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Estimated Plasma Volume Status in Heart Failure:

Clinical Implications and Future Directions

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Abbreviations and Acronyms

PV=plasma volume

ePVS=estimated plasma volume status

HF=heart failure

CHF=chronic heart failure

AHF=acute heart failure

ADHF=acutely decompensated heart failure

HFrEF=heart failure with reduced ejection fraction

HFpEF=heart failure with preserved ejection fraction

HFmrEF=heart failure with mid-range ejection fraction

Abstract

Congestion is one of the main predictors of poor outcome in patients with heart failure (HF). Assessing and monitoring congestion is essential for optimizing HF therapy. Among the various available methods, serial measurements of estimated plasma volume (ePVS) using routine blood count and/or body weight (e.g. the Strauss, Duarte, Hakim formulas) may be useful in HF management. Further prospective study is warranted to determine whether ePVS can help optimize decongestion therapy (loop diuretics, mineralocorticoid receptor antagonists, SGLT2i) in various HF settings. This narrative review summarizes the recent evidence supporting the association of ePVS with clinical congestion and outcome(s) and discusses future directions for monitoring ePVS in HF.

Introduction

Congestion is one of the main mechanisms underlying worsening heart failure (HF) and is associated with poor outcome. Insufficient decongestion is associated with higher rates of HF re-admission and death.[1] Therefore, it is of paramount importance to better detect and monitor congestion before progression to decompensation [2] and to assess the intensity of decongestion for an optimal tailoring of HF therapy. International guidelines have long recommended assessing "volume status" in order to adapt diuretic doses [3]. However, congestion can be difficult to assess, especially when extrapulmonary signs of congestion are mild, or in patients with residual congestion at discharge from a HF hospitalization [2].

According to the principle of total body volume distribution, all fluid compartments are balanced, and plasma volume (PV) would interact with the interstitial and intracellular compartments [4-7]. PV expansion in patients with HF is associated with increases in all fluid compartments. In particular, PV in patients with decompensated HF may increase by 40% compared with that in healthy controls [8]. In addition to accumulated fluid volume, the fluid redistribution from splanchnic venous system to pulmonary circulation also contributes to expand PV, subsequently leading to urgent HF hospitalization [2, 4, 9]. Decongestion therapy reduced greatly body weight/net fluid balance, but had less impact on PV owing to plasma refilling from interstitial space to intravascular space [10, 11]. This therefore warrants a reliable and actionable assessment of PV.

Hemoconcentration (or hemodilution) gauged by a change in hemoglobin or hematocrit concentrations as an indirect marker of changes in PV has been shown to trend with clinical assessments of congestion [12-14]. For instance, an analysis of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial investigated baseline-to-discharge increases in hematocrit, albumin and total protein values. Patients with 2 or more of the 3 aforementioned variables with values in the top tertile were considered to have evidence of hemoconcentration, which was found to be associated with greater net weight or fluid loss and

greater reduction in right atrial pressure and pulmonary capillary wedge pressure, along with a substantially lower risk of mortality [12]. More recently, hemoglobin was found to be significantly negatively correlated with all tested biological and ultrasound measurements of congestion in a chronic HF population across a large spectrum of ejection fractions [15]. In a meta-analysis from a systematic review including 18 studies and a total of 368 patients with HF, hemoglobin was found negatively associated with measured PV (Beta=-6.66 ; SE=2.53, p=0.008)[16]. Direct quantification of PV accurately depicts the severity of congestion in patients with chronic HF [10, 17]. However, clinical utility of direct PV measurement-guided management has not been well documented [18]. The procedure, in addition, requires specialized equipment with relatively high cost and exceedingly high logistical issues to implement, which may not readily available for clinicians. Therefore, PV estimated from a routine blood count and/or body weight may be more clinically relevant for repeat use given its low cost and practicability. Estimated PV status (ePVS) might provide a phenotypic characteristic to tailor personalized therapy in the different settings of HF.

This narrative review summarizes the recent evidence supporting the association of ePVS with clinical congestion and outcome and discusses future directions for monitoring ePVS in HF.

Estimated and Measured Plasma Volume Status

Formulae for Estimating Plasma Volume

Among recent reports in HF settings, two representative methods are available for estimating PV. Both express relative values of PV and use routinely available variables (*i.e.*, hemoglobin and body weight).

Strauss Formula

The concept of estimating PV was first reported by Strauss et al. in 1951 [19]. This seminal research of the Strauss formula demonstrated the association between the infusion of saline into human bodies and rapid changes in their estimated PV. In 1970's, Dill et al. reported the association of a decrease in

body weight after exercise with a steep decrease in ePVS using hemoglobin and hematocrit [20]. This formula was validated against a radiolabeled gold standard method and has been routinely used over decades for the estimation of plasma volume in patients scheduled for plasma exchanges [21, 22].

