ADHF POCUS research proposal

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Title: Does serial ultrasonographic assessment for extravascular lung water and IVC measurement affect outcomes in inpatient heart failure management?

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Introduction:

Patients with admitted to hospital with Acute Decompensated Heart failure (ADHF) suffer a significant morbidity and premature mortality. In the United States, cardiovascular disease is listed as the leading cause of death, accounting for nearly 836,546 deaths per year and heart failure accounts for nine percent of these deaths (1). The management of ADHF is challenging, complex and diuretic therapy serves as the cornerstone for acute management of these patients. However, administration of intravenous (IV) diuretics is largely guided by clinical judgment based on physical exam, net fluid measurement, changes in daily weights and chest x-ray findings.

Serum laboratory measurements supplement these findings and include blood urea nitrogen (BUN), serum creatinine (Cr), brain natriuretic peptide (BNP) and serum bicarbonate levels. The key objective is to promote adequate diuresis while improving symptoms, without compromising renal function. Observational studies have identified worsening renal failure (WRF) in patients admitted for heart failure as an important clinical entity. Despite the lack of consensus definition for WRF, renal dysfunction is common among patients admitted for ADHF with an incidence as high as twenty to forty percent. (2-5) Patients who develop WRF are subjected to increased length of stay, in-hospital death, all-cause mortality and increased rates of cardiovascular death. (4, 6) The use of recommended medications such as angiotensive converting enzyme inhibitors (ACEi) is limited in patients with WRF complicating their care even further. (5)

To add to the challenges of diuretics and renal function, other commonly utilized measures of successful diuresis are inadequate. For example, studies suggest that daily weight and net fluid loss poorly correlate with symptom relief in ADHF. (7) Laboratory tests demonstrating hemo-concentration, increasing BUN, and increasing creatinine have been proposed as positive prognostic indicators in patients receiving IV diuretic therapy (8, 9) but these methods suffer from inadequate predictive value. Despite the considerable deficits in these techniques for monitoring diuretic use in ADHF, they continue to be used by clinicians. This has led to the unmet need to develop and utilize novel bedside monitoring to improve outcomes for patients who are receiving diuretic therapy for ADHF.

Point of care Ultrasound (POCUS) has the potential to fill this unmet need. POCUS provides clinicians with immediate diagnostic information obtained and interpreted at bedside that can augment and enhance the physical examination. Numerous studies have examined POCUS assessment of pulmonary edema and measurement of the Inferior Vena Cava (IVC) to estimate hemodynamic parameters for patients with acute decompensated heart failure (ADHF). Studies show that IVC diameter and variation in diameter during respiratory cycles correlate with right atrial pressures and can aid in the initial diagnosis of ADHF. Measurement of the IVC with POCUS correlates with prognosis and have been found to identify individuals who are at risk of being readmitted to the hospital. (10-15)

POCUS of the lung is a reliable and accurate diagnostic modality that is both sensitive and specific for pulmonary edema due to ADHF. (16, 17) Identification of interstitial syndrome, which is defined as the presence of multiple, diffuse and bilateral B-line artifacts can help differentiate pulmonary edema from other causes of dyspnea and hypoxemia in ADHF patients. Resolution of interstitial syndrome has been shown to better correlate with relief of symptoms in real time, and correlates to decrease in brain natriuretic peptide level in patients with ADHF compared to other methods. (18-24)

The 2013 American Heart Association and American College of Cardiology Foundation guidelines for heart failure management recommend diuretic therapy for patients that are admitted to hospital for ADHF and the use of intravenous (IV) diuretic therapy is a cornerstone of inpatient therapy. Monitoring with serum renal function tests and clinical assessment is also recommended. However, current guidelines do not address the use of Point of Care Ultrasound (POCUS) for the monitoring of patients admitted for ADHF. (25)

Combining serial examination of IVC and lung ultrasound in patients hospitalized with ADHF and correlating with relief of symptoms based on a standardized ADHF congestion score may be a novel approach to guide diuretic therapy and aid in monitoring and predicting improved outcomes. (26)

Despite abundance of data in use of POCUS as an initial diagnostic modality and possible treatment tool for ADHF, there is no study to date that has validated the longitudinal use

of POCUS to guide intravenous diuretic therapy. In this study we propose to examine use of serial POCUS on ADHF and its effect on the rate of worsening renal function, length of stay and rehospitalization rates in hospitalized patients.

Hypothesis:

The use of POCUS for serial assessment of volume status with IVC measurement and lung ultrasound evaluation for interstitial syndrome reduces incidence of WRF attributed to diuretic administration in patients admitted for ADHF as compared to usual care.

