Recommendations and Guidance for Introducing and Using Daxor BVA-100® (Blood Volume Analyzer) in the Clinical Setting and Achieving the Best Outcomes and Values

Blood Volume Analysis for Heart Failure Patients: Expert User Panel Recommendations for Improving Outcomes and Providing Value

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Preamble

AS TECHNOLOGIES are introduced and used in clinical practice, what emerges at some point is a set of best practices. Best practices help guide current and unpracticed users of that technology to reap the full potential of the technology and enhance the efficiency and process of integrating it into clinical practice for the benefit of patients. After 20 years of clinical use and more than 60,000 tests, multiple best practices have emerged. Clinicians from leading centers within the U.S. have crafted the best practices applicable to blood volume analysis (BVA), interpretation, and application and are sharing those with you within this document.

This Consensus document has gone through multiple iterations over one year. As the applications of BVA in heart failure patients and beyond continue to expand, more best practices and insights will emerge. Therefore, the current document is planned as a living document to be updated and expanded regularly.

We are grateful to our Advisory Board members, who have dedicated their time and wisdom to creating this initial installment of the Consensus document. We look to all who read and use the document to be future contributors and promote the vision of using BVA to improve healthcare outcomes, improve patient safety, and reduce the cost of care.

Background on Blood Volume Analysis

One question that often arises is whether there are expert guidelines to teach how to use and interpret blood volume analyses **(BVA)**, accelerate the introduction of BVA, and support the path to the best outcomes. The answer is yes!

Many of the earliest clinical users of BVA were based in academic centers and began the BVA studies in a wide range of applications and clinical settings. As a result, a series of practical and key recommendations for best practices evolved. More than 100 medical publications detail process and flow learned after extensive experience. This report condenses this information into a usable and immediately helpful format. Short summaries are provided to help with the learning process by providing an evidence base and a supporting bibliography. The intent is that this will be a helpful tool to familiarize each user with BVA best practices and share them with team members.

Blood Volume Analysis is at the Heart of Heart Failure

The integrity of a patient's circulatory system is largely dictated by cardiac function and the intravascular volumes defined by plasma volume **(PV)** and red blood cell volume **(RBCV)**, which together comprise total blood volume **(TBV)**. Heart failure **(HF)** is a complex syndrome marked by wide heterogeneity and derangements in intravascular volumes.[1-9] While homeostasis in intravascular volume is generally integrated with other body fluid compartments (intracellular and interstitial), even this integration is disrupted in heart failure.[1-10]

The measurement of blood/plasma volume was used to study various disease states, with some of the early work of Gibson and Evans in 1937 using colorimetric dyes.[11] In 1977, several advancements occurred, including documentation of a bedside procedure using a single isotope and the creation of a revised nomogram that allowed individualized patient normative BVA values to be generated by the Daxor BVA-100® (Blood Volume Analyzer). This device and procedure have become the gold standard for blood volume analysis and have been clinically available, FDA-cleared, and reimbursed in the inpatient and outpatient settings.[12, 15-16]

Currently, many sites across the U.S. perform BVA in many different clinical and research settings, with more than 60,000 BVA tests performed to evaluate blood volume to date. For HF patients, key metrics provided by BVA have a proven benefit and value guiding care in the wide range of HF phenotypes (HFpEF, HFrEF, and mid-range EF.).[16-22] It is important to note, the key BVA metrics of total intravascular volume and RBCV are fundamental in evaluating an HF patient but are not quantitatively known without BVA.

Consensus Report

With more than 20 years of clinical use, careful validation, and expanded application of BVA in a range of HF scenarios, expert clinicians and investigators (core user group) have identified the value in creating a consensus document. This document will ease the way for centers to understand the central importance of the precise and individualized measurements reported, including TBV, PV, and RBCV, and the associated measurements of a normalized hematocrit (nHct) and the capillary albumin transudation rate **(TR)**. Understanding these values is the first step for a clinical team to get the needed insights into the patient's clinical status and create a treatment plan to improve care and outcomes.

The entire HF syndrome, from the earliest to the more advanced stages of the disease, BVA may be applied in clinical practice, quality improvement processes, offices, clinics, and hospitals across the nation. This document brings forward the evidence and utility of using BVA in a wide range of HF scenarios; the goal is to provide distinct insights into the pathophysiological derangements and provide actionable steps for treatment and monitoring.

Standardized, "routine" treatment plans are commonly applied to HF populations; however, HF is a complex disease process with multiple overlying comorbidities. Because of this complexity, empiric care plans such as intravenous diuretic administration based on history or HF clinical signs and symptoms lack objective data. They may, in some cases, exacerbate the disease severity.[23-26]

BVA applied as an early diagnostic in inpatient or outpatient settings allows a reset in the thoughtful planning process needed to create an informed care plan that helps avoid over or under treatment and prevent risky therapeutic missteps.[10,21-22,26]

How and Where to Perform BVA

BVA is based on the indicator dilution technique using an I^{131} tagged human serum albumin (HSA) tracer combined with various patented processes and technologies, including uniquely well-validated patient-specific norming to deliver a 98% accurate quantitative measurement of TBV, RBCV, and PV and calculate the volume excess or deficit versus patient-specific normal expected volumes.[13-14]

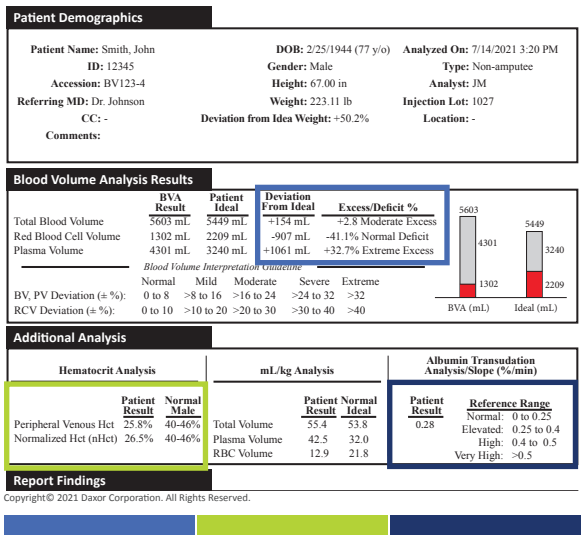
Following intravenous injection of the tracer at time zero, a 12-minute diffusion period through the circulation is

followed by blood draws six minutes apart. The samples are then centrifuged to separate red cells from plasma. Finally, plasma aliquots and standards are placed in the analyzer carousel, generating results within 60-90 minutes. The ease of administration, sampling, and processing allow BVA to be performed in multiple settings, including emergency departments, surgical suites, critical care units, hospital wards, offices, clinics, ambulatory, and even home care settings. Processing typically takes place on-site where the BVA analyzer is installed; however, sample shipment to the Daxor BVA Reference Lab is also routinely performed.[12,15-16]

What does the BVA Measure and What Data is Provided in the BVA Test Report

The value of blood volume measurement is delivered in key metrics that are patient-specific, accurate, and actionable.[12,15,21-22-27-30] A sample BVA report, below, highlights these metrics:

Fig. 1. Intravascular total blood volume, plasma volume, and red blood cell volume



Excess/Deficit %

Degree of volume derangement relative to calculated patient-specific norms.

