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## **Congestive Heart Failure: How should we manage this in the ED?**

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### **I. Scope of the problem**

Heart failure is a worldwide problem and is responsible for a tremendous cost to the healthcare system.<sup>1</sup> The American Heart Association estimates that nearly 5 million individuals are living in the United States with congestive heart failure.<sup>2</sup> Approximately 550,000 new cases are diagnosed each year and acute heart failure (AHF) is the most common cause for hospital admission in patients greater than 65 years of age.<sup>3</sup> Overall, there are over 1,000,000 admissions to US hospitals for AHF each year, accounting for >6,000,000 hospital days and \$12 billion in costs (4). Approximately 80% of patients hospitalized for acute heart failure syndromes are admitted through the Emergency Department.<sup>4</sup> Of even greater concern is the poor prognosis of patients admitted with AHF, with >20% of patients being readmitted with heart failure (HF) and >20% dying during the first year after admission.<sup>4</sup> Couple the significant increase in the aging population and the dramatic decrease in EDs and hospital beds in the US from 1993 to 2003 (decreased by 425 and 198,000 respectively)<sup>4-6</sup>, one can expect more “boarding” of patients forcing emergency physicians to be comfortable with delivering both acute and ongoing heart failure care.<sup>5,7</sup>

### **II. Definitions: Exactly who are we talking about?**

A review of the basic pathophysiology of AHF will not be covered here, but it is important to highlight more recent classifications and terminology adopted by the major national and international societies regarding heart failure as they directly affect the management of patients presenting to the ED.<sup>7</sup> The term “acute heart failure [AHF] syndromes”

emerged from an international workgroup to establish uniform terminology and definitions in heart failure. The workgroup defined acute heart failure syndromes as the “gradual or rapid deterioration in heart failure signs and symptoms resulting in a need for urgent therapy”<sup>2</sup> and was incorporated in 2005 by the European Society of Cardiology.<sup>8</sup> The most recent ACC/AHA guidelines from 2005 define heart failure as a “complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.”<sup>9</sup> The American College of Emergency Physicians Clinical Policies Committee reviewed the current terminology and definitions and agreed to use the term “acute heart failure syndromes” in their updated guidelines in 2007.<sup>2</sup>

More recently, two separate categories of AHF syndromes have been adopted by the European Society of Cardiology in their guidelines on the diagnosis and treatment of AHF.<sup>8,10</sup> The first is termed *acute decompensated cardiac failure*. Patients have progressive, relatively slow (days to weeks) deterioration of chronic heart failure that is typically attributed to non-compliance with medications or dietary indiscretions or myocardial dysfunction.<sup>7</sup> These patients are typically fluid-overloaded, benefiting from diuretic therapy, fluid restriction, dietary education, pharmacotherapy adjustments or other interventions (such as revascularization or resynchronization).<sup>3</sup>

The second is termed *acute vascular failure* or dysfunction. In comparison, this is a rapidly progressive condition associated with high blood pressure and severe acute dyspnea, a common ED presentation in patients with acute heart failure syndromes.<sup>7</sup> These patients are most likely symptomatic due to a combination of increased vascular resistance and decreased cardiac contractility (even in the setting of a relatively good baseline ejection fraction).<sup>7</sup> Therefore, these patients have a largely vascular problem and not necessarily a fluid overload problem. Recent data from registries such as ADHERE suggests that this second category is actually the most common type of AHF in unselected populations.<sup>4</sup> Steep increases in afterload combined with poor systolic function result in an acute increase in left ventricular end-diastolic pressure and a decrease in cardiac output.<sup>7</sup> This may explain the presence of pulmonary congestion despite [only] modest fluid accumulation.<sup>7</sup>

The above distinctions are important as standard teaching in the US has typically been that acute heart failure is mainly due to fluid overload (*acute decompensated heart failure*). However, in many cases an acute increase in afterload is often the precipitant of AHF in many patients, leading to the rapid development of pulmonary congestion (*acute vascular failure*) without signs and symptoms of systemic congestion (edema). More than 50% of patients presenting with cardiogenic pulmonary edema can be *euvolemic* or *hypovolemic*.<sup>3</sup> Therefore, the key to treatment of AHF in many cases (especially patients with flash pulmonary edema) is to focus on afterload reduction and fluid redistribution rather than aggressive diuresis.