Specific Aims:

The overall guiding aim for our project is to determine the effectiveness of POCUS assessment in improving clinical outcomes in our patients admitted with ADHF.

To test our hypothesis, we will conduct our experiment with the following specific aims:

Primary aim: To determine if bedside written assessments of IVC and interstitial syndrome with POCUS provided to clinicians caring for patients admitted for ADHF improves outcomes compared to usual care as demonstrated by decrease in incidence of WRF while inpatient.

Secondary aim: To determine if bedside written assessments of IVC and interstitial syndrome with POCUS provided to clinicians caring for patients admitted for ADHF improves outcomes compared to usual care as demonstrated by decreased length of stay and decreased 30-day readmission rates.

Study Design

Randomized control trial open label study

Study Population

Patient's admitted to Riverside University Health Systems Medical Center, a tertiary care center located in Moreno Valley, CA. Our patient population is predominately residents of Riverside and San Bernardino counties. These patients are most often lower socioeconomic status with little access to healthcare resources. Our population selected is greater than 18 years old admitted with acute heart failure exacerbation as primary admission diagnosis from Emergency department to the general internal medicine service.

Inclusion Criteria

Age >18 admitted for acute decompensated heart failure exacerbation as primary admission diagnosis from Emergency department to General Medicine ward that are administered diuretic therapy expected to be admitted for two days or more.

Exclusion Criteria

1) Decline consent for study
2) If admitted and research team not available for consent and initial evaluation prior within 6 hours of first diuretic administration
3) Patients in whom diuretics will not be utilized (i.e. anuric, ESRD on HD)
4) Inability to assess IVC (surgical anatomy, body habitus, Ileus, etc.)
5) Patients admitted to ICU
6) Patients currently on positive pressure ventilation (BiPAP)
7) Patients discharged from the emergency department
8) Patients discharged prior to evaluation by the POCUS team

Human Subjects Protection

The risk of ultrasound to for study purposes was determined to be non-significant based on the opinion of facility experts and ultrasounds history as a diagnostic modality prior to study design. This study will be submitted to the RUHS-IRB for review and approval prior to patient enrollment. After approval, informed written consent will be obtained from each research subject or their surrogate per local federal, state and county regulations. Research data will be collected and stored electronically for this study. The collected data will be entered into a data collection sheet which will be a password protected EXCEL spreadsheet and stored in the RUHS server under additional password protection. Unique identifiers will be removed from the data collection sheet and each subject assigned a random number. This number will serve to link the identity to the subject as a data linkage log. The subject identity will be kept in a separate EXCEL case book under a different password. Access to the subject information will be limited to the PI, sub PI and RUHS IRB.

Subject Recruitment

Subjects will be recruited while in the RUHS Emergency Department or RUHS Medicine ward by the PI, SubPI and Collaborators. Consent will be obtained in the RUHS Emergency Department or RUHS medicine ward by the PI, SubPI and collaborators with clinical privileges at RUHS. Resident physicians obtaining consent for the study will do so under the direct supervision of PI, SubPI and collaborators with clinical privileges at RUHS. Further, the PI will meet with Emergency and Internal Medicine Hospitalist Staff and inform them of the study. Any potential subjects will be reported to and screened for inclusion by the PI and SubPI.

Sample Size

Literature review was conducted with regard data for the incidence of worsening renal failure in patients with acute decompensated heart failure. Incidence of WRF in patients admitted for ADHF was as high as 20-40% (2-5) based on our review. Assuming an incidence of worsening renal failure of 30% in the control group, an alpha equal to 0.05 and a beta of 0.20, to detect a 25% reduction in worsening renal failure (or a 23% incidence of worsening renal failure in the intervention group), our study will require a sample size of 129 patients in each arm. To account for patients lost to follow up, who

choose to withdraw or may have an alternative diagnosis to ADHF proposed we plan to enroll up to 200 patients per arm in our study.

Methodology:

Emergency physicians and house staff will determine the diagnosis of ADHF exacerbation based on history, clinical exam, elevated BNP levels, radiology and bedside POCUS evaluation. Prior to diuretic administration patients will be screened for inclusion or exclusion in the study by checklist. If the patient or their surrogate decision maker consents to the study, they will then be randomized by random number generator to usual care or POCUS experimental arms. The POCUS team members in the ED will evaluate these patients and obtain baseline POCUS measurements.

