Blood Volume Analysis - Guided Heart Failure Management

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1. Protocol Title

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2. Background

Heart failure (HF) is a leading cause of morbidity and mortality in the US. Simply put, the numbers are alarming. HF affects more than 6 million adults in the United States (US) alone.[1] It is the most common cause of hospitalization among Medicare beneficiaries and outcomes remain unacceptably poor. The key hallmark of acute heart failure (HF) is vascular congestion. Despite its central role in the pathophysiology of HF, our understanding of congestion remains limited. The current HF pathophysiologic model suggests that congestion is the result of volume retention, and therefore therapies (such as diuretics and ultrafiltration) have generally targeted a suspected volume overload. Despite this, the therapeutic benefits of fluid removal strategies on short and long term outcomes have been modest or absent. More recently the concept of fluid gain as cause of cardiac decompensation has been challenged. Our recent work proposed a new concept of cardiac congestion and decompensation, which may play a critical role in the pathophysiology of congestion in a significant portion of patients. This disruptive concept suggests that cardiovascular congestion is the result of blood redistribution from the abdominal (splanchnic) compartment to the heart and lungs. To allow a personalized treatment of patients with HF it is imperative to understand whether a patient has fluid overload and if so to what extent. To date the assessments of congestion is often limited to surrogates of intravascular pressure and volume, which often provide an incomplete and, in some instances, a false impression of a patient's congestion status. Volume overload, based on clinical examination parameters (presence of jugular venous distension, peripheral edema and orthopnea, an S3 and positive hepato-jugular reflex)[1, 2] increases in body weight,[3, 4] natriuretic peptides[5], estimates of plasma volume[6] and even invasive hemodynamic measurements[7, 8] lack sufficient sensitivity and specificity to accurately assess a patient's intravascular volume status. Yet, the use of blood volume analysis (BVA) via I131-labeled human serum albumin indicator-dilution technique, the gold-standard test to determine the intra-vascular volume, could overcome many of the limitations of conventionally used surrogate markers.

While it is well recognized that the extent of fluid volume congestion is closely associated with clinical outcomes,[9-12] the extent to which decongestion is achieved with diuretic therapy is highly variable and often less than clinically suspected.[11, 13, 14] Our **preliminary data** supports that current surrogate markers of congestion lack accuracy to estimate the true blood volume.[6] Given the limitations in clinical assessment of congestion and volume overload, an accurate assessment of blood volume using a standardized indicator-dilution technique with I-131-labeled albumin could provide distinct clinical benefit. This technique is considered to be the gold-standard for the quantitative assessment of plasma and total blood volume analysis given its precision, reproducibility, and clinical validity.[17] Retrospective studies using this technique have

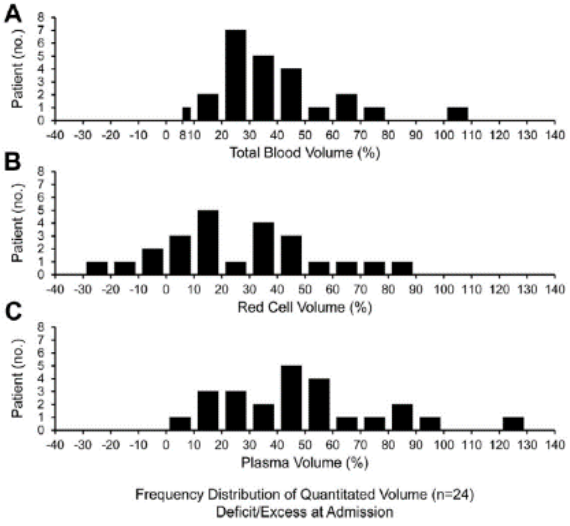


Figure 1: Heterogeneity in blood volume parameters. From Miller W, et al. *JACC HF* 2014

demonstrated marked heterogeneity in volume status in patients with acute and chronic HF[11, 13, 15] and uncovered unrecognized subclinical hypervolemia in asymptomatic and symptomatic HF patients (**Figure 1**).[15, 16] Most recent retrospective evidence now suggests that BVA- guided HF management could improve clinical outcomes such as HF rehospitalization and mortality in patients admitted with acute HF.[16] Consistent with our paradigm shifting hypothesis and **preliminary data**, inappropriate redistribution of intra-vascular volume might be an additional important driver of cardiac decompensation and can explain an increase in central filling pressures in the absence of weight gain or total body volume increase [11, 17, 18]. Supportive evidence is provided by body volume analysis using the I131-labeled human serum albumin indicator-dilution technique. Using this technology studies found that chronic HF patients with persistent symptoms are in 35% of cases hypovolemic or euvolemic[11] and the same was even true for patients admitted for decompensated HF (34%).[19, 20]

In an attempt to gather **preliminary experience** with the Daxor BVA technology, we enrolled and performed BVA measurements in 14 patients with acute and chronic HF within a 3 months window as part of a Duke approved IRB protocol (Pro00100536, Adrian Hernandez).

