Clinical and Research Considerations for Patients with Hypertensive Acute Heart Failure

A Consensus Statement form the Society of Academic Emergency Medicine and the Heart Failure Society of America Acute Heart Failure Working Group

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This is the author's manuscript of the article published in final edited form as:

Collins, S. P., Levy, P. D., Martindale, J. L., Dunlap, M. E., Storrow, A. B., Pang, P. S., … Butler, J. (2016). Clinical and Research Considerations for Patients With Hypertensive Acute Heart Failure: A Consensus Statement from the Society of Academic Emergency Medicine and the Heart Failure Society of America Acute Heart Failure Working Group. Journal of Cardiac Failure, 22(8), 618–627. https://doi.org/10.1016/j.cardfail.2016.04.015

ABSTRACT

Management approaches in emergency department (ED) patients with acute heart failure (AHF) have largely focused on intravenous diuretics. Yet, the primary pathophysiological derangement underlying AHF in many patients is not volume overload. Patients with hypertensive AHF (H-AHF) represent a clinical phenotype with distinct pathophysiologic mechanisms that lead to elevated ventricular filling pressures. To optimize treatment response and minimize adverse events in this subgroup of patients, clinical management likely needs to be tailored to a conceptual model of disease that is based on these mechanisms. This consensus paper reviews the relevant pathophysiology, clinical characteristics, approach to therapy, and considerations for clinical trials in ED patients with H-AHF.

PATHOPHYSIOLOGY OF HYPERTENSION IN ACUTE HEART FAILURE

Hypertensive AHF (H-AHF) is defined as pulmonary congestion in the setting of a systolic blood pressure over 160 mmHg.[1] Many patients with H-AHF have a history of poorly controlled hypertension.[2] The consequences of longstanding hypertension include changes to both the vasculature as well as the ventricle, resulting in increased stiffness and reduced compliance across the cardiovascular system. [3] Such stiffening increases systolic load on the left ventricular myocardium, triggering intra- and extra-cellular adaptations that tend to normalize systolic and diastolic sarcomere stress.[1] Many of these changes occur at the expense of left ventricular compliance and ultimately lead to clinically significant diastolic dysfunction. [4] [5] As the functional ventricular-vascular relationship becomes uncoupled, the left ventricle has insufficient cardiac reserve to compensate for the increases in afterload and preload that accompany hypertensive episodes, exertion and muscle contraction. [6] As a result, the poorly compliant cardiovascular system with chronic hypertension responds with larger changes in left ventricular filling pressure for a given change in preload or afterload.[7] Thus, it is important that therapy for H-AHF includes interventions to both improve vascular compliance and reduce intravascular filling pressure.

VASCULAR DYSFUNCTION AND ITS ROLE IN ACUTE HEART FAILURE

Normal cardiovascular function requires close integration between the heart and vasculature to provide adequate distribution to the vital organs and periphery.[8] A compliant aorta acts as a capacitor, reducing the peak pressure generated during ventricular systole and promoting continuous forward flow throughout the cardiac cycle. Central aortic pressure is further augmented during diastole by the reflected pressure wave generated downstream at the junction of the medium and small resistance arterioles. These reflected waves effectively represent the recoil of arteriolar expansion resulting from the force of contraction during systole. The net effect is a dynamic process of ventricular-arteriolar coupling that serves as a major determinant of cardiac output, providing a mechanism for adaptive changes in response to metabolic needs.[8]

In patients with chronic hypertension the aorta and large arteries stiffen, enhancing the amplitude and velocity of the reflected pulse wave generated by resistance arterioles.[9] Arterioles also adapt to chronic increases in arterial pressure associated with hypertension through smooth muscle hypertrophy; a process that normalizes end-arteriolar pressure at the expense of a further increase in large artery pressure and increased pulse wave velocity. The reflected wave, which normally reaches the central aorta after aortic valve closure, can increase

velocity enough to return to the proximal aorta in late systole. This results in increased load for ventricular contraction and may trigger early aortic valve closure. An immediate consequence of shortened left ventricular systole due to premature aortic valve closure is increased diastolic volume and pressure, resulting in increased pulmonary venous pressures, predisposing the patient to pulmonary congestion.

