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Optimal Endpoints of Acute Heart Failure Therapy

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Introduction

Over one million hospitalizations for acute heart failure (AHF) occur yearly and hospitalization remains a strong predictor of mortality in heart failure.[1 2] Hospitalization for AHF should begin with an evaluation of volume status and perfusion, in addition to identifying reversible exacerbating factors such as ischemia, arrhythmia, medication non-adherence, and co-existing pulmonary disease.[3] Most commonly, patients present with pulmonary and systemic congestion and sufficient perfusion. Exam findings in these patients predominantly rely on recognizing evidence of elevated right heart pressures, such as elevation of jugular venous pressure, presence of lower extremity edema, and hepatomegaly. These findings are often used as surrogates of elevated left heart pressures which are better characterized by the presence of rales, and complaints of shortness of breath, cough or orthopnea. These initial signs and symptoms are often the first suggestion of AHF and need for intensification of therapy and possible admission.

Many tools are used to objectively determine if a patient’s symptoms may be related to AHF. Initial laboratory evaluation in urgent care or emergency department (ED) setting should include laboratory evaluation for hyponatremia, acute renal failure and evidence of hepatic congestion. Natriuretic peptides should be checked as when low they are sufficiently sensitive to exclude AHF. Elevated natriuretic peptides are less specific indicators of AHF in a dyspneic patient as they may be chronically elevated in compensated chronic heart failure.

[4–6] Further evaluation includes echocardiography for assessment of ventricular size and function, mitral regurgitation, as well as, inferior vena cava size and collapsibility which may be performed in the ED at the bedside as a focused study or as a comprehensive study. [7 8] A subset of patients may also have right heart catheterization (RHC) or pulmonary arterial catheter (PAC) placement to measure filling pressures and to quantify congestion, as well as evaluate need for inotropic therapy, optimize afterload reduction and diuresis. Patient selection for these interventions is crucial, however, because the impact of PAC on mortality has been mixed.[9 10]

Despite the various modalities to evaluate congestion in patients with AHF, there is no consensus as to what changes during hospitalization are sufficient to safely discharge a patient. There are multiple data points to consider when making the discharge decision, including changes in labs, physical exam, imaging and invasive measures. Defining safe endpoints of therapy is a critically unmet need, as readmission is more likely when signs of volume overload are still present at discharge.[11–14] However, what defines adequate decongestion is currently unclear. The definition of decongestion used in clinical trials includes: jugular venous distention <8cm of water, no more than trace peripheral edema and the absence of orthopnea.[12 15] Many objective measures have been used to attempt to quantify the level of congestion, however, the use of a standardized method to evaluate decongestion beyond clinical signs and symptoms is necessary to ensure safe and durable discharge.

Different phases of congestion exist in acute heart failure and occur progressively with worsening degree of illness and severity of volume overload. Hemodynamic congestion represents increased left ventricular filling pressures as measured by elevated left ventricular end diastolic pressure (LVEDP) or surrogate pulmonary capillary wedge pressure (PCWP). Pulmonary congestion more specifically refers to the presence of extravascular lung water (EVLW), a downstream effect of hemodynamic congestion in AHF, but also exacerbated when there are increased right sided filling pressures and reduced lymphatic drainage. Clinical or systemic congestion refers to fluid accumulation outside of the lung, and creates many of the common exam findings used to assess for AHF.[16] Systemic congestion is represented by findings of increased right sided filling pressure, such as jugular venous distention, edema, hepatomegaly, and, in some patients, acute renal failure and congestive hepatopathy. Patients with the same LVEDP can have variable severity of pulmonary congestion, from complete absence of EVLW to alveolar pulmonary edema and resulting hypoxic respiratory failure. Similarly, varying levels of systemic congestion occurs at different levels of hemodynamic and pulmonary congestion relating to chronicity of disease, comorbidities, as well as, valvular and RV function.[17 18] Residual congestion is the presence of ongoing hemodynamic, pulmonary or clinical congestion that is present on discharge for AHF hospitalization, this has been defined by Orthoedema scores >0 indicating the presence of orthopnea, elevated JVP or peripheral edema. Presence of residual congestion on discharge by orthoedema score correlated with a 60-day increased risk of death, re-hospitalization or emergent office visit.[19]

In the cascade of congestion there are multiple possible targets for AHF therapy. We propose the treatment during hospitalization should target hemodynamic congestion, not the

traditional and more easily, non-invasively identified clinical decongestion. Below we identify possible tools to objectively monitor levels of hemodynamic congestion in a hospitalized AHF patient population.

