Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: January 31, 2024

Citation: Begos, D., G., 2024. The Use of Plasma Volume Calculations to Manage Acute Heart Failure: History, Current Status, and Future Directions. Medical Research Archives, [online] 12(1). https://doi.org/10.18103/mra.v12i1.5004

DOI: https://doi.org/10.18103/mra.v12i1.5004

ISSN: 2375-1924

RESEARCH ARTICLE

The Use of Plasma Volume Calculations to Manage Acute Heart Failure: History, Current Status, and Future Directions

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ABSTRACT

The use of calculated formulas for plasma volume based on hemoglobin and hematocrit (H&H) and other physiologic parameters is being increasingly used to gauge prognosis in patients with heart failure.

Many formulas exist, but they can be simplified into those which rely solely on H&H, and others which rely on H&H plus parameters such as weight and sex. The formulas that rely solely on H&H are the Strauss and Duarte formulas, while those which incorporate other parameters include the Hakim and Kaplan formulas.

There is now a large body of evidence that demonstrates these simple formulas can convey prognosis and may be valuable as a prospective measurement to guide therapy.

This review lays out the evidence for using plasma volume calculations in patients with heart failure and the benefits that can be derived from utilizing them in the management of heart failure.

Introduction

Heart failure (HF) continues to be a challenging problem for the global medical community and represents a significant and persistent cause of morbidity and mortality worldwide, with nearly 65 million people afflicted[1]. Lethality is high, with a mortality in the US of over 40% at 5 years[2]. Costs continue to rise, with a projected increase of 127% from 2012 to 2030, and it is estimated in the US that by 2030 it will cost the healthcare system nearly $70 billion[2]. Readmission within 30 days and 1 year of discharge, which is a metric often used to assess hospital systems, and which is a major driver of cost, remains stubbornly high, at roughly 20% and over 50%, respectively[3-6], although these vary widely by country and within various demographic groups. Despite significant resources being devoted to reducing readmissions, the rate has not changed appreciably in decades, and may be increasing according to some reports[4,6].

One calculated metric that has been retrospectively studied in HF is plasma volume (PV). There are several methods of calculating PV and many different terms for it, but there are two basic formulas: the Strauss formula, which uses 2 measures of hemoglobin and hematocrit (H&H) to calculate the change in estimated plasma volume status or ΔePVS[7]; and the Hakim or Kaplan formula, which incorporates body weight and sex in addition to hematocrit[8,9] (see Figure 1). The Strauss formula has been modified by Duarte to reflect PV at a single point in time, or estimated plasma volume status (ePVS)[10]. These formulas were not developed specifically for HF, but rather for plasmapheresis in the case of Hakim, and in healthy volunteers in the case of Strauss. The Strauss formula was "discovered" for HF by Duarte and colleagues in 2015 [10] to retrospectively examine patients enrolled in the EPHESUS study and found it to have prognostic value. Most HF researchers favor the Strauss formula over the Hakim formula because of the difficulty in estimating the dry body weight in this patient population.

Figure 1—Formulas to calculate Plasma Volume

STRAUSS FORMULA

$$\Delta ePVS = 100 \times \frac{\text{hemoglobin (g/dL)(before)}}{\text{hemoglobin (after)}} \times \frac{100 - \text{hematocrit (\%)(after)}}{100 - \text{hematocrit (before)}} - 100$$

DUARTE FORMULA

ePVS = (100 − hematocrit (%))/hemoglobin (g⁄dL)

HAKIM FORMULA

$$\text{actual PV} = (100 - \text{hematocrit (\%)})/100 \times [a + (b \times \text{dry weight (kg)}]$$

$$\text{ideal PV} = c \times \text{dry weight (kg)}$$

(males: a = 1530, b = 41, c = 39; females; a = 864, b = 47.9, c = 40),

KAPLAN FORMULA

ePV(in ml)=(0.065×body weight(in kg))×(1−haematocrit)×1000

PVS CALCULATION

PVS= [(ePV−ideal PV)/ideal PV]×100 (%), where ideal PV=c×BW (c=39 in males and 40 in females)

Since that publication in 2015 there have been numerous retrospective studies which have shown prognostic benefit in assessing PV in HF patients, however no study which has

examined PV prospectively to aid in clinical decision making. This paper seeks to review the available evidence in using PV calculations for prognosis in HF patients, and explore the rationale of using it prospectively in real-time to manage patients with HF.

