Clinical Investigation

The Optimal Plasma Volume Status in Heart Failure in Relation to Clinical Outcome

PIETER MARTENS, MD,[1,2] PETRA NIJST, MD, PhD,[1] MATTHIAS DUPONT, MD,[1] AND WILFRIED MULLENS, MD, PhD[1,3]

Genk, and Diepenbeek, Belgium

ABSTRACT

Background: Progressive plasma volume (PV) expansion is a hallmark of chronic heart failure (HF), ultimately contributing to decompensated heart failure. Monitoring PV might offer prognostic information and might be a target for tailored therapy.

Methods and Results: The correlation between technetium-99 (^{99}Tc)−labeled red blood cell measured PV and calculated PV was first determined in a validation cohort. The relationship between PV status (PVS; a marker how much actual PV deviated from the ideal PV) and outcome was analyzed with the use of Cox proportional modeling in a prospective chronic HF (CHF) population (the outcome cohort). Thirty-one HF patients were included in the validation cohort. Calculated PV correlated well with ^{99}Tc-measured PV ($r = 0.714$; $P = .001$). A total of 1173 patients (HF with reduced ejection fraction [HFrEF]: n = 872; HF with mid-range EF [HFmrEF]: n = 229; HF with preserved EF [HFpEF]: n = 72) were prospectively included in the outcome cohort. The mean PVS in the outcome cohort was −6.7% ± 10%, indicating slight PV contraction. Higher PVS was independently associated with increased risk for HF hospitalization and all-cause mortality (hazard ratio 1.016; 95% confidence interval 1.006−1.027 per 1% increase in PVS; $P = .002$). Receiver operating characteristic curve analysis indicated that a PVS of −6.5% optimally predicted absence of adverse outcome. Hazard ratio analysis indicated that CHF patients were less equipped in tolerating PV expansion in comparison to PV contraction. The use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and mineralocorticoid receptor antagonists were independently associated with a higher odds of having an optimal PVS in HFrEF and HFmrEF (all $P < .05$), but not in HFpEF.

Conclusions: Calculated PV correlates well with measured PV in HF patients. An increase in PV is independently associated with a higher risk of adverse outcome, and a slight contraction of the predicted PV seems to be related to less adverse events. Higher dosages of renin-angiotensin-aldosterone blockers are associated with higher odds of having an optimal PV status. (*J Cardiac Fail 2019;25:240−248*)

Key Words: Plasma volume, heart failure, outcome.

Plasma volume expansion is a hallmark of the heart failure syndrome and contributes to the development of congestion (ie, an increase in filling pressures).[1] Unrestrained chronic neurohormonal activation in heart failure induces a situation of plasma volume expansion.[2] If the subsequent plasma volume expansion overwhelms the decreasing venous capacitance as a result of increased neurohumoral activation, an increase in filling pressures ensues with

From the [1]Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; [2]Doctoral School for Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium and [3]Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium.

Manuscript received April 17, 2018; revised manuscript received October 30, 2018; revised manuscript accepted November 29, 2018.

Reprint requests: Wilfried Mullens, MD, PhD, Department of Cardiology, Ziekenhuis Oost-Limburg Schiepse Bos 6, 3600 Genk, Belgium. Tel: +32-89-327160. Fax: +32-89-327918. E-mail: wilfried.mullens@zol.be

Funding: Pieter Martens is supported by a doctoral fellowship by the Research Foundation—Flanders (FWO, grant no. 1127917N). Pieter Martens, Petra Nijst, and Wilfried Mullens are researchers for the Limburg Clinical Research Program (LCRP) UHasselt-ZOL-Jessa, supported by the Limburg Sterk Merk (LSM) foundation, Hasselt University, Ziekenhuis Oost-Limburg, and Jessa Hospital.

See page 248 for disclosure information.

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2018.11.019

progressive deterioration to acute heart failure.[3] Recent analysis has indicated that patients with a clinical picture of volume overload and acute heart failure exhibit an expanded plasma volume compartment.[4] Furthermore, Testani et al demonstrated that hemoconcentration, as a surrogate for plasma volume reduction, is associated with improved outcome during the treatment of acute heart failure.[5] Therefore, plasma volume expansion might be an indication of the transition from stable to decompensated heart failure.[6]

Nuclear techniques based on labeling of albumin or red blood cells can precisely determine plasma volume.[4,7] However, these techniques are cumbersome in clinical practice owing to the need of frequent venous blood sampling and a processing delay. Several formulas have been validated to accurately calculate the plasma volume in healthy individuals and subjects with heart failure.[8,9] The goals of the present analysis were: (1) to validate the use of a calculated method of plasma volume determination; (2) to assess the distribution of plasma volume and its relationship with adverse outcome in a large contemporary optimally treated heart failure population; and (3) to determine pharmacologic predictors associated with an optimal plasma volume status.