Clinical Endpoints

Exam findings are the most commonly used endpoint to assess decongestion. However, recognition of clinical findings of systemic congestion are difficult to identify for many providers.[20 21] Unfortunately, clinical signs and symptoms can misrepresent true volume status, such as ongoing edema in a patient with malnutrition and hypoalbuminemia, or dyspnea in patients with co-morbid lung disease. Exam findings typically used are not reliable markers of adequate hemodynamic decongestion, given these findings are manifestations of elevated right sided pressures (Table 1). Right sided congestion in left heart failure generally appears once volume overload has advanced past the point of hemodynamic and pulmonary congestion. Scoring systems have attempted to objectify congestion without much benefit, most including measures such as orthopnea, edema or JVP.[22] Therefore, exam findings of right sided congestion often resolve prior to decreasing left sided pressures, giving the illusion of sufficient decongestion.

An additional clinical measure of prognosis and readmission risk may lie in exercise capacity, specifically 6-minute walk distance (6MWD). This metric is often used as a functional status surrogate and quality of life indicator. A study of 6MWD of patients with AHF and systolic dysfunction at ED presentation found 6MWD increased as hospitalization progressed. This study demonstrated the feasibility of performing this measure throughout hospitalization in AHF admissions.[23] 6MWD has been shown to be predictive of 30-day readmission rates. For every 100 feet further a patient walked the 30-day readmission rate decreased by 16%.[24] In AHF hospitalizations, shorter 6MWD is associated with significantly higher rates of readmission, especially when patients walk less than 390 meters. [25] In chronic heart failure, changes in 6MWD predict both hospitalization and mortality. [26 27] Further evaluation of 6MWD in the acute setting may find this to be an objective marker of decongestion.

Daily weights and weight change during admission are classically used as a surrogate for effective diuresis and decongestion. A modest correlation has been shown between fluid loss and weight loss with worsening correlation as the hospital course progresses.[28] Weight loss and fluid loss do not correlate well with relief of dyspnea in AHF admissions.[29] Alternatively, increases in body weight during AHF hospitalization correlate with a 16% per kilogram risk of 30-day mortality and readmission.[30] Further, patients with diastolic HF may have symptoms related to fluid redistribution rather than total body fluid accumulation, and it may not be necessary to target significant weight loss in this patient population.[31] While weight loss appears to be measure of adequate diuresis and has been traditionally used as a tool to evaluate decongestion, data do not support the use of weight loss as a reliable correlative of decongestion or volume loss during inpatient therapy.

Laboratory Evaluation

Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are two of the most frequently used and extensively studied laboratory values in AHF. BNP alone has been shown to correlate with LVEDP in a small study of patients with systolic heart failure and both BNP and NT-proBNP have shown diagnostic utility in ED patients with undifferentiated dyspnea (Table 1).[32–34] Natriuretic peptides may be chronically elevated in patients with chronic HF and, as a result, an elevated BNP without a known baseline is less helpful to detect an acute change in filling pressures. However, when compared to a baseline BNP for a given patient, changes in BNP do correlate with changes in filling pressures.[35] Currently there is not a validated method for using natriuretic peptides to guide diuretic therapy or discharge timing. The STARBRITE study looked at BNP guided therapy during AHF hospitalization, finding no difference in days alive and not hospitalized with BNP guided treatment strategy when compared to standard care without the use of BNP guided medication titration. The BNP-guided strategy did result in increased use of evidence based medications, however.[36] The utility of BNP is in initial differentiation of causes of dyspnea in the ED, as opposed to guiding diuretic therapy during AHF hospitalization.

