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Calculated Estimates of Plasma Volume in Patients with Chronic Heart Failure – Comparison to Measured Volumes

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Abstract

Background: Calculated estimates of plasma volume (PV) have been developed using hemoglobin/hematocrit-body weight based methods. The accuracy of such formula-derived values has not been thoroughly evaluated. The objective of this analysis is the comparison of calculated vs. a quantitative measure of PV in patients with chronic heart failure (HF).

Methods: PV was measured using a standardized computer-based indicator-dilution labelled albumin technique in 110 patients with clinically stable chronic HF and correlated with paired Kaplan-Hakim (K-H) and Strauss formula estimates of PV.

Results: The K-H formula underestimated (3.4 ± 0.7 L) and Strauss formula overestimated (5.3 ± 1.5 L) PV relative to the measured volumes (4.3 ± 1.1 L). Calculated PV was only moderately correlated with measured PV by the K-H formula ($r=0.64$, $p<0.001$) and weakly by Strauss formula ($r=0.285$, $p=0.003$). Strauss formula estimates of change (%) in PV were also poorly correlated with paired measured changes in PV ($r=0.162$, $p=0.999$, $N=40$).

Conclusions: Calculated estimates of PV demonstrate limited association with measured volumes. These findings indicate that while formula-based estimates of PV have been shown to have prognostic value they are limited in their reliability for volume management in patients with chronic HF.

Keywords

formula estimated plasma volume; measured plasma volume; chronic heart failure

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Conflicts of Interest
None.

INTRODUCTION

Volume overload with clinical congestion remains a prominent issue in the management of patients with chronic heart failure (HF) and has significant prognostic implications.^{1,2} While direct quantification of plasma volume (PV) has been shown to have clinical utility to reveal the often unrecognized marked heterogeneity and relative severities in volume overload of patients with chronic HF,³⁻⁶ this methodology has not always been readily available to clinicians. Therefore, multiple surrogates have been advanced and utilized to provide an assessment of intravascular volume status. These surrogates have included physical signs and symptoms, hemodynamic parameters, and various biomarkers. One other form of surrogate volume assessment which is the focus of this analysis is the calculated estimates of PV commonly based on formulae incorporating venous hemoglobin or hematocrit and commonly body weight parameters.⁷⁻⁹ These estimates of PV have also been reported to be markers of clinical congestion and indices of long-term risk in patients with HF.¹⁰⁻¹² Hemoconcentration gauged by change in hemoglobin concentration over time as an indirect marker of change in PV has also been shown to trend with clinical assessments of congestion and decongestion.^{13,14} Accordingly, we undertook an analysis to compare calculated estimates of PV with quantitative measurements of PV with the intent to determine how well and reliably calculated estimates of PV and changes in PV compare with quantitative measurements of PV in patients with chronic HF. Our hypothesis was that calculated estimates of PV would demonstrate limited association with the “gold standard” quantitative method of PV measurement.

METHODS

Study cohort

Clinically stable patients with known chronic HF, NYHA Class III-IV, who were undergoing outpatient evaluation to assess their candidacy for LVAD implantation or cardiac transplantation or were being dismissed from hospital after diuretic therapy and stabilization for HF exacerbation (post-acute status) composed the cohort for this analysis of prospectively collected data. All patients had a quantitative measure of intravascular volume (blood volume analysis, BVA) obtained under stable hemodynamic conditions. A subset of patients who had BVA obtained at time of hospital dismissal or shortly thereafter also received a BVA at the time of hospital admission. All patients were receiving standard oral HF medical therapy at goal or highest tolerated doses including beta-blockers, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRA), and oral loop diuretics at the time of data collection. Standard blood laboratory test results were available clinically for all patients including venous hemoglobin (Hb) and hematocrit (Hct) values. Clinically available echocardiographic data obtained within 3 months of the BVA were also collected. Patient exclusion criteria were 1) age <18 years; 2) chronic kidney disease requiring hemodialysis or ultrafiltration; 3) symptomatic coronary artery disease; or 4) patients requiring advanced pharmacologic or device therapy for hemodynamic support; 5) females who were pregnant or of child-bearing potential. The study protocol was approved by the Mayo Foundation

Institutional Research Review Board as required by Minnesota Statute 144.335/CFR 21 (Part 50).