Methods

Study Population: Validation and Outcome Cohort

Two cohorts were prospectively collected; a validation cohort and an outcome cohort. The validation cohort was designed to determine the relationship between the measured and calculated plasma volume. The outcome cohort was used to determine the relationship between calculated plasma volume and adverse clinical outcome. All patients were recruited in a single tertiary care center (Ziekenhuis Oost-Limburg, ZOL Genk). The validation cohort was included from September 2014 to September 2015. Inclusion criteria for the validation cohort consisted of (1) age >18 years, (2) heart failure with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] <40% at the time of diagnosis), (3) stable guideline-recommended heart failure therapy for >3 months, (4) absence of an acute heart failure episode in the past 6 months, and (5) mildly symptomatic heart failure, defined as New York Heart Association (NYHA) functional class I or II. The outcome cohort was collected from August 2008 to January 2016. Inclusion criteria for the outcome cohort consisted of (1) a previous heart failure hospitalization in the past 6 months, and (2) HFrEF (LVEF <45%) or HF with preserved ejection fraction (HFpEF; LVEF >45%, with 1 additional echocardiographic alteration: left ventricular hypertrophy, left atrial dilation, or diastolic dysfunction). However, to adhere with the 2016 European Society of Cardiology-guidelines for the diagnosis and treatment of heart failure, patients were afterward classified as HF with reduced (LVEF <40%), mid-range (HFmrEF; LVEF 40%−50%), and preserved (LVEF >50%) EF. The study protocols of the validation and outcome cohorts were approved by the Institutional Review Board, and every patient provided written informed consent. This study complies with the Declaration of Helsinki. The manuscript was drafted according to the STROBE statement for observational studies.[10]

Measurement of Plasma Volume

In the validation cohort, total blood volume was measured with the use of nuclear techniques using technetium-99 (^{99}Tc)−labeled red blood cells, according to the International Committee of Standardization in Hematology. In brief, after adaptation in supine position for 60 minutes, patients received 2 peripheral venous catheters. First, venous blood was sampled and labeled with ^{99}Tc in the nuclear laboratory. The labeled blood (22.8 ± 4.2 mCi) was reinjected into the patient. Afterward, 5 mL blood was collected at 10-minute intervals for 30 minutes. Radioactivity was measured in an automated counter (Veenstra/Comecer, Joure, The Netherlands). Blood volume was calculated as the zero-time volume of distribution of the radiolabeled red blood cells obtained by semilogarithmic extrapolation of values measured from the 3 samples. Plasma volume was derived from the measured blood volume and venous hematocrit, corrected for the trapped plasma and mean body hematocrit.[7]

Calculation of Plasma Volume

In both the validation cohort and the outcome cohort, plasma volume was calculated with the use of a validated formula based on curve-fitting analysis of the subjects' hematocrit and body weight.[9] Actual plasma volume (aPV) was determined as $(1 - \text{hematocrit}) \times (a + [b \times \text{weight in kg}])$,
with hematocrit being expressed as a fraction, and a and b equaling a fixed value varying according to sex (male: a = 1530, b = 41; female: a = 864, b = 47.9). In the validation cohort, the correlation between the measured plasma volume and the calculated aPV was determined. Afterward, the calculated aPV was used in larger numbers in the outcome cohort. In addition to the calculated aPV, the ideal plasma volume (iPV) was calculated according to the established formula: weight in kg multiplied by 39 in men and by 40 in women). This iPV was used to calculate the relative plasma volume status (PVS), which indicates how much the calculated aPV deviates from the iPV: $\text{PVS} = [(\text{aPV} - \text{iPV})/\text{iPV}] \times 100$). The PVS was used in the outcome cohort to determine the population distribution of plasma volume, its predictors, and the relationship with outcome.

Baseline Data Collection

In both the validation cohort and the outcome cohort, each patient underwent collection of detailed baseline characteristics, including weight (with the use of a validated weight scale), severity of heart failure (NYHA functional class), and registration of comorbidities, baseline

medication, and clinical parameters after completion of the informed consent. The dose of baseline therapy with angiotensin converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and beta-blockers were expressed as percentage of target dose as previously published.[11] Loop diuretics were expressed as furosemide equivalents, with 1 mg of bumetanide equaling 20 mg torsemide and 40 mg furosemide.[12] Afterward, peripheral venous blood was sampled. Hematologic indices were assessed from fresh venous blood collected in an EDTA tube (Siemens Healthcare Diagnostics, Deerfield, Illinois).

Clinical Follow-Up and End Point in the Outcome Cohort

Patients enrolled in the outcome cohort were followed clinically every 6−9 months in the outpatient cardiology department, as previously described.[13] Follow-up was censored at the last medical visit or death. Vital status was checked with the use of the electronic health record. A combined end point of heart failure hospitalization and all-cause mortality was used as the clinical outcome end point. Heart failure hospitalization was defined as an acute hospitalization lasting for >24 hours necessitating the need for intravenous diuretics in the presence of ≥2 signs or symptoms of congestion or due to a state of low cardiac output.

Statistics

Continuous variables were expressed as mean ± SD if normally distributed or median and interquartile range if nonnormally distributed. Normality was checked by means of the Shapiro-Wilk statistic. Categoric data were expressed as percentages and compared by means of the Pearson χ^2 test when a large sample size was present or Fisher exact test when a small sample size was present ($n < 100$). Continuous variables were compared by means of the Student *t* test, Mann-Whitney *U* test, and analysis of variance (ANOVA) as appropriate. Receiver operating characteristic (ROC) curves were used to determine the PVS with the lowest risk for the combined clinical end point (the optimal plasma volume point) by identifying the Youden point (optimal cutoff point) with the lowest risk for the combined end point. The Cox proportional hazards model was used to calculate the hazard ratio with corresponding 95% confidence interval. Hazard ratios were calculated for PVS as a continuous variable and as a categoric value (small discrete groups of PVS). Small discrete groups for PVS were made of 2%, except that at both end of the PVS spectra patients were clustered to ensure that sufficient patients were present, because PVS is normally distributed. The discrete PVS group that contained the optimal plasma volume point was set as the reference value by which hazard ratios were compared. Adjusted hazard ratios were calculated in a Cox proportional hazard model after adjusting for important covariates. A multivariate binary logistic regression model was used to determine the pharmacologic predictors of an optimal plasma volume status. Statistical significance was always set at a 2-tailed probability level of <.05. All statistics were performed with the use of SPSS version 24 (IBM, Chicago, Illinois).