Markers of hemoconcentration have also been investigated in AHF hospitalization, including hemoglobin, hematocrit, albumin and total protein along with estimated glomerular filtration rate (eGFR) and creatinine. Analysis of the ESCAPE trial found greater changes in albumin, total protein and hematocrit in patients who had worsening in their eGFR during AHF admission. Despite worsening renal function, patients with laboratory evidence of hemoconcentration were shown to have greater total weight loss, larger total volume of diuresis and greater reduction in right atrial pressure (RAP) and PCWP.[37] Similar findings have been reported from an analysis of the EVEREST placebo arm where patients with worsening renal function were more likely to have significant hemoconcentration as marked by increases in hematocrit. Patients with evidence of hemoconcentration also had larger decreases in weight and BNP, suggesting greater degrees of diuresis.[38] Increases in hematocrit during an inpatient stay were associated with a decreased post-discharge risk of all-cause and cardiovascular mortality and HF hospitalization.

Hyponatremia is another marker of congestion that is an ominous sign in chronic systolic HF, portending a poor prognosis. In AHF the associated hypotonic hyponatremia is an issue with impaired water excretion rather than sodium depletion. Reduced serum osmolality is mediated by increased circulating Arginine Vasopressin levels, increasing renal water reabsorption which may contribute to persistent congestion.[39] As such, in parallel hyponatremia and lower serum osmolality may be markers of residual congestion in the AHF patient population.[40] Patients admitted with AHF with presentation serum sodium <132mmol/L have higher rates of adjusted in-hospital and 60-day mortality. [41 42] Improvement in serum sodium 2mmol/L during hospitalization in the ACTIV in CHF trial was associated with significantly lower 60-day mortality (11.1% vs. 21.7%, p=0.0195).[43] It is yet to be seen if serum sodium is measure that can be used as a true marker of hemoconcentration.

Worsening renal function (WRF) is common during treatment of AHF and has been associated with decreased survival and increased re-hospitalization.[44] In recent years WRF in the setting of guideline-directed medical therapy (GDMT) with ACE inhibitors and ARBs as well as aggressive diuresis has not been shown to have the same adverse outcomes.[45] While greater hemoconcentration is associated with worsening renal function, those patients with evidence of hemoconcentration had lower 180-day mortality. [37 46] Changes in renal function associated with clinical improvement, decongestion and RAAS blockade have different effects on prognosis compared with worsening renal function independent of these findings and treatments. Thus, it is important to consider the clinical scenario when determining the importance of WRF. Monitoring renal function related to decongestion is an important part of the treatment process and further research is needed to help guide clinicians regarding the interaction of diuresis and WRF.

Imaging Modalities

Bedside ultrasound is a relatively inexpensive and rapidly interpretable modality to aid in identifying patients with AHF. The finding of pulmonary congestion is important given the associated poor prognosis in heart failure.[17] Lung ultrasound can be used to identify interstitial pulmonary edema by the appearance of B-lines (artefactual vertical lines arising from the pleural surface), with three or more B-lines in at least 2 intercostal spaces bilaterally diagnostic of pulmonary edema (Figure 1).[47] B-lines appear to be dynamic in nature, as they decrease in proportion to the amount of fluid removed in patients undergoing dialysis and have been shown to decrease with diuresis and treatment of AHF.[48 49] Further investigation is needed to determine the utility of B lines as a measure of decongestion. Inferior Vena Cava (IVC) diameter and collapsibility is a bedside ultrasound measure that can be used as a surrogate of central venous pressure. With ever improving and less expensive portable ultrasound devices, IVC measurements can easily be performed serially at the bedside without the expense of a full echocardiogram. This can be used to augment clinical findings of the level of right atrial pressure elevation and has been shown to be much more accurate than physical exam assessment of JVP.[50] IVC collapsibility on bedside ultrasound has been validated in ED patients in aiding a diagnosis of AHF, where less than 33% decrease in IVC diameter during inspiration corresponded to a diagnosis of AHF.[51] IVC collapse >50% versus 50% has been shown to discriminate between right atrial pressure <10mmHg and 10mmHg respectively.[52 53] Despite the theoretical benefits of using serial IVC measurements as a marker of congestion, one small study examining the use of serial IVC ultrasound showed no significant change during hospitalization and treatment of patients with AHF.[54] Point of care IVC ultrasound appears to be useful in estimating RAP, however, further investigation is needed to correlate changes in IVC with advanced heart failure therapies and resolution of symptoms.[54]