To estimate relative changes in PV between 2 independent time points, the Strauss formula uses changes in hemoglobin and hematocrit which need to be measured at both independent time points (before and after) [19]:

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

In a recent report, Duarte et al. used a single time-point 'instantaneous'-derived measurement of plasma volume (Duarte's formula) for estimating PV derived from the Strauss formula as follows [23]:

$$\text{ePVS} = (100 - \text{hematocrit (\%)}) \,/\, \text{hemoglobin (g/dL)}$$

Hakim Formula

The Hakim formula is also used for calculating actual and ideal PV and ePVS derived from hematocrit and dry body weight using the following equations [24]:

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

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

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

Relative PV status, an index of the extent to which patients have deviated from their ideal PV, was subsequently calculated from the following equation:

$$\text{ePVS} = [(\text{actual PVS} - \text{ideal PV})/\text{ideal PV}] \times 100\%$$

One caveat with the Hakim formula is that it warrants dry body weight which is a major potential confounder in the HF setting, where there is a complex interplay between congestion and loss in body weight ("cachexia"), both associated with poor prognosis [25].

Measured Plasma Volume

Radioisotope assays are considered as the gold-standard, as they accurately assess PV status along with red blood cell and total blood volume, using the concomitant determination of hematocrit. The latter provides relevant information, since red blood cell abnormalities (non-hemodilutional anemia or polycythemia) may coexist with PV abnormalities in patients with HF and may challenge its isolated interpretation [7, 18]. Notwithstanding, the radioisotope assays are expensive and impractical for serial monitoring, due to the need of frequent venous blood sampling and processing delays [26] .

131I-labeled albumin method [18]

The 131I-labeled albumin method (Volumex, Daxor Corporation, New York) is a validated and standardized clinically available technique. Low-dose iodinated I-131-labeled albumin is injected, and from a contralateral forearm venous catheter, blood samples are collected at time 0 (pre-injection), and at 12, 18, 24, 30, and 36 min post-injection. This technique may measure PV more quickly than 125 I-HSA method [27]. Hematocrit is determined from each sample, and the plasma radioactivity of each sample is measured (in duplicate) in a semi-automated counter (Food and Drug Administration approved BVA-100 Blood Volume Analyzer, Daxor Corporation). Subsequent to an initial assessment in patients with acutely decompensated HF (ADHF), it was proposed that the readily available peripheral hematocrit test results may provide an updated view of the patients' volume status, such that, in those cases where it could be assumed that the red blood cell volume was reasonably stable (absent bleeding or interventions to correct anemia), an increase in peripheral hematocrit could be interpreted as a true (decongestive) decrease in PV [18].

125I-HSA method [28]

The International Committee for Standardization in Hematology recommends the 125I-HSA method [28]. A 125I-labeled albumin is injected peripherally, and blood is collected from a different vein (usually the opposite arm) at 10-, 20- and 30-min post-injection. The radioactivity of the plasma samples and the standard are determined in a scintillation counter. PV is calculated by the following equation:

$$\mathrm{PV} = \frac{\text{Radioactivity of standard (cpm/ml)} \times \text{dilution of standard} \times \text{volume injected (ml)}}{\text{Radioactivity of postinjection sample (cpm/ml, adjusted to time zero)}}$$

99mTc-HSA method [7, 26]

Technetium (99Tc)-labeled red blood cells is injected peripherally after 60 min in supine position. Thereafter, blood is collected at 10-min intervals for 30minutes. Radioactivity is measured in an automated counter. PV is calculated from the measured blood volume, venous hematocrit, corrected for the trapped plasma and mean body hematocrit.

IV-administered visible fluorescent injectate (VFI)™ (FAST BIOMedical) [29]

Recently, a non-isotopic (fluorescent) method to rapidly quantify PV and renal function was developed. The method consists of 12mg of a 150-kDa carboxy-methylated dextran, conjugated to a rhodamine dye (plasma volume marker), and 35mg of a 5-kDa carboxy-methylated dextran, conjugated to fluorescein (renal clearance marker), in a total volume of 3.0 ml. As the large molecule is retained in the intravascular space, its concentration reflects real-time plasma volume, and since the small molecule is freely filtered across the glomerulus, its change represents the glomerular filtration rate. The injectate is infused intravenously over 30s. Dye concentrations are quantified at only 1-time point, 15 min after the injections for initial PV measurements using the indicator-dilution principle, and this timing may have less influence on the value of PV [29]. Blood volumes are calculated based on PV and the subject's hematocrit. Samples are also taken at 60 and 170 min for determination of glomerular filtration rate by the FAST BioMedical technique [29]. Validation results were recently

published using data from 16 healthy subjects and 16 subjects with chronic kidney disease. Additionally, this technique accurately tracked dynamic changes in PV induced by a volume challenge following an intravenous bolus of 350 mL of a 5% albumin solution in normal saline in 8 healthy subjects [29]. The ongoing EMPAKT-CHF (Estimating versus Measuring Plasma Volume and Kidney Function in Acute Decompensated Congestive Heart Failure) study is a one-armed, phase 2 clinical trial using (VFI)™ to assay and assess measured PV and measured glomerular filtration rate in hospitalized patients with acute decompensated congestive HF (NCT03808948).