Circulatory failure can also occur in high output states, such as patients with acute infections, anemia or thyrotoxicosis.<sup>11</sup>

### **III. Diagnosis**

In the majority of cases the diagnosis of AHF is based on a patient's presenting signs and symptoms. Concerning symptoms include breathlessness, progressing fatigue, anorexia, confusion, weakness, and reported cold extremities. Following a thorough history and physical exam, confirmation and refinement of the diagnosis is made based on further testing including an electrocardiogram, chest radiograph, and laboratory studies (routine chemistries, blood gases, specific biomarkers).<sup>11</sup>

#### **Physical exam**

A thorough history and the assessment of mental status, peripheral perfusion, skin temperature and venous filling pressures are important in the initial evaluation in patients with suspected AHF syndromes. One study found that age >75, systolic BP  $\leq 140$  mm Hg and the inability to obey commands on initial presentation to the ED predicted early mortality (<7 days) in patients with acute cardiogenic pulmonary edema.<sup>12</sup> Identifying patients in cardiogenic shock, defined as evidence of tissue hypoperfusion induced by AHF, should be made early in the evaluation.<sup>11</sup> Typically, cardiogenic shock is characterized by reduced systolic blood pressure (SBP < 90 mmHg or a drop of mean arterial pressure > 30 mmHg from baseline) and absent or low urine output (< 0.5 mL/kg/h).<sup>11</sup>

The cardiovascular exam should focus on identifying murmurs or the presence of a third or fourth heart sound (S3, S4). An S3 is highly specific (99%) for congestive heart failure, and is almost never associated with other conditions.<sup>13</sup> Aortic stenosis or insufficiency is important as these patients are preload dependent and may have significant hypotension if vasodilator therapy is used. The presence of jugular venous distention (often seen with elevated right heart filling pressures), hepatojugular reflux and peripheral edema and tachycardia > 120 beats per minute are also important criteria for diagnosing CHF based on Framingham Studies.<sup>13</sup> On pulmonary exam the presence of increased work of breathing, bilateral rales or crackles and diminished breath sounds (suggestive of pulmonary effusion) usually indicates elevated left heart filling pressures.<sup>11</sup>

#### **Diagnostic studies**

Recommendations for specific testing are largely based on expert consensus opinion rather than well documented evidence.<sup>11</sup>

### **1. Electrocardiogram (ECG)**

An ECG is an essential test to perform early in the ED setting. The electrocardiogram is more useful for examining the cause or precipitant of heart failure rather than for diagnosing AHF syndromes. The presence of atrial fibrillation has a high positive likelihood ratio (3.8) for diagnosis of heart failure and new t-wave changes are also associated with the diagnosis of heart failure (+LR 3.0).<sup>15</sup>

### **2. Chest radiograph**

A chest X-ray should be performed early for all patients with suspected AHF to assess the degree of pulmonary congestion and to evaluate other pulmonary or cardiac conditions (cardiomegaly, effusion, or infiltrates).<sup>11</sup> While a 2 view upright posterior-anterior and lateral provides better visualization, clinicians may be limited to performing a portable or supine film (if intubated) in an acutely ill patient. Radiographic signs of congestion such as cephalization, interstitial edema, and alveolar edema are highly specific (96%, 98%, and 99%, respectively) for acute heart failure syndromes but have low sensitivity (41%, 27%, and 6%, respectively).<sup>17</sup> A recent study found that ED physicians are excellent at identifying CHF on X-ray when present but under-call it frequently (specificity 96%, sensitivity 59%).<sup>18</sup> However up to 18% of ED patients with acute heart failure syndromes will have no findings of congestion on chest radiographs (especially in patients with late-stage heart failure despite elevated wedge pressures)<sup>17</sup> reiterating the point that no single test can “rule in” or “rule out” AHFS.<sup>19</sup>

### **3. Bedside ED Echocardiography**

Additional testing may include bedside echocardiography to estimate an ejection fraction or to evaluate for possible wall motion abnormalities suggesting an acute coronary syndrome. Studies on the use of bedside ultrasound (US) in the ED setting have shown good correlation of wall motion and ejection fraction with definitive testing.<sup>20,21</sup> Bedside thoracic US for B-lines (suggest thickened interstitial or fluid-filled alveoli seen commonly in CHF patients) as markers of CHF alone or in combination with natriuretic peptide levels can assist with the diagnosis of CHF.<sup>22</sup> However, these more advanced echocardiography skills may be beyond the scope of many practicing ED physicians.