Hematocrit Analysis

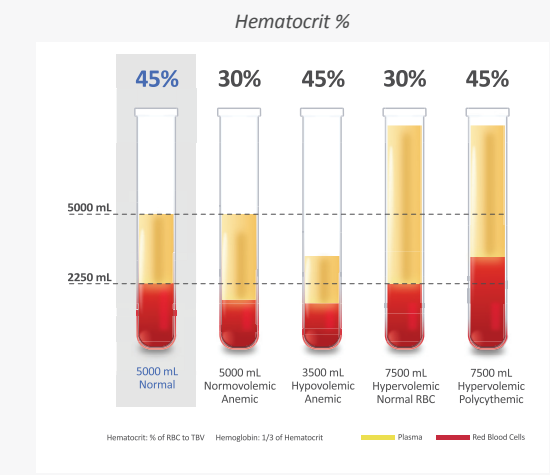
Normalized Hct what the hematocrit would be if TBV was normal by only correcting the plasma volume.

Albumin Transudation Slope

Provides the rate at which the albumin transudates out of the circulation through the capillary bed.

The BVA-100 test report provides a comprehensive overview of TBV, PV, and RBCV status unique for each patient. In HF patients, large, often unexpected, volume variations are common.[1-10] The variation from the patient-specific norms is reported in milliliters (ml) and as a percentage of excess or deficit, providing a quantitative evaluation of the degree of derangements.[12,15] This information can help guide specific therapeutic targets and inform approaches to intravascular volume status. Importantly, studies directly comparing the BVA measured RBCV show that the peripheral hematocrit (pHct) measurement does not accurately predict RBCV. BVA often identifies unsuspected red blood cell derangements, including anemia and polycythemia, impacting HF outcomes.[31-42]

Fig. 2. Patients with the same hematocrit (Hct) may be highly discordant in true red blood cell volume status



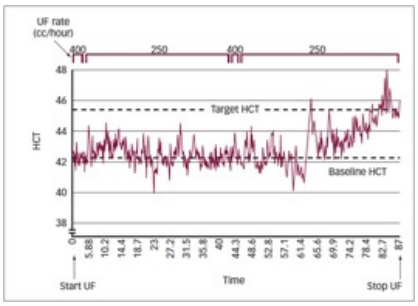
Adapted from Manzone et al. "Normalized Hematocrit" from Blood Volume Analysis Offers Enhanced Accuracy over Peripheral Hematocrit in Assessment of Red Blood Cell Volume. Poster presentation, SNM, 2010.[43]

Normalized Hematocrit (nHct)

The hematocrit (Hct) analysis compares the pHct to a unique metric, the normalized hematocrit (nHct). For example, the nHct would be the Hct if TBV were adjusted to normal by adjusting the PV. The nHct is a crucial part of determining the true derangement of RBC, such as true anemia versus dilutional anemia and true polycythemia. In addition, the nHct allows evaluation of the RBCV as it relates to the TBV and PV.[43]

The pHct, as first described, relates the PV and RBCV and expresses the relationship as a ratio or fraction; in healthy individuals, the red cells typically comprise 40-45% of the blood volume. This relationship can be obtained with a peripheral finger stick but only detects the ratio RBC to PV and not the RBCV.[44-45] Clinical underestimations of the actual red cell volumes can greatly influence patients' signs, symptoms, functional status, and prognosis. Furthermore, the nHct is extremely valuable in monitoring hemoconcentration and hence guiding diuretic strategies; movement of a pHct towards a target nHct guides normalizing an expanded TBV/PV.[35]

Fig. 3. Realtime hematocrit monitoring during ultrafiltration therapy



Time is represented on the x-axis and hematocrit (Hct) data on the y-axis. The baseline and target Hct, which are derived from blood volume analysis, are represented by dashed lines. As ultrafiltration (UF) progresses and the plasma refill rate falls below the UF rate, Hct begins to rise. In response, the UF rate is gradually reduced in a step-wise fashion and ultimately stopped once the target Hct has been achieved. Reproduced from Saltzberg MT, Blood Volume Analysis Coupled with Ultrafiltration in the Management of Congestive Hear Failure-Guided Therapy to Achieve Euvolemia. *US Cardiology* 2010;7(1):72-75.[28]

Set a Rational Target by the Normalized Hct, then Monitor Diuresis Adequacy by the Peripheral Hct

Decreased RBCV may worsen HF patient status in multiple ways, including decreased oxygen tissue delivery and decreased intravascular oncotic pressure.[46] It is increasingly clear that anemia and polycythemia in HF patients is a significant comorbidity that can and must be identified and addressed during hospital admissions.[30-41]

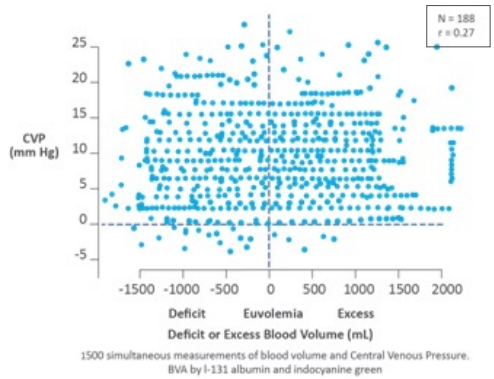
Albumin Transudation Rate (TR)

The BVA test report also captures the rate of albumin transudation, the rate at which the albumin transudates out of circulation through the capillary bed. The TR is a key circulation function, and albumin is the lead carrier protein for hundreds of important ligands and supports health. A rate of approximately 0.25% per minute is considered normal and is one of the unique metrics on the BVA report. In a patient with increased capillary permeability, this rate may increase. An increased TR has been associated with worsening clinical outcomes in certain disease states.[46-49]

Superiority of BVA Measurement to Indirect or Surrogate Estimates of Blood Volume

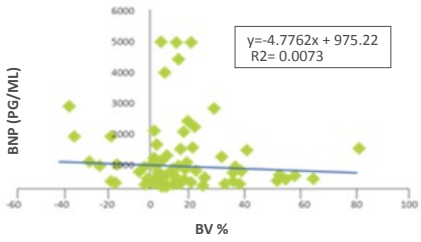
Recognizing the critical role of knowing intravascular and red cell volumes, clinicians have long attempted to correlate various clinical signs and symptoms seen in HF and several laboratories and diagnostic measurements with direct BVA measurements. Multiple studies have shown that surrogate or indirect measures for volume status (such as heart pressure indices, heart rate, cardiac output, stroke volume, hemoglobin/hematocrit, blood pressure, ultrasound, clinical assessment, and natriuretic peptide biomarkers, etc.) do not provide actual volume status. Furthermore, they are neither sensitive nor specific indicators of actual volume status. Surrogates are unable to provide the true red cell volume nor the albumin transudation measure that the BVA provides.[39,46-60] Most clinical signs (i.e. edema, lung rales, hepatomegaly) and symptoms (dyspnea, bendopnea, early satiety) are related more to interstitial volume expansion and thus have similarly lacked useful correlation with simultaneous BVA measurement.[23-24,61-63]

Fig. 4. 1500 simultaneous measurements of blood volume and central venous pressure



Heterogeneous cohort of 188 ICU patients demonstrating no association between these two variables (r=0.27). The correlation between ΔCVP and change in blood volume was 0.1 (r2=0.01). This Study demonstrates that patients with a low CVP may have volume overload and likewise patients with a high CVP may be volume depleted. Adapted from Shippy CR, et al. Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med*. 1984;12(2):107-112. doi:10.1097/00003246-198402000-00005[39]

Fig. 5. Brain-type natriuretic peptide (BNP) as predictor of blood volume



Relationship between BNP and BV. Takahishi EA, et al. Brain-type natriuretic pepetide and right ventricular end-diastolic volume index measurements are imprecise estimates of circulating blood volume in critically ill subjects. *J Trauma Acute Care Surg*. 20013;75(5):813-818. doi:10.1097/TA.0b013e3182a85f3a[59]

Mandates to Measure Blood Volume and Red Cell Volume in Heart Failure Patients

For nearly 20 years, patients with HF undergoing BVA testing have demonstrated clinically unanticipated and wide-ranging variability in TBV, PV, and RBCV. In populations clinically suspected to be hypervolemic, BVA has detected significant deviations in intravascular volume, which include normovolemia, hypovolemia, and varying degrees of hypervolemia. Thus, the BVA provides clinicians with actionable targets for their treatment

plans. Additionally, similar variation has been observed in stable, mildly, or asymptomatic ambulatory HF patients, aside from significant deviations in hospitalized inpatients.