Results

Study Populations

A total of 31 patients were included in the validation cohort and 1173 patients in the outcome cohort. Of the patients included in the outcome cohort, 872 patients had HFrEF, 229 HFmrEF, and 72 HFpEF. Baseline characteristics of the patient populations and subgroups according to ejection fraction classification are presented in Table 1. Characteristics are indicative of a large optimally treated contemporary heart failure population.

Correlation Between Measured and Calculated Plasma Volume

Figure 1A illustrates the correlation between the measured plasma volume with the use of the described nuclear technique versus the calculated plasma volume. The aforementioned formula to calculate aPV demonstrated a moderate to good correlation with the validated (criterion standard) nuclear technique. In addition, Fig. 1B illustrates a Bland-Altman plot, showing good agreement between measured and calculated plasma volume.

Plasma Volume Status in the Outcome Cohort

Figure 2 demonstrates the relative PVS in the outcome cohort. The *x*-axis illustrates how much the actual calculated plasma volume has deviated from the ideal plasma volume. The mean PVS in our cohort was −6.7% ± 10%, indicating that most heart failure patients in our cohort had a lower actual calculated plasma volume than what was predicted by the ideal plasma volume formula. In addition, as illustrated in Fig. 2, PVS is relatively normally distributed in a large heart failure cohort.

Relationship Between Plasma Volume Status and Outcome

During a mean follow-up of 33 ± 21 months, a total of 440 events (330 heart failure hospitalization and 110 deaths) occurred for the primary end point of heart failure admission and all-cause mortality. The median duration between inclusion and a first event was 301 days (interquartile range 100−699 days). The event rates between HFrEF, HFmrEF, and HFpEF were not significantly different (log-rank $P = .155$). To assess the relationship between PVS and adverse clinical outcome in the entire outcome cohort, PVS was first handled as a continuous variable in a Cox proportional model (Table 2). Even after adjusting for covariates that all carry prognostic information (Table 2), higher PVS was an independent predictor of the combined end point of heart failure admission and all-cause mortality or heart failure hospitalization independently. To further study the relationship between PVS and outcome, we identified the

Table 1. Baseline Characteristics of Validation and Outcome Cohorts

Parameter	Validation Cohort (n = 31)	Outcome Cohort (n = 1173)	Outcome Cohort Subgroups		
			HFrEF (n = 872)	HFmrEF (n = 229)	HFpEF (n = 72)
Age, y	60 ± 18	70 ± 12	70 ± 12	71 ± 11	72 ± 9
Sex					
Male	25 (81%)	829 (71%)	635 (73%)	167 (73%)	27 (37%)
Female	6 (19%)	344 (29%)	237 (27%)	62 (27%)	45 (63%)
Functional class					
NYHA I	8 (26%)	92 (8%)	59 (7%)	25 (11%)	9 (14%)
NYHA II	23 (74%)	401 (34%)	292 (34%)	87 (38%)	22 (34%)
NYHA III/IV	–	680 (58%)	466 (59%)	112 (49%)	34 (52%)
Cardiomyopathy					
Nonischemic	11 (35%)	479 (41%)	358 (41%)	89 (40%)	32 (50%)
Ischemic	20 (65%)	628 (58%)	514 (59%)	136 (60%)	32 (50%)
Comorbidities					
Atrial fibrillation	8 (26%)	441 (38%)	311 (36%)	96 (42%)	34 (48%)
Diabetes	5 (16%)	326 (28%)	238 (27%)	66 (29%)	22 (31%)
Hypertension	16 (52%)	711 (61%)	515 (59%)	145 (63%)	51 (71%)
COPD	8 (26%)	241 (21%)	173 (20%)	49 (21%)	19 (26%)
Smoker/history of smoking	16 (52%)	597 (51%)	449 (51%)	120 (52%)	28 (39%)
Echocardiography					
LVEF, %	42 ± 14	32 ± 11	26 ± 7	43 ± 4	59 ± 4
Laboratory analysis					
Hemoglobin, g/dL	13.4 ± 1.3	13.3 ± 1.9	13.2 ± 1.7	13.4 ± 2.7	12.7 ± 1.7
Hematocrit, %	39.4 ± 3.9	39.8 ± 12.3	39.8 ± 13.8	39.7 ± 5.8	38.4 ± 5.2
eGFR, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	66 ± 24	61 ± 25	60 ± 25	61 ± 25	61 ± 22
Sodium, mmol/L	138 ± 3	139 ± 7	139 ± 8	140 ± 4	139 ± 3
Heart failure therapy					
ACE-I or ARB	24 (77%)	861 (73%)	657 (75%)	167 (73%)	37 (56%)
Beta-blocker	26 (84%)	937 (80%)	727 (83%)	169 (74%)	41 (62%)
MRA	21 (67%)	649 (55%)	527 (60%)	103 (45%)	19 (29%)
Loop diuretics	17 (55%)	576 (49%)	439 (50%)	115 (50%)	23 (35%)
CRT or ICD	22 (71%)	730 (62%)	572 (66%)	136 (59%)	22 (30%)

NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; eGFR, estimated glomerular filtration rate; NT-proBNP, NT-terminal pro–type B natriuretic peptide; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonist; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator. Values are presented as mean ± SD or n (%).

optimal plasma volume point with the use of ROC analysis. A PVS of −6.5% best predicted the absence of heart failure hospitalization and all-cause mortality. Afterward, PVS was divided into discrete groups. Figure 3 illustrates the hazard curve of the discrete PVS groups with the group containing the optimal plasma volume point as a reference.