### **4. Laboratory testing**

#### **Arterial blood gas**

An arterial blood gas enables assessment of oxygenation (pO<sub>2</sub>), respiratory function (pCO<sub>2</sub>), and acid–base balance (pH) in patients with severe respiratory distress.<sup>11</sup> A venous blood gas to assess for hypercapnia and acidosis may be a reasonable alternative in critically ill patients as it may be obtained more quickly with IV placement (or drawn from pre-hospital

placed IV), rather than the more invasive, painful and often more difficult to obtain arterial blood gas. Findings of acidosis (due to poor tissue perfusion) or CO<sub>2</sub> retention are associated with a worse prognosis.<sup>11</sup> Non-invasive measurement with pulse oximetry can often replace arterial blood gas analysis but clinicians should remember that it is unreliable in very low output syndromes or vasoconstricted, shock states.<sup>11</sup>

## Chemistries

A low sodium, elevated blood urea-nitrogen (BUN) and creatinine, and anemia (Hemoglobin < 12mg/dL in men and <11gm/dL in women) are associated with adverse outcomes in patients with AHF.<sup>11,23</sup> Cardiac enzymes including a troponin level should be considered in patients with suspected acute coronary syndromes based on history and initial ECG findings.

## Natriuretic peptides

The myocardium produces natriuretic peptides, which have diuretic, natriuretic and vascular smooth muscle relaxing properties and are released in response to wall stretch, ventricular dilatation and/or increased filling pressures.<sup>24</sup> Over the past 10 years the measurement of B-type natriuretic peptides (BNP and NT-proBNP) has steadily increased in the ED and ICU setting. They have a reasonably high negative predictive value for excluding AHF.<sup>11</sup> One of the largest studies was the Breathing Not Properly study of 1586 patients presenting to the ED with shortness of breath, finding a BNP cut-off value of <100pg/mL having a sensitivity of 90% for differentiating heart failure from other etiologies of dyspnea.<sup>25,26</sup> Furthermore a value <50pg/mL had a negative predictive value of 96%. While no consensus exists internationally regarding the reference values for BNP and NT-proBNP, recent amended ACEP 2007 guidelines are listed here:<sup>2</sup>

**Level B recommendations.** The addition of a single BNP or NT-proBNP measurement can improve the diagnostic accuracy compared to standard clinical judgment alone in the diagnosis of acute heart failure syndrome among patients presenting to the ED with acute dyspnea.

- BNP <100 pg/mL or NT-proBNP <300 pg/mL acute heart failure syndrome unlikely (Approximate LR- =0.1)
- BNP >500 pg/mL or NT-proBNP >1,000 pg/mL acute heart failure syndrome likely (Approximate LR+=6)

BNP and NT-proBNP appear to be equally sensitive and specific for diagnosing AHF.<sup>27</sup>

However, while studies have shown a theoretical improvement to the accuracy of HF diagnosis in the ED with BNP testing, a recent large study found that availability of BNP levels did not significantly improve the accuracy of a *clinical* diagnosis of HF.<sup>28</sup> In other words, the ED

physician's clinical suspicion (based on medical history and physical examination) appears overall as accurate in diagnosing a patient with AHF as a single BNP level.<sup>29</sup> Amazing! BNP levels appear most helpful in patients with an intermediate or low pretest probability of AHF and the test results are either very high or very low.<sup>17</sup>

Clinicians should also be careful in interpreting natriuretic peptide levels as they can be affected by age, sex, body mass index and many underlying medical conditions.<sup>17</sup> Natriuretic peptide levels have an inverse relationship with body mass index, a finding that may be related to an increase in clearance receptors in adipocytes in obese patients ( $BMI > 30 \text{ kg/meter}^2$ ).<sup>30</sup> Future study is needed as no specific changes in cut-off parameters have been recommended by major medical specialties for BNP and NT-proBNP in obese patients. Patients with flash pulmonary edema may not have elevated levels because they are often evaluated before natriuretic peptides are released from the left ventricle.<sup>30</sup> Because the half-lives of BNP and NT-proBNP are relatively short (BNP= 23 minutes, NT-proBNP= 60-120 minutes) the time needed to reflect meaningful changes in hemodynamic status is approximately 2 hours for BNP and 12 hours for NT-proBNP.<sup>31</sup> Patients with acute mitral regurgitation<sup>32</sup> due to papillary muscle rupture<sup>33</sup> may also have lower than expected levels as the heart failure is located "up-stream" from the left ventricle.<sup>30</sup>

Conversely, many disease processes can cause significantly elevated BNP levels.<sup>34</sup> Levels can be elevated in patients with acute coronary syndromes, atrial fibrillation, hypoxemia and various hyperdynamic states, including sepsis, hyperthyroidism, and cirrhosis. They can also be elevated with right ventricular dysfunction as a result of pulmonary embolus, pulmonary hypertension, or severe lung disease (COPD).<sup>30</sup> Levels may also be elevated due to renal dysfunction and advanced age.<sup>11</sup> Clinicians should be aware that NT-proBNP is primarily cleared by the kidneys, and plasma concentrations are greatly elevated by renal failure.<sup>31</sup> Therefore, interpreting NT-proBNP levels in the setting of renal insufficiency or failure is difficult, and in many of the larger clinical trials, subjects with elevated creatinines were not included in data sets.<sup>31</sup> Women tend to have higher levels than their age-matched male counterparts.<sup>30</sup>

Elevated BNP and NT-proBNP on admission are important for risk stratification in patients with congestive heart failure.<sup>11</sup> Measurement of BNP or NT-proBNP may also assist the clinician in prompting further evaluation for other conditions when a low or normal BNP level is found.