Baseline characteristics of sex, age, body mass index (BMI), new york heart association (NYHA) heart failure Class and stage, etiology of heart failure, ejection fraction, presence of diastolic dysfunction, diabetes mellitus, hypertension, chronic kidney disease and stage, home diuretic regimen, home ACEi, home ARB, IV contrast administration, guideline directed medical therapy (GDMT) for heart failure and antibiotic (piperacillin-tazobactam, Vancomycin, Aminoglycosides) administration will be recorded for patients enrolled.

POCUS team consists of attending physicians, resident physicians and medical students. POCUS team members undergo formal training, by facility experts, for IVC assessment and B-line identification. Training for POCUS team members consists of 2 hours of classroom didactics followed by bedside teaching of standardized patients and technical skills training. Team members who collect data will be subjected to multiple choice examination with 25 standard images. Individuals certified to collect data must pass standard image exam with 95% result on two attempts. Individuals who do not pass will be directed to retake didactic and hands on sessions and then allowed to retake this examination.

In addition to their initial POCUS evaluation patients in the experimental group will immediately have a protocol-based evaluation (checklist) for interstitial syndrome (b-lines) and IVC evaluation by POCUS team. These examinations take place daily in the morning at 6am before the primary team rounds on their patient and findings are reported directly to the primary team via copy of the data sheets and verbal/written interpretation of exam results. Thoracic ultrasound examination will be performed with a Philips Sparq or Philips Lumify device with a C6-2 or C5-2 Curvilinear probe set to 15cm depth with a frequency of 48Hz. Ultrasound of the chest will be conducted on 4 regions of each lung bilaterally per international chest consensus guidelines from 2012. Positive exam is denoted by the presence of greater than three b-line artifacts in the intercostal space bilaterally, confluent B line artifact bilaterally or bilateral pleural effusions. Cardiac and subsequent IVC measurement will be conducted with a C6-2 or C5-2 curvilinear probe set to 15cm depth with a frequency of 48Hz in the subcostal view. IVC measurement will be conducted per American society for echocardiography guidelines for assessment of the

right heart. Either sagittal or transverse views will be obtained and IVC will be measured for collapsing with snif maneuver.

Data scoring sheet with reflect anatomic regions of findings in binary yes/no answers. Interpretation of data on volume status will be indicated at the bottom of data sheets as high dose diuretic tolerant, high dose diuretic intolerant or consider alternative diagnosis with disclaimer.

Patients in each arm will be monitored with daily diuretic administration with dosing, intake and output, daily weight measurements and serum electrolyte levels. Additionally, patients in both arms will be monitored for ACEi/ARB prescription, hospital day of ACEi/ARB prescription, antibiotics known to cause WRF (piperacillin-tazobactam, Vancomycin, Aminoglycosides). Incidence of WRF will be monitored with daily serum creatinine levels. WRF will be defined as development of: increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) or increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred during admission. In addition to the above variables in hospital mortality, all-cause mortality, cardiovascular mortality, length of stay in hospital days and readmission to hospital within 30 days for the same diagnosis related group (e.g. Heart failure exacerbation, heart failure or ADHF) will be recorded. Data will be exported to an excel spreadsheet and the research team with statistician will perform descriptive and quantitative analysis.

The choice of diuretic, dose and timing of administration will be left to the discretion of the primary physician. The control group will consist of patients receiving usual care for ADHF +/- bedside ultrasound assessment, with ultrasound assessment being performed at the primary physician discretion.

Data analysis

Baseline variables will be compared using descriptive statistics (e.g. chi-square for nominal data and t-test for continuous data). A multiple logistic regression will be performed for the primary study outcome (presence or absence of worsening renal failure) as well as the secondary outcome of hospital readmission within 30 days. A multiple linear regression will assess the secondary outcome of hospital length of stay.

Data safety and monitoring

Training in the pertinent diagnostic ultrasound techniques will be conducted for all individuals who collect data on the team. This training process is composed of bedside verification of skills, classroom didactics and online instructional videos. Certification to collect data will be granted to team members after passing an examination with standard images and bedside assessment by core investigators. This is a training program developed by the PI and faculty members based on clinical experience in ultrasound and clinical teaching.

The data examining training and competency for POCUS are heterogeneous with many studies examining learners of various levels and several modalities. Both individual

studies and systematic review support the use of classroom didactics with standard imaging and competency testing. Further, there is evidence to suggest excellent interrater agreement for B-lines utilizing the approach outlined (27, 28).

Incidental findings will be reported to primary team immediately and verification for these findings. Interim data analysis will be conducted by PI and collaborators every 6 months.

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Conflict of Interest Disclosure

The authors declare that there is no conflict of interest regarding the publication of this paper.

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