Diuretic Response: Clinical and Hemodynamic Predictors and Relation to Clinical Outcome

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ABSTRACT

Objective: The aims of this work were to investigate the clinical and hemodynamic profile underlying the response to loop diuretics in acute decompensated heart failure (ADHF), and to compare the relative usefulness of measures of diuretic resistance for predicting mortality.

Methods and Results: We studied 475 patients with ADHF, of whom 241 underwent right heart catheterization. Linear regression models were used to identify factors that affected urine output. Loop diuretics response was estimated as 1) net fluid loss per 40 mg furosemide equivalents and 2) urine output produced per 40 mg furosemide equivalents. In a multivariable regression model, key independent predictors of urine output included diuretic dose (partial $r = 0.44$), baseline renal function (partial $r = 0.38$), systolic blood pressure (partial $r = 0.26$), and fluid intake (partial $r = 0.31$; all $P < .0001$). Among hemodynamic variables, elevated right atrial pressure was associated with greater urine output (partial $r = 0.19$; $P = .002$). The partial correlation attributable to diuretic dose (partial $R^2 = 0.19$) accounted for approximately one-half of the variance in urine output explained by the model (model $R^2 = 0.40$).Cox regression models demonstrated inverse relationships between quartiles of net fluid loss ($P = .004$) and quartiles of urine output ($P = .04$) per 40 mg furosemide and 6-month mortality. When comparing nested models, the model based on net fluid loss was better than the model based on urine output for the prediction of mortality ($\chi^2 = 8.1$; 3 *df*; $P = .04$).

Conclusions: In patients with ADHF, beyond diuretic dose, other parameters including renal function, hemodynamic status, the degree of volume overload, and fluids intake also affect urine output. Measures of loop diuretic response are associated with short-term mortality. (*J Cardiac Fail 2016;22:193−200*)

Key Words: Acute heart failure, Diuresis, central venous pressure, congestion.

The ability to sustain filtration and tubular functions of the kidneys during therapeutic interventions in patients with acute decompensated heart failure (ADHF) is vital to successful alleviation of congestion. The Acute Decompensated Heart Failure National Registry (ADHERE) and other studies have shown that most ADHF hospitalizations are due to congestion in patients refractory to oral diuretics.[1−3] Despite use of intravenous loop diuretics, the average hospitalization for ADHF is 4.3 days, with 42% of the patients discharged with unresolved symptoms, 50% losing ≤5 pounds, and 20% gaining weight during the hospitalization.[1] Unresolved congestion contributes to high readmission rates seen in this patient population.[4−6]

In >90% of patients who are hospitalized for ADHF, intravenous loop diuretics are used to relieve congestion.[7] During loop diuretic therapy, particularly in the acute setting, a marked reduction in efficacy frequently occurs, which is described as "diuretic resistance." However, there is no clinically vetted and commonly applied measure of diuretic resistance. Thus, although patients are frequently perceived as having an unsatisfactory response to diuretic treatment, the underlying causes remain unclear.

Recent studies have argued that the amount of urine produced indexed to the diuretic dose,[8] or weight loss per unit loop diuretic[9,10] should be used to assess the response to diuretics. In the present study, we sought to determine

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the clinical and hemodynamic profile associated with reduced urine output among patients admitted for ADHF. In addition, we compared the relative usefulness of various measures of diuretic resistance for the prediction of mortality.

Methods

Patients

The study population included patients enrolled in the Vasodilation in the Management of Acute Congestive Heart Failure study (VMAC), a randomized multicenter trial comparing the hemodynamic and clinical effects of nesiritide and nitroglycerin in patients with ADHF. Study design and main results have been published previously.[11]

Briefly, inclusion criteria included dyspnea at rest, while supine or immediately upon minimal activity, and signs of congestion or measured elevation of cardiac filling pressures (pulmonary capillary wedge pressure [PCWP] ≥20 mm Hg in catheterized patients).[11] The protocol was approved by the Institutional Review Board of the participating hospitals. Written informed consent was obtained from each patient before initiation of therapy.