## **Troponin**

An elevated troponin is seen in up to 40% of patients admitted for acute decompensated

heart failure present.<sup>14</sup> In addition to aiding in diagnosis of possible acute coronary syndrome as a precipitant of AHFS, an elevated cardiac troponin I level appears to be a predictor of 30-day and 1-year mortality.<sup>14</sup> In the ADHERE trial, a combination of a BNP above the median (> 840 pg/mL) with increased troponin was associated with twice the in-hospital mortality compared with patients with solely elevated BNP.<sup>35</sup>

## **5. Invasive monitoring**

The indications for arterial line catheter placement are the need for either continuous analysis of arterial blood pressure due to hemodynamic instability (i.e. hypotension or cardiogenic shock requiring inotropic support) or the need for frequent arterial blood samples (i.e. intubated patient).<sup>11</sup> Central venous lines (CVL) placements are useful for the delivery of fluids and drugs, and monitoring of the central venous pressure (CVP) and venous oxygen saturation (SVO<sub>2</sub>), which provides an estimate of the body oxygen consumption/delivery ratio but are not mandatory in all patients with AHFS syndromes.<sup>11</sup> The insertion of a pulmonary artery catheter (PAC) for the diagnosis of AHF is usually unnecessary in the acute ED setting, but may be useful in hemodynamically unstable patients who are not responding as expected to traditional treatments.<sup>11</sup>

## **IV. Treatment**

Treatment and diagnosis of AHFS often proceeds in parallel. The cornerstone of initial resuscitative efforts remains airway management, support of breathing, and circulatory support, especially in dramatic presentations of AHFS (e.g. flash pulmonary edema or cardiogenic shock).<sup>16</sup> In addition to symptom improvement, prevention of myocardial or renal injury, decreased coronary perfusion, increased heart rate, and/or further neurohormonal activation is critical, requiring close monitoring of heart rate, cardiac rhythm, and blood pressure.<sup>16</sup> Other life threatening conditions requiring timely intervention, such as ST-elevation MI, arrhythmias, or aortic vascular catastrophes (dissections) should be promptly identified and managed according to established guideline and protocols.<sup>16</sup>

In the published acute heart failure trials, many agents have been shown to improve hemodynamics but no agent has been shown conclusively to reduce mortality.<sup>16</sup> Potential limitations in these trials include the heterogeneous populations studied and the delay between hospital presentation (ED setting where a significant portion of AHF care is initiated) and therapeutic intervention of the study (study drug often started after admission from the ED or patients in ED excluded for various reasons from studies).<sup>16</sup>

## Ventilatory support

In patients not maintaining oxygen saturations >95% with oxygen supplementation (>90% in patient with COPD), additional ventilatory support will be required.<sup>11</sup> The main priority in patients presenting with AHF syndromes with acute respiratory failure is to achieve adequate oxygenation levels to prevent organ dysfunction and the onset of multiple organ failure.<sup>11</sup> Numerous randomized trials have evaluated the application of non-invasive ventilation (NIV) by continuous positive airway pressure (CPAP), Bi-PAP, or non-invasive pressure support ventilation (PSV) for the treatment of patients who fail to respond to standard medical treatment and require respiratory assistance for severe respiratory failure due to acute cardiogenic pulmonary edema (ACPE).<sup>11</sup> The addition of NIV to standard treatment has been shown to result in rapid improvements in gas exchange, lung mechanics, work of breathing, and in left ventricle afterload reduction.<sup>11</sup> Multiple studies have shown that PaO<sub>2</sub>, FiO<sub>2</sub>, pH, RR, HR, and SpO<sub>2</sub> improve with NIV.<sup>11</sup> A small number of studies have also observed that nPSV may be more effective than CPAP to unload respiratory muscles in ACPE, showing a more rapid improvement in gas exchange with nPSV in hypercapnic patients.<sup>36</sup> Three meta-analyses reported that early application of NIV in patients with acute cardiogenic pulmonary edema reduces both the need for intubation and short-term mortality.<sup>37-39</sup> However, in 3CPO, a large randomized control trial, NIV improved clinical parameters but not mortality.<sup>40</sup>