Echocardiographic findings in AHF can be helpful in objectifying adequate decongestion (Figure 2).[55] Mitral valve inflow velocities are used to evaluate increased left atrial filling pressures as the E wave represents early diastolic filling and as filling pressures increase, so does the early mitral inflow velocity. The E'-wave evaluated by tissue Doppler imaging of the lateral mitral annulus detects early reduction in diastolic filling associated with increased filling pressures as well. E/E' ratio > 15 is predictive of PCWP >15mmHg with a sensitivity

of 85% and specificity of 88%.[56] The E/a ratio is less reliable in the prediction of PCWP and change in E/a ratio is not useful in predicting changes in PCWP.[57] Severity of mitral regurgitation (MR) is also an important part of the echocardiographic evaluation of AHF. Functional MR is a common complication of heart failure due to left ventricular dilation, annulus distortion and leaflet tethering, and often worsens with decompensation. In parallel, with treatment of AHF, functional MR measured by color Doppler jet area has been shown to improve along with mitral inflow Doppler parameters. While mitral inflow parameter changes have not been associated with mortality, both baseline and discharge severity of MR are associated with increased risk of AHF hospitalization or death at 6 months.[8] Improvement in MR occurs with decongestion and GDMT in AHF hospitalization and those patients with less MR have better morbidity and mortality.[8 58]

Non-invasive imaging technologies to evaluate volume overload are being investigated in clinical practice. Bioreactance and bioimpedance are two non-invasive methods to measure cardiac output, of which bioreactance is more robust and resistant to artifact.[59] Thoracic bioimpedance is one method to measure EVLW, this technology is available in one form as Remote dielectric sensing (ReDs). ReDs expresses EVLW as a percentage of lung volume and is FDA approved for monitoring fluid status in heart failure patients.[60] EVLW correlates with invasively measured PCWP in 145 patients undergoing clinically indicated RHC. Specifically, a ReDs value $\geq 35\%$ predicted a PCWP $>17\text{mmHg}$ with sensitivity of 80% and specificity of 75%.[61] In the vulnerable period of post-hospitalization care for AHF a study of 50 patients found the mean reading at hospital admission was 35.3% ($\pm 7.5\%$) and at discharge was 30.6% ($\pm 7.5\%$), correlating with an average weight reduction of 2.3 kg and decrease in BNP by 254 pg/mL ($\pm 655\text{ pg/mL}$).[60] Another newly revitalized modality of evaluating volume overload is nuclear determination of total blood volume (TBV) using radiolabeled albumin (I-131). TBV is measured by I-131 tagged albumin injection with subsequent serial blood draws over a total of 36 minutes. Results are reported as absolute values and percent excess or deficit from reference ranges, in addition to reporting red blood cell mass and plasma volume. Miller and Mullan studied HF patients admitted with clinical volume overload, measuring TBV at admission and discharge. They found that systolic HF patients saw significant decline in TBV when compared to diastolic HF at discharge, however, both remained hypervolemic compared to reference ranges.[62] Miller and colleagues are currently investigating correlations between TBV patterns in diastolic HF and systolic HF in relation to RHC measurements.[63] Further research is needed evaluate the utility of these technologies in AHF hospitalization.