Hemodynamic Evaluation

In the VMAC trial, randomization was stratified based on the investigator's clinical decision, before randomization, to use a right heart catheter to manage decompensated heart failure (''catheterized'' or ''noncatheterized'' strata). In the catheterized group, PCWP, mean pulmonary arterial pressure (mPAP), cardiac output (CO), and mean right atrial pressure (RAP) were measured at baseline (before the initiation of study drugs) and at several time points during the 1st 24 hours.[11,12]

Assessment of Renal Function

Venous blood samples for creatinine levels were obtained at baseline and on days 2, 5, 14, and 30 of the study. Estimated glomerular filtration rate (eGFR) was derived with the use of the abbreviated Modification of Diet in Renal Disease study equation.[13]

Fluid Balance

Fluid balance was rigorously monitored: the recording period for urine output/fluid intake was from the void just before the start of study drug to the void ≥24 hours after the start of study drug. Net fluid balance was defined as the sum of daily fluid intake minus total output,[14] with negative values indicating net fluid loss and positive values indicating net fluid gain.

Diuretic Response

Furosemide-equivalent doses (as intravenous) were calculated with the use of the following conversion factors: bumetanide: 1 mg = 40 mg; torsemide: 1 mg = 2 mg; furosemide oral: 1 mg = 0.5 mg.[9,10] The effectiveness of the response to loop diuretics was determined as urine output during the 1st 24 hours of the study per 40 mg furosemide administered.[8] We also assessed diuretic response based on net fluid removal per 40 mg furosemide, because this metric assesses the overall effectiveness of diuretic-induced decongestion, akin to weight change per 40 mg furosemide.[9,10]

Statistical Analysis

Continuous variables are presented as mean (SD) or median (interquartile range [IQR]), categoric variables as n (%). Baseline characteristics of the groups were compared by means of analysis of variance (ANOVA) for continuous variables and χ^2 statistic for noncontinuous variables. When continuous data was not normally distributed, groups were compared with the use of the nonparametric 1-way ANOVA (Kruskal-Wallis test). The nonparametric Jonckheere-Terpstra (nonparametric) test for linear trend was performed to determine the association between increasing quartiles of diuretic dose and urine output.

The distribution of urine output and other variables, such as diuretic dose, was skewed. Therefore, logarithmically transformed values were used. The associations between urine output and clinical characteristics, biochemical variables, and hemodynamic data were assessed with the use of univariable linear regression of ln urine output on each variable separately. Variables found to have a univariable association with urine output at the $P < .1$ level (Wald test), were used in a multiple linear regression with backward selection. Baseline variables considered for inclusion in the model included: age, sex, body mass index, New York Heart Association functional class, history of hypertension, history of diabetes, atrial fibrillation, eGFR, baseline systolic and diastolic blood pressures, left ventricular ejection fraction, randomization to nesiritide (vs nitroglycerin), dose of loop diuretic, use of metolazone, use of inotropes, and vasoactive therapy assignments (nesiritide or nitroglycerin). We also considered fluid intake, change in blood pressure, and change in eGFR from day 1 to day 2.

Similar models limited to the catheterized stratum (n = 241) were constructed to include the following hemodynamic variables: RAP, PCWP, mPAP, CO, and cardiac index. Specification of continuous covariates (linear vs categoric) was guided by each covariate's observed association with outcome with the use of restricted cubic splines.[15] Partial correlation coefficients were used to estimate the proportion of variance of dependent variables explained by each independent variable.

Survival curves were constructed with the use of the Kaplan-Meier method, and compared with the use of the log-rank test. Stepwise Cox proportional hazards models with backward selection were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for quartiles of urine output per 40 mg furosemide and quartiles of net fluid loss per 40 mg furosemide. The multivariable models were adjusted for all the variables listed in Table 1 that showed a univariable association with mortality at the $P < .10$ level.

Nested models were compared with the use of likelihood ratio tests to determine whether the Cox regression models that included quartiles of urine output per 40 mg furosemide and quartiles of net fluid loss per 40 mg furosemide provided significantly better fit than did Cox regression models limited to quartiles of urine output per 40 mg furosemide and vice versa. In addition, comparison of non-nested models that included either quartiles of urine output per 40 mg furosemide or quartiles of net fluid loss per 40 mg furosemide was performed by calculating the Akaike information criterion (AIC).

All statistical analyses were performed with the use of Stata statistical software version 13.1 (College Station, Texas).