Based on available studies, ACEP recommends CPAP (Level B) or BiPAP (level C) in acute heart failure syndromes in the ED.<sup>2</sup> The lower recommendation for BiPAP is based on one study showing BiPAP having a trend toward a higher rate of myocardial infarction as defined by elevated cardiac markers.<sup>2</sup> The reasons for the potential excess of myocardial infarction with bilevel ventilation were not immediately apparent; patients' numbers were small (only 27 patients total) and there were many confounding factors.<sup>42,43</sup> More patients with chest pain were randomized to BiPAP than CPAP (10 vs. 4 respectively) and a larger number had a left bundle-branch block at the time of study entry, making it unclear as to whether the infarctions preceded or were a consequence of therapy.<sup>43</sup> Two patients in the BiPAP group also had increased creatine kinase MB fractions at the time of study entry, and a number of patients had creatine kinase concentrations that peaked within 12 hours of study enrollment, suggesting that their myocardial infarctions were already underway before enrollment into the BiPAP study group.<sup>41</sup> As far as an explanation for the reported increase, some authors have suggested that it could be a function of more rapid correction of PaCO<sub>2</sub> values with potential coronary vasoconstriction and asynchrony between patient and bilevel ventilator, which could induce adverse physiological changes.<sup>43</sup> The authors of the study also suggest that the significantly lower systemic BP in the bilevel positive airway pressure group seen early after the initiation of



therapy raises the possibility that a relative decrease in myocardial perfusion could have extended areas of incipient infarction.<sup>41</sup>

Subsequent studies comparing BiPAP with CPAP in patients presenting with pulmonary edema and acute respiratory failure of heterogeneous causes failed to demonstrate an increase in MI or mortality in patients receiving BiPAP.<sup>2</sup> Two additional studies have directly compared CPAP and BiPAP for patients with acute heart failure syndrome and neither modality was found to be superior to the other.<sup>42,43</sup>

The ESC recommends initiating NIV (CPAP) with a positive end-expiratory pressure (PEEP) of 5–7.5 cm H<sub>2</sub>O and titrated to clinical response up to 10cm H<sub>2</sub>O with FiO<sub>2</sub> delivery  $\geq 40\%$ . Duration will be based on clinical response or more specifically until a patient's dyspnea and oxygen saturation remain improved without NIV. Contraindications to NIV include patients who have an obvious immediate need of endotracheal intubation due to progressive life-threatening hypoxia or those who cannot cooperate (unconscious patients, severe cognitive impairment, or overwhelming anxiety).<sup>11</sup> Potential complications of NIV include worsening of severe right ventricular failure, anxiety or claustrophobia, pneumothorax or aspiration.<sup>11</sup> Overall the success of noninvasive ventilator support is largely based on the skills of the medical team, physician experience and time to application in treating patients with acute respiratory failure. Objective measures to determine the need for mechanical ventilation can include persistent hypoxia (SaO<sub>2</sub> < 90) despite supplemental oxygen, hypercarbia (PaCO<sub>2</sub> > 55 mm Hg), and acidosis (pH < 7.25).<sup>44,45</sup>

### **Morphine Sulfate**

Opioids have been used for the management of congestive cardiac failure and acute pulmonary edema for centuries, but there is little definitive evidence that they improve morbidity or mortality.<sup>46</sup> On the contrary, a large study published in 1999 stated otherwise, finding opioid use was associated with higher intubation and intensive care admissions rates.<sup>47</sup> Therefore, the routine use of opioids in the management of AHFS appears to be unjustified and is no longer recommended.<sup>7</sup> The use of morphine in the management of AHFS was not addressed in the ACEP 2007 guidelines.

### **Bronchodilators**

A large study of more than 10,000 patients from the Acute Decompensated Heart Failure National Registry Emergency Module evaluated the effects of bronchodilators during acute treatment (prehospital setting or in the ED). The use of bronchodilators in patients who did not have a history of COPD was associated with a greater need for “aggressive interventions,” including mechanical ventilation and the need for IV vasodilators.<sup>48</sup> It is unclear if the bronchodilator use was causing adverse outcomes or was perhaps a marker of sicker

patients. A recent review of the literature on the use of bronchodilators patients with heart failure found no increase in clinically significant dysrhythmias or cardiac ischemia but did not report specifically on clinical outcomes including mortality, length of hospital stay or self-reported symptom scores.<sup>49</sup> Further research is needed to answer these questions.