Quantitative Measurement of Plasma Volume

PV was quantified using the indicator-dilution method at the Mayo Clinical Nuclear Medicine Laboratory. The standardized computer-based clinically available technique was undertaken to administer low-dose (micro-Curie) ^{125}I -labeled albumin intravenously (Volumex, Daxor Corp., New York, New York).¹⁵ Expected normal reference volumes for the individual patient are incorporated into the computer analysis as previously described.¹⁶ This technique has been recommended for the quantitative assessment of plasma and total blood volume analysis for its precision, reproducibility, and **clinical validity**.¹⁷ The specifics of the technique and procedure have been previously reported.^{3,15,18} Volumes are reported as absolute values (in liters) and as percentage volume deficit (–) or excess (+) from the normal expected volumes. Normal quantitated PV and total blood volume (TBV) are defined as measured volume within –10% to +10% and –8% to +8%, respectively, of expected normal volumes.^{15,18} Therefore, volume deviations above or below these values reflect clinically significant intravascular volume overload or volume contraction, respectively.

Formula Calculations of Plasma Volume

Plasma volume and changes in PV were calculated from the following equations which have been previously reported and have been the principal formulations where utilized in clinical studies.^{7,8,10-12} **These formula-derived estimates of PV and related values were compared to quantitative PV measurements obtained in the same patient with data collected on the same day (paired data).**

Point Estimate of Plasma Volume

The Kaplan-Hakim formula⁷ calculates PV using data derived by curvefitting techniques of subjects' hematocrit and dry body weight. PV is defined as calculated PV (cPV) = $(1 - \text{hematocrit}) \times [a + (b \times \text{weight in kg})]$ where adjustment factors were $a = 1,530$ in males and 864 in females, and $b = 41$ in males and 47.9 in females. The ideal PV (iPV) which is the normal expected PV was calculated from a formula based on body weight: $\text{iPV} = k \times \text{weight (kg)}$ where the adjustment factor for k was 39 in males and 40 in females.¹¹

Relative plasma volume status (PVS) has been developed as an index of the degree to which a patient's calculated PV (cPV) has deviated from their ideal PV (iPV), which was calculated from data obtained from the Kaplan-Hakim formula⁷ and expressed as percent change: $\text{PVS} = [(cPV - iPV)/iPV] \times 100\%$.

Change in Estimated Plasma Volume

In a subset of the patient cohort where BVA was also obtained at the time of hospital admission as well as at discharge, the Strauss formula^{8,11} was used to calculate changes in PV over time using Hb and Hct concentrations which provide an estimate of relative change in PV (% change) over a specified period of time (ePVS) which for this analysis was change in PV from hospital admission to time of discharge or immediate post-discharge. Patients were in a steady-state hemodynamically stable status for all testing. Quantitated

measures of change in PV were obtained in relation to the calculated parameters. The formula^{8,11} used for calculating change in PV is the following: $ePVS = 100 \times [(Hb\ A/Hb\ D) \times (1 - Hct\ D)/(1 - Hct\ A)] - 100$, where A= admission and D=discharge/post-discharge. A calculation of estimated PV at the time of discharge was also derived from the Strauss formula and compared to the measured PV at the time of discharge or immediate post-discharge. The formula used is the following: $estimated\ PVS = [(1 - Hct)/(Hb \times 0.01)] \times 1000\ (mL)$.¹¹

Statistical Analysis

Categorical variables are reported as number and percentage, while continuous variables are expressed as mean $\pm$ standard deviation (SD) if normally distributed or as median (interquartile range [IQR]) if not normally distributed. To assess differences, **volume variables were compared using Wilcoxon sign-rank test for paired analyses**. The associations between measured and estimated variables of PV were assessed using Spearman's correlation coefficients and **Lin's concordance correlation coefficient (CCC) for assessing level of agreement between two measures. A CCC value of <0.90 indicates poor agreement (i.e., discordance of paired parameters)**. All statistical analyses were performed using JMP and SAS version 9.3 and p-values <0.05 were considered to be statistically significant.