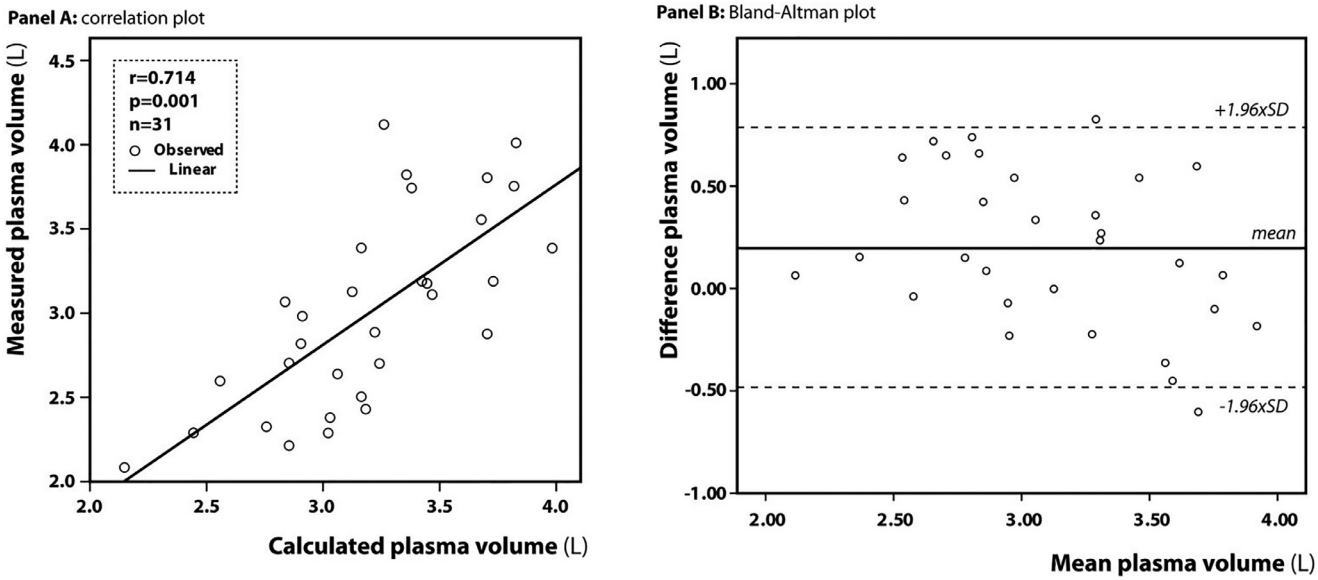

Fig. 1. Relationship between measured and predicted plasma volume.

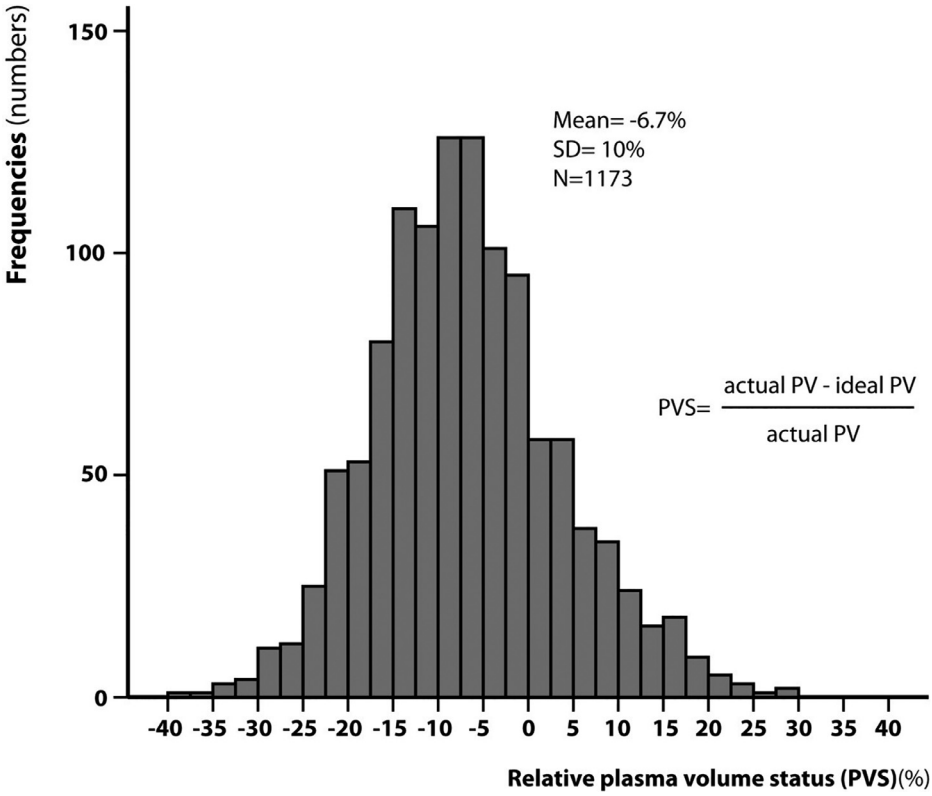

Fig. 2. Distribution of estimated plasma volume in the outcome cohort.