Hypertension contributes to vascular stiffness and increases left ventricular afterload. Further increases in vasoconstriction may precipitate H-AHF. Increases in sympathetic tone leading to vasoconstriction can be seen in instances such as: 1) physical exertion (via central command and the muscle-metabolic reflex) [10]; 2) hypoxia associated with acute respiratory infection; 3) chronic obstructive pulmonary disease; 4) obstructive sleep apnea; 5) pulmonary hypertension; 6) psychosocial stress/anxiety; 7) substance abuse (e.g. cocaine); or 8) abrupt cessation of antihypertensive medication.

BLOOD PRESSURE AND ITS RELATIONSHIP TO ACUTE HEART FAILURE

Large registries have shown that heart failure patients are most commonly hypertensive upon presentation to the ED. [11, 12] (**Table 1**). Moreover, the initial systolic blood pressure is a strong predictor of outcomes, with an association between higher presenting blood pressures and lower in-hospital mortality, 30-day myocardial infarction, death, or rehospitalization, as well as a greater likelihood of discharge within 24 hours.[13, 14] These associations are likely corresponding anatomic implications and contractile reserve, as higher systolic blood pressure [15] is more often linked to heart failure with preserved ejection fraction, with the likelihood of an ejection fraction >40% increasing 3% for every 1 mmHg presenting systolic blood pressure >120 mmHg (**Table 2**).

However, patients presenting with AHF can manifest a wide range of blood pressures. While there is a clear association between presenting blood pressure and outcomes, there is no direct relationship between blood pressure and ejection fraction, which explains why patients with AHF across the spectrum of underlying cardiac function can appear similar clinically. Ultimately, blood pressure summarizes cardiac contractile force relative to the vascular resistance it encounters.[16, 17] On the ventricular side, ejection capability is determined by myocardial function, while on the vascular side, resistance to flow reflects arterial health, the degree of vasoconstriction resulting from neurohormonal stimulation, and volume status.

Blood pressure largely determines organ perfusion. Maintenance of blood pressure is tightly regulated by baroreceptors, primarily in the aorta and carotid arteries, though renal mechanisms are also involved. Changes in cardiac output and systemic vascular resistance are

triggered by sympathetic nervous system and neurohormonal activation in response to baroreceptor mediated detection of alterations in vascular pressure. Thus, when confronted with increased arterial resistance, a heart with normal contractile reserve is able to maintain cardiac output with a net increase in systolic blood pressure.[18, 19] However, in the setting of chronic hypertension and heart failure, baroreceptor responses shift to be more tolerant to greater tonic pressure and expected responses to acute perturbations may be altered. [20-22] This contributes to a ventricular-vascular uncoupling, where acute changes in blood pressure associated with excess venous return or vasoconstriction are not met with the same cardiac contractile response. As a result, a poorly functioning myocardium is unable to maintain cardiac output in response to elevated systemic vascular resistance, making elevated blood pressure a *de facto* impediment to forward flow.

INTRAVASCULAR VOLUME AND ITS ROLE IN ACUTE HEART FAILURE

Elevated cardiac filling pressures are a hallmark of patients presenting the AHF. While total body sodium and water retention has traditionally been implicated as the main driver for elevated filling pressures, recent studies have shown that many patients do not gain weight prior to AHF onset.[23] [24] This has led investigators to suggest that redistribution rather than net volume gain is an important mechanism underlying AHF, likely driven by perturbations of the autonomic nervous system.[25] This finding is supported by studies showing changes in heart rate variability occurring weeks prior to presentation for AHF, a time during which cardiac filling pressures begin to rise, in the absence of a change in weight, and prior to the development of symptoms. [26] Thus, while symptoms drive most patients with HF to seek treatment, there is at least a moderate degree of discordance between symptoms, cardiac filling pressures, and intravascular volume.

