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Timing of Hemoconcentration During Treatment of Acute Decompensated Heart Failure and Subsequent Survival

Importance of Sustained Decongestion

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Objectives This study sought to determine if the timing of hemoconcentration influences associated survival.

Background Indicating a reduction in intravascular volume, hemoconcentration during the treatment of decompensated heart failure has been associated with reduced mortality. However, it is unclear if this survival advantage stems from the improved intravascular volume or if healthier patients are simply more responsive to diuretics. Rapid diuresis early in the hospitalization should similarly identify diuretic responsiveness, but hemoconcentration this early would not indicate euvolemia if extravascular fluid has not yet equilibrated.

Methods Consecutive admissions at a single center with a primary discharge diagnosis of heart failure were reviewed ($N = 845$). Hemoconcentration was defined as an increase in both hemoglobin and hematocrit levels, then further dichotomized into early or late hemoconcentration by using the midway point of the hospitalization.

Results Hemoconcentration occurred in 422 (49.9%) patients (41.5% early and 58.5% late). Patients with late versus early hemoconcentration had similar baseline characteristics, cumulative in-hospital loop diuretic administered, and worsening of renal function. However, patients with late hemoconcentration versus early hemoconcentration had higher average daily loop diuretic doses ($p = 0.001$), greater weight loss ($p < 0.001$), later transition to oral diuretics ($p = 0.03$), and shorter length of stay ($p < 0.001$). Late hemoconcentration conferred a significant survival advantage (hazard ratio: 0.74 [95% confidence interval: 0.59 to 0.93]; $p = 0.009$), whereas early hemoconcentration offered no significant mortality benefit (hazard ratio: 1.0 [95% confidence interval: 0.80 to 1.3]; $p = 0.93$) over no hemoconcentration.

Conclusions Only hemoconcentration occurring late in the hospitalization was associated with improved survival. These results provide further support for the importance of achieving sustained decongestion during treatment of decompensated heart failure. (J Am Coll Cardiol 2013;62:516–24) © 2013 by the American College of Cardiology Foundation

The primary therapeutic objective in the majority of patients hospitalized with acute decompensated heart failure (ADHF) is optimization of volume status (1,2). Unfortunately, determining the optimal stopping point for decongestive therapies remains a major challenge (1). Notably, the increase in concentration of red blood cells and plasma proteins induced by intravascular volume contraction, known as hemoconcentration, provides a surrogate for changes in intravascular volume status during fluid removal (3–5). In the setting of ADHF treatment, hemoconcentration seems to identify patients who have undergone aggressive decongestion and has been associated with better post-discharge survival (6–8). However, hemoconcentration merely indicates that the plasma refill rate has been exceeded (i.e., fluid has been removed from the intravascular space faster than it could be replaced by extravascular fluid). As a result, hemoconcentration in isolation does not inform total body volume status. Importantly, previous studies of hemoconcentration focused on hemoconcentration at the time of

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discharge, a time when overall volume status should have been optimized. As such, the majority of patients with hemoconcentration in these studies had objective evidence of improvement in intravascular volume (hemoconcentration) in addition to having the treating physician deem their overall volume status sufficiently optimized to permit discharge.

Interpretation of these observations is challenging because it is unclear to what degree this survival advantage stems from a cause-and-effect association with aggressive decongestion or simply from the fact that hemoconcentration may occur more commonly in patients who are diuretic responsive and are therefore healthier. However, if a patient underwent diuresis early in an ADHF hospitalization with sufficient rapidity to exceed the plasma refill rate, intravascular volume contraction and hemoconcentration would occur. This outcome would be true even if extravascular volume overload persisted at the time of hemoconcentration. However, as diuresis was slowed (perhaps prematurely in response to the improved signs of intravascular volume status), extravascular fluid would equilibrate, leading to recurrence of intravascular volume overload and loss or reduction in the degree of hemoconcentration. Importantly, both early hemoconcentration (early HC) and late hemoconcentration (late HC) should identify treatment-responsive patients. However, the degree of volume optimization achieved over the hospitalization would likely be superior in patients with the peak degree of hemoconcentration in proximity to discharge, when extravascular volume status should be optimized to a greater degree. As a result, comparing the survival of patients with peak hemoconcentration early versus late in the hospitalization could provide some insight into the relative importance of aggressive decongestion versus treatment responsiveness in the improved survival associated with hemoconcentration. As such, the primary objective of the current study was to evaluate the association between the timing of peak hemoconcentration and subsequent survival.

