Volume Overload and Quantitated Blood-Plasma Volume: How Effective is Intravenous Diuretic Therapy in Patients Hospitalized for Decompensated Chronic Heart Failure?

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Abstract

Background: The assessment and management of fluid volume overload has been a recurrent and perplexing issue in the management of patients hospitalized and often re-hospitalized with decompensated heart failure (DHF). The objective of this study was to quantitate plasma volume (PV) status in patients with DHF, and to determine the effectiveness of standard in hospital diuresis management in reducing volume overload, and if the quantitation of PV could serve as a tool to guide more effective in-hospital diuretic therapy to achieve practice guideline-recommended euvolemia.

Methods: TBV-PV was measured in patients with a history of chronic HF admitted to hospital for management of clinically determined volume overload. Intravascular volume was determined by a validated radiolabeled-albumin dilutional technique (Volumex, Daxor Corp., NY, NY) at hospital admission and at hospital discharge. Normal PV is defined pre hoc as measured volumes within ±8% of the expected normal value; mild-moderate volume expansion is ≤20% of predicted normal value. Volume status reported as absolute value and percentage of the normal value for the individual patient. Changes in quantitated volume status pre-post diuretic therapy were compared to clinical parameters of volume assessment [(body weight change; net fluid input and urine output (I/Os)].

Results: Twenty-six patients were evaluated (73±9 yrs, sCr 1.8±0.9 mg/dL, LVEF 38±18%, LOS 6.3±2.1 days). All patients except 3 received intravenous loop diuretic therapy (furosemide) at 10-20mg/hr for average of 5±2 days. The remaining 3 patients received oral furosemide equivalent of 80-160mg per day. Admission to discharge PV and clinical parameters are shown below:

	Admission	Discharge
Measured PV	4.7±1.1 Liters	4.3±1.0 Liters
Normal Expected PV	3.2±0.4 Liters (Euvolemia)	
PV Expansion	+46±30%	+34±22% (p=0.214)
Change in Body weight		-7.0±4.6 kg
Net I/Os		-7.4±6.5 Liters

Conclusions: Quantitated PV demonstrates that patients with DHF are significantly intravascularly volume expanded and that usual clinically-guided diuretic therapy only marginally impacts volume status at discharge despite large reductions in body weight and high net negative I/Os. Mobilization of interstitial volume intravascularly likely accounts for this disparity and suggests that DHF patients require longer periods of, or more effective diuretic therapy, to achieve euvolemia. Longer LOS may, however, be compensated by lower rates of 30-day re-hospitalization.

No Disclosures to Report

Introduction

- Volume overload and abnormal fluid distribution are front-line features of the syndrome of decompensated chronic heart failure (DHF). The clinical assessment of total blood volume (TBV), particularly in determining euvolemia in the context of aggressive diuretic therapy, remains a significant challenge for most clinicians. Surrogate markers such as the presence or absence of elevated JVP, dyspnea, edema, or S3, however, lack sensitivity and reliability.
- The interplay of multiple factors [TBV, interstitial fluid volume, oncotic pressures (albumin concentration), absolute systolic blood pressure, anemia (dilutional or true anemia), diuretic and vasodilator therapies, and intrinsic renal function] significantly affect fluid distribution of interstitial and intravascular volume expansion.
- The aim of the study was to determine TBV status at the time of hospital admission for DHF in patients considered clinically volume overloaded. Also, using serial measurements of TBV, we sought to evaluate the response to standard loop diuretic therapy in achieving guideline-recommended euvolemia prior to hospital dismissal, and to assess the intravascular-interstitial contribution of overall body fluid loss.
- Our study hypothesis is that DHF patients will, by the quantitation of TBV, demonstrate hypervolemia characterized by heterogeneity in TBV, RCV, and PV distributions. Additionally, serial TBV measurements will demonstrate persistent hypervolemia, despite standard diuretic therapy and the presence of clinical indicators of volume reduction [reduced body weight and net negative urine output minus oral intake (negative I/Os)].

Methods

- Total Blood Volume (TBV) was measured in patients with a history of chronic HF admitted to hospital for management of clinically determined volume overload.
- Intravascular volume was determined by a validated radiolabeled-albumin dilutional technique (Volumex, Daxor Corp., NY, NY) at hospital admission and at hospital discharge.
- Normal TBV was defined pre hoc as measured volumes within ±8% of the expected normal value. Volume status reported as absolute value and percentage of the normal value for the individual patient. The TBV-PV measurement technique has an accuracy of ±2.5%.
- Changes in quantitated volume status pre-post diuretic therapy were compared to clinical parameters of volume assessment [(body weight change; net fluid input and urine output (I/Os)].