Estimated Plasma Volume Status as a Congestion Marker

Comparison between Estimated Plasma Volume Status and Direct Plasma Volume

Several reports have assessed the correlation between ePVS and conventional radioisotope-labeled albumin or red blood cell assays. Ling et al. compared ePVS derived from the Hakim formula and actual PV using the gold standard 125Iodine labeled human serum albumin method [30]. Results showed a moderate correlation between measured PV and estimated PV ($r=0.51$, $p=0.006$) in 30 patients with CHF ($r=0.68$, $p<0.001$ in 119 healthy subjects). Martens et al. also compared ePVS derived from Hakim and PV expansion using Technetium (99Tc)-labeled red blood cells in stable patients with HFrEF, showing moderate to good correlation ($r=0.71$, $p<0.001$) and a good agreement between measured and calculated PV [26]. Furthermore, Fudim et al. compared ePVS and measured PV in 110 stable CHF patients with NYHA class III or IV [31]. The authors used both the Hakim formula and Strauss formulae (change and instantaneous), compared to low-dose ^{131}I-labeled albumin intravenously. They reported moderate-to-strong correlation of the Hakim formula with the measured quantitative PV ($r=0.51$, $p=0.006$ and $r=0.64$, $p<0.001$), while the Strauss formula ePVS was weakly correlated with measured PV ($r=0.29$, $p=0.003$). A recent report comparing Strauss-derived ePVS and PV measured by ^{125}I-human serum albumin in 10 patients with type 2 diabetes showed good correlation (Lin's concordance index of 0.6 ($p< 0.01$) between both PV measurements) [32].

Association between Clinical Congestion Markers and Estimated Plasma Volume Status

Clinical predictors of higher estimated or measured PV, including demographics, comorbidities, ultrasound/hemodynamic parameters and biomarkers are presented in **Table 1**. Similar clinical characteristics have been reported between ePVS derived from the Strauss and Hakim formulae. Patients with higher ePVS were older, had more frequent ischemic heart disease, more severe clinical congestion, poorer renal function, higher natriuretic peptide and were less likely to be on HF medications [30, 33-35]. Recent published data showed the Duarte-derived ePVS was associated with left-sided congestion such as E/e' [36], and with pulmonary artery pressure as assessed by an implanted home monitoring device [37]. In addition, other data showed the significant association between ePVS and echocardiographic parameters (i.e. tricuspid regurgitation) during decongestion therapy [38]. Of note, some available data in the HF cohort studies demonstrated good correlations between instantaneous and/or changes in ePVS and natriuretic peptide. Using data from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial, Rossignol et al. showed a relatively weak correlation between baseline to 1-month changes in ePVS and BNP ($r=0.284$; $p<0.001$), independently of study drug and renal function variations [39]. Not surprisingly, significant associations between ePVS and congestion markers such as natriuretic peptide were also observed in HFpEF [35].

These findings therefore strengthen the evidence of ePVS as a clinically relevant congestion marker.

Association of Estimated Plasma Volume Status with Clinical Outcomes in the Different Settings of Heart Failure

Patients with acute heart failure (AHF) have more interstitial fluid volume due to fluid accumulation/re-distribution compared to those with chronic heart failure (CHF) [9, 40, 41], whereas fluid volume profiles show a different distribution between patients with HFpEF and HFrEF [42, 43]. Androne

et al. showed that, in patients with CHF with absence of clinical congestion, increased measured blood volume, as assessed by intravenous administration of iodine 131-labeled albumin, was associated with an increased risk of death or urgent cardiac transplantation [17]. A number of other reports also found independent associations between an increase in estimated PV level and a higher risk of clinical outcomes, consistently and across a wide HF spectrum (acute/chronic, HFpEF/HFrEF) (**Table 2**). Furthermore, across these HF phenotypes, ePVS improved consistently patient risk stratification on top of established clinical-based models [23, 44, 45]. Both formulas incorporated hemoglobin and/or hematocrit. Several underlying diseases (inflammation and renal impairment) may lead to anemia and influence the value of ePVS. However, the prognostic value of ePVS persists regardless of the presence of anemia in patients with de novo HF following acute myocardial infarction or in those with acute HF [23, 33, 44]. Importantly, HFpEF manifested more often with anemia compared with HFrEF or HFmrEF [46, 47]; therefore, further research is needed to explore whether prognostic value of ePVS would be influenced by anemia or anemia-related diseases in HFpEF.

Chronic Heart Failure

The associations of ePVS with clinical outcomes have been well documented in patients with CHF irrespective of LV systolic function.