Figure 3 shows that heart failure patients are perhaps better at tolerating a contraction in their plasma volume compartment than an expansion above PVS >0%, because all discrete groups above PVS >0% had a significantly higher risk for adverse outcome. Figure 4 illustrates the same hazard curve but plotted against the PVS distribution in the outcome cohort, indicating that many heart failure patients fall into PVS categories associated with higher risk for adverse outcome. Finally, we assessed if PVS (handled as a linear variable) offers additional prognostic information on top of a well established prognostic risk score in heart failure, the MAGGIC-HF risk score.[14] Table 3 presents the results of a Cox proportional hazard model, showing that every increase in percentage of PVS indicates higher risk for the combined end point of heart failure admission and all-cause mortality in addition to all individual components of the MAGGIC-HF risk score.

Predictors of Optimal Plasma Volume Status

Because PVS might be a modifiable risk factor associated with adverse outcome in heart failure, we tried to identify which pharmacologic therapies were associated with an optimal plasma volume status. For this analysis, the optimal plasma volume status was defined as the range of discrete PVS groups that did not exhibit a statistically higher risk for adverse outcome. This is illustrated in Fig. 3 as the area between the 2 vertical lines indicating statistical divergence (lower range point −20% to −18% and upper range point 0 to +2%). Table 4 presents the results of the binary logistic

Table 2. Plasma Volume Status as Predictor for Outcome

	Unadjusted Risk			Adjusted Risk*		
Parameter	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Heart failure hospitalization and all-cause mortality	1.028	1.019−1.038	<.001	1.016	1.006−1.027	.002
Heart failure hospitalization	1.025	1.014−1.036	<.001	1.014	1.004−1.026	.014

HR, hazard ratios; CI, confidence interval. HRs are for every 1% increase in plasma volume status.

*Adjusted for, age, sex, history of atrial fibrillation, chronic obstructive lung disease, diabetes, ischemic etiology of heart failure, use of renin-angiotensin-aldosterone system blockers, beta-blockers, mineralocorticoid receptor antagonists, and loop diuretics, New York Heart Association functional class, ejection fraction, and estimated glomerular filtration rate.

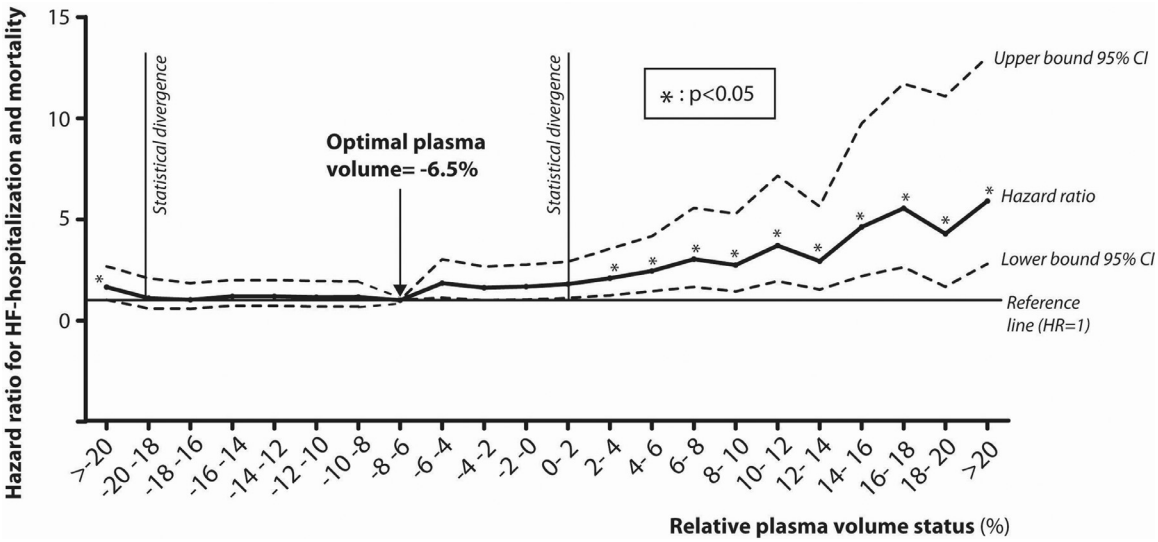

Fig. 3. Relationship between plasma volume status and risk of heart failure (HF) hospitalization and all-cause mortality.

model determining which pharmacologic baseline therapy was associated with higher odds of having an optimal plasma volume status. Neurohormonal blockers and loop diuretics were entered as continuous covariates, taking drug dosage into account (instead of binary covariates, intake yes or no). Because the benefit of neurohormonal blockers differ according to ejection fraction strata, patients were further classified in HFrEF, HFmrEF, and HFpEF. Our data indicate that a higher dose of renin-angiotensin-aldosterone system (RAAS) blocker (ACE-I or ARB) and a higher dose of a mineralocorticoid receptor antagonist (MRA) are associated with an independent higher odds of having an optimal plasma volume status in HFrEF and HFmrEF, but not in HFpEF.