Methods

Consecutive admissions from 2004 to 2009 to non-interventional cardiology and internal medicine services at the Hospital of the University of Pennsylvania with a primary discharge diagnosis of congestive heart failure were reviewed. Inclusion into this single-center study required an admission B-type natriuretic peptide (BNP) level of >100 pg/ml within 24 h of admission along with serial hematocrit (Hct) and hemoglobin (Hgb) levels. To focus primarily on the physiology and timing of decongestion, patients with a length of stay <3 days (who likely underwent limited decongestion) and patients with length of stay >14 days (who likely had either atypical degrees of congestion or nondiuresis-related problems driving the length of stay) were excluded. Patients undergoing renal replacement therapy were also excluded. In the event of multiple hospitalizations for a single patient, only the first admission meeting the aforementioned inclusion criteria was retained. Online Figure 1 provides additional details on patient selection.

Abbreviations and Acronyms

ADHF = acute decompensated heart failure
BNP = B-type natriuretic peptide
CI = confidence interval
eGFR = estimated glomerular filtration rate
HC = hemoconcentration
Hct = hematocrit
Hgb = hemoglobin
HR = hazard ratio
IQR = interquartile range
OR = odds ratio
WRF = worsening renal function

Hemoconcentration was defined as an increase in both Hct and Hgb levels above admission values at any time during the hospitalization. Two positive markers of hemoconcentration were required to improve the signal-to-noise ratio and to maintain some consistency with our previous hemoconcentration definition (7). For the primary analyses, the timing of hemoconcentration was determined by averaging the percentage of the hospital stay that had elapsed at the time of the peak Hct and Hgb levels, then dichotomizing this value into early HC and late HC by using the 50% point. The relative timing of hemoconcentration was chosen to focus on a patient's overall improvement in intravascular volume status, rather than the degree of euvolemia achieved after an arbitrary period of time. This distinction is of practical importance for 2 reasons: 1) the amount of baseline extravascular volume overload present in each patient is highly variable; and 2) extravascular and intravascular volumes are in equilibrium. As a result, intravascular euvolemia will on average take longer to achieve if severe extravascular volume overload is present at baseline and therefore confound the absolute time to peak hemoconcentration by the degree of baseline volume overload. Secondary analysis focused on the absolute time to peak hemoconcentration with adjustment for length of stay.

Estimated glomerular filtration rate (eGFR) was calculated by using the 4-variable Modification of Diet in Renal Disease equation (9). Worsening renal function (WRF) was defined as a ≥20% decrease in eGFR at any time during the hospitalization (7,10–14). All-cause mortality was determined via the Social Security Death Index (15). Loop diuretic doses were converted to furosemide equivalents with 1 mg of bumetanide = 20 mg of torsemide = 80 mg of furosemide for oral diuretics, and 1 mg of bumetanide = 20 mg of torsemide = 40 mg of furosemide for intravenous diuretics. Average daily loop diuretic doses were calculated by dividing the total dose of loop diuretics over the hospitalization (in furosemide equivalents) by the hospital length of stay. Given that hospital admissions over a 5-year period were analyzed, a sensitivity analysis was undertaken to ensure that the primary findings were consistent over this observation period and thus the cohort could be analyzed as a whole. There was no significant difference in the findings between the first quartile enrolled and the fourth quartile enrolled (p interaction = 0.52) or continuously across the enrollment interval (p interaction = 0.23). The study was approved by the institutional review board of the Hospital of the University of Pennsylvania.