## **Vasodilators**

Vasodilators are recommended early in the treatment of AHFS. Improvement in pulmonary congestion occurs due to decreased left- and right-heart filling pressures, lowered systemic vascular resistance, resulting in improved dyspnea.<sup>11</sup> Caution is recommended in patients with a systolic BP between 90-110mm Hg as hypotension may develop after initiation of therapy.<sup>11</sup> A second category of patients who may develop significant hypotension from vasodilator therapy are patients with aortic stenosis. Multiple studies have shown an association between the use of high dose nitrates and improved clinical outcomes in acute decompensated heart failure,<sup>50-54</sup> including lower rates of endotracheal intubation, need for BiPAP, and ICU admissions with relatively few adverse events.<sup>55</sup> Alternatives to intravenous vasodilators include nitroglycerine spray of 400 mcg (2 puffs) every 5–10 min, buccal nitrate (isosorbide dinitrate 1 or 3 mg), or 0.25–0.5 mg sublingual nitroglycerine.<sup>11</sup> Topical nitrates (nitropaste) may be less effective than oral and intravenous routes due to patient diaphoresis and the nature of transdermal absorption.<sup>7</sup>

Nitrates are not recommended in hypotensive patients or patients presently taking sildenafil or other similar medications for erectile dysfunction due to concerns of a precipitous drop in blood pressure.<sup>7</sup> Furthermore, nitrates are generally not recommended in patients with aortic stenosis or pulmonary hypertension due to their dependence on preload to maintain adequate perfusion.<sup>7</sup>

## **Angiotensin converting enzyme inhibitors (ACEI)**

While there have been no large, randomized controlled trials of ACEI use in acute pulmonary edema, limited data suggest short-term benefit. A series of small studies has demonstrated that early use of ACE inhibitors in the sublingual (captopril) or intravenous (captopril, enalapril) formulation are associated with rapid improvements in preload, afterload, cardiac output, and dyspnea, and perhaps also a significant decrease in need for ICU use and intubation.<sup>47,57-63</sup> Improvements of both hemodynamics and subjective dyspnea can occur within 6 to 12 minutes.<sup>7</sup> There is no consensus on the ideal timing for initiation of ACEI therapy in AHF, but registry data suggests that early administration may decrease hospital length of stay.<sup>11,64</sup>

In patients with AHFS and pulmonary edema, along with intravenous nitroglycerin, ACEI can be used in patients with blood pressure >140/90mmHg.<sup>65</sup> The ACEP Guidelines for acute heart failure syndromes give a level C recommendation for the use of ACE inhibitors, stating

they may be used for vasodilation in the initial management of acute heart failure syndromes, although patients must be monitored for first dose hypotension.<sup>2</sup> ACE inhibitors can also be useful for the hemodialysis patient who presents in pulmonary edema as a bridge to hemodialysis in the fluid overloaded patient.<sup>7</sup>

Patients with heart failure and progressing dyspnea and fluid overload ankle or typically benefit from diuretic and ACE inhibitors. (New York Heart association Class III (moderate) or IV(severe)).<sup>13</sup> Contraindications for using ACEI include: history of angioedema, bilateral renal artery stenosis, serum potassium concentration >5.0 mmol/L, serum creatinine >2.5 mg/dL, or a history of severe aortic stenosis.<sup>11</sup>

### **Nesiritide**

The Prospective Randomized Outcomes study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Netrekor (PROACTION) trial was an ED-based study involving nesiritide versus placebo for acutely decompensated congestive heart failure.<sup>66,67</sup> While the admission rate for acutely decompensated congestive heart failure was lower in the nesiritide group nonstatistically higher number of deaths in the nesiritide-treated cohort were seen. A subsequent study showed that administration of nesiritide for acutely decompensated congestive heart failure was no better than standard therapy alone for the composite endpoint of return to the ED or hospitalization at 30 days.<sup>68</sup> Based on the limited available ED-based evidence, the routine use of nesiritide for the management of acute decompensated congestive heart failure in the ED is not recommended.<sup>2,69</sup>

### **Diuretics**

Patients who have decompensated CHF (especially cardiogenic pulmonary edema) have decreased renal blood flow due to markedly increased afterload, resulting in delays in the diuretic and preload-reducing effect for between 90 to 120 minutes.<sup>70</sup> In patients with significantly elevated blood pressures, proportional greater use of nitrate therapy with lower dose diuretic therapy as opposed to low-dose nitrates and high-dose diuretics has been suggested to improve outcomes.<sup>71</sup> Exact dosing and goals of loop diuretics remain largely empiric as rigorous studies are lacking in the management of AHFS.<sup>16</sup> The recommended initial dose is a bolus of furosemide 20-40mg intravenously, with a total dose no greater than 100mg in the first 6 hours.<sup>16</sup> Urine output should be monitored frequently to assess initial response to diuretic therapy<sup>16</sup> (excludes ESRD patients who are anuric baseline).