For nearly two decades, Guidelines for HF have called for and provided Level I recommendations to evaluate a patient's "volume status" at each clinical encounter. For hospitalized patients, the initial evaluation of volume status informs the initial and subsequent treatment plans and, as such, sets the course for post-acute care and subsequent risk of readmission.[64-67]

A recent 2019 American College of Cardiology (ACC) Expert Consensus Decision Pathway for Hospitalized HF patients repeatedly calls out the importance of volume measurement and its tightly connected role in crafting a treatment approach.[67]

Additionally, the contribution and mandate to identify and treat iron deficiency anemia (IDA) in HFrEF patients upon hospital discharge have proven safe and positively impacted further HF hospitalizations.[68-69] Yet, while IV iron replacement addresses the iron deficiency syndrome, it does not restore a significantly depleted RBCV. Ongoing and future clinical trials of anemia in HF would be strengthened by using BVA-derived RBCV as the key metric to identify true anemia and provide a threshold for treatment rather than general, population-based treatment triggers.[70-73]

Consensus Statements

Expert Panel Guidance on Initiating or Expanding BVA Use in Clinical Practice/Expert Panel Consensus Statements

Experienced and expert clinicians and educators who have incorporated and studied BVA within their research and clinical practices have identified the need to summarize and bring forward key topics to increase awareness of the value, clinical utility, and cost-effectiveness of BVA. That is the focus of this Consensus document.

Organization of the Statements. These statements support several key areas of BVA testing and its applications. The following topic is used to provide focus and flow to each key consensus statement:

1. **What is BVA?**
2. **What does BVA allow us to do?**
3. **Who is appropriate for BVA?**
4. **When to do BVA?**
5. **How to use BVA (phenotypes)?**
6. **How NOT to use BVA?**
7. **Where to do BVA (inpatient/outpatient/ambulatory)?**
8. **What about red blood cells?**
9. **What Value does BVA bring to Value-Based Care and Healthcare Economics?**

Key Consensus Statements (1-10)

What is BVA?

STATEMENT 1

BVA provides a 98% accurate measure of congestion and intravascular volumes – informing optimal individualized treatment pathways.[12-15] Indirect measures of BV are neither sensitive nor specific to intravascular blood or red cell volume and do not provide the accuracy or precision of direct measurement with BVA.[21-22,38-42,50-60] Indirect measures do not provide actionable steps towards managing decongestion or evaluating and treating anemia. Furthermore, while indirect measures do not correlate well with intravascular volumes, they can contribute to an overall clinical picture of hemodynamics. for example, when considering the need to measure and address each of the intravascular volumes, BVA is unique in quantifying critical volumes – and cannot be replaced by a surrogate or indirect measure

What does BVA Allow Us to Do?

STATEMENT 2

The BVA report provides key measurements that create an actionable BVA phenotype to achieve the target of euvolemia – normal blood volume and component volumes of red cells and plasma.[1-9,16-22,27-28] A stepwise approach in considering each metric adds precision to planning an optimal treatment pathway. It also assures that key information is not overlooked, which may impact the next steps and accurate therapeutics.

Who is Appropriate for BVA?

STATEMENT 3

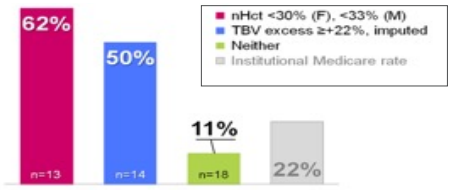
BVA is appropriate across the entire HF spectrum, including NYHA functional classes I-IV in symptomatic and asymptomatic patients with HFrEF and HFpEF. Regardless of etiology structure or function, BVA provides otherwise unrecognized outcome-related insights.[1-10,16-25,27-29-36] Numerous studies have shown that volume derangement of TBV and component volumes of plasma and red cells are common in both ambulatory and hospitalized patients with HF and acute decompensated HF.[1-10] Studies also show that HF patients discharged from the hospital are often significantly volume deranged despite weight loss and clinical assessment of euvolemia and symptom relief leading to worsening outcomes.[9,18-19,29] Volume derangement is common and often unrecognized.[1-10]

Research demonstrates that clinicians miscategorize volume status in 50% of patients.[3,7,21,63] Data from populations as diverse as hypertension patients, mechanical circulatory support (MCS) patients with LVADs, hospitalized and ambulatory HF patients show significant volume derangement and heterogeneity of volume status.[1-9,74-80]

Many clinicians have found BVA of great value in their "difficult" patients. They have struggled to understand why the patient was still failing, being readmitted, or rapidly headed for ventricular support, transplant, or palliative care. Unfortunately, these "difficult" patients are the tip of the iceberg. Multiple studies have demonstrated that most patients have consistent, unrecognized variances in volumes.[1-9,16,18-25,27,29,31-36] Inpatients and outpatients across the HF spectrum, including those treated to "dry weight" or clinically assessed euvolemic using standard of care approaches, display wide residual derangements in BVA measurements; these derangements ultimately predict increased risk for hospital admission or readmission.[1-10,19,23-24,29,36,75] The derangements include both PV and RBCV.[1-10,18-22-24,29,32-33,36] Additionally, in a cohort of stable, non-edematous ambulatory patients, data demonstrated hypovolemia in (5%). Physical findings in these patients were rare and were not related to blood volume. However, importantly, residual hypervolemia was found in 65% of patients.[3,7] The finding of hypotension related to residual hypervolemia impacts patient functional status and the ability to optimize goal-directed medical therapy (GDMT).[81] The BVA measured hypervolemia was associated with a greatly increased risk of death or urgent cardiac transplantation risk.[3,7,82-83]

Recently, teams managing large LVAD programs have looked at BVA results in patients clinically stable after short, medium, and longer-term LVAD support and have found similar derangements in blood PV and RBCV.[76-80]

Fig. 6. Impact of anemia or hypervolemia at discharge on 30-day read mission rates in hospitalized heart failure (HF) patients



nHct, or normalized Hct, is adjusted for plasma volume to reflect true RBCV. Not shown: polycythemia (n=1); neither was readmitted. Reproduced with permission from Droogan CJ, et al. 30-day readmissions associated with persistent congestion or anemia at discharge in the first heart failure (HF) cohort (n=47) to receive blood volume analysis (BVA) at Lakenau Medical Center. Poster presented at: 20th Annual Scientific Meeting of the Heart Failure Society of America (HFSA); Sep 17-20, 2016; Orlando, FL.,USA.[29]

Table 1. Blood volume variances across the heart failure spectrum

HF Population (n)	TBV Range of % Deficit (-)/Excess (+)	RBCV Range of % Deficit (-)/Excess (+)	Reference
Stable, OP FC I-II (46)	-14 to +56	-31 to +50	Miller, 2018[2]
Ambulatory, FC II-IV, Non-Edematous (43)	-20 to +30	--	Androne, 2004[3]
Hospitalized HF (245)	-31 to +117	-55 to +74	Strobeck, 2018[19]
Implanted LVAD Pts (24)	-19 to +87	-43 to +80	Yaranov, 2021[76]

TBV=Total Blood Volume, RBCV=Red Blood Cell Volume

Volume adjustment and optimization is a key feature of homeostasis and is a repeated guideline-level recommendation for all patients[28-31] – accurate and precise volume measurement with BVA is the optimal diagnostic to inform care.