Methods

A literature search using the terms "plasma volume" "volume status", and "heart failure" were performed. Papers which evaluated outcomes based on calculated plasma volume formulae were identified and evaluated.

For clarity, we will use the terms Strauss Formula to identify formulae that use H&H alone to calculate PV, and Hakim or Kaplan formula for those that use weight and/or sex and hemoglobin. We will use the terms PV and PVS interchangeably.

Results

A total of 19 papers were identified from 2015 to September 2023 which evaluated the relationship between heart failure and calculated plasma volume values, using either the Strauss or the Hakim formula.

Duarte and colleagues in Nancy, France did a post-hoc analysis of the EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), evaluating the 4957 of the 6632 patients enrolled in the study who had the available data to calculate ePV using the Strauss formula[10]. The EPHESUS study enrolled patients who developed HF after MI and had an ejection fraction (EF) of 40% or less (heart failure with reduced ejection fraction or HFrEF). Endpoints included cardiovascular death or hospitalization for HF between 1-3 months after myocardial infarction (MI). Assessments were made at enrollment, and at 1 month, 3 months, and then every 3 months after enrollment. In univariate analysis, both ΔePVS between enrollment and 1 month and ePVS at enrollment and at 3 months were associated with cardiovascular (CV) events, with ΔePVS and ePVS at 1 month being retained in multivariate analysis. As ePV increased, so did the risk of CV events. Perhaps surprisingly, ΔePVS did not correlate with weight, and patients who lost weight during the time interval had an increase in CV events.

Ling and colleagues in the United Kingdom evaluated patients in the Val-HeFT trial (Valsartan in Heart Failure) using the Hakim formula[11]. These patients had HFrEF, and 4404 of the 5010 patients enrolled had sufficient data to calculate ePV at baseline and at 4 months. They also evaluated the relationship of ePV to other biomarkers of volume status including brain natriuretic peptide (BNP), N-terminal pro b-type natriuretic peptide (NT-proBNP), and plasma renin activity. They stratified patients into change in PVS over time and correlated with mortality and cardiac events. They found a "J-shaped" curve, reflecting increased events in the lowermost end of PVS (> -4%) and in the higher groups. These also correlated with BNP and NT-proBNP, but PVS remained an independent predictor even after adjusting for those variables. In addition, they measured PV in 119 healthy volunteers and found a correlation ($r = 0.68$, $p < 0.0001$) between the measured PV and the calculated PV.

Bilchick and colleagues used the Strauss formula to evaluate patients enrolled in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization

Effectiveness trial (ESCAPE)[12]. They calculated the ePV on admission and discharge and found that patients who had an increase in ePV or no change had a higher mortality at 6 months than those whose ePV decreased during admission.

A group at Virginia Commonwealth University retrospectively used the Strauss formula and BNP in 218 patients who had been hospitalized at their institution with HF and seen within 2 weeks after discharge[13]. Both mortality and readmission at 90 days were seen in patients with higher ePV and BNP. The ePV also remained an independent predictor of events after controlling for BNP. Patients in the lowest tertile of ePV had a 12% incidence of death or readmission, as compared to 29% and 27% in the middle and highest tertile, respectively (p=0.02). There was no difference in any of the variables in these groups on admission.

A cohort of 449 patients in Taiwan with HF with preserved ejection fraction (HFpEF) were evaluated using the Strauss formula to calculate ePV and ΔePVS (the timing for the ΔePVS was unclear)[14]. Higher baseline ePV and higher ΔePVS were predictive of increased mortality and hospitalization for HF.