3. Purpose of the Study

Our objective is to develop personalized treatment approaches to the treatment of acute HF. The central hypothesis is that BVA will allow improved congestion phenotyping of acute HF patients given the ability to directly and accurately measure blood volume. Knowledge of specific congestion phenotypes will be the basis for targeted treatment algorithms. **The specific objectives are:**

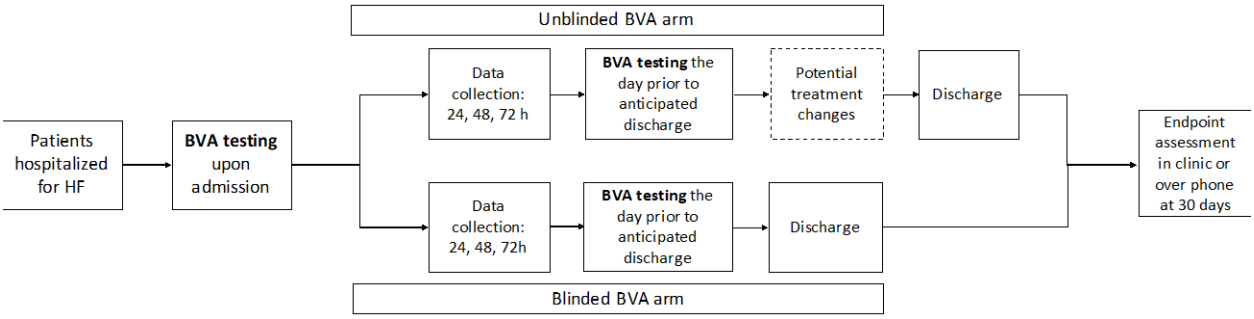
Perform a pragmatic randomized pilot study (N=50) with blood volume analysis (BVA) – guided treatment strategy vs standard of care in patients admitted for acute decompensated HF
***A:** Study effects of unblinded BVA results on provider treatment choices and clinical endpoints*
***B:** Develop a new BVA-guided treatment algorithm based on the observed experience with BVA at Duke*

4. Design & Procedures

Perform a pragmatic randomized pilot study (N=50) with BVA- guided treatment strategy vs standard of care in patients admitted for acute decompensated HF.

The main intent for this pilot study is to gather information on optimal study design, treatment recommendations and sample size for a future planned pivotal trial.

Design: Pragmatic pilot study of patients admitted with acute HF. Upon enrollment patients will be randomized to either the unblinded arm (BVA- guided treatment), or blinded arm (Standard of care treatment), where BVA results will not be provided to patients or provider team. The study is planned to start in the Spring, 2020 and be open for enrollment for 1 year. (**Figure 2**)



Population: Patients presenting to Duke Hospital with a history of HF and worsening symptoms of HF will be enrolled in the study. Exclusion criteria are: Ongoing pregnancy, age <18 years, post heart transplantation or ongoing mechanical circulatory support, and end stage renal disease.

Treatment protocol: A pre-determined assortment of demographic and medical information will be gathered for all patients upon admission, 24h, 48h, 72h and upon completion of repeat BVA and upon discharge. See flow chart below (**Table 1**).

Table 1: Patient assessments during the study. SOC indicates standard of care and CS indicates clinical study related procedures.

Required Assessment	Baseline	Day 1	Day 2	Day 3	Day before discharge	Discharge	30 days post discharge
Consent/Randomization	X (CS)						
Medications	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (CS)
Vitals (BP, HR, RR, SpO2, weight)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	
Orthostatic vitals	X (CS)				X (CS)	X (CS)	
Urine output	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	
Labs: BMP, NT-proBNP, urine sodium, CA-125	X (SOC/CS)	X (SOC/CS)		X (SOC/CS)	X (CS)		
BVA	X (CS)				X (CS)		
Dyspnea Questionnaire	X (CS)	X (CS)	X (CS)	X (CS)	X (CS)	X (CS)	X (CS)
Impedance and lung fluid content measurement	X (CS)				X (CS)	X (CS)	
Echocardiogram	X (SOC/CS)				X (SOC/CS)		
Pulse Wave Analysis	X (CS)				X (CS)		
Physician questionnaire	X (CS)				X (CS)		

Phone Call							X (CS)

Following enrollment, subjects will undergo the following tests/measurements. Some procedures occur as part of standard of care testing (SOC) while some testing will be performed as part of the clinical study (CS). All of the following tests have been approved in the present combination in Pro00100536, PI: Adrian Hernandez.