When to Perform a BVA and Evidence of Benefit?

STATEMENT 4

In hospitalized patients with decompensated heart failure (ADHF), early performance and BVA-guided treatment improve outcomes related to both mortality and readmission. The sooner the patient is accurately diagnosed, the faster they will be correctly treated.[6,15-17,33-34,40,48,73-74]

Lessons learned from a recently published study, with the hypothesis of using BVA-guided therapy, found that early BVA performance provides clinicians with patient-specific information related to blood volumes informing optimal treatment plans, avoiding early missteps, and positively impacting patient outcomes. The recently published retrospective outcome analysis of 245 consecutive acute heart failure admissions with mixed ejection fractions compared with propensity-matched controls explored the insights around volume heterogeneity using BVA measurement at hospital admission to create and guide in-hospital care. This study demonstrated both heterogeneity of volume status, and significantly improved outcomes with BVA-guided treatment: 82% reduction in 30-day mortality (2.0% vs. 11.1%; $p < 0.001$), and 56% reduction in 30-day readmissions (12.2% vs. 27.7%; $p < 0.001$).[17-19]

Fig. 7. Blood volume analysis significantly reduced heart failure mortality & readmissions

Propensity matched control trial in community hospital | n=245, Mixed HFpEF/HFrEF
Adapted from Strobeck et al. *JACC Heart Fail.* 2018;6(11):940-948[17]

So be it in the Emergency Department (ED), an Intensive care unit (ICU), or general care unit (GCU), all clinical teams, including Hospitalists, Resident based teams, Fellows, and Cardiologists, can apply the key information about a patient using BVA metrics. Hospitalized patients are critically ill, and delays or early missteps impact patient outcomes significantly.[21-22,27,35,38-39,57,82]

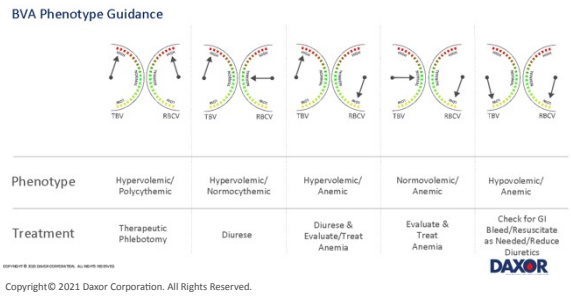
Hospitalization for HF is at once a biomarker for disease severity and disease progression and a phase that carries a significant impact on short and long-term morbidity, readmission, and impact on mortality.[83-86] Additionally, hospitalization is a primary driver of HF and health care costs. Despite nearly 40 years of therapeutic innovations, HF admission remains a pain point for all centers providing care for HF patients. Admission of patients with symptomatic HF, while often attributed to advanced disease severity or non-compliance with medications or dietary restrictions, is missing the key piece in understanding how best to manage these patients. The core understanding of their intravascular volume status is an initial diagnostic step in creating a treatment plan.[1-10,16,18-19,23-24,27,31,33-35,41,56]

How to Use BVA Phenotypes?

STATEMENT 5

Identifying the BVA phenotype allows clinicians to create guideline-directed treatment pathways to improve patient outcomes. Previous and current HF guideline statements identify as fundamental, primordial steps to identify volume status and anemia; without BVA, neither can be done with precision.[63-66]

Fig. 8. Blood volume analysis phenotype guidance



How NOT to Use BVA?

STATEMENT 6

There is a right way and a wrong way to integrate BVA with other clinical tests to optimize patient care. BVA results must be recognized as the guiding determinant of volume status. Pressure is not volume, and clinical signs and biomarkers are not measures of intravascular volume nor sufficient for optimal discharge readiness.[16,21-22,27,36-39,40-42,49-59]

Care teams which incorporate BVA as "another signal" to be considered among their existing indirect metrics of volume status achieve sub-optimal outcomes as BVA is 98% accurate and other tests have minimal to zero correlation with volume. Typical examples include teams which ignore BVA results which contradict RH Cath measures or clinical symptoms of overload such as JVP or edema or rely on weight loss for sufficiency of diuresis.[3,7,23-24,27,32,35,62] It is precisely those instances where BVA provides the unique clinical insight which contradicts those metrics that lead to better treatment pathways – a 98% accurate measure should not be weighed equally with indirect measures of little to no accuracy. If the BVA indicates a volume status that contradicts hemodynamic pressures or clinical signs, BVA is the accurate guide, always.[21-22,38,49-50,56,59] However, when BVA shows euvolemia and hemodynamics are elevated, an optimal choice of therapy for dilator adjustment is the natural and optimal care pathway, informed by a correct use of both diagnostic tests.

Patients having received standard HF hospitalization care and considered to be euvolemic at discharge may still be volume deranged.[3,7,18-19,23-24,29] While a favored approach in performing the BVA, teams looking at a discharge BVA in patients whom they felt were optimized during a HF admission found considerable residual derangements in volume excess and red blood cell volume deficit in the BVA done at discharge; both derangements contributed to early readmission and mortality.[17-19,27] (See Lankenau Figure above)

Where to Do BVA (Inpatient/Outpatient/ Ambulatory)?

STATEMENT 7

Large opportunities exist to manage patients in an outpatient heart failure care structure, including physician or nurse-led programs, clinics, and advanced heart failure ambulatory settings, and participation in ongoing clinical studies. BVA-guided management is a unique diagnostic for a variety of scenarios seen in outpatients, including, but not limited to, new patient evaluation, post-acute care visits, optimizing patient's volume, and RBCV prior to referral for advanced HF therapies, including left ventricular assist devices (LVADs) or implantable hemodynamic monitors. Several studies (MOVE-HF, VA-HF study, and Duke University Medical Center) are underway quantifying further the benefit of optimizing patient care with BVA to initiate and better titrate indicated and life-saving guideline-directed management.[87] Also under

study, Geisinger Medical Center is looking at the impact of a BVA-centered ambulatory approach to delimit hospital admission/readmission and lengthen patients' days alive and out of the hospital.