Rossignol et al. investigated the prognostic value of changes in PV using the Strauss formula in 6,820 patients with HFrEF in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF trial) [48]. During a median follow-up of 3.9 years, increased PV (>0%) from baseline was independently associated with a higher incidence of all-cause mortality (adjusted HR [95%CI]=1.010 [1.002-1.018], p=0.017) and cardiovascular mortality (adjusted HR [95%CI]=1.012 [1.003-1.020], p=0.007), independent of a significant decrease in body weight. A post-hoc analysis of the Valsartan Heart Failure Trial (Val-HeFT) assessed ePVS derived from the Hakim formula in 5,002 patients with HFrEF [30]. After a median follow-up of 716 days (during which 20.0% of patients died), the highest ePVS quartiles were associated with increased all-

cause mortality after adjusting for clinical covariates including BNP (adjusted HR [95%CI]=1.26 [1.05-1.52], p=0.01). Similar prognostic implication of Strauss-derived or Hakim-derived ePVS is in line with reports in HFpEF [35, 49]. In a post-hoc analysis of Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT), ePVS derived from the Hakim formula was assessed in 3,414 patients with HFpEF, in which increased ePVS was associated with a higher risk of the composite of all-cause death or HF re-hospitalization [35].

Heart Failure with Reduced Ejection Fraction and Post-myocardial Infarction

In 6,080 patients with HFrEF following acute myocardial infarction from the EPHESUS study database, after a mean follow-up of 16 months, a significant decrease in ePVS as assessed by the Strauss-formula (delta ePVS) from baseline to 1 month was associated with a lower risk of clinical outcomes [39]. Furthermore, in another report of the EPHESUS, Duarte et al. assessed the prognostic value of instantaneous ePVS at 1 month as well as ePVS change from baseline to 1 month [23]. They found that instantaneous ePVS at 1 month was a better predictor of cardiovascular events than change in ePVS from baseline to 1 month over a follow-up period of 6 months. The fact that the Hakim formula was not associated with outcomes in this analysis may arise from the integration of body weight in this formula. Indeed, Hakim-derived ePVS increases when hematocrit decreases and conversely decreases when weight decreases, whereas patients with events displayed lower weight and hemoglobin. Ideally, dry weight (i.e., the body weight measured in non-congested patients), which was not assessed in this latter study and is difficult to estimate in routine practice because of frequently persisting edema in HF patients, should have been used to run this formula [23].

Acute Heart Failure

A study assessing change in Strauss-derived ePVS from admission to discharge in 712 patients with AHF [44] found that an increase in ePVS at discharge was associated with poor prognosis, and provided a significant improvement in prognostic reclassification, on top of standard clinical prognostic models. This is in keeping with findings of several smaller studies in AHF, showing the prognostic value of

discharge ePVS and of ePVS change from admission and discharge, likely depicting residual congestion [50-52]. Other reports showed that patients with increased in admission ePVS also have worse prognosis [33, 53]. In a recent report from the Effect of Nesiritide in Patients with Acute Decompensated Heart Failure (ASCEND-HF) trial including 7,141 patients with decompensated HF, Duarte- and Hakim-derived ePVS at baseline was associated with cardiovascular mortality or HF rehospitalization at 30 days.

Non-Heart Failure

PV may manifest subclinical congestion, and its expansion may play crucial role of the perioperative or emergency management even in patients without HF. In a retrospective cohort study including 1,887 patients undergoing coronary artery bypass graft surgery, preoperative assessment of Hakim-derived ePVS ≥5.6% was associated with worse prognosis in a post-operative period [54]. Similarly, worse prognostic value of higher ePVS was reported in patients undergoing transaortic valvular intervention or mitral valvular intervention[55, 56]. In addition, in 1,369 acute dyspneic patients admitted to the emergency department, the highest tertiles of admission Duarte-derived ePVS was associated with AHF diagnosis (adjusted OR [95%CI]=1.64 [1.16–2.33], p=0.005) as the main cause of dyspnea. A value of ePVS >5.12 ml/g identified patients who, concomitant with infection or chronic renal failure, were diagnosed with AHF in the emergency department. In this study, higher Duarte-derived ePVS in dyspneic patients was associated with a higher risk of in-hospital mortality irrespective of the presence of HF [57].

Hemoconcentration and Worsening Renal Function

Aggressive decongestion as documented by a decrease in PV and hemoconcentration, improves clinical outcomes in patients with HF [12-14, 58, 59]. Incident hemoconcentration, across a large range of definitions, is frequently associated with worsening renal function [12-14, 58, 60-63](**Supplementary table 1**), which has little negative prognostic influence [61, 64, 65]. In contrast, worsening renal function without

hemoconcentration, i.e. with persistent congestion, is associated with worse outcomes [66, 67]. Importantly, in most of the aforementioned studies, hemoconcentration was derived from changes in hemoglobin or hematocrit.