- **IV line** will be placed (SOC)
- If the subject is female and childbearing potential and has not had a **pregnancy test** since the arrival to the hospital, a blood pregnancy test will be done (SOC). If positive the subject will be excluded from the study.
- **Blood work:** Basic metabolic panel (BMP) (SOC), N-terminal pro-brain natriuretic peptide (NT-proBNP) (CS), urine sodium (CS), CA-125 (CS). This will require an extra lab draw. Expected blood loss is <20ml.
- **Blood volume analysis** The described BVA technique is an FDA approved technology for the purpose of volume measurement. It is currently used in clinical practice on patients with syncope, heart failure and sepsis to determine the exact intravascular volume and their components such as plasma volume and red blood cell volume.

  BVA will be completed within 24h of admission and again within 24h before anticipated discharge. Each blood volume analysis will take about 60 minutes to complete. The agent will be delivered to the radiopharmacy and prepared by the radiopharmacy. The agent will be then transported and stored at the DMP/ Radiology. On the study day the agent will be taken from the DMP to the patient's room for the injection. An intravenous line connected to a 50 ml saline solution will be inserted in an arm. This line will be used to inject a small amount of diagnostic radioactive material into the patient's circulatory system. A second IV line will be placed to collect small samples of blood at timed intervals 15 min after injection of drug, then every 6 minutes for an additional 3 samples (18, 24, and 30 minutes). Blood collection timeframes do not have to be exact but time of blood draw will be documented. Approximately 15 ml of blood will be drawn total. The collected blood samples will be processed in the DMP in the device provided by the company.

  On the report, values will be expressed as percentage (%) deviation from ideal volumes and the predicted normal BV was determined from patient's height, weight and deviation from ideal body weight. The output on the BVA results will be shared with the clinical teams within an hour of processing as outlined in **Figure 2.** BVA results will be provided only to patients and providers in the unblinded/BVA- guided arm. In the BVA- guided arm the medical team will also be provided with data to inform the medical management of their patients based on observed BVA results (admission and prior to discharge).

  The current data supports that ideal patient-specific euvolemic target should be 8-10% above euvolemia. All recommendations will not be binding.

  Further, if there is a red-cell deficit of >20% the team in encouraged to consider therapies to augment the red blood cell pool. Treatment is up to the physician discretion.

  Similarly, the test might reveal red blood cell overload (polycythemia) which ideally is addressed by the medical team using whatever options are clinically available.

- **Vital Signs:** Recorded vital signs including weight, blood pressure, heart rate, respiratory rate, SpO2
- **Dyspnea questionnaire** using a 7-point Likert scale and Visual Analog Scale (CS)
- Orthostatic heart rate and blood pressure (5 minutes supine, 1+5 minutes sitting and 1+5 minutes standing) on the day before procedure if the subject is an inpatient and again within 1 hour before procedure (CS). Also we will document whether subjects have symptoms bending over for 10 seconds (bendopnea).
- **Non-invasive Testing**
  - **Fluid Lung Content** measurement of chest fluid content using the ReDS™ unit (Sensible Medical, Tenafly, NJ). The ReDS unit is a vest that emits radiofrequency waves to measures fluid content. The device is FDA approved. The measurement requires 10 minutes.
  - **Impedance** for lung water volume measure using the Cardioset which uses electrical impedance technique to determine intra-thoracic blood volume.
  - **Arterial stiffness assessment (Pulse Wave Analysis):** We will use the Sphygmocor™ (AtCor Medical, Itasca, IL) to measure arterial stiffness. It is measured through a brachial cuff. This measurement requires 5 minutes.
- **Bedside ultrasound** will be performed of the heart and abdomen. We will assess: left ventricular function, inferior vena cava dimensions and collapsibility.

A phone call at 30 days will evaluate the vital status of the patient, potential changes in medications after discharge, and assess the patient's symptoms via the standardized questionnaires.

Physicians will be interviewed with a questionnaire at the time point of the BVA testing. The questionnaire will explore whether the unblinded BVA results changed the perception of the patients' congestion status and if they will result in a change in management.

Randomization process: Randomization will be performed by the study coordinator using computer software.

Potential complications:

- The radiation effective dose from a single administration of I-131 albumin for blood volume measurement is 0.60 mSv which is equal to three chest x-ray exams. It is equivalent to about 2 months of natural background exposure.

5. Selection of Subjects

For this study we seek to enroll heart failure patients admitted for acute decompensated heart failure to the cardiology service at the Duke Hospital. All patients irrespective of gender, race, and ethnicity will be considered for the study.