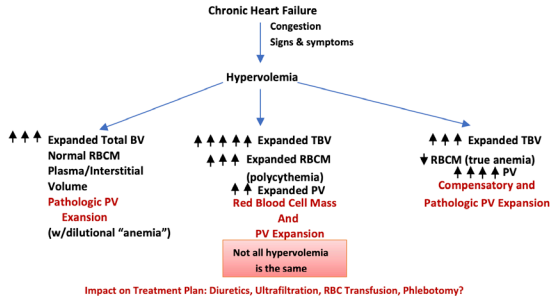
Due to the ability to obtain samples with a single venipuncture and obtain actionable results within 60 minutes, the BVA test can be performed in any situation or location where precise information on a patient's intravascular volume will improve clinical decision-making patient outcomes.[12-15]

What About Red Blood Cells? ANEMIA AND POLYCYTHEMIA

STATEMENT 8

Differentiating between true and dilutional anemia is a key differential diagnosis to optimize HF treatment.[15,25,27,30-36,41-42,82] HF patients are routinely PV deranged and, with even mild decrements in RBCV, homeostatic mechanisms rapidly increase the PV in an attempt to restore a normal intravascular volume and perfusion pressure.[1-9] These shifts in PV dramatically disrupt normal ratios between red blood cells and PV and misleading measured hematocrit values.
The BVA report provides a Hct analysis that compares the pHct to a unique metric, the nHct.[12,42] The nHct would be the target Hct if TBV were adjusted to normal by changing the PV. The BVA allows for evaluation of the RBCV in relation to the TBV/PV and provides a useful individualized target for treatment. For hypervolemic patients, the added value of the nHct is; unless RBCVs have been adjusted (transfusion, EPO, etc.) clinicians can more safely target the nHct to guide effectiveness and adequacy of diuretic strategies.

Fig. 9. Marked heterogeneity in volume overload profiles



Used with publisher & author permission from, Miller WL. Assessment and Management of Volume Overload and Congestion in Chronic Heart Failure: Can Measuring Blood Volume Provide New Insights? *Kidney Dis (Basel)*. 2016;2(4):164-169. doi:10.1159/000450526[1]

Further, for the patient who is hypervolemic and polycythemic, BVA alerts to the risk of only addressing the PV status, which may further hemoconcentrate the patient's blood and contribute to hyperviscosity and thrombosis. Euvolemia for these patients can only be achieved through addressing the overload in both components of the BV, PV and RBCV.[3,5-6,8,27,31-32,34-35]

STATEMENT 9

Interest in the complex interaction of "anemia" in HF patients has had several iterations. Still, investigation has been hindered using pHct/Hgb as a proxy measure for the RBCV of the patient populations studied. The interest comes, understandably, from the relationship of anemia to worsening HF outcomes and its role in disease progression. An early linkage of "anemia" defined by a low Hgb or Hct, measured from a peripheral venous sample, triggered early investigators to correct the laboratory finding with a combination of erythrocyte stimulating agents (ESA's) or IV iron replacement.[68-69] This approach led to the development of large-scale clinical trials exploring the use of ESA's only.[70-73] However, lack of substantially improved outcomes, adverse events, and concern over thrombotic events tempered interest in focus on anemia.

Recently several smaller and now larger clinical trials explored the role of IV iron regardless of laboratory measures of anemia.[67,79] The most accurate, personalized, and meaningful measurement of anemia is the patient-specific RBCV which BVA uniquely provides. The ability of the BVA algorithms to correct for expanded PV is important due to the compensatory response to anemia and the expanded volume related to the HF state.[42]

What Value Does BVA Bring to Value-Based Care and Healthcare Economics?

STATEMENT 10

BVA is highly cost-effective and is covered by both private and public insurance, cost-effectively delivering optimal care to the populations of patients with HF. Due to the enormous cost of care for both hospitalized and ambulatory HF patients, many strategies have been implemented by clinicians and payers of healthcare costs. Similarly, multiple drugs and devices have been envisioned to interrupt the cycle of HF.[81,88-89] Despite these, HF continues its cycle of pain, suffering, and cost.

A recent health economic analysis was performed on a cohort of HF patients (HFrEF and HFpEF) admitted to a hospital with initial early BVA; care was targeted to manage PV and RBCV. The clinical outcomes in BVA-guided patients were dramatically improved compared to a propensity-matched cohort when these outcomes included early and late hospital readmissions and 1-year mortality.[90]

In HF, one of the largest cost-drivers of the national healthcare system, found the use of BVA showed an "extremely cost-effective," incremental cost-effectiveness ratio (ICER) of $10,200 over a 30-year simulation. BVA was 80% less costly than other therapies that are considered "good value" by common quality metrics. In addition to the cost savings, the data revealed an average life extension of 2.32 quality-adjusted life years (QALYs). The authors also found a 12% reduction in mortality and readmission (HR = 0.88).[90]

For all scenarios considered, the ICER values were far below the threshold of $50,000, which is generally taken to represent good value for health care, including scenarios in which the hazard ratio improvement due to blood volume analysis-guided treatment is as little as 12%.[90] The additional cost of the test itself is small (comparable to other much less impactful diagnostic measurements currently undertaken). Indeed, BVA can also provide early insight and direction that may reduce the application of many more expensive therapies for certain patients, identify better candidates for some of the treatments, and slow and prevent disease progression with the knowledge of BVA vital metrics.

In an era focused sharply on value-based care, it is apparent that a low cost yet, precise diagnostic, providing critical metrics that are immediately actionable, describes the essence of value-based care.[91-92] For heart failure, inpatient and outpatient opportunities to use BVA as the foundational diagnostic for value-based care programs abound across the entire HF spectrum.[42]

Fig. 10. Retrospective analysis in hospitalized heart failure patients n=245, Mixed HFpEF/HFrEF

Blood volume-guided treatment was found to be extremely cost effective in a cohort of hospitalized heart failure patients. Adapted and used with permission from: Strobeck et al. Cost-effectiveness Analysis of Early Blood Volume-Guided Management in Hospitalized Heart Failure Patients. Abstract Presented at: 24th Annual Scientific Meeting of the Heart Failure Society of America (HFSA); Sep 30 - Oct 6, 2020:Virtual[90]

Advice for Teams

It is useful to review the BVA report as a team and have a standardized approach to interpretation and sharing the results.[17-18,21,74] By consulting with experienced users to assist with understanding and using the measurements provided by BVA, protocols can be developed to guide treatment and ensure that the entire care team agrees with treatment goals. Some teams have employed a weekly session to review tests done over the last few days. Depending on the center, the report may go directly into an electronic medical record system, come in as a facsimile, or be entered manually by the technologist. Teams should be aware of the full report content as every aspect of the report is designed to simplify and guide accurate interpretation.

In HF patients with implanted LVADs, significant heterogeneity of intravascular blood volume and red cell volume is common and often not apparent without BVA measurement.[76-80] Many centers have found it useful to record clinical evaluation of a patient's volume status before reviewing results from the BVA and then comparing them to clinical evaluation determinants.[21-22] These centers then document how often the enhanced accuracy results in a different clinical pathway. This approach is an active learning process and leads the team to trust and value BVA results which are the gold standard of accuracy.