Discussion

The present analysis adds novel and important information about the relationship between plasma volume status and outcome in a large optimally treated contemporary heart failure population. The core messages can be summarized as follows: (1) calculated actual plasma volume correlates well with the measured plasma volume; (2) plasma volume status is normally distributed, yet widely variable,

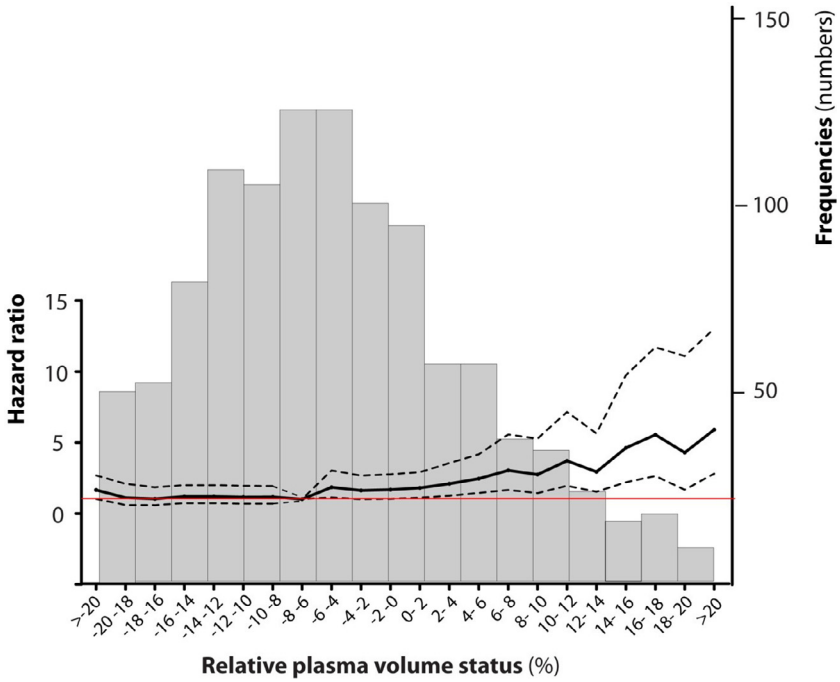

Fig. 4. Plasma volume frequencies plotted against discrete risk for adverse outcome. Red line indicates the reference hazard ratio of 1. Black solid line indicates hazard ratio and dotted black lines indicate 95% confidence interval.

Table 3. Additive Prognostic Impact of PVS in Addition to MAGGIC-HF Risk Score*

	Adjusted Risk for Combined End Point of HF Admission and All-Cause Mortality		
Parameter	HR	95% CI	*P* Value
PVS, %	1.022	1.007−1.037	.003
Diabetes mellitus	1.746	1.294−2.350	< .001
Ischemic etiology	1.083	0.752−1.559	.670
SBP, mm Hg	0.995	0.987−1.002	.178
Heart rate, beats/min	1.002	0.994−1.009	.679
LVEF, %	1.008	0.996−1.021	.191
Female sex	0.916	0.652−1.285	.611
Creatinine, mg/dL	1.118	0.964−1.297	.139
NYHA functional class	1.812	1.489−2.205	< .001
Active smoking	0.736	0.574−0.944	.016
COPD	1.202	0.861−1.679	.279
Beta-blocker use	1.051	0.727−1.520	.792
ACE-I/ARB use	0.651	0.473−0.895	.008

HR, hazard ratio; CI, confidence interval; PVS, relative plasma volume status**;** SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

*Duration of heart failure (one of the components of the MAGGIC-HF risk score) was not available in our database and could not be used in this model.

in a large patient population with a population mean indicating plasma volume contraction; (3) plasma volume expansion is associated with adverse outcome; and (4) higher dosages of RAAS blockers and MRA are associated with an optimal plasma volume status in HFrEF and HFmrEF, but not in HFpEF.

In a majority of decompensated heart failure patients, plasma volume expansion due to chronic sodium and water retention contributes to the worsening congestion.[15] It is well recognized in heart failure patients awaiting transplants that even subclinical volume expansion is associated with a higher risk for heart failure hospitalization and mortality.[16] Data from implantable pressure monitors indicate that small rises in filling pressures are often detectable weeks before the admission for an acute heart failure episode.[15,17] Interventions with the use of loop diuretics (which reduce plasma volume) or vasodilators (which increase venous capacitance) both reduce filling pressures and were associated with lower risk for heart failure admissions in the CHAMPION trial.[18] In aggregate, these data suggest that the plasma volume might be a very attractive target for tailored patient care. However, the inability to easily determine plasma volume might hamper its use in clinical practice.

Table 4. Pharmacologic Predictors of Optimal Plasma Volume Status in Overall Outcome Cohort and Subgroups

	Binary multivariate logistic model		
Parameter	OR	95% CI	*P* Value
Overall outcome cohort (n = 1173)			
RAS-I dose	1.623	1.010−2.367	.008*
Beta-blocker dose	1.020	0.980−1.062	.384
MRA dose	1.132	1.038−1.219	.004*
Loop diuretic dose	0.942	0.869−1.020	.093
Outcome-HFrEF subgroup (n = 872)			
RAS-I dose	1.051	1.010−1.094	.026*
Beta-blocker dose	1.041	0.990−1.094	.139
MRA dose	1.147	1.038−1.250	.009*
Loop diuretic dose	0.942	0.852−1.020	.160
Outcome-HFmrEF subgroup (n = 229)			
RAAS-I dose	1.091	1.000−1.184	.047*
Beta-blocker dose	0.970	0.886−1.062	.473
MRA dose	1.190	1.013−1.395	.037*
Loop diuretic dose	0.961	0.818−1.150	.721
Outcome-HFpEF subgroup (n = 72)			
RAS-I dose	0.942	0.801−1.105	.476
Beta-blocker dose	1.030	0.851−1.243	.780
MRA dose	1.105	0.807−1.537	.529
Loop diuretic dose	0.522	0.245−1.127	.101

RAAS-I, renin-angiotensin-aldosterone system blockers; MRA, mineralocorticoid receptor antagonists. Changes are for 10% in target dose for RAS-I and beta-blocker and for 12.5 mg in dose for MRA and 20 mg furosemide equivalents for loop diuretics.