Although hypertensive patients who are aggressively diuresed may appear to initially improve, they are more likely to develop subsequent dehydration, renal insufficiency, increased hospital lengths of stay, and higher morbidity rates.<sup>72</sup> Clinicians should be careful with aggressive diuresis in patients with abrupt onset of acute pulmonary edema who do not have

underlying chronic HF, as they may in fact have low plasma volumes at ED presentation.<sup>73</sup> For example, certain patients may not present with signs of right-sided heart failure (e.g., jugular venous distention, peripheral edema, and hepatomegaly) and may have baseline volume depletion due to pressure diuresis.<sup>74</sup> Further diuresis may actually exacerbate the underlying pressure natriuresis and increase stimulation of the renin-angiotensin axis in these “dry failure” patients.<sup>74</sup>

Approximately 35% of patients will present with mild, subacute worsening of their symptoms during several days to weeks, primarily a result of gradual total body fluid overload, as opposed to respiratory distress from acute hypertension and pulmonary edema.<sup>5</sup> These patients benefit from more aggressive diuresis, with a therapeutic goal of relieving congestion and reducing total body fluid and peripheral edema. Patients with blood pressure in the low to normal range (90 to 120 mm Hg) may “run out” of blood pressure after initial diuresis, and should be monitored closely after initial diuretic administration.<sup>17</sup>

## Inotropes

In the ED setting, inotropic agents are typically indicated in patients with low output states or in the presence of signs of hypoperfusion (cold, clammy skin, in patients who are vasoconstricted with acidosis, renal impairment, liver dysfunction, or impaired mentation). Inotropes may also be considered if congestion persists despite the use of vasodilators and/or diuretics to improve presenting symptoms. Although inotropes may acutely improve the hemodynamic and clinical status of patients with AHF, they can cause further myocardial injury and arrhythmias, leading to increased short- and long-term mortality.<sup>11</sup> In patients with cardiogenic shock, inotropic agents may stabilize patients at risk of progressive hemodynamic collapse or serve as a life-sustaining bridge to more definitive therapy such as mechanical circulatory support, ventricular assist devices, or cardiac transplantation.

Dobutamine, acts by stimulation of  $\beta_1$ -receptors to produce dose-dependent positive inotropic and chronotropic effects, initiated with a 2–3 mcg/kg/min infusion rate without a loading dose.<sup>11</sup> Dopamine also stimulates  $\beta$ -adrenergic receptors both directly and indirectly with a consequent increase in myocardial contractility and cardiac output. Infusion of low doses of dopamine (<2–3 mcg/kg/min) has been shown to have limited effects on diuresis.<sup>11</sup> Higher doses of dopamine may be used to maintain systolic blood pressure, but with an increasing risk of tachycardia, arrhythmia, and  $\alpha$ -adrenergic stimulation with vasoconstriction.<sup>11</sup> Both dopamine and dobutamine should be used with caution in patients with a heart rate >100 beat-per-minute as  $\alpha$  stimulation at higher doses may lead to vasoconstriction and elevated

systemic vascular resistance.<sup>11</sup> Low-dose dopamine may be combined with higher doses of dobutamine to achieve improved perfusion and cardiac output.

### **Phosphodiesterase Inhibitors**

Milrinone and enoximone are the two type III phosphodiesterase inhibitors (PDEIs) that inhibit the breakdown of cyclic AMP and have both inotropic and peripheral vasodilating effects.<sup>11</sup> Benefits include an increase in cardiac output and stroke volume, as well as a concomitant decline in pulmonary artery pressure, pulmonary wedge pressure, and systemic and pulmonary vascular resistance.<sup>11</sup> Caution should be used with the administration of PDEIs in patients with CAD, as it may increase medium-term mortality.<sup>75</sup>

### **Calcium Sensitizer**

Levosimendan is a calcium sensitizer that improves cardiac contractility by binding to troponin-C in cardiomyocytes and promotes significant vasodilatation mediated through ATP-sensitive potassium channels and mild PDEI action.<sup>11</sup> It increases cardiac output and stroke volume and reduces pulmonary wedge pressure, systemic vascular resistance, and pulmonary vascular resistance. More importantly, the inotropic effect is independent of  $\beta$ -adrenergic stimulation, it represents an alternative for patients on  $\beta$ -blocker therapy.<sup>11</sup> Levosimendan infusion can begin with a bolus dose (3–12 mg/kg) over 10 minutes followed by a continuous infusion (0.05–0.2 mcg/kg/min for 24 h).<sup>11</sup> In patients with SBP <100 mmHg, the infusion should be started without a bolus dose to avoid hypotension.<sup>11</sup>