Invasive Measurements

RHC to determine right sided filling pressures and PCWP is the gold standard to measure volume status in acute and chronic HF. However, RHC is invasive with risk of complications including vascular injury and pneumothorax. The ACC/AHA guidelines recommend considering RHC in AHF patients with unclear volume or perfusion status, hypotension, worsening renal function or those undergoing evaluation for advanced therapies. These guidelines currently recommend against routine RHC in patients with AHF, normal blood pressure and improvement in symptoms with current therapies.[64] Trends for PAC use in recent data suggests patients who receive PACs are more likely to be younger, female and

have cardiogenic shock, acute myocardial infarction, cardiac arrest or require mechanical ventilation.[65] PACs are used more frequently in larger, urban teaching hospitals with advanced heart failure centers and higher acuity patients. These patients had higher mortality rates (13.1% vs. 3.4%) and longer hospital stays (9.9 vs. 5.1 days) compared to those who did not receive a PAC.[65] However, in a non-randomized analysis such as this, selection bias can heavily influence results.

The CardioMEMs device is an invasive, implantable device used to monitor pulmonary arterial pressures, specifically PA diastolic pressure, to evaluate degree of hemodynamic congestion. This is a wireless, radiofrequency, pressure-sensitive capacitor that is implanted in the pulmonary artery and requires calibration with RHC. The CHAMPION trial validated the utility of this implantable PA pressure monitor to manage heart failure and hospital readmissions. CHAMPION found the number of AHF hospitalizations at 6 months was reduced by 28% in the CardioMEMs group when compared to standard care.[66] In patients who have one of these implantable devices, the use of PA diastolic pressure during an inpatient hospitalization for AHF is an important tool to assess adequate decongestion prior to discharge but has not yet been thoroughly studied in this capacity.

Future Directions

Assessment of adequate hemodynamic decongestion is an important part of the evaluation of patients with AHF prior to hospital discharge, as residual congestion increases the risk of re-hospitalization and mortality. Traditionally we have relied on signs and symptoms of clinical decongestion to determine readiness for discharge. However, these findings have proven to be unreliable and subjective. As a result, we suspect that a large proportion of patients have residual congestion at discharge. Thus, hemodynamic and not clinical decongestion should be a target of hospitalization interventions. The practicality of CardioMEMs or RHC to evaluate decongestion is limited due to procedural risks, cost and logistics. Additionally, PACs have not been shown to improve mortality or readmissions. Rather, finding a feasible, non-invasive, cost-effective surrogate or series of surrogates to objectively determine how well a patient has been decongested is an ambitious but achievable goal.

Currently there is no standardized, non-invasive method to evaluate hemodynamic decongestion. With no single measure currently existing to quantify decongestion, we suggest two important directions. First, while we await further research to define optimal endpoints, it is important to incorporate labs and imaging techniques in a systematic manner. One method to accomplish this would be to implement a discharge checklist documenting surrogates of decongestion in a similar fashion at a similar time on each patient during their hospitalization (Figure 3). This checklist would include traditional measures such as jugular venous pressure, presence of dyspnea, orthopnea and edema, as well markers of hemoconcentration and perhaps natriuretic peptides. Bedside ultrasound to determine IVC size and collapsibility to confirm jugular venous pressure is another potential addition. Further research is needed to determine other objective endpoints to augment the discharge checklist. This would include determining how changes in bedside lung and IVC ultrasound or ReDs examination augment traditional measures of decongestion, identify appropriate levels of diuresis, and decrease risk of readmission.