Signals activating vasoconstriction induce acute and subacute increases in intravascular volume and contribute to the pulmonary congestion of H-AHF. Neurohormonal factors associated with chronic heart failure activate renal sodium and water retention leading to increase in intra- and extra-vascular volume. This may be accompanied by abrupt redistribution of blood volume from venoconstriction, especially in the splanchnic vascular bed, mobilization of fluid into the central and pulmonary circulation, and a dramatic rise in intravascular volume from an acute surge in sympathetic tone. Such increases in filling volume also trigger the Frank-Starling mechanism in the right ventricle (RV), which combines a catecholamine mediated increase in RV contractile force to drive up pulmonary artery and capillary wedge pressure. [27]

While abnormal volume distribution is responsible for many of the cardinal signs and symptoms of AHF, the history and physical exam findings of dyspnea, elevated jugular venous pulse, S3 gallop, hepato-jugular reflux and peripheral edema have low sensitivity for detecting volume overload.[28] Direct measurement of blood volume using a radionucleotide-dilution technique demonstrated a wide range of fluid distribution patterns in subjects with AHF and low ejection fraction,[29] with most, though not all, showing elevated total body volume. With a net diuresis of 8.4±5.2 liters, the majority of fluid loss was from the interstitial compartment, accounting for 85±15% of the total fluid reduction, with only a slight decrease in intravascular volume despite patients being clinically judged to be euvolemic. Therefore, trans-capillary mobilization of interstitial fluid is responsible for the weight reduction during treatment for AHF, with little impact on intravascular volume

Zelis et al explored this link between fluid status, hypertension and heart failure in a canine model where the arterial sodium and water content were pathologically elevated over control animals.[30] The elevation of tissue sodium and water content, specifically vascular tissue, was found to be the likely mechanism for increased arteriolar stiffness and thus decrease capacitance in heart failure. This was then studied in a human model using mineralocorticoid-induced sodium and water retention [31]. These findings laid the groundwork for the theory that decreased arteriolar capacitance in AHF is driven by elevated tissue sodium and water and may serve as a therapeutic target. Studies suggest residual intravascular hypervolemia portends a poor prognosis. In 43 clinically compensated chronic HF patients, 65% were found to have expansion of the intravascular space using the labelling technique.[32] Increased total body volume was associated with lower systolic blood pressure, increased pulmonary capillary wedge pressure and increased risk of death or transplantation at one year. This suggests a diuresis endpoint, such as subcutaneous edema, is misleading and not representative of intravascular congestion.

OTHER CONSIDERATIONS

Age: HF is predominantly a condition of the older population in developed countries where the prevalence increases markedly with age, rising sharply at age 75.[33] Elderly patients, particularly women are more likely than younger adults to develop heart failure with preserved ejection fraction, elevated systemic vascular resistance, and impaired ventricular-arteriolar coupling.[34] Pulmonary edema in the setting of severe systolic hypertension is a common presentation of AHF in patients with advanced age. Evidence supporting treatment options

targeted for elderly patients is limited by their exclusion from and underrepresentation in randomized trials in the acute care setting.

Renal Function: Chronic kidney disease is common and associated with persistent congestion during AHF, and portends worse prognosis. [35] Approximately 30% of patients with heart failure have moderate to severe renal impairment.[36] Maladaptive mechanisms that contribute to progressive renal disease are also important therapeutic targets in the management of H-AHF. In chronic kidney disease, activation of the renin-angiotensin-aldosterone system leads to a compensatory increase in filtration fraction but at the expense of intraglomerular hypertension, hypertrophy and sclerosis of remaining nephrons. Detrimental effects of renin-angiotensin-aldosterone system activation extend to the myocardium and the vasculature, contributing to the pathophysiology in both chronic HF and H-AHF. ACE-inhibitors or angiotensin receptor blockers are widely recommended for patients with renal insufficiency and AHF unless renal dysfunction is severe [37]. However, patients with heart failure with reduced ejection fraction and severe renal insufficiency (creatinine clearance <30 mL/min) who were treated in-hospital with a renin-angiotensin-aldosterone system antagonist appear to have been better 1-year survival, [38] suggesting that such an approach should not be absolute. Despite this, ACE-inhibitors and angiotensin receptor blockers are administered less frequently during heart failure hospitalizations in patients with severe kidney dysfunction, [39, 40] and more data are needed if current recommendations and clinical practice are to be altered. Mineralocorticoid receptor antagonists have been shown in subgroup analyses to confer mortality benefit in patients with renal dysfunction and moderate to severe heart failure.[41] Mineralocorticoid receptor antagonists are recommended in patients with reduced ejection fraction and a creatinine <2.5 mg/dL[37, 42]. Further studies are required to clarify the benefit these medications might confer early in the course of AHF management.