Plasma Volume as an Actionable Biomarker to Guide (De)-congestion Therapeutic Strategies in Heart Failure

Half a century ago, furosemide infusion was shown to consistently increase hematocrit and decrease estimated (Strauss formula) and measured (isotopic) plasma volume [68]. In the 1990's, venovenous ultrafiltration in chronic HF was found to decrease estimated PV (hematocrit-based formula) [69] along with pulmonary wedge pressure and right atrial pressure, two established biomarkers of congestion. Importantly, immediately after ultrafiltration, mean pulmonary wedge pressure decreased by 29% and right atrial pressure decreased by 46%. Both variables remained unchanged in the next two days. PV was reduced by 22% immediately after the procedure and by 10% after 24 hours, and subsequently fully recovered in the next 24 hours. This differential kinetics may reflect a modest correlation between ePVS changes and pulmonary wedge pressure changes. However, more importantly, changes in ePVS and pulmonary wedge pressure were directionally and consistently concordant and were simultaneously reduced by the ultrafiltration process**.** Ultimately, in HF, hemoconcentration, which is easily and continuously measured by an in-line hematocrit sensor during ultrafiltration therapy, is considered as an appropriate surrogate indicating when the plasma refill rate is exceeded by the rate of fluid removal [70]. More recently, several contemporary HF cohort studies showed correlations between volume depletion due to diuretic response and decreases in ePVS [30, 43, 44].

The EPHESUS data in HF patients post-MI showed that the mineralocorticoid receptor antagonist (MRA) eplerenone induced a diuretic-like effect compared to placebo, as assessed by decreased ePVS (Strauss Formula) after one month, an effect associated with improved clinical outcomes [39]**.** In patients with chronic HF, a higher dose of renin-angiotensin-antagonist-blocker

(RAS-blocker; ACE-I or ARB) and a higher dose of a MRA have moreover been associated with an independent higher odds of having an optimal ePVS in HFrEF and HFmrEF [26]. In addition, Sacubitril/Valsartan generally increases endogenous peptides with natriuretic effects, which may lower circulating levels of aldosterone [71, 72]. Sacubitril/Valsartan, therefore, may theoretically decrease the value of ePVS. Further research is warranted.

SGLT2 inhibitors are likely to become part of the life-saving drug armamentarium in HF, downstream of the DAPA-HF trial in HFrEF [73], while HFpEF trials are ongoing [74]. In a randomized, placebo-controlled, double-blind trial, 75 subjects with type 2 diabetes were assigned either placebo, the SGLT2 inhibitor dapagliflozin 10mg/day, or hydrochlorothiazide 25mg/day. SGLT2 inhibitor dapagliflozin treatment resulted in a 7.3% reduction in measured (isotopic) PV from baseline, with parallel consistent increases in hematocrit and hemoglobin [75]. In a pooled database of 13 phase 2b/3 placebo-controlled clinical trials involving 4,533 patients with type 2 diabetes and randomized to dapagliflozin 10mg daily or matched placebo, dapagliflozin decreased estimated plasma (Strauss Formula) by 9.6% (95% confidence interval 9.0 to 10.2) compared to placebo after 24 weeks [32]. Of note, the increase in hematocrit, consistent with the rise in serum albumin levels, mediated a major part of the beneficial effect in the EMPA-REG cardiovascular outcome trial [75, 76]. Interestingly, SGLT2 was reported to suppress sympathetic hyperactivity, leading to less hemodynamic changes despite a significant increase in hematocrit [77, 78].

Whether monitoring PV, hematocrit or hemoglobin may enable optimization of HF therapy and therefore improve cardiovascular outcomes warrants dedicated randomized clinical trials. Interestingly, a provocative retrospective analysis of a single center database supported both the short (30-day readmission and mortality) and long-term benefit (365-day mortality), unrestricted by ejection fraction category, of a volume-guided HF therapy versus propensity-matched controls in patients hospitalized for HF. The HF treatment strategy was individualized and guided by initial blood volume analysis with DAXOR. Their goal was to normalize measured total blood volume and/or red blood cell volume disturbance, using a rise in peripheral hematocrit in relation to the patients' peripheral

hematocrit. Both blood compositions were considered as a surrogate marker of interstitial fluid volume decongestion or increase in red blood cell volume, depending on the primary treatment strategy. As rightly pointed out by W. Tang in an accompanying editorial [79], "Such hypothesis-generating insights require independent validation with a randomized controlled trial design to demonstrate rigor and reproducibility of the findings. Translating in clinical practice, the blood volume analysis is not an inexpensive test, and requires logistic solutions for its administration. Hence, beyond demonstrating incremental benefits by a blood volume analysis-guided approach in ADHF management, clinical adaptability and practical use of such a strategy will also depend on its cost-benefit assessment at a time when there is growing concerns regarding the increasing costs of health care".