The group from Nancy, France, also evaluated ePV and ΔePVS in 3 different cohort studies using the Strauss formula[15]. There were 383 patients from a study at Tokyo University Hospital, 165 from Centro Hospital de Porto, and 164 from the Insuffisance CARdiaque en LORraine (ICALOR) study at their home institution. Primary outcome was rehospitalization for HF or mortality. In all 3 study cohorts, ePV at discharge was an independent predictor of readmission or all-cause mortality, even after controlling for confounding factors such as BNP. Dividing ePV into tertiles showed significantly worse outcomes for those in the highest tertile in the Tokyo and Porto cohorts, although in the ICALOR study this did not reach significance.

Tamaki and colleagues from Osaka, Japan analyzed 384 consecutive patients at their institution admitted with HF who survived to discharge. They used the Hakim, Kaplan, and Strauss formulas to calculate ePV and relative PVS[16]. Primary endpoints were mortality and rehospitalization for HF. Of all the calculations, the PVS on admission and discharge as calculated by the Hakim formula were the only ones predictive of outcomes.

In another post hoc trial analysis, patients enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT) were evaluated[17]. Using the Hakim formula, 3414 patients in this study, who had HFpEF, had PVS calculated and assessed against the primary endpoints of mortality, HF hospitalization, and cardiac mortality. Each 5% increase in PVS was associated with an increase in all-cause mortality and HF hospitalization, but not cardiac mortality. When adjusted for BNP, only HF hospitalization remained significant. Because of regional variation noted in the TOPCAT study[18], a subset of 1747 patients from North and South America from this study were evaluated using both Strauss and Hakim formulae for ePV, and outcomes included cardiovascular mortality, HF hospitalization, or cardiac arrest[19]. In this analysis, patients were divided into quartiles based on ePV, and the Strauss-derived highest quartile (> 5.5 mL/g) was associated with the primary outcome

when compared with the lowest quartile. The Hakim-derived ePV did not afford any prognostic significance. The Strauss ePV maintained its ability to predict outcomes even after correcting for BNP.

A group in Xian, China prospectively evaluated 231 consecutive patients admitted with HF to their institution. They calculated the ePV on admission using the Strauss formula, and its relation to the outcomes of all-cause mortality or HF readmission[20]. Dividing the group into terciles, they found that each tercile had an increasingly higher incidence of the outcomes, which held true on multivariate analysis.

In a study of 252 patients comparing ePV (Strauss) to a semi-quantitative congestion score index (CSI), which is a scoring system based on a chest radiograph, there was no correlation between ePV and CSI [21]. However, when combined, patients in the high CSI and high ePV groups had a four-fold higher risk of in-hospital mortality compared with the low CSI and low ePV group. This same prognostic value was not seen in either group individually.

A group in Germany evaluated 36 patients admitted to the hospital with HF who had a measured plasma volume (mPV) using a fluorescent biomarker on admission and on hospital day 3 [22]. Patients also had ePV calculated by both the Strauss and Kaplan formulas at the same time intervals and were being actively treated with diuretics. The authors found that mPV at admission correlated moderately well with the Hakim formula (r = 0.75), however mPV at 3 days did not correlate well (r = 0.24 Strauss, r = 0.23 Hakim). In a subgroup of 19 patients with a stable measured red cell volume (mRCV), the Strauss formula did correlate well with the change in mPV (r = 0.78). Changes in hemoglobin and hematocrit also did not correlate with mPV, however 4 patients in the cohort had a bleeding event or required a transfusion, so it is unclear how this affected the data[23].

A study evaluating outpatients with HF in the UK compared 2 cohorts of patients using ePV measurements (both Hakim and Strauss) with ultrasound measures of congestion[24]. Cohort 1 (n=3505) consisted of patients referred to a heart failure specialty clinic, while cohort 2 (n=341) was patients already enrolled who were seen in routine follow-up. All patients had echocardiography done, and cohort 2 underwent comprehensive ultrasound assessment of congestion: inferior vena cava (IVC) diameter, jugular vein distensibility (JVD) ratio, and lung B-line count. Both Hakim and Strauss ePV correlated well with each other. The Hakim ePV correlated with symptoms, but after multivariate analysis, only association with lung B-line count > 14 was significant. Hakim ePV also correlated with all-cause mortality in cohort 1 after multivariate analysis. The Duarte ePV did not correlate with any of the ultrasound signs of congestion after multivariate analysis but did correlate with all-cause mortality in cohort 2. In this study, log NT-proBNP was strongly associated with clinical and ultrasound measures of congestion, NYHA class III or IV symptoms, and both endpoints in both cohorts after multivariable adjustment.