*$P < .05$.

Our analysis supports the analysis by Ling et al indicating that a calculated plasma volume carries a good correlation with the measured plasma volume according to validated nuclear techniques.[9] Furthermore, our analysis is in line with studies from direct plasma volume assessment indicating that the plasma volume status is normally distributed (though often with a wide distribution) and that many stable well treated heart failure patients demonstrate a plasma volume under the predicted point of "euvolemia" (PVS 0).[7,19,20] Interestingly, just as in the Val-HeFT dataset, a slight volume contraction best predicted the absence of heart failure hospitalization and all-cause mortality.[9] However, it is important to bear in mind that the population in the Val-HeFT trial might not reflect a contemporary heart failure population, as illustrated by the absence of the use of MRAs, cardiac resynchronization therapy, implantable cardioverter-defibrillators, and beta-blockers use in 35% of the cohort.[21] Therefore, reconfirming the analysis of Ling et al might be welcome in a contemporary heart failure population.

Using the patients with an ROC curve−identified optimal plasma volume (PVS −6.5%) as a reference, we demonstrated that patients with heart failure are perhaps more equipped in tolerating plasma volume contraction than

plasma volume expansion, because a plasma volume up to −20% of the "ideal calculated" plasma volume was not associated with worse outcome, whereas even a slight plasma volume expansion (>0% increase above the "ideal calculated" plasma volume) was associated with a higher risk for heart failure hospitalization and all-cause mortality. In addition, PVS expansion independently predicted increased risk for heart failure admission and all-cause mortality on top of the individual components of the MAGGIC-HF risk score.[14] Several mechanisms might explain this finding. As alluded to, heart failure hospitalizations are most often for worsening of congestion and only in a minority of cases for low cardiac output.[1] Although plasma volume expansion is often used synonymously for congestion, it should be noticed that congestion in its essence indicates an increasing of filling pressures that result in vascular crowding of capillaries and development of edema. Moreover, congestion can theoretically occur owing to an increase in plasma volume, but also a decrease in venous capacitance,[3] because the filling pressures in a biologic system are the interaction between an intravascular volume and the capacitance function of the vasculature. Indeed, many patients do not exhibit weight gain before a heart failure hospitalization with congestion, indicating that in some patients a reduced venous capacitance due to venoconstriction plays a role in the development of increased filling pressures.[22,23] However, chronic neurohormonal activation has been shown to decrease the venous capacitance in heart failure as well as increase sodium/fluid retention, with a corresponding increase in plasma volume.[3]

Furthermore, our analysis generates the hypothesis that RAAS blockers might partially mediate their beneficial effects by restoring the volume set-point in heart failure in patients with HFrEF and HFmrEF (in which the role of neurohormones are well established), because higher doses of ACE-I, ARB, and MRA were associated with higher odds of having an optimal plasma volume status in HFrEF and HFmrEF. Indeed, the RAAS is implicated in heart failure as the culprit for inducing plasma volume retention. Chronic inhibition of the RAAS might allow for a more stable (contracted) plasma volume, at least in the patient population in which the role of neurohormonal activation is well established, such as those with HFrEF. Interestingly, research assessing the role of neurohormonal blockers in HFmrEF indicate that HFmrEF more closely fits the profile of HFrEF regarding effectiveness of pharmacotherapy than HFpEF.[24] Nevertheless, it must be recognized that the number of patients with HFpEF is the present cohort was small. Therefore, we should also acknowledge the possibility that the nonsignificant *P* value is the result of a type II error (inability to reject a false null hypothesis).

More strikingly, the use of loop diuretics was not independently associated with a higher odds of having an optimal plasma volume. This could obviously be the result of prescription bias, because loop diuretics are used in patients with signs of volume overload. However, loop diuretics might also induce RAAS activation, potentially preventing an optimal plasma-volume in the long run. Clearly these results are only hypothesis generating and do not illustrate causality. Nevertheless, our data might generate the hope for other therapies that effectively reduce plasma volume (without compensatory RAAS activation) to improve outcomes in heart failure. One such therapy that fits this profile are sodium glucose-linked transporter 2 (SGLT2) inhibitors.[25] The SGLT2 inhibitor dapagliflozin, eg, results in a 7.3% reduction in plasma volume without compensatory sympathetic nerve activation or inhibiting macula densa activity.[26] Finally, our data might support the use of calculated plasma volume as a metric of volume status to prospectively tailor therapy. Additional well designed prospective studies are necessary to determine if calculated plasma volume−guided therapy is superior to clinical judgement in preventing heart failure admissions or all-cause mortality.