Clinical Perspectives. Monitoring Plasma Volume for Therapy Optimization

The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial highlighted the benefit of HF management according to pulmonary pressure data derived from wireless devices on HF re-hospitalization in ambulatory patients with HF [80]. Importantly, in this trial, changes in treatment prompted by persistent hemodynamic congestion were overwhelmingly dominated by an increase in diuretic doses [80]. This invasive outpatient monitoring, however, may not be widely available in all patients with HF in the context of elderly, high comorbidity burden and economic concerns. Monitoring congestion status, using plasma volume estimation, based on changes in serial hemoglobin/hematocrit measurements could hence represent a low-cost and easy-to-use alternative, which may enable to its applicability in routine clinical practice.

On the basis of the available retrospective data, specific target hemoconcentration goals have yet to be defined, and it is unclear whether the same targets should be applied to different patient subsets [81]. Based on the latest published data with the Duarte's Strauss-derived instantaneous assessment of ePVS (Strauss-Duarte) in acutely decompensated or chronic HF, an actionable threshold

of >5.5ml/g may be proposed to define an excessive congestive status, associated with poor outcomes [44, 49, 57], which may allow prospective evaluation as a trigger for therapeutic action. Interestingly, in a recent study, capillary blood samples were drawn by study nurses at home 5 days a week for two months after an acute decompensation in 15 patients with HFrEF. Hematocrit and hemoglobin (along with creatinine and potassium) were measured using an approved home-based device (ABOTT iSTAT). An ePVS >5.5ml/g, suggestive of undiagnosed residual congestion, was observed at discharge in 3 out the 15 patients. It was possible to document a number of episodes of re-congestion (mean ± standard deviation; 1.4 ± 1.5 for an ePVS rise>10%, 2.3 ± 2.4 for an ePVS rise>15%, 1.8 ± 2.6 for an ePVS>5.5ml/g)[82]. Adequately powered prospective clinical trials using hematocrit/hemoglobin and ePVS are however needed to investigate this hypothesis.

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Graphic abstract

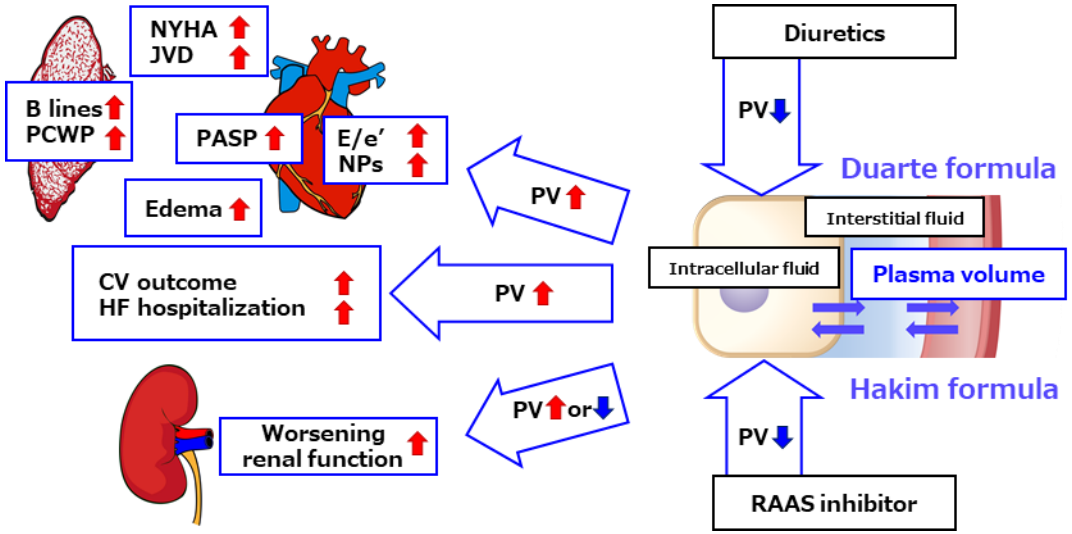


Table 1. Clinical Predictors for Higher Estimated Plasma Volume (derived from Strauss/Duarte or Hakim formula) or Higher Measured Plasma Volume

NYHA, New York Heart Association; JVD, jugular venous distention; BP, blood pressure; RAAS, renin-angiotensin-aldosterone-system; ADHF, acutely decompensated heart failure; TRV, tricuspid regurgitation velocity; PASP, pulmonary artery systolic pressure; EF, ejection fraction; TAPSE, tricuspid annular plane systolic excursion; PCWP, pulmonary capillary wedge pressure; CHF, chronic heart failure; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate.

Table 2. Prognostic Value of Estimated Plasma Volume Status

BS: baseline; M: month; HF, heart failure; ePVS, estimated plasma volume status; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CHF, chronic heart failure; ADHF, acutely decompensated heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction; ACM, all-cause mortality; CVM, cardiovascular mortality; LVAD, left ventricular assistance device.