Leahova-Cerchez and colleagues evaluated 50 consecutive patients over 75 years old admitted to the hospital with HF [25]. They assessed clinical signs, inferior vena cava (IVC)

diameter measured by ultrasound, NT-proBNP, and ePV using the Strauss formula during decongestive therapy. All patients had a non-compliant IVC on admission. They found the strongest correlations between IVC and jugular vein distention (r = 0.8), and IVC and edema (r = 0.6). IVC and NT-proBNP had a weak correlation (r = 0.3), and there was no correlation between ePV and signs of congestion.

A group from Jakarta, Indonesia evaluated 208 patients admitted with right HF, and calculated their ePV using the Hakim formula[26]. Patients were divided into low and high groups based on ePV, and the in-hospital mortality in the high group was nearly triple that of the low group (18.3% vs 6.7%, respectively).

Guvenc and colleagues evaluated patients in a national HF registry-- the Snapshot of Heart Failure in Turkey (SELFIE-TR), which included the entire spectrum of HF patients: acute or chronic, normal or low ejection fraction, etc[27]. A total of 769 patients in the database had ePV calculated using the Strauss, Kaplan, and Hakim formulas, as well as the relative PV (rPV) (ePV (Hakim) divided by the ideal PV). Both ePV (Strauss) and rPV tertiles correlated with mortality, with those in the highest tertile of rPV having significantly higher mortality than the lowest 2, and for ePV (Strauss) the higher 2 tertiles both had significantly higher mortality than the lowest tertile. Both ePV (Strauss) and rPV also weakly but significantly correlated with signs and symptoms of congestion. The ePV as calculated by the Hakim formula did not correlate with any of the variables.

Chen and associates evaluated 253 patients who were admitted to Putian Hospital in China with HF[28]. Patients had echocardiographic measurement of left atrial diameter (LAD), as well as NT-proBNP and ePV calculated using the Strauss formula, with outcomes of HF readmission and cardiac death evaluated. On regression analysis, ePV (OR = 2.061, 95% CI 1.322~3.214, p = 0.001), was the strongest predictor of outcomes, with LAD (OR = 1.054, 95% CI 1.012~1.098, p = 0.011), and NT-proBNP (OR = 1.006, 95% CI 1.003~1.010, P = 0.036) weaker predictors. In addition, increasing ePV increased the risk of cardiogenic mortality.

A group in Kashihara, Japan retrospectively evaluated 466 patients who had been admitted for HF[29]. They combined ePV using the Strauss formula with the fractional excretion of urea nitrogen (FEUN), and divided patients into 4 groups based on low or high ePV and FEUN. The patients were roughly evenly distributed among the groups, with 99-134 patients per group. End points were all-cause mortality and HF readmission. Analysis showed that the high- FEUN/low-ePVS group had a better prognosis than the other groups. In the multivariable Cox regression analysis, the low- FEUN/high- ePV group had a higher mortality than the high-FEUN/low- ePV group (hazard ratio, 2.92 [95% CIs, 1.73– 4.92; p<0.001]). An analysis was not performed looking at just ePV, however, so it is unclear if this was an independent predictor of outcomes.

The value of the Strauss-derived ePV was also affirmed by Wu and colleagues from Beijing, China[30]. They evaluated 195 patients with advanced HF using right heart catheterization to measure hemodynamics. The sum of right atrial pressure (RAP) and pulmonary arterial wedge pressure (PAWP)>30 mmHg was considered hemodynamic congestion.