Worsening renal function during AHF is of particular concern in those with baseline renal insufficiency. Diuretics and vasodilators are commonly used to achieve pulmonary decongestion, but may be associated with the risk of increasing renal dysfunction. Higher doses of diuretics have been associated with worsening renal function in patients with AHF, [43] and activation of the renin-angiotensin-aldosterone system has been suggested as a possible underlying mechanism. This may be of greater importance in patients with H-AHF, where volume redistribution may be more prominent than volume overload. While higher levels of diuretics may be required to achieve decongestion in patients with renal dysfunction, blood pressure control is also important. Improving symptoms and avoiding hypovolemia is crucial in

this cohort. Patients with AHF and comorbid renal disease should be monitored for large and persistent increases in serum creatinine during and after inpatient diuresis.

TREATMENT

Expert opinion, supplemented by small cohort and randomized studies, suggests initial therapy might best be informed by clinical parameters rather than a typical diuretic-only approach.[44-46] While there is no randomized trial evidence evaluating initial treatment strategies for patients with AHF based on hemodynamics, systolic blood pressure plays a central role in AHF as a predictor of morbidity and mortality.[47] Accordingly, we suggest initial treatment may be most effective if it is based on presenting systolic blood pressure.[44, 46, 48-52]

Stabilization with noninvasive positive pressure ventilation (NIPPV) is useful in patients with H-AHF and significant work of breathing. Meta analyses suggest it decreases the need for intubation in both ED and hospitalized patients with AHF. [53] [54] A randomized trial of NIPPV in the prehospital settting suggests it may not impact mortality or the need for intubation, but it does improve work of breathing. [55] Whether it has additive value to aggressive use of intravenous vasodilators in H-AHF patients is unclear. [56]

The OPTIMIZE-HF investigators reported ≈50% of patients with AHF had a systolic blood pressure of >140 mmHg at presentation; in-hospital mortality was lowest among those with the highest value (between 189-300 mmHg).[47] Intravenous diuretics are the cornerstones of AHF therapy.[57] However, the failing heart is sensitive to afterload and some patients may develop pulmonary edema with a systolic blood pressure as low as 150 mmHg. Prompt recognition and afterload reduction with vasodilators may avoid the need for intubation.[58] Until recently, evidence regarding the safety and efficacy of vasodilator therapy in AHF was limited. [59, 60] However, data from contemporary studies suggests specific phenotypes of AHF patients, such as those with H-AHF benefit from intravenous vasodilators.[50, 51, 61]

Nitrovasodilators: Nitroglycerin is a short-acting, rapid-onset, venous and arterial dilator. It decreases mean arterial pressure by preload reduction, and at higher doses, afterload as well. Nitroglycerin has coronary vasodilatory effects, decreasing ischemia and improving cardiac function. The choice between intravenous, sublingual, or transdermal routes is often based on symptoms. Sublingual is easily administered, rapidly bioavailable, and can be given as needed. There is no consensus, but often a 10-20% reduction in blood pressure, leading to reduction in filling pressures, is sufficient to improve symptoms of dyspnea. One initial approach is repeated administration of a 0.4 milligram sublingual nitroglycerin tablet every 3-5 minutes until symptom

relief, replacement with intravenous nitroglycerin, or a blood pressure target is reached. Transdermal nitroglycerin has been demonstrated to reduce filling pressure in patients with HF who had pulmonary artery catheters in place. [62] [63] The available data suggest the transdermal ointment has clinical effect within one hour of application, and should be reapplied every 6 hours. A typical starting dose is 1-2 mg every 6 hours. When using the intravenous formulation, a starting dose of 0.5 to 0.7 mcg/kg/min is common and titrated upwards every few minutes, up to 200-400 mcg/min based on blood pressure (avoiding large drops) and symptoms (**Tables 3 and 4**). High doses (2 mg by repeated intravenous bolus) may be beneficial acutely and adverse events are uncommon. [51] Transdermal nitroglycerin 0.5-2 inches on the chest wall is sometimes used, but is hampered by slow onset, should be reserved for after initial therapy has improved conditions, or in patients with minor symptoms. Hypotension may occur though it is often transient with the intravenous and sublingual forms, and usually resolves after cessation of the nitroglycerin. If hypotension is persistent, consideration should be given to volume depletion, right ventricular infarct, or an etiology other than AHF causing the current symptoms, and a saline fluid bolus may be administered. Headache is frequent and usually responds to acetaminophen. Methemoglobinemia is theoretically possible, but typically not a concern unless high-doses are used for extended intervals. Despite common use and targeting appropriate pathophysiologic derangements, nitroglycerin has little published efficacy evidence beyond its effects on symptom resolution.[64] [65]