Results

- The study cohort consisted of 26 patients admitted to St Mary's Hospital, Mayo Clinic, Rochester, MN for DHF and considered to require aggressive diuretic therapy by the primary hospital service for symptomatic volume overload, and who also met inclusion/exclusion criteria.
- The clinical characteristics and demographics for this cohort are shown in Table 1.
- TBV analysis was undertaken at admission in this group, and of this group, 17 patients also had BV quantitated at hospital discharge. Two of the 26 patients were, by pre-hoc definition (total BV expansion ≤8%), euvolemic at admission with a mean deviation from normal expected TBV value of +4±5%; and 24 were hypervolemic (Table 2).
- The frequency of volume distributions (Total Blood, Red Cell, and Plasma Volumes) for the patients with hypervolemia at admission are shown in Figures 1A, 1B, and IC. No patients demonstrated volume contraction hypovolemia at admission.

Table 1. Baseline Characteristics of Patients Hospitalized for Decompensated Chronic HF (N=26)

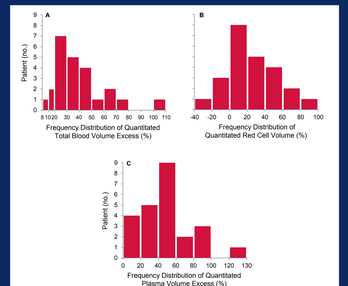
Variable		Variable	
Age, years	73±9	Etiology of HF	Ischemic: 15 Non-Ischemic: 11
Gender, male	18	NT-proBNP, pg/mL	4886 (2522, 12361)
BMI, kg/m²	35±9	Albumin, g/dL	3.7±0.3
LVEF, %	38±18	K+, mEq/L	4.4±0.5
LOS, days	6.0±2.4	Na+, mEq/L	139±4.3
Blood Pressure, systolic, mmHg	120±18	sCr, mg/dL	1.8±0.9
Diabetes, %	12	BUN, mg/dL	44±23
Hypertension, %	20	Hemoglobin, g/dL	12.2±2.2
CAD, %	18	Hematocrit, %	38±6.2
Afib, %	15	Plasma glucose, mg/dL	111±24

Table 2. Blood Volume Analysis in Patients with Decompensated Chronic Heart Failure – Hospital Admission (N=24)

Variable	Total Blood Volume	Red Cell Volume	Plasma Volume
Admission, liters	7.4±1.6 (5.0-11.9) 72mL/kg (CL 66-85)	2.6±0.8 (1.4-4.7)	4.8±1.0 (2.9-7.8)
Expected Normal, liters	5.3±0.7 (3.8-6.5)	2.1±0.3 (1.4-2.7)	3.2±0.4 (2.5-3.9)
Volume Expansion, Admission, %	+39±22% (+9.5 to +107%) (2.1±1.2 L)	+25±27% (-24 to +65%) (0.5±0.7 L)	+49±28% (+13 to +128%) (1.6±0.9 L)

Data Expressed as Mean ± SD and (range of values)

Figure 1



A. Total Blood Volume in Hypervolemic Chronic Heart Failure Patients Admitted to Hospital with Clinically Determined Volume Overload (n=24). **B.** Red Cell Volume in Hypervolemic Chronic Heart Failure Patients Admitted to Hospital with Clinically Determined Volume Overload (n=24). **C.** Plasma Volume Excess in Hypervolemic Chronic Heart Failure Patients Admitted to Hospital for Clinically Determined Volume Overload (n=24).

Results *(cont)*

- Changes in Volume and Fluid Distribution in Response to Diuretic Therapy – Admission and dismissal characteristics of the 17 patients who had TBV quantitated both at hospital admission and discharge are shown in Table 3, and the changes in TBV, RCV, and PV with diuretic therapy are shown in Table 4.
- The diuretic regimen resulted in relatively minor changes in the quantitated TBV at dismissal with less than 1 liter of net fluid demonstrated to be reduced from the intravascular compartment.
- The relatively minor quantitated intravascular volume change was, however, in the setting of large reductions in body weight (-6.9±5.2 kg) and net negative I/Os (- 8.4±5.2 liters) during this same period. The change in body weight over the short duration of this study was assumed to be equivalent to changes in total body water. Thus, the change in observed body weight in liters less the reduction in TBV reflects fluid loss from the interstitial compartment occurring as a result of transcapillary refill to the intravascular compartment. The calculated volume is shown in Table 4.
- However, even with this diuretic-induced fluid loss, the quantitated TBV and PV at hospital discharge remained persistently expanded by +30±16% and +38±18%, respectively. This reflects a persistent hypervolemia of TBV 1.5±0.9 liters and PV 1.2±0.6 liters. The frequency distributions of the TBV and PV at dismissal are shown in Figure 3A and 3B.