References

1. Miller WL. Assessment and Management of Volume Overload and Congestion in Chronic Heart Failure: Can Measuring Blood Volume Provide New Insights? *Kidney Dis (Basel*). 2017;2(4):164-169. doi:10.1159/000450526
2. 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*. 2018;24(7):417-424. doi:10.1016/j.cardfail.2017.09.010
3. 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(10):1254-1259. doi:10.1016/j.amjcard.2004.01.070
4. Miller WL, Mullan BP. Volume Overload Profiles in Patients With Preserved and Reduced Ejection Fraction Chronic Heart Failure: Are There Differences? A Pilot Study. *JACC Heart Fail*. 2016;4(6):453-459. doi:10.1016/j.jchf.2016.01.005
5. Cohen R, Wajahat R, Titova I, Coromilas E, Maurer MS, et al, Anemic Patients with HFNEF Have a Reduced Red Cell Volume, True Anemia and Concomitant Plasma Volume Expansion. Poster presented at: 11th Annual Scientific Meeting, Heart Failure Society of America (HFSA). Sep 16 - 19, 2007; Washington, DC.,USA.
6. 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(3):298-305. doi:10.1016/j.jchf.2014.02.007
7. Androne AS, Katz SD, Lund L, et al. Hemodilution is common in patients with advanced heart failure. *Circulation*. 2003;107(2):226-229. doi:10.1161/01.cir.0000052623.16194.80
8. Miller WL. Fluid Volume Overload and Congestion in Heart Failure: Time to Reconsider Pathophysiology and How Volume Is Assessed. *Circ Heart Fail*. 2016;9(8):e002922. doi:10.1161/CIRCHEARTFAILURE.115.002922
9. Miller WL, Grill D. Prognostic Impact of Intravascular Volume Heterogeneity on Post-Hospital Outcomes in patients with Chronic Heart Failure. *J Card Fail*. 2017;23(8)S16-S17.
10. Costanzo MR. The Cardiorenal Syndrome in Heart Failure. *Heart Fail Clin.* 2020;16(1):81-97. doi:10.1016/j.hfc.2019.08.010
11. Gibson JG, Evans WA. Clinical studies of the blood volume in the relation of plasma and total blood volume to venous pressure, blood velocity rate, physical measurements, age, and sex in ninety normal humans. *J Clin Invest*. 1937;16(3):317-328. doi:10.1172/JCI100860
12. Manzone TA, Dam HQ, Soltis D, Sagar VV. Blood volume analysis: a new technique and new clinical interest reinvigorate a classic study. *J Nucl Med Technol*. 2007;35(2):55-79. doi:10.2967/jnmt.106.035972
13. Feldschuh J, Katz S. The importance of correct norms in blood volume measurement. *Am J Med Sci.* 2007;334(1):41-46. doi:10.1097/MAJ.0b013e318063c707
14. Feldschuh J, Enson Y. Prediction of the normal blood volume. Relation of blood volume to body habitus. *Circulation.* 1977;56(4 Pt 1):605-612. doi:10.1161/01.cir.56.4.605
15. Dworkin HJ, Premo M, Dees S. Comparison of red cell and whole blood volume as performed using both chromium-51-tagged red cells and iodine-125-tagged albumin and using I-131-tagged albumin and extrapolated red cell volume. *Am J Med Sci.* 2007;334(1):37-40. doi:10.1097/MAJ.0b013e3180986276
16. Feldschuh J. Blood Volume Measurements in Critical Care. In: Layon JA, Gabrielli A, Yu M, Wood KE, eds. C*ivetta, Taylor, & Kirby's Critical Care, 5th ed.* Wolters Kluwer; 2018:302-309. ICCN 2017033400|ISBN 9781469889849.
17. Strobeck JE, Feldschuh J, Miller WL. Heart Failure Outcomes With Volume-Guided Management. *JACC Heart Fail*. 2018;6(11):940-948.
18. Strobeck JE, Miller WL. Impact of Blood Volume Quantification on Decongestion Strategy, Readmission Rates (RR), and Mortality in Hospitalized Heart Failure Patients (HHF). Poster presented at: 65th Annual Scientific Session of the American College of Cardiology (ACC); Apr 02-04, 2016: Chicago, IL., USA. Abstract 1160M-01.
19. Strobeck JE, Feldschuh J, Miller WL. Propensity score matched-controlled study of impact of blood volume quantification on decongestion strategy, readmission rates, and mortality in hospitalized heart failure patients. Abstract presented at: 67th Annual Scientific Session and Expo of the American College of Cardiology (ACC); Mar 10-12, 2018; Orlando, FL.,USA.
20. Pillon L, Tseng C-H. Blood Volume Monitoring Improves Volume Assessment and Cardiovascular Parameters in Hemodialysis Patients. Poster presented at: Spring Clinical Meetings of the National kidney Foundation (NKF); Apr 10-14, Orlando, FL.,USA.
21. Yu M, Pei K, Moran S, et al. A prospective randomized trial using blood volume analysis in addition to pulmonary artery catheter, compared with pulmonary artery catheter alone, to guide shock resuscitation in critically ill surgical patients. *Shock*. 2011;35(3):220-228. doi:10.1097/SHK.0b013e3181fc9178.
22. Pakanishi DM Jr, Biuk-Aghai EN, Yu M, et al. The availability of circulating blood volume values alters fluid management in critically ill surgical patients. *Am J Surg.* 2009;197(2):232-237. doi:10.1016/j.amjsurg.2008.01.016
23. Miller WL. Volume Overload and Quantitative Blood-Plasma Volume: How Effective is Intravenous Diuretic Therapy in Patients Hospitalized for Decompensated Chronic Heart Failure? Poster presented at: 17th Annual Scientific Meeting of the Heart Failure Society of America (HFSA); Sep 22-25, 2013; Orlando, FL., USA.
24. Miller W. "Why is Diuresis-related Weight Loss Not a Consistent Predictor Of Clinical Outcomes in Heart Failure?" - Need to Account For Variability in Volume Status. Poster presented at: Annual Scientific Meeting of the Heart Failure Society of America (HFSA); Sep 30 - Oct 6, 2020; Virtual
25. Miller WL, Grill DE, Qian Q. Intravascular Volume Modulates the Outcome Predictive Capacity of Clinical Renal Function Biomarkers in Clinically "Euvolemic" Chronic Heart Failure Patients. *Kidney Dis (Basel)*. 2020;6(1):50-58. doi:10.1159/000502210
26. Cioffi G, Tarantini L, Pulignano G, et al. Prevalence, predictors, and prognostic value of acute impairment in renal function during intensive unloading therapy in a community population hospitalized for decompensated heart failure. *J Cardiovasc Med (Hagerstown)*. 2007;8(6):419-427. doi:10.2459/01.JCM.0000269715.95317.33

27. Pillon L, Tseng C-H. Accuracy of Anemia Evaluation is Improved in a Wide Variety of Acute and Chronically Ill Patients by Accounting for Volume Status. Poster presented at: Renal Week: American Society of Nephrology Annual Meeting (ASN). Nov 04-09, 2008; Philadelphia, PA.,USA.

28. Saltzberg MT. Blood Volume Analysis Coupled with Ultrafiltration in the Management of Congestive Heart Failure-Guided Therapy to Achieve Euvolemia. *US Cardiology* 2010;7(1):72–75.

29. Droogan CJ, Domsky SM, McNeill GE, Strobeck JE. 30-day readmissions associated with persistent congestion or anemia at discharge in the first heart failure (HF) cohort (n=47) to receive blood volume analysis (BVA) at Lankenau Medical Center. Poster presented at: 20th Annual Scientific Meeting of the Heart Failure Society of America (HFSA); Sep 17-20, 2016; Orlando, FL.,USA.

30. Malha L, Fattah H, Modersitzki F, Goldfarb DS. Blood volume analysis as a guide for dry weight determination in chronic hemodialysis patients: a crossover study. *BMC Nephrol*. 2019;20(1):47. Published 2019 Feb 11. doi:10.1186/s12882-

31. Strobeck JE, Feldschuh J, Silver M, Miller WL. Red Cell Volume Phenotypes in Hospitalized Heart Failure Patients. Poster presented at: The Annual Scientific Meeting of the Heart Failure Society of America; Sep 30- Oct 6, 2020. Virtual.

32. Silver MA, Strobeck J, Feldschuh JA. The Common Phenotype of Polycythemia And Hypervolemia In Hospitalized Heart Failure Patients. Poster presented at: 25th Annual Scientific Meeting of the Heart Failure Society of America (HFSA); Sep 10-13, 2021; Denver, CO., USA.