RESULTS

For this analysis, BVA and clinical data were available in 110 patients who were prospectively identified. Table 1 shows the clinical and demographic features of this patient cohort. Table 2 shows specific intravascular volume profile data for the cohort based upon measured and estimated volume parameters. Marked heterogeneity in volume distribution profiles of both measured and estimated values was demonstrated with a wide range in PV from marked deficit (hypovolemia) to severe volume excess (hypervolemia). Measured PV was on average significantly expanded at $+31 \pm 25\%$ above normal expected volume but with marked heterogeneity (range: -12% to $+100\%$ of normal expected volume). In contrast, calculated PV (Kaplan-Hakim) reflected mild volume contraction at $-6.1 \pm 12\%$ but also with much heterogeneity (range: -46% to $+37\%$). Absolute volumes (Table 2) revealed that Kaplan-Hakim estimated PV underestimated ($3.4 \pm 0.7\ L$) and Strauss formula overestimated ($5.3 \pm 1.5\ L$) PV relative to the measured PV ($4.3 \pm 1.1\ L$). Calculated PV by the Kaplan-Hakim formula was moderately correlated with measured PV ($r=0.64$, **$p<0.001$, Fig. 1A**) but **did not have good accuracy (CCC=0.40 $\pm$ 0.10, Fig. 2B)**. **Calculated PV by the Strauss formula was very weakly correlated with measured PV ($r=0.285$, $p=0.003$, Fig. 2A) and also demonstrated poor accuracy (CCC=0.20 $\pm$ 0.13, Fig 2B)**. Kaplan-Hakim formula estimates of percent PV deviation from normal volume were also poorly correlated with measured PV values ($r=0.141$, $p=0.149$, Fig. 3).

In this cohort of 110 patients, 29 had HFpEF defined by LVEF $\geq 50\%$ and 81 with HFrEF ($<50\%$). While patient number was limited for the HFpEF subgroup we pursued an assessment of associations between measured and estimated PV for these subgroups with the

findings as shown in Table 3. No significant differences were identified from the cohort as a whole.

Forty patients, a subset of the whole cohort, had BVA and clinical lab data available at the time of hospital admission, as well as, at the time of hospital discharge/post-discharge. This subgroup was initially treated for clinically determined volume overload but at the time of hospital discharge or shortly after discharge was at clinical baseline for each patient, considered clinically euvolemic, and demonstrated no clinical or laboratory differences from the cohort as a whole (data not shown). Strauss formula estimates of change (%) in PV from the time of admission to discharge/post-discharge evaluation (6 ± 2 days) were compared to paired-in-time measured changes in PV and found to show a weak association ($r=0.162$, $p=0.999$, $N=40$, Fig. 4). As an additional comparison, absolute changes in venous hemoglobin reflecting hemoconcentration over this same time period were analyzed in relation to paired quantitated changes in PV and a weak association was also demonstrated ($r=0.456$, $p=0.003$, $N=40$, Figure 5).

DISCUSSION

To our knowledge, this is the first report to evaluate the association between multiple calculated estimates of PV and directly measured PV in a large cohort of patients with chronic HF. In the present study, we demonstrated that 1) PV calculated by formulae using hemoglobin/hematocrit and body weight parameters correlated at best only moderately well with the gold-standard quantitation of PV, 2) calculated estimates of PV consistently underestimate (Kaplan-Hakim) volume status relative to measured volume, and 3) calculated changes in PV over time relative to measured changes show poor associations.

These findings suggest that formula estimates of PV should not be considered accurate measures of PV or changes in PV, and further suggest a systematic error in the calculated values that does not reflect the intrinsic dynamics of PV expansion or contraction and variability in body composition in patients with HF. Further, these findings indicate that hemoglobin/hematocrit-based formula estimates of PV are limited in reliability to reflect absolute or relative change in PV status compared with a clinically available quantitative measure of PV (BVA). This has implications for guiding volume management where decisions based upon such PV estimates can result in overly or inadequately aggressive diuretic therapy that could strongly impact clinical outcomes.

While our findings are in agreement with previous work by Ling et al.¹⁰ their study was in a cohort of healthy adults and a smaller cohort of patients with HF (N=30). Their study found a moderate correlation between directly measured and the point estimate Kaplan-Hakim PV formula ($r=0.51$, $p=0.006$) with a bias of -281mL . Our study, however, extends these findings in a larger cohort of hemodynamically steady state and stable NYHA Class III-IV patients with chronic HF and to also include data from other formulations assessing changes over time. We demonstrated a more pronounced deviation in estimated and measured differences in PV of approximately 1 liter vs. 281mL as reported by Ling et al.¹⁰ Further, we report that the discrepancies in

calculated and measured PV extend to other commonly used estimates of PV such as the Strauss formula estimates and measures of hemoconcentration.