Nitroprusside is a potent arterial and venous vasodilator that produces a decrease in blood pressure and left ventricular filling pressure leading to increases in cardiac output. Nitroprusside is generally considered to be more effective than nitroglycerin, despite a small study comparing LV filling that suggested their hemodynamic response profiles are similar. [66] The initial dose is 0.3 mcg/kg/min, titrated upward every five to ten minutes based on blood pressure and clinical response (maximum 10 mcg/kg/min). The major complication is hypotension. It is also rarely associated with cyanide toxicity, typically with high doses, prolonged (longer than three days) use, and hepatic or renal impairment. Such toxicity can be prevented by concurrent administration of sodium thiosulfate. Though uncommonly used in the acute setting, a historical goal of nitroprusside therapy is rapid reduction of systemic vascular resistance and wedge pressure in an effort to prevent the need for endotracheal intubation. Logistical considerations related to the need for close monitoring, often with an arterial line and/or in the intensive care unit setting and keeping the infusion protected from light make it less convenient to use.

Loop Diuretics: With vasodilator therapy and blood pressure control, patients may require diuretics (**Table 4**) based on continued symptoms or evidence of excess fluid accumulation. As discussed previously, not all patients with H-AHF are volume overloaded, therefore routine diuretic administration may not be necessary when treating this phenotypic variant. Moreover, diuretics administered alone without vasodilators for H-AHF may increase mortality [50] and worsen renal function. Successful management of blood pressure and filling pressure often results in marked improvement in respiratory status before any diuresis. Furosemide has been used most commonly, but alternatives including bumetanide (1 mg equivalent to 40 mg furosemide) or torsemide (20 mg equivalent to 40 mg furosemide) can also be used. All trigger rapid diuresis after an intravenous dose, often within 10 to 15 minutes.

Natriuretic Peptides: Smaller studies have shown a benefit of nesiritide (exogenous b-type natriuretic peptide) on dyspnea relief, but the pivotal mortality trial [67] found no significant difference in rehospitalization or mortality. Although initial studies did not demonstrate any increased risk of hypotension, hypotensive events were over 2 hours duration in the VMAC trial[68], and the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failrue (ASCEND-HF) study reported an increased risk of both symptomatic and asymptomatic hypotension in patients randomized to nesiritide.[67] This may have occurred because the ASCEND-HF study did not specifically target H-AHF, with a mean baseline systolic blood pressure of enrolled patients of 124 mm Hg. Nesiritide does not result in substantial clinical improvement when added to standard care and is a second line agent, utilized when nitroglycerin is ineffective or contraindicated. Carperitide has also been studied in AHF patients with systolic blood pressure above 90 mmHg. While small studies suggest it may have efficacy and it is used in other parts of the world, it is not currently available in the United States. [69] [70]

Calcium Channel Blockers: Clevidipine is a rapidly acting intravenous calcium channel blocker that lowers blood pressure by selective arteriolar vasodilation and, without venous capacitance effects, increases cardiac output as peripheral vascular resistance declines. It is metabolized in the blood and has a one-minute half-life, allowing for rapid titration. Because it has no negative inotropic or chronotropic effects it may be beneficial in H-AHF. In a trial of patients presenting with H-AHF, clevidipine was demonstrated to be more effective than nitroglycerin or nicardipine for rapid control of blood pressure and dyspnea relief.[52] This trial was open label and there

have been concerns about reflex tachycardia and increased atrial fibrillation, which will need to be addressed in large scale trials. [71]

ACE Inhibitors and Angiotensin Receptor Blockers: The use of these drugs has received widespread adoption for hypertension and chronic heart failure, however the utility of intravenous formulations for AHF is understudied. While studies of intravenous ACE inhibitors for pulmonary edema unrelated to infarction and H-AHF suggest safety and beneficial hemodynamic effects, and their properties make them attractive for consideration in the acute setting, their small sample sizes and settings limit extrapolation to the emergency care setting. [64]

Contraindications and Alternatives to Vasodilation in Select Settings: Because all vasodilators lower blood pressure they are not recommended if there are signs of hypoperfusion or existing hypotension. Flow-limiting, preload-dependent states such as right ventricular infarction, aortic stenosis, hypertrophic obstructive cardiomyopathy, anaphylaxis or volume depletion increase the risk of hypotension associated with vasodilator use.[72] Combined with acute pulmonary edema, these pre-load dependent states can be extremely difficult to manage. Therapy is aimed at decreasing the outflow gradient by reducing heart rate and cardiac contractility. Although this can be accomplished with intravenous β-blockers, some prefer this to be done with invasive hemodynamic guidance.

