical volume removal. Although the same principles are likely operative over a longer time scale during a heart failure hospitalization, the optimal timing to assess for hemoconcentration is uncertain given heterogeneity in the diuretic response and plasma refill rate from the extravascular space. The assessment of hemoconcentration based solely on small changes in concentration of albumin, total protein, and hematocrit may be influenced by other factors that alter concentration of these markers during therapy (improved hepatic function in response to relief of right-sided congestion and subclinical bleeding events, including repeated phlebotomy for laboratory monitoring). Moreover, use of hemoconcentration as a measure of treatment effectiveness cannot be readily translated to clinical practice because the target values for increased albumin, total protein, and/or hematocrit are unknown for individual patients. One potential approach to resolve this dilemma is to directly measure the red blood cell volume and plasma volume with a radiolabeled dye dilution technique.\textsuperscript{10} Such direct blood volume measurements in addition to existing measures of intravascular volume, or other clinical and pharmacological factors related to reduction of vascular congestion remains unknown.

Disclosures
Dr Katz is the principal investigator for the multicenter TEAM-HF study sponsored by Daxor Corp. He receives no payments from Daxor.

References


**KEY WORDS:** Editorials heart failure loop diuretics outcomes assessment
The Plot Thickens: Hemoconcentration, Renal Function, and Survival in Heart Failure
Stuart D. Katz

_Circulation_. 2010;122:233-235; originally published online July 6, 2010;
doi: 10.1161/CIRCULATIONAHA.110.965293

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/122/3/233

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/