Study Limitations

Several limitations should be addressed to fully interpret the data. First, in the outcome cohort we collected data regarding only heart failure hospitalization and all-cause mortality. No outcomes data were collected for hospitalizations in relation to worsening of renal function. This might be relevant because patients with a very low plasma volume might exhibit an increased risk for hospitalizations in relation to worsening of renal function. Second, the plasma volume status analysis is only a baseline snapshot in the disease trajectory of the patient with heart failure. We were not able to correlate dynamic changes in plasma volume status with outcome. However, this has previously been demonstrated by Duarte et al.[8] Third, in the small validation cohort, we have previously noted that the intake of neurohormonal blockers was not associated with plasma volume.[7] However, because of the small sample size of the validation cohort, definitive conclusions are not possible. Fourth, some differences were present between the validation cohort and the outcome cohort. The reason for this difference is that the validation of ^{99}Tc-labeled red blood cell plasma volume measurement with calculated plasma volume occurred in a cohort that required elective hospitalization for measurement and were therefore clinically more stable. Nevertheless, this difference is not expected to have had an impact on the validity of calculating PVS in the outcome cohort. Fifth, our data provide only an association between plasma volume status and outcome. Prospective studies are necessary to determine if reducing plasma volume status in patients with increased plasma volume status is associated with improved clinical outcome. Finally, the formula, though validated previously, used only weight, sex, and hematocrit. However, a low hematocrit can occur in the setting of true anemia or in the setting of volume overload. In addition, obesity and cachexia are 2 conditions often associated with heart failure in which weight changes are not a result of fluid changes. The formula used is perhaps not capable of differentiating these mechanisms.

Conclusion

Calculated plasma volume correlates well with measured plasma volume in heart failure patients. In a large patient cohort, plasma volume expansion was independently associated with worse outcome. PVS −6.5% from the ideal calculated plasma volume best predicted absence of heart failure hospitalization and all-cause mortality. Such optimal PVS was associated with higher doses of ACE-I/ARB and MRA in HFrEF and HFmrEF, but not HFpEF.

Disclosures

None.

References

1. Martens P, Nijst P, Mullens W. Current approach to decongestive therapy in acute heart failure. Curr Heart Fail Rep 2015;12:367–78.
2. Kalra PR, Anagnostopoulos C, Bolger AP, Coats AJ, Anker SD. The regulation and measurement of plasma volume in heart failure. J Am Coll Cardiol 2002;39:1901–8.
3. Verbrugge FH, Dupont M, Steels P, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol 2013;62:485–95.
4. Miller WL, Mullan BP. Understanding the heterogeneity in volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: role for blood volume quantitation. JACC Heart Fail 2014;2:298–305.
5. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation 2010;122:265–72.
6. Zile MR, Bennett TD, St John SM, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation 2008;118:1433–41.
7. Nijst P, Verbrugge FH, Bertrand PB, et al. Plasma volume is normal but heterogeneously distributed, and true anemia is highly prevalent in patients with stable heart failure. J Card Fail 2017;23:138–44.
8. Duarte K, Monnez JM, Albuisson E, Pitt B, Zannad F, Rossignol P. Prognostic value of estimated plasma volume in heart failure. JACC Heart Fail 2015;3:886–93.
9. Ling HZ, Flint J, Damgaard M, et al. Calculated plasma volume status and prognosis in chronic heart failure. Eur J Heart Fail 2015;17:35–43.
10. von EE, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370(9596):1453–7.
11. Martens P, Verbrugge FH, Nijst P, et al. Feasibility and association of neurohumoral blocker up-titration after cardiac resynchronization therapy. J Card Fail 2017;23:597–605.
12. Martens P, Verbrugge FH, Nijst P, Dupont M, Mullens W. Changes in loop diuretic dose and outcome after cardiac resynchronization therapy in patients with heart failure and reduced left ventricular ejection fractions. Am J Cardiol 2017;120:267–73.
13. Martens P, Nijst P, Verbrugge FH, Smeets K, Dupont M, Mullens W. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. Acta Cardiol 2018;73:115–23.
14. Pocock SJ, Ariti CA, McMurray JJ, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J 2013;34:1404–13.
15. Nijst P, Verbrugge FH, Grieten L, et al. The pathophysiological role of interstitial sodium in heart failure. J Am Coll Cardiol 2015;65:378–88.
16. Androne AS, Hryniewicz K, Hudaihed A, Mancini D, Lamanca J, Katz SD. Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. Am J Cardiol 2004;93:1254–9.
17. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377(9766):658–66.
18. Costanzo MR, Stevenson LW, Adamson PB, et al. Interventions linked to decreased heart failure hospitalizations during ambulatory pulmonary artery pressure monitoring. JACC Heart Fail 2016;4:333–44.
19. Feigenbaum MS, Welsch MA, Mitchell M, Vincent K, Braith RW, Pepine CJ. Contracted plasma and blood volume in chronic heart failure. J Am Coll Cardiol 2000;35:51–5.
20. Miller WL, Albers DP, Gansen DN, Mullan BP. Intravascular volume profiles in patients with class I and II systolic heart failure: heterogeneity and volume overload are common even in mild heart failure. J Card Fail 2017, October 2.
21. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667–75.
22. Kociol RD, McNulty SE, Hernandez AF, et al. Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. Circ Heart Fail 2013;6:240–5.
23. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. Circ Heart Fail 2011;4:669–75.
24. Nauta JF, Hummel YM, van Melle JP, et al. What have we learned about heart failure with mid-range ejection fraction one year after its introduction? Eur J Heart Fail 2017;19:1569–73.
25. Martens P, Mathieu C, Verbrugge FH. Promise of SGLT2 inhibitors in heart failure: diabetes and beyond. Curr Treat Options Cardiovasc Med 2017;19:23.
26. Lambers Heerspink HJ, de ZD, Wie L, Leslie B, List J. Dapagliflozin, a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes Metab 2013;15:853–62.