33. Ramnauth SD, Teruya S, Helmke S, et al. Masked Polycythemia in Patients with Heart Failure and a Preserved Ejection Fraction: An underappreciated phenotype? Poster presented at: 16th Annual Scientific Meeting of the Heart Failure Society of America (HFSA) 16th; Sep 09-12, 2012; Seattle, WA., USA.

34. Abramov D, Cohen RS, Katz SD, Mancini D, Maurer MS. Comparison of blood volume characteristics in anemic patients with low versus preserved left ventricular ejection fractions. *Am J Cardiol*. 2008;102(8):1069-1072. doi:10.1016/j.amjcard.2008.05.058

35. Noumi B, Teruya S, Salomon S, Helmke S, Maurer MS. Blood volume measurements in patients with heart failure and a preserved ejection fraction: implications for diagnosing anemia. *Congest Heart Fail.* 2011;17(1):14-18. doi:10.1111/j.1751-7133.2010.00208.x

36. Miller WL. The Importance of Defining Red Blood Cell Mass in the Management of Volume Overload Chronic Systolic Heart Failure. *J Card Fail.* 2015;21(8S)S126.

37. Van PY, Riha GM, Cho SD, et al. Blood volume analysis can distinguish true anemia from hemodilution in critically ill patients. *J Trauma.* 2011;70(3):646-651. doi:10.1097/TA.0b013e31820d5f48

38. Takanishi DM, Yu M, Lurie F, et al. Peripheral blood hematocrit in critically ill surgical patients: an imprecise surrogate of true red blood cell volume. *Anesth Analg.* 2008;106(6):1808-1812. doi:10.1213/ane.0b013e3181731d7c

39. Shippy CR, Appel PL, Shoemaker WC. Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med.* 1984;12(2):107-112. doi:10.1097/00003246-198402000-00005

40. Edwards K, Yu M, Lurie F, Takanishi D, Tan A, Chih Ho H, Apte S, Koss W. Does Hematocrit Reflect Red Cell Volume when Adjusted for Plasma Volume. Poster presented at the 35th Congress of the Society of Critical Care Medicine (SCCM) Jan 07 - 11, 2006; San Francisco, CA., USA.

41. Lee, JW; Sheikh F; Patel A; Inouye D; Takanishi D; Zhao F; Yu M; Severino R; Hayashi M. Peripheral blood hematocrit is an inaccurate index of red cell volume in critically ill subjects. *Crit Care Med*: 2019;47(1)72. doi.org/10.1097/01.ccm.0000550936.02784.b0

42. Silver MA, Strobeck JE, Feldschuh JA. True Anemia in Heart Failure Patients: Peripheral Hematocrits Lack Sensitivity and Specificity as a Predictor of Measured Red Blood Cell Volumes in a Mixed-LVEF Cohort. Abstract presented at: 25th Annual Scientific Meeting of the Heart Failure Society of America (HFSA); Sep 10-13, 2021; Denver, CO., USA

43. Manzone T, Dam H, Howard-Sachs J. ``Normalized Hematocrit" from Blood Volume Analysis Offers Enhanced Accuracy over Peripheral Hematocrit in Assessment of Red Blood Cell Volume. Poster presented at: Annual Meeting of the Society of Nuclear Medicine (SNM); Jun 05-09, 2010; Salt Lake City, UT.,USA

44. Recommended methods for measurement of red-cell and plasma volume: International Committee for Standardization in Haematology. *J Nucl Med.* 1980;21(8):793-800.

45. Dean L. Blood Groups and Red Cell Antigens [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2005. Chapter 1, *Blood and the cells it contains*. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2263/

46. Chores JB, Holt DW. Colloid Oncotic Pressure, Monitoring its Effects in Cardiac Surgery. *J Extra Corpor Technol.* 2017;49(4):249-256.

47. DeFrancesch, D., et al. Is There a Relationship between SOFA scores and Albumin Leak Rates as a Marker of Endothelial Dysfunction? Poster presented at: 40th Congress of the Society of Critical Care Medicine (SCCM); January 15-19, 2011; San Diego, CA.,USA.

48. Harvey S, McKnight CL, Musikasinthorn C, Inouye D, Hayashi M, Nakagawa K, Takanishi D, Yu M. Persistently High Albumin Leak is Associated with Mortality. *Crit Care Med.* 2014;42(12)A1383. doi:10.1097/01.ccm.0000457593.23 715.a0.

49. Inouye D, Yu M, Hayashi M, et al. Elevated Transcapillary Albumin Escape: A Marker of Increased Mortality. Poster presented at: 40th Congress of the Society of Critical Care Medicine (SCCM); January 15-19, 2011; San Diego, CA.,USA.

50. Chakko S, Woska D, Martinez H, et al. Clinical, radiographic, and hemodynamic correlations in chronic congestive heart failure: conflicting results may lead to inappropriate care. *Am J Med.* 1991;90(3):353-359. doi:10.1016/0002-9343(91)80016-f

51. Alrawi SJ, Miranda LS, Cunningham JN Jr, Acinapura AJ, Raju R. Correlation of blood volume values and pulmonary artery catheter measurements. *Saudi Med J.* 2002;23(11):1367-1372.

52. De Vecchis R, Baldi C. Inferior Vena Cava and Hemodynamic Congestion. *Res Cardiovasc Med.* 2015;4(3):e28913. doi:10.5812/cardiovascmed.28913v2.

53. Domino S, Yu M, Osborne M, et al. A Comparison of Pulse Pressure Variation and Blood Volume Measurement. Poster presented at: 38th Congress of the Society of Critical Care Medicine (SCCM). January 31 through February 4, 2009; Nashville, TN.,USA.

54. Furuta S, Inouye DS, Hayashi MS, Takanishi DM Jr, Yu M. Blood volume measured by ultrasound and radioisotope dilution in critically ill subjects. *J Surg Res.* 2017;207:77-84. doi:10.1016/j.jss.2016.08.077.

55. Furuta S, Pei K, DeFrancesch D, Nishiguchi B, et al. A Comparative Study of Systolic Pressure Variation and Blood Volume Measurement. Poster presented at: 39th Congress of the Society of Critical Care Medicine (SCCM). January 9-13, 2010. Miami Beach, FL.,USA.

56. James KB, Troughton RW, Feldschuh J, Soltis D, Thomas D, Fouad-Tarazi F. Blood volume and brain natriuretic peptide in congestive heart failure: a pilot study. *Am Heart J*. 2005;150(5):984. doi:10.1016/j.ahj.2005.07.031

57. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest.* 2008;134(1):172-178. doi:10.1378/chest.07-2331

58. Strobeck JE, Giordano R. Lack of Correlation Between I-131 Labeled Albumin Measurements of Blood Volume and Serum B-Natriuretic Peptide Levels in Heart Failure Patients. Poster presented at: 14th Annual Scientific Meeting of the Heart Failure Society of America (HFSA); September 12-15, 2010; San Diego, CA.,USA.

59. Takahashi EA, Moran SE, Hayashi MS, Inouye DS, Takanishi DM Jr, Yu M. Brain-type natriuretic peptide and right ventricular end-diastolic volume index measurements are imprecise estimates of circulating blood volume in critically ill subjects. *J Trauma Acute Care Surg.* 2013;75(5):813-818. doi:10.1097/TA.0b013e3182a85f3a

60. Yamauchi H, Biuk-Aghai EN, Yu M, et al. Circulating blood volume measurements correlate poorly with pulmonary artery catheter measurements. *Hawaii Med J.* 2008;67(1):8-11.