CONSIDERATIONS FOR CLINICAL TRIAL DESIGN

Similar to other biomarkers, use of systolic blood pressure as a criterion for inclusion or exclusion efficiently discriminates AHF patients. Thus clinical trials use systolic blood pressure in conjunction with other criteria to identify patients that will ideally have the most benefit and least risk to a novel therapy. Another consideration for clinical trial enrollment is whether H-AHF is the primary cause of symptoms, or a secondary cause as a result of another primary problem such as acute hypertension, worsening renal function or acute coronary syndrome. Recent trials of novel agents with vasodilatory properties have reported precipitous drops in blood pressure may lead to worse outcomes, and have used higher systolic blood pressure inclusion criteria. [61, 73] Importantly, vasodilation may be the cause of some poor outcomes; in large trials spanning multiple sites and countries, hypotension in patients who may not have AHF or only mild heart failure may precipitate sufficient adverse events to offset any potential benefits of a novel therapy.

The upper limit of systolic blood pressure for entry into clinical trials has also been debated. Patients with very high systolic blood pressure (>185mmHg) tend to improve quickly with appropriately dosed nitrate therapy, making symptom improvement beyond standard care difficult. Focusing enrollment on such patients would thus make conduct of clinical trials especially challenging as prompt dyspnea resolution may preclude eligibility if mechanisms to identify potential subjects early in the course of treatment are not in place. Further, a rapid response to usual therapy makes it more difficult to achieve a clinically significant effect size. This highlights a paradox in AHF that the sickest appearing patient at presentation may have the best outcome, e.g. flash pulmonary edema. While aggressive management is required, treatment usually results in rapid improvement. In contrast, a patient with AHF patient and advanced HF may have a low systolic blood pressure at presentation and present with milder symptoms, such as fatigue and dyspnea on exertion, yet these patients are at the greatest risk for adverse events.

Other vasodilators are generally prohibited in clinical trials at the time of enrollment or allowed only at lower doses. Despite their infrequent use in practice, the absence of 'head-to-head' comparisons of novel agents vs. traditional vasodilators (i.e. nitrates) in patients with very high systolic blood pressure is a frequent criticism, raising questions as to whether the novel agent is truly going against usual standard therapy. Regardless, the ideal systolic blood pressure range for both current and novel therapies has yet to be determined. Studies such as Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) study [74] that have targeted patients with systolic blood pressures > 125 mm Hg, have shown both clinical and biomarker evidence of benefit with novel agents (e.g., serelaxin, a vasomodulator with favorable renal blood flow properties), suggesting that there may be effect modification within phenotypic subgroups. **Table 5** shows the more recent AHF trials and their systolic blood pressure entry criteria as well as time of enrollment.

CONCLUSION AND FUTURE DIRECTIONS

The hallmark of patients presenting to the ED with H-AHF is an altered relationship between ventricular and vascular function, leading to reduced cardiovascular reserve and an inability to adequately accommodate increases in venous return. Arterioles also adapt to chronic increases in arterial pressure associated with hypertension, resulting in an increased load for ventricular contraction triggering early aortic valve closure. An immediate consequence of shortened left ventricular systole due to premature aortic valve closure is increased diastolic volume and pressure. Subsequent increases in pulmonary venous pressures may result in pulmonary

congestion. Many of these patients are older with concomitant renal disease. Preliminary data raises the possibility that future treatment might be better focused on preload and afterload reduction with vasodilators rather than volume removal with diuretics. Clinical trial design has begun to account for patients with H-AHF by raising the minimum blood pressure to be enrolled, thus limiting the proportion of patients who are likely to develop symptomatic hypotension. Results from several clinical trials will be available in the next few years and will provide insight into safety and efficacy in this cohort. It is still unclear whether an upper blood pressure limit is necessary, but reasons to exclude may be more a function of logistics rather than clinical concern. Future investigations should investigate a diuretic sparing approach in this cohort, as the pathophysiology strongly supports volume redistribution rather than volume overload. The lower limit of blood pressure for clinical trial enrollment should be investigated to determine the optimal response to investigational agents in this cohort of patients. Similarly, further data are needed to assess the similarities and differences the pathophysiology and management of H-AHF with heart failure and reduced versus preserved ejection fraction.[7]