Table 1. Clinical Predictors for Higher Estimated Plasma Volume (derived from Strauss/Duarte or Hakim formula) or Higher Measured Plasma Volume

		Estimated Plasma Volume				Measured Plasma Volume		
Predictor category	**Factors**	**Strauss/ Duarte**	**reference**	**Hakim**	**reference**	**I-131 labeled albumin**	**reference**	**Comments**
Clinical parameters	Older age	◯	44, 49, 53, 57, 83, 84	◯	33, 35, 84, 85			
	Female sex	◯	44, 57, 83, 84					
	Higher body weight	◯	34					
	Lower body mass index			◯	30, 33, 84, 85			
	Prior history of HF	◯	57 83					acute dyspneic patients with higher ePVS had a more frequent prior HF hospitalization [57]
	Ischemic heart disease	◯	44, 49, 52	◯	35			
	More severe congestion (NYHA, JVD and leg edema)	◯	44, 49, 57, 83, 84	◯	30, 33, 84			
	Lower systolic BP	◯	57	◯	30, 33, 35, 84, 85	◯	17	
	No use of RAS inhibitor			◯	33			
	No use of beta-blocker					◯	17	
	No use of aldosterone antagonist	◯	44					
	Use or higher dose of furosemide	◯	44, 57	◯	30			association between higher ePVS and increased furosemide doses at discharge in ADHF [44]
Echo/ hemodynamics	Higher TRV or PASP	◯	37, 38, 44	◯	35			association between higher ePVS and higher TRV in HFpEF [35] ; Duarte-derived ePVS was correlated with home monitoring-based PAP [37]
	Higher TAPSE	◯	53					
	Higher E/e'	◯	86	◯	33			Duarte-derived ePVS was associated with E/e', whereas ePVS derived from Hakim was not [86]
	Higher PCWP					◯	17, 69	PCWP in ambulatory patients with CHF with absence of edema was correlated with measured blood volume (r=0.69, p=0.01) [17].
Biomarkers	Higher BNP or NT-proBNP	◯	23, 39, 44, 57, 84, 87	◯	30, 33, 35, 84	◯	17	correlation between change BNP and ePVS (r=0.28) [39]; correlation between Duarte-derived ePVS and BNP (r=0.23 or 0.25) [23;] correlation between Hakim-derived ePVS and BNP (r=0.21, p<0.01) [30]
	Lower eGFR (or higher creatinine)	◯	34, 44, 52, 53, 57, 83, 84	◯	35, 84, 85			
	Lower sodium			◯	33, 35, 84			
	Lower albumin			◯	85			

Table 2. Prognostic Value of Estimated Plasma Volume Status

Author/year	n	HF phenotype	ePVS timing	Age (yearrs)	NYHA III/IV(%)	LVEF (%)	Follow-up	Outcome	Comments
Strauss/Duarte (change or instantaneous)									
Rossignol 2015[48]	6,820	CHF with HFrEF	Change from BS to follow-up visit (within 1yr)	67	36	33	3.9 years (median)	ACM, CVM	PVS change>0 was associated with a higher incidence of outcomes
Rossignol 2011[39]	6,080	HFrEF and post-MI	Change from BS to 1M	64	—	33	16 months (median)	ACM, CVM or HF hospitalization etc	decreased ePVS was associated with 11% to 19% to better outcomes
Duarte 2015[23]	4,957	HFrEF and post-MI	BS, 1 mo. and change from BS to 1 mo.	65	17	35	within 6 months	CVM or HF hospitalization	ePVS at 1 month was a better predictor than ePVS change
Kobayashi 2020[83]	1,747	CHF with HFpEF	BS	72	35	58	2.5 years (median)	ACM or HF hospitalization	ePVS was associated with congestion status, study-outcomes, and improved risk stratification regardless of renal function.
Kobayashi 2018[44]	712	ADHF	Admission, discharge and change from admission to discharge	73	69	41	1 year	ACM or HF hospitalization	higher ePVS at discharge had worse prognosis in three independent cohorts from three countries (Japan, France and Portugal)
Kobayashi 2019[53]	117	ADHF	Admission	74	55	40	90 days	ACM or HF hospitalization	combination of higher ePVS and higher congestion score assessed by chest X-ray had 5-fold higher risk of outcome
Fudim 2020 [84]	6,373	ADHF	Admission	67	76	28	30 days & 180 days	CVM or HF hospitalization	Duarte-ePVS tended to be associated with with 30-day, but not 180-day outcomes. Continuous KH-ePVS>0 (per 10 unit increase) was associated with improved 30-day outcomes.
Balderston 2018[50]	218	ADHF	Discharge and 1st visit at outpatient clinic	68	—	34	90 days	ACM or HF hospitalization	ePVS at post-discharge had prognostic value of outcome
Hudson 2016[51]	967	ADHF	Change from admission to discharge	74	93	—	from 4.9 to 8.7 yrs	ACM, ACM or HF hospitalization	highest ePVS tertile was associated with a higher risk of outcomes
Bilchick 2017[52]	324	ADHF	Change from admission to discharge	56	—	—	within 6 months	ACM, cardiac transplantation or LVAD	increased ePVS was associated with a higher risk of outcomes
Massari 2019[87]	436	184 AHF + 252 CHF	Admission	75	56	42	463 days (median)	ACM	ePVS>5.3dl/g had worse prognosis
Chouihed 2018[88]	1,369	Acute dyspnea (including 288 AHF)	Admission	77	—	—	in-hospital	In-hospital mortality	higher ePVS tertile was associated with higher incidence of in-hospital mortality
Huang 2019[49]	449	CHF with HFpEF	BS and change from BS to date of event (or end of follow-up period)	66	42	69	10.7 yrs (median)	ACM or HF hospitalization	ePVS>5.5dl/g at baseline or an increase in ePVS was associated with a higher risk of outcomes
Hakim									
Ling HZ 2015[30]	5,002	CHF with HFrEF	BS	61	36	27	716 days	ACM or HF re-hospitalization	ePVS>-4% was associated with a higher risk of primary outcome
Grodin 2019[35]	3,414	CHF with HFpEF	BS	69	33	61		CVM, HF re-hospitalization or aborted cardiac arrest	higher ePVS was associated with a higher risk of HF hospitalization
Martens 2018[26]	1,173	CHF	BS	70	58	32	33 months (mean)	ACM or HF re-	ePVS>0% was associated with a higher risk