While it is well recognized that the extent of fluid volume congestion is closely associated with clinical outcomes,^{1,2,4,19} the extent to which decongestion is achieved with diuretic therapy is highly variable and often less than clinically suspected.^{3,4,20-22} Therefore, assessments of volume status need to accurately reflect intravascular volume in order to effectively impact decongestion and, therefore, clinical outcomes. The assessments of volume overload, however, based on clinical examination parameters (e.g., presence of jugular venous distension, peripheral edema, orthopnea, an S3 and positive hepato-jugular reflex)^{23,24} increases in body weight,²⁵ levels of natriuretic peptides^{25,26} and even invasive hemodynamic measurements^{27,28} lack sufficient sensitivity and specificity to accurately assess a patient's intravascular volume status. Therefore, an accurate assessment of PV achieved using a standardized indicator-dilution technique with I-131-labeled albumin is more clinically relevant. Studies using this technique have demonstrated marked heterogeneity in volume status in patients with chronic HF^{3,4,29} and uncovered unrecognized subclinical hypervolemia in asymptomatic and mildly symptomatic Class I and II patients with HF,²⁹ as well as, in patients with non-edematous advanced HF.⁵

The distribution of PV deviations from normal volume towards negative values as demonstrated using the Kaplan-Hakim formula would suggest that patients would potentially be identified as having a lower than expected PV despite clinical assessment to the contrary as has been observed in other contemporary reports using this formula.¹⁰⁻¹² The quantitative measure of PV in the current analysis revealed significant PV expansion (volume excess) in the majority of patients with HF in this cohort. This suggests that calculated PV by the Kaplan-Hakim formula would consistently underestimate PV. Such findings have also been reported in normal subjects.³⁰ The explanation for the discrepancies between measured and calculated PV likely relates in part to the non-linear relationship of the formula-calculated ideal PV, where patients with lower body mass have an inappropriately high calculated ideal PV (biasing PVS towards lower values with the Kaplan-Hakim formula). Further, the Kaplan-Hakim formula was validated in a historic cohort of renal dysfunction patients and assumes the measure occurs at dry weight which has limited applicability to a population with chronic HF. This is contrasted by the overestimation of PV expansion when calculated by the Strauss formula where hemoglobin concentrations and hematocrit levels may not reflect true PV status. Efforts are ongoing for revision of formulae to improve alignment with measured PV.³¹ **This will require validation studies but may help in appropriate calibration and more reliable application of such formulae.**

It should be noted that despite the identified discrepancies of formulae relative to estimates of PV and hemoconcentration in this analysis, recent work suggests that estimates of intravascular congestion are strong predictors of clinical outcomes in patients with HF.^{10,11,14,32,33} This in concept is similar to the use of natriuretic peptides (e.g., B NP, NT-proBNP) which also serve as markers of outcome and risk stratification but do not accurately or quantitatively reflect the actual volume state they are monitoring. Thus, these estimates of PV can be markers of events but not measures of Volume.

Limitations

First, **whether the findings of this analysis can be extrapolated to all classes of patients with HF cannot be concluded from these data but given that data are within individual measurements it would be expected that such associations would be consistent across classes of HF severity.** The finding of this analysis do suggest caution in interpreting volume-specific data derived using calculated estimates of PV particularly where recommendations for clinical management strategies are being considered. Second, while the patient cohort was composed of outpatients and patients at the time of hospital discharge or shortly thereafter, all patients were stable NYHA class III/IV, at steady state for their volume status at the times of concurrent BVA and Hb/Hct measurements with calculated estimates of PV, and receiving stable oral medication regimens. **Also, no subset differences relative to the cohort as a whole were identified to include comparisons of HF_rEF and HF_pEF subgroups.** Therefore, given these consistencies and the fact that the data collected were paired within each patient the estimated and measured volumes reflect consistent clinical circumstances for the collected data. Third, the patient number is sufficient at 110 to adequately test the proposed hypothesis particularly given that paired within patient comparisons were undertaken.

CONCLUSIONS

Calculated estimates of PV correlate only moderately well with measured PV and consistently underestimate or overestimate measured PV depending upon the formula used. These findings indicate that hemoglobin/hematocrit-based formula estimates of PV should be considered cautiously as accurate measures of PV or changes in PV and suggest a systematic error in the calculated values that do not reflect the intrinsic dynamics of PV expansion and contraction in patients with chronic HF. Such calculated values, however, may still have prognostic significance but do not reflect accurate measures of intravascular volume.