### **Vasopressors**

Vasopressors are not recommended as first-line agents. They are only indicated in patients in cardiogenic shock as a rescue agent after the combination of an inotropic agent and possible fluid challenge fails to restore SBP >90 mmHg<sup>11</sup> and until other therapies to improve cardiac function can be instituted.<sup>32</sup> These therapies may include angioplasty, intra-aortic balloon pumping, or cardiac surgery.<sup>73</sup> Norepinephrine is probably the pressor of choice for the following reasons: it improves coronary perfusion in the presence of severe hypotension; it has the least overall increase in heart rate and contractility that could further increase myocardial oxygen demands; and it is particularly useful in patients with low blood pressure and “inappropriate” vasodilation (low blood pressure in the presence of normal or high cardiac output).<sup>32</sup> Caution is advised with concomitant dopamine use that already exerts a vasopressor effect.<sup>11</sup> Epinephrine is not recommended in cardiogenic shock and should be restricted to use as rescue therapy in cardiac arrest.<sup>32</sup>

## Disposition

Critically-ill patients with AHFS are best managed in the ICU with invasive monitoring to closely track their hemodynamic status and allow precise titration of the medications. These would include patients on any drips, intubated patients or those requiring continued NIV, as well as patients with associated acute coronary syndromes.

Evidence-based data to guide and facilitate risk-stratification and ultimate disposition of other AHFS patients from the ED setting is lacking.<sup>16</sup> A large review of studies in JAMA isolated systolic blood pressure level as a broadly applicable method to determine in-hospital mortality risk.<sup>76</sup>

In-hospital mortality rates by admission systolic blood pressure deciles (n= 48 567).<sup>76</sup> *Permission Pending*

Variables that have been shown in multiple studies to predict high risk of subsequent morbidity and mortality include the following: low serum sodium level, ischemic ECG changes, significant hypotension at presentation, poor diuresis in the hypervolemic patient, abnormal renal function, poor health care behavior (poor access to health care, dietary and medication non-compliance) and possibly increased natriuretic peptide values.<sup>17</sup> Multiple scoring systems have been proposed for the diagnosis of heart failure using components of the history and physical examination, but these are based on the outpatient and not the ED setting.<sup>17</sup> Hsieh and colleagues recently completed a validation of the acute heart failure index clinical prediction rule that identifies a group of patients with heart failure at low risk for inpatient deaths and serious complications (< 2% risk).<sup>77</sup> Although the high-risk patient has been characterized in studies, the absence of high-risk criteria does not necessarily equate to a low-risk patient overall.<sup>17,78-81</sup> Current NHLBI funded studies are exploring risk stratification from the ED, but recent initial studies support stratification of patients to the observation unit setting.<sup>82-84</sup>

## Future therapies

Multiple novel therapeutic agents are under development for short term management (hours to days) to target signs and symptoms, improve hemodynamic stabilization, as well as potentially protect or prevent organ injury.<sup>16</sup> While a majority of these medications are still being evaluated through basic science research or Phase I trials, it is worth mentioning a medication called *Relaxin*, which is currently under investigation for its systemic and renal vasodilatory actions.<sup>16</sup> A Phase II trial has demonstrated improvement in dyspnea with a single dose in patients with AHFS and elevated blood pressures, with a Phase III trial currently in progress.<sup>85</sup>

## Summary

Acute decompensated heart failure treatment has a renewed focus on the use of aggressive use of nitrates and optimization of airway support including the use of NIV, while the use of high dose furosemide and morphine has become de-emphasized.<sup>70</sup> Diuretics seem to be most beneficial in patients who have substantial volume overload but often a normal SBP.<sup>86</sup> Vasodilator therapy is recommended as first-line therapy in patients with acute pulmonary edema associated with an elevated SBP.<sup>86</sup> The use of ACEI in acute management of heart failure is still being defined but available data suggests possible benefits in the ED setting and ACEI are being utilized and recommended by numerous authors. Patients in cardiogenic shock need emergent enhancement of cardiac contractility and inotropes are effective in restoring hemodynamic stability.<sup>86</sup> However, the use of inotropes may lead to increased short- and long-term mortality. Successful treatment of AHFS has been limited because no agent has been shown to reduce post-discharge mortality or readmission rates, and patients frequently remain symptomatic after treatment.<sup>86</sup> Further research may give us the answers as to which of the “standard”, controversial and future therapies are the best for ED patients with AHF syndromes.

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