								hospitalization	of primary outcome
Yoshihisa 2018[33]	1,115	AHF	Admission	67	16	50	1007 days (mean)	ACM, CVM, CVM or HF re-hospitalization	Highest ePVS tertile was associated with a higher risk of clinical outcomes
Okonko 2019[85]	459	CHF with HFrEF	BS, weeks 4, 12 and 24	68	83	32	within 24 weeks	ACM or HF hospitalization	• a decrease in ePVS from BS to week 24 was associated with an increase in 6-min walk and improvement of NYHA class. • ePVS>-4% at baseline was an independent predictor of outcome.
Tamaki 2019[89]	384	ADHF	Admission, discharge and change from admission to discharge (Strauss formula)	76	28	39	743 days (median)	ACM or HF hospitalization	ePVS both at admission and discharge had worse prognosis

Supplementary table 1. Association between Hemoconcentration and Worsening Renal Function

					Baseline		Hemoconcentration		Baseline	WRF (or renal impairment)		Comments
Author/year	N	Age (yrs)	LVEF (%)	Follow-up period for Hemoconcentration/WRF	Hb (g/dl)	Hct (%)	Definition	Incidence (%)	eGFR (ml/min/1.73m²)	Definition	Incidence (%)	
Testani 2010 [1]	336	56	19	during hospital index	12.5	37.8	the highest tertile of changes in ≥2 of 3 markers (total protein, ALB or Hct)	32.5	58	≥20% decrease in eGFR	—	Hemoconcentration was associated with 5-fold higher risk of WRF
van der Meer 2013 [2]	1,969	70	32	from admission to day 7	12.7	40.2	increase in Hb level	69.4	51	—	—	Hemoconcentration was significantly associated with an increase in Cr level
Grenne 2013 [3]	1,684	65	28	from baseline to day 7 or discharge (whichever occurred first)	—	42.0	Hct change ≥ 3%	26.4	55	≥0.3mg/dl increase in Cr, ≥25% increase in BUN or ≥25% decrease in eGFR	11.6 (by worsening eGFR)	Highest quartile of absolute change in Hct was associated with worsening Cr, BUN and eGFR
Davila 2011 [4]	295	79	46	during hospital index	12.1	—	the upper quartile of changes in Hb	25.4	1.27 (Cr, mg/dl)	≥0.3mg/dl increase in Cr	20.0	Hemoconcentration was associated with a higher risk of WRF after adjustment for covariates including Hb and Cr at baseline
Darawsha 2016 [5]	704	76	45	during hospital index	12.1	37.1	increase in both Hb and Hct levels	39.2	49	—	—	Hemoconcentration was significantly associated with an increase in Cr level
Testani 2013 [6]	845	63	28	during hospital index	12.1	36.6	increase in both Hb and Hct levels	49.9	60	≥20% decrease in eGFR (at any time during the hospitalization)	—	Incidence of WRF was similar between patients with early hemoconcentration (<a mean of LOS) and late hemoconcentration (<a mean of LOS).
Rao 2019 [7]	105	69	37	from admission to day 4	10.8	—	increase in Hb level	54.2	35	≥median of renal tubular injury biomarker score [44]	50.5	Increase in renal tubular injury biomarkers was associated with a higher incidence of hemoconcentration

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