The timing of pre-discharge congestion evaluation is also an important component and is preferably performed prior to the planned day of discharge, allowing for at least 24 hours to modify the discharge plan. Given variable bioavailability of diuretics in different disease states, we propose that a more rapid assessment of diuretic dosing is important to the discharge process.[67 68] This may be facilitated by checking urinary sodium levels shortly after diuretic dosing to allow faster up-titration of dosing or nursing driven diuretic protocol based on fluid balance to facilitate faster discharge.[69]

Beyond optimizing clinical status on discharge are issues of comorbidity management, care coordination and adherence, all of which are important to preventing readmission. Exacerbations of comorbidities are a common cause of readmission in heart failure patients and timely follow-up with appropriate specialists is important for management of diseases such as diabetes, kidney disease and pulmonary disease.[70] Care coordination is an important factor in managing these comorbidities and can ease some of the financial burden of chronic disease. Some suggestions are to coordinate laboratory testing, appointment timing and imagine amongst providers. Medication adherence may also be able to be improved by understanding patient's limitations to access and minimizing costs by using generic when possible, splitting tabs or involving a pharmacist to aid with patient assistance programs. [71] All of these interventions may improve overall patient experience and decrease risk for readmission.

Conclusions

Ensuring hemodynamic decongestion is an essential goal of AHF hospitalization. Currently there is no standardized and objective method of evaluating hemodynamic congestion prior to discharge. We suggest that a necessary first step is to synthesize a standard method to use the currently available modalities to optimize the assessment of the near-discharge patient. This evaluation will then be augmented by future research to devise an effective, non-invasive and feasible method for quantification of pre-discharge decongestion.

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Figure 1.

Lung ultrasound showing two different lung fields with B lines. Arrows point to B-lines that are vertical lines that begin at the pleural and extend to the bottom of the imaging field.

Figure 2.

Ultrasound and Echocardiographic findings in acute decompensated heart failure. A. Mitral valve inflow pulse wave Doppler showing high E/A ratio of 3.9. B. Tissue Doppler Imaging showing reduced excursion of the lateral mitral annulus as a low Lateral e' and a high E/e' ratio (E wave of 114cm/s in a different patient). C. Parasternal long axis view of a severely dilated left ventricle which distorts the mitral valve architecture. D. Color Doppler of Moderate Functional mitral regurgitation in the same patient. E. Severely dilated IVC in the same patient. LV: left ventricle, LA: left atrium, IVC: Inferior Vena Cava.

Pre-Discharge Checklist			
Clinical Endpoints	Result	Medications	Dose/Reason Not Prescribed
JVP $\leq$ 8 cm H ₂ O		Diuretic Dosing	
Absence of Edema		Beta Blocker	
US: IVC < 2.1 cm and > 50% collapse with sniff ⁴⁷		ACEI/ARB/ARNI	
Decrease in Weight		Aldosterone Antagonist	
Total I/O balance		Aspirin/Anticoagulation	
30% decrease in NP		Hydralazine/Nitrates	
Renal Function trend		Statin	
Hematocrit trend		Digoxin/Ivabradine	
Education	Date	Follow-up	Date
Daily home weight		Primary Care Follow-up	
Diet/Fluid restrictions		Cardiology follow-up	
BP monitoring		Cardiac Rehab	
Smoking Cessation		Device	Present/Reason Not A Candidate
Medication Education		ICD	
Importance of Follow-up		Indication for CRT-D	

Figure 3.

Proposed Discharge checklist.[71] JVD: Jugular venous distention, IVC: Inferior Vena Cava, I/O: Intake to Output ratio, BNP: brain natriuretic peptide, BP: Blood pressure; ACEI: Angiotensin-converting-enzyme inhibitor, ARB: Aldosterone Receptor Blocker.

Table 1

Sensitivity and Specificity of clinical and laboratory markers of congestion. Adapted from Gheorghiade et al[17] and Martindale et al[6].

Signs and Symptoms	Sensitivity (%)	Specificity (%)
Dyspnea on Exertion	66	52
Orthopnea	52–66	47–70.5
Rales	24–75	68–84
Edema	46–52	73–75
JVD	37–70	79–87
S ₃ gallop	13–73	42–97
Laboratory Values		
BNP >100 ng/L[6, 33, 72]	93–95	53–76
NT-proBNP >300 ng/L[6, 34, 72]	90–99	38–68

JVD: Jugular venous distention, BNP: brain natriuretic peptide, NT pro-BNP: N-terminal proBNP.