61. Baeza-Trinidad R, Mosquera-Lozano JD, El Bikri L. Assessment of bendopnea impact on decompensated heart failure. *Eur J Heart Fail*. 2017;19(1):111-115. doi:10.1002/ejhf.610

62. Thibodeau JT, Turer AT, Gualano SK, et al. Characterization of a novel symptom of advanced heart failure: bendopnea. *JACC Heart Fail*. 2014;2(1):24-31. doi:10.1016/j.jchf.2013.07.009

63. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA*. 1989;261(6):884-888.

64. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. *J Heart Lung Transplant*. 2002;21(2):189-203. doi:10.1016/s1053-2498(01)00776-8

65. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation [published correction appears in Circulation. 2010 Mar 30;121(12):e258]. *Circulation.* 2009;119(14):e391-e479. Doi:10.1161/CIRCULATIONAHA.109.192065

66. Heidenreich PA, Fonarow GC, Breathett K, et al. 2020 ACC/AHA Clinical Performance and Quality Measures for Adults With Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *J Am Coll Cardiol.* 2020;76(21):2527-2564.

67. Hollenberg SM, Warner Stevenson L, Ahmad T, et al. 2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized With Heart Failure: A Report of the American College of Cardiology Solution Set Oversight Committee [published correction appears in J Am Coll Cardiol. 2020 Jan 7;75(1):132]. *J Am Coll Cardiol.* 2019;74(15):1966-2011. doi:10.1016/j.jacc.2019.08.001

68. Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial [published correction appears in Lancet. 2021 Nov 27;398(10315):1964]. *Lancet*. 2020;396(10266):1895-1904. doi:10.1016/S0140-6736(20)32339-4

69. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009;361(25):2436-2448. doi:10.1056/NEJMoa0908355

70. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol.* 2000;35(7):1737-1744. doi:10.1016/s0735-1097(00)00613-6

71. Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol*. 2001;37(7):1775-1780. doi:10.1016/s0735-1097(01)01248-7

72. Lindquist DE, Cruz JL, Brown JN. Use of erythropoiesis-stimulating agents in the treatment of anemia in patients with systolic heart failure. *J Cardiovasc Pharmacol Ther*. 2015;20(1):59-65. doi:10.1177/1074248414541841

73. Kang J, Park J, Lee JM, Park JJ, Choi DJ. The effects of erythropoiesis stimulating therapy for anemia in chronic heart failure: A meta-analysis of randomized clinical trials. *Int J Cardiol.* 2016;218:12-22. doi:10.1016/j.ijcard.2016.04.187

74. Fudim M, Blumer VL, Lopes RD, et al. Correlation of Quantitated Intravascular Volume with Blood Pressure in Patients with Systemic Hypertension. *J Cardiovasc Transl Res.* 2020;13(4):528-530. doi:10.1007/s12265-019-09910-4

75. Fudim M, Miller WL. Calculated Estimates of Plasma Volume in Patients With Chronic Heart Failure-Comparison With Measured Volumes. *J Card Fail.* 2018;24(9):553-560. doi:10.1016/j.cardfail.2018.07.462

76. Yaranov DM, Jefferies JL, Edwards TD, et al. Value of Blood Volume Analysis in Patients with Left Ventricular Assist Devices. Poster presented at: 25th Annual Scientific Meeting of the Heart Failure Society of America (HFSA); Sep 10-13, 2021; Denver, CO., USA.

77. Yaranov DM, Silver MA, Thompson S, et al. Blood Volume Analysis Phenotypes in Heart Failure Patients Supported with Left Ventricular Assist Device. Abstract presented at: 25th Annual Scientific Meeting of the Heart Failure Society of America (HFSA); Sep 10-13, 2021; Denver, CO., USA.

78. James KB, McCarthy PM, Jaalouk S, et al. Plasma volume and its regulatory factors in congestive heart failure after implantation of long-term left ventricular assist devices. *Circulation*. 1996;93(8):1515-1519. doi:10.1161/01.cir.93.8.1515

79. Vieira JL, Ventura HO, Mehra MR. Mechanical circulatory support devices in advanced heart failure: 2020 and beyond. *Prog Cardiovasc Dis*. 2020;63(5):630-639. doi:10.1016/j.pcad.2020.09.003

80. Miller L, Birks E, Guglin M, Lamba H, Frazier OH. Use of Ventricular Assist Devices and Heart Transplantation for Advanced Heart Failure. *Circ Res.* 2019;124(11):1658-1678. doi:10.1161/CIRCRESAHA.119.313574

81. Fiuzat M, Ezekowitz J, Alemayehu W, et al. Assessment of Limitations to Optimization of Guideline-Directed Medical Therapy in Heart Failure From the GUIDE-IT Trial: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol.* 2020;5(7):757-764. doi:10.1001/jamacardio.2020.0640

82. Katz SD. Blood volume assessment in the diagnosis and treatment of chronic heart failure. *Am J Med Sci*. 2007;334(1):47-52. doi:10.1097/MAJ.0b013e3180ca8c41

83. Carry BJ, Katz SD. Subclinical Volume Overload Across the Spectrum of Heart Failure: Lessons From Total Blood Volume Measurements. *J Card Fai*l. 2018;24(7):425-427. doi:10.1016/j.cardfail.2018.04.007

84. Omar HR, Guglin M. Longer-than-average length of stay in acute heart failure: Determinants and outcomes. *Herz*. 2018 Mar;43(2):131-139. English. doi: 10.1007/s00059-016-4532-3

85. Cheema B, Ambrosy AP, Kaplan RM, et al. Lessons learned in acute heart failure. *Eur J Heart Fai*l. 2018;20(4):630-641. doi:10.1002/ejhf.1042

86. Miñana G, Bosch MJ, Núñez E, et al. Length of stay and risk of very early readmission in acute heart failure. *Eur J Intern Me*d. 2017;42:61-66. doi:10.1016/j.ejim.2017.04.003

87. Feldschuh J, Thompson S, Kohl N, et al. Monitoring Outpatient Blood VolumE in Heart Failure (MOVE-HF). Abstract presented at: Poster presented at: 25th Annual Scientific Meeting of the Heart Failure Society of America (HFSA); Sep 10-13, 2021; Denver, CO., USA

88. Gierula J, Kearney MT, Witte KK. Devices in heart failure; diagnosis, detection and disease modification. *Br Med Bull*. 2018;125(1):91-102. doi:10.1093/bmb/ldx051

89. Zeitler EP, Abraham WT. Novel Devices in Heart Failure: BAT, *Atrial Shunts, and Phrenic Nerve Stimulation.* JACC Heart Fail. 2020;8(4):251-264. doi:10.1016/j.jchf.2019.11.006

90. Strobeck JE, Feldschuh J, Williams BA, Miller WL. Cost-effectiveness Analysis of Early Blood Volume-Guided Management in Hospitalized Heart Failure Patients. Abstract Presented at: 24th Annual Scientific Meeting of the Heart Failure Society of America (HFSA); Sep 30 - Oct 6, 2020:Virtual

91. Dombrádi V, Bíró K, Jonitz G, Gray M, Jani A. Broadening the concept of patient safety culture through value-based healthcare. *J Health Organ Manag*. 2021;ahead-of-print(ahead-of-print):10.1108/JHOM-07-2020-0287. DOI. doi:10.1108/JHOM-07-2020-0287