Exclusion criteria are:
- Ongoing pregnancy
- age <18 years
- Recent acute MI or hemodynamic instability: Acute MI (STEMI or Type I NSTEMI) within 7 days
- post heart transplantation or ongoing mechanical circulatory support
- Progressive cardiogenic shock

- Patients with Ventricular Assist Devices
- End stage renal disease

6. Subject Recruitment & Compensation

Potential subjects will be identified via two potential pathways.

Inpatients will be identified within 24 h of the admission via screening of the admission logs and inpatient census. Consent process will occur in the subjects' hospital rooms on Duke Hospital Divisions 7700/7100/7300/7200/3100/3300/7 East.

Patients considered for this study will be identified within 24 h of admission. Prior to approaching the patient we will discuss the patient and his/her eligibility with the primary cardiology team. Study team will be introduced by the primary team. Ample time will be given to the patient to review the consent and have all questions answered. After the patient has consented to the study we will begin study related activities. The primary enrollment target is up to =50.

Subjects will be informed that their participation is strictly voluntary. They will be assured that the decision to decline participation will have no impact on their care or the perceptions of their providers.

The subject will be compensated $100 for participation in this clinical study.

7. Consent Process

Candidate subjects will be informed of the risks and benefits of participation in the study. They will be informed of the study process and demands. They will be given a copy of the informed consent document to review and afforded adequate time to do so.

Informed consent will be obtained prior to the study. Consent will be obtained by the study Principal Investigator (PI), Duke Heart Center study coordinators who are trained on the study and who have been trained on the informed consent process, and other key personnel as designated by the PI. Consent will be obtained in the subjects' rooms. A subject is considered enrolled in this clinical study at the time at which the subject and investigator or authorized designee have personally signed and dated the Informed Consent Form.

8. Subject's Capacity to Give Legally Effective Consent

Subjects must to be able to understand the English language and understand the study process, including all potential risk and benefits. Any subject for whom the study personnel or treatment team has cause for concern regarding the subject's ability to understand the study process or follow the consent process, will be excluded from the study.

9. Study Interventions

- Lab draws
- Vital signs
- Orthostatic vital signs
- Non-invasive imaging with ultrasound
- Non-invasive hemodynamic monitoring (heart rate variability, Sphygmocor ReDS,

Cardioset)
- Blood volume analysis

10. Risk/Benefit Assessment

This study is associated with only small risks and has the potential to provide significant insight into the physiology of the patient's congestion. Risks are limited to the intravenous line placement, and radiation exposure.

Anticipated benefits to the subject include detailed information on congestion status and extent of fluid overload, otherwise not captured with standard clinical care diagnostic methods. This newly obtained data will be provided back to the patient and provider which then can result in a change in clinical care. However the study or protocol does not have an influence on the clinical care the patient will receive as a result of the newly obtained information.

11. Costs to the Subject

Study-specific activities and assessments will be conducted at no additional cost to the subject. Subjects will still be responsible for standard of care procedures related to hospitalization for heart failure.

12. Data Analysis & Statistical Considerations

Descriptive statistics of continuous outcomes will include sample size, mean, median, standard deviation, minimum and maximum. For categorical outcomes, the number and percentage of subjects in each category will be presented. Statistical comparisons will be made using t-tests for continuous outcomes and chi square or Fisher's exact test (depending on overall event rates) for categorical outcomes.

13. Data & Safety Monitoring

Significant adverse events associated with the study procedures are not expected. 30 day follow-up is planned. Should complications be encountered, they will be reported to the IRB within 10 working days or per IRB policy. The Principal Investigator will also provide an annual report of any side effects or problems to the IRB during the study renewal process.

No protected health information associated with the study procedures will be sent outside of Duke. PHI (subject ID, height, weight, and gender) will be used internally for measuring the blood volume. Additionally, we will capture the birth year of the patient to perform the pulse wave analysis.

14. Privacy, Data Storage & Confidentiality –

Data will be obtained by approved study personnel. An enrollment log will also be maintained in an Excel Spreadsheet on the Heart Center's secured S:drive. The subject ID will also be stored on the folder to track subject enrollment and collection of data. Data will be recorded in Excel. Only deidentified data will be available for statistical analysis. All subject identifiers will be removed for database storage, statistical analysis and data reporting. This data will be stored on a study specific folder on the Duke server behind the

Duke firewall. The subject ID code will be destroyed after data analysis is completed. Protected health information will not be used for any other purposes than those described in this protocol without obtaining further IRB approval. This information will be used for research purposes only and subjects will never be contacted regarding information obtained through chart review. A designated statistician from the DCRI will provide support with statistical analysis.

The adequacy of the Research Data Security Plan (RDSP) will be evaluated and approved by the Cardiology CRU prior to study conduct.

Any publications or presentations that result from this research will not identify any subjects individually, and will present data in aggregate form only.

Gathered data will be stored for at least 6 years.

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