Table 3. Admission and Dismissal Characteristics (N=17)

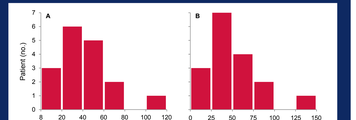
Variable		Variable	
Age, years	74±10	Albumin, g/dL	A: 3.6±0.3 D: 3.5±0.4
Gender, male	13	Na+, mEq/L	A: 138±5 D: 139±4
BMI, kg/m²	34±8	K+, mEq/L	A: 4.3±0.4 D: 4.0±0.4
LVEF, %	34±16	sCr, mg/dL	A: 2.0±1.1 D: 2.0±1.1
LOS, days	6.7±1.4	BUN, mg/dL	A: 50±27 D: 52±23
Change in weight, kg	-6.9±5.2 (-1.3 to -17.9kg)	Hemoglobin, g/dL	A: 12.6±2.4 D: 12.8±2.2
Net I/Os, liter	-8.4±5.2 (-1 to -19.8 liters)	Hematocrit, %	A: 40±6.8 D: 39±6.3
NT-proBNP, pg/mL	5458 (CL 3657, 12361)	Normalized Hematocrit, %	A: 55±14 D: 52±12
BP, systolic, mmHg	A:122±17 D: 116±16	Plasma glucose, mg/dL	A: 113±22 D: 117±28

Table 4. Change in Volumes in Response to Diuretic Therapy in Hypervolemic Patients (N=17)

Variable	Total Blood Volume	Red Cell Volume	Plasma Volume
Admission, liters	7.4±1.6 (4.6-11.9)	2.6±0.9 (1.5-4.7)	4.7±1.2 (2.7-7.8)
Dismissal, liters	6.7±1.3* (4.9-8.9)	2.4±0.7* (1.3-4.4)	4.3±0.8* (3.0-5.9)
Net Change, liters	-0.7±1.1	-0.2±0.3	-0.5±0.8
Expected normal, liters	5.3±0.8	2.1±0.4	3.2±0.4
Volume expansion, admission	+40±27% (2.1±1.5 L)	+25±20% (0.5±0.7 L)	+49±32% (1.6±0.9 L)
Volume expansion, dismissal	+30±16% (1.5±0.9 L)	+21±20% (0.3±0.4 L)	+38±18% (1.2±0.6 L)

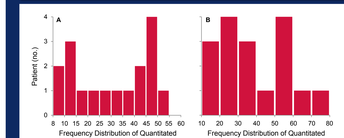
Interstitial Trans-capillary Refill Volume, 6.2±4.0 Liters
Percent of total Volume Loss Derived from the Interstitial Space, 85±15%
(Change in Body Weight (in Liters) minus Change in Total BV)
*p>0.05, NS

Figure 2



A. Total Blood Volume in Hypervolemic Chronic Heart Failure Patients at Admission to Hospital (n=17) **B.** Plasma Volume Excess in Hypervolemic Chronic Heart Failure Patients at Admission to Hospital (n=17)

Figure 3



A. Total Blood Volume Status at Hospital Dismissal in Hypervolemic Chronic Heart Failure Patients Post-Diuretic Therapy (n=17) **B.** Plasma Volume Status at Hospital Dismissal in Hypervolemic Chronic Heart Failure Patients Post-Diuretic Therapy (n=17)

Summary

- There is marked heterogeneity in intravascular volume composition and overload (range 10% to over 100%) in patients with DHF.
- Pathologic red cell volume expansion, as well as, plasma volume expansion are common in DHF patients.
- Despite large total body fluid loss with diuretic therapy as reflected in large reductions in body weight and net negative I/Os, persistent intravascular hypervolemia (+30%) was present at hospital dismissal.
- The major component of volume loss with diuretic therapy is derived from the interstitial compartment (85% in this cohort).

Conclusions

- The quantitation of TBV, RCV, and PV in individual HF patients, particularly serial quantitative measurements, would appear to permit a better pathophysiologic-based understanding of the distribution and heterogeneity of expanded fluid volume and provide a direct measurement to guide appropriate volume management and support a tailored approach to diuretic therapy.
- The persistent TBV expansion at discharge suggests that DHF patients may require additional adjustments of their diuretic and/or vasodilator medications to achieve euvolemia.
- Whether longer length of hospital stays to achieve euvolemia in DHF patients can be justified is not clear at present, but a hypothesis that longer lengths of stay with quantitated TBV-guided management would be compensated by reductions in 30-day re-hospitalization rates and better long-term outcomes merits study - A randomized clinical trial of TBV analysis-guided vs. standard clinically-guided volume management to assess long-term and short-term outcomes to include 30-rehospitalization rates in DHF patients.

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