Patients with an ePV of greater than 4.08 dL/g were more likely to have clinical signs of congestion (e.g., rales) and had a higher mortality regardless of their catheterization pressures. This led the authors to advocate using ePV as an independent prognostic marker for patients with HF.

Discussion

Managing patients with HF is a challenging clinical task[31]. There are many different phenotypes of HF, and many different modes of presentation. Patients can be categorized and evaluated according to EF, exercise tolerance, filling pressures, radiologic parameters, laboratory measures, clinical signs and symptoms, pulmonary function, and renal function, among others. Most often, clinicians use a combination of some or all of these parameters to assess and treat these complex patients[32], but treatment remains suboptimal. Mortality and readmission from HF continue to remain at levels that are considered unacceptable to most practitioners and payors[1,3,32]. What is clear from the data is that there is no simple solution or "magic bullet" yet available to tackle this problem.

Where ePV fits in to the myriad potential data points is unclear at present, but its utility is being recognized by multiple authors across a wide variety of HF patients. Current evidence seems to advocate for its role in assessing prognosis of HF, but the possibility of using it to monitor treatment and facilitate clinical decision making is intriguing. It has several benefits:

- It is inexpensive.
- It is readily calculated from the hemoglobin and hematocrit, a test which is often performed daily or more frequently in HF patients.
- There are currently devices on the market that will automatically calculate ePV from a 60 microliter sample in approximately a minute[33].
- It is backed by evidence across multiple geographic regions.
- It has been studied in heterogenous HF groups.

For these reasons, it would seem logical to incorporate ePV as another data point in the clinical armamentarium to help with managing these patients. There is no one who would argue that ePV, however calculated, is a definitive or absolute measure of volume status, but, in time, it may become a useful adjunct in patient management.

Some future directions for refining the role of ePV in HF could include:

- Prospective studies using ePV to assist in clinical management and decision making.
- The value of serial ePV measurements in patient care.
- Studies to evaluate which HF subgroups would most benefit from ePV use.
- How ePV may fit into outpatient management.
- If ePV can be leveraged to reduce readmission rates.
- How ePV responds to various pharmacologic and therapeutic modalities.

One intriguing area of future study would be how red blood cell mass (RBCM) impacts HF and the role of ePV in this particular HF cohort. In one thoughtful study, Miller and colleagues at the Mayo Clinic evaluated RBCM in HF patients[34]. They evaluated 132 HF patients just prior to discharge after being admitted for HF exacerbation and treated

with diuresis. A standardized nuclear medicine study was performed to assess the RBCM of these patients, and the authors found that 27% had RBCM deficit (true anemia), 41% had RBCM excess, and 32% had a normal RBCM. In following these groups, the cohort with the RBCM excess had the best survival, while those with the RBCM deficit had the poorest survival. It may be that RBCM, or RBCV as shown by Swolinsky, et al. [22] may be important factors in the utility of ePV to accurately prognosticate HF patients.

Although HF seems to have the most robust literature at the moment, calculation of ePV and its surrogates seems to show benefits in other, wide-ranging pathologies. Some are cardiovascular related, such as pulmonary hypertension[35,36], peripheral vascular disease[37,38], pulmonary embolism[39], trans-catheter aortic valve replacement[40-42], and myocardial infarction[43], while others are seemingly not, including hemodialysis[44], Covid-19[45,46], diabetic ketoacidosis[47], primary myelofibrosis[48], sepsis[49,50], polycythemia vera[51], and ARDS[52]. There are even links to population health and all-cause mortality in Japan and the US[53,54].

It is therefore likely that in the near-future ePV's role in HF and other pathologies will become clearer and its utility in these conditions will be recognized.

Conclusions

The use of calculated plasma volume measurement for HF prognosis and management is a growing area of data driven practice. Further clarification of its role in guiding treatment for HF, including prospective studies, are warranted to better define its place in this complex and heterogenous disease process.

Conflicts of Interest Statement:

Dennis Begos is an employee of Nova Biomedical, a point-of-care blood testing device company.

Acknowledgements Statement:

None

Funding Statement:

None

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