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Highlights

- Formula-derived estimates of PV show poor correlation with quantitative measurements
- Calculated estimates of PV should be considered cautiously to guide volume management
- Quantitative measurements of PV provide “gold standard” accurate assessments
- More work is needed to make calculated values more accurate indicators of volume

Figure 1. Relationship of Formula Estimated (Kaplan-Hakim) to Measured Plasma Volume in a Cohort of Patients with Chronic Heart Failure (N=110). **Agreement of plasma volume methods: Spearman's correlation (A) and Bland-Altman Plot (B).**

Figure 2.

Relationship of Formula Estimated (Strauss) to Measured Plasma Volume in a Cohort of Patients Chronic Heart Failure (N=110). **Agreement of plasma volume methods: Spearman's correlation (A) and Bland-Altman Plot (B).**

Figure 3. Relationship of Kaplan-Hakim Formula Calculated to Measured Plasma Volume Expressed as Percent Deviation from Normal Expected Plasma Volume in a Cohort of Patients with Chronic Heart Failure (N=110).

Figure 4. Strauss Formula Calculated Percent Change in Plasma Volume vs. Measured Percent Change in Plasma Volume Hospital Admission to Discharge in Patients with Chronic Heart Failure (N=40).

Figure 5.
Relationship of Absolute Change in Venous Hemoglobin (g/dL) to Change in Measured Plasma Volume (mL) Hospital Admission to Discharge in Patients with Chronic Heart Failure (N=40).

Table 1.

Demographic and Clinical Characteristics (N=110)

Variable	
Age, years	64±13
Gender, female/male	31/79
Body Mass Index, kg/m ²	32±8
Systolic blood pressure, mm Hg	112±18
Duration of Heart Failure, months	44±30
LVEF, % Range	36 ±17 14 to 70
Diabetes, %	40%
Hypertension, %	61%
Coronary artery disease, %	49%
Atrial fibrillation, %	49%
Hemoglobin, g/dL	12.4±2.1
Hematocrit, %	37±6
Serum creatinine, mg/dL	1.6±0.8
eGFR, mL/min/1.72m ²	51±24
BUN, mg/dL	36±23
Plasma Albumin, g/dL	3.8±±0.6
Plasma glucose, mg/dL	116±32
NT-proBNP, pg/mL	3412(1175, 7506)

Mean ± SD, median with 25th, 75th percentile, or percent in category

Table 2.

Profiles of Paired Measured and Estimated Intravascular Volumes in the Cohort of Patients with Heart Failure (N=110)

Variable	Measured Volumes	Estimated PV: Kaplan-Hakim Formula	Estimated PV: Strauss Formula
PV, Liters Range Median (25 th , 75 th)	4.3±1.1 2.4 to 7.4 4.2 (3.6, 5.2)	3.4±0.7 2.2 to 5.8 3.3 (2.9, 3.8) p<0.001	5.3±1.5 2.2 to 9.7 5.0 (4.3, 5.9) p<0.001
PV, % Excess (+)/Deficit(-) Range Median (25 th , 75 th)	+31.0±25.3% -12% to +100% +26% (+10%, +48%)	-6.1±12.1% -46% to +37% -6.5% (-14%, +37%) p<0.001	
RBCM, Liters Range Median (25 th , 75 th)	2.2 ± 0.7 0.83 to 5.1 2.2 (1.7, 2.6)		
RBCM, % Excess (+)/Deficit (-) Range Median (25 th , 75 th)	+3.1±25.7% -38% to +100.6% -14% (-15%, +21%)		
TBV, Liters Range Median (25 th , 75 th)	6.5±1.6 3.2 to 10.1 6.6 (5.1, 7.7)		
TBV, % Excess (+)/Deficit (-) Range Median (25 th , 75 th)	+20.3±21% -17% to +70% +20% (-4%, +38%)		

PV=plasma volume; RBCM=red blood cell mass; TBV=total blood volume Data presented as mean±SD and range of values; p-values reflect comparisons to measured volume.

Table 3.

Comparisons of Measured and Calculated Plasma Volumes (PV) by HFpEF (N=29) and HFrEF (N=81).

HFpEF			HFrEF		
Measured PV vs. Kaplan-Hakim calculated PV	r=0.729	p=0.001	Measured PV vs. Kaplan-Hakim calculated PV	r=0.632	p<0.001
Measured PV vs. Strauss Formula calculated PV	r=0.440	p=0.017	Measured PV vs. Strauss Formula calculated PV	r=0.200	p=0.080
Percent deficit/excess in Measured PV vs. Kaplan Hakim calculated PV	r=0.198	p=0.325	Percent deficit/excess in Measured PV vs. Kaplan Hakim calculated PV	r=0.123	p=0.279