Table 1. Systolic Blood Pressure On Presentation In Acute Heart Failure

Dataset	N	Hospitals	SBP mmHg (IQR)	SBP >140 mmHg (%)	SBP <90 mmHg (%)
ADHERE [12]	107,362	274	144±33	50	3
OPTIMIZE [47]	48,612	259	143±33	50	--
GWTG-HF	110,621	275	138 (118,159)	--	--

SBP = systolic blood pressure

Table 2. Heart Failure with Preserved Ejection Fraction by Presenting Blood Pressure

Systolic Blood Pressure (mmHg)	Proportion with Heart Failure with Preserved Ejection Fraction
110	43.5
120	46.6
130	47.8
140	48.0
160	58.7
180	63.6
200	73.3

Table 3: Suggested Management of Hypertensive Acute Heart Failure[+]

Stepwise Approach	Comments
1. Administer oxygen as needed to keep saturation 95% or greater, give sublingual nitroglycerin.	Sublingual nitroglycerin may be repeated up to one per minute
2. If severe dyspnea, consider NIV or intubation.	
3. If blood pressure >150/100 mm Hg, add IV nitroglycerin or nitroprusside; if blood pressure falls below 100 mm Hg, stop nitrates, monitor for persistent hypotension or symptoms. If blood pressure<150/100 after sublingual administration and if improved, consider transdermal nitroglycerin.	See text for discussion of these agents.
4. Start IV loop diuretic (furosemide or bumetanide or torsemide) in the setting of volume overload.	Initiate nitrates before diuretics.
5. Assess for severity of illness/high risk: altered mental status persistent, hypoxia despite NIV, hypotension, troponin elevation, ischemic ECG changes, blood urea nitrogen over 43, creatinine over 2.75, tachycardia, tachypnea, or inadequate urine output.	
6. Admit to ICU if high severity of illness or risk of decompensation.	
7. Choose discharge or emergency department observation unit admission if good response to therapy and no need for on-going intravenous vasodilators, no high-risk features, and good social support. Admit the rest, ICU if any ongoing cardiorespiratory compromise or acute ischemia.	Scoring systems may not reliably identify all patients at risk.

Abbreviations: blood pressure = blood pressure; NIV = noninvasive ventilation; systolic blood pressure = systolic blood pressure.
*Adapted from Collins SP, Storrow AB[72] [+] Inclusion: systolic blood pressure >140 mm Hg

Table 4: First-Line Medications for Acute Heart Failure

Vasodilators for Acute Heart Failure			
Vasodilator	**Dose**	**Titration End Point**	**Complications**
Sublingual NTG	0.4 milligram every 1–5 min	Blood pressure	Hypotension
Transdermal NTG	1-2 mg of topical NTG every 6 hours	Blood pressure	Possible prolonged hypotension
IV NTG	0.5–0.7 microgram/kg/min (starting dose)	Symptoms	Headache, hypotension
Nitroprusside	0.3 microgram/kg/min (starting dose), 10 micrograms/kg/min (maximum)	Blood pressure	Hypotension, cyanide/thiocyanate toxicity, coronary steal
		Symptoms	
Diuretics for Heart Failure			
Diuretic	**Dose (IV)**	**Effect**	**Complications**
Furosemide	No prior use: 20-40 mg IVP	Diuresis starts within 15–20 min	↓ K^+, ↓ Mg^{2+}, hyperuricemia, hypovolemia
	If prior use: total daily IV dose 1 to 2.5 times the patient's previous total daily oral dose, divided in half and given IV bolus every 12 hours	Duration of action is 4–6 h	
			Ototoxicity, prerenal azotemia, sulfa allergy
	If no effect by 20–30 min, increase subsequent dose		
Bumetanide	1–3 milligrams IV	Diuresis starts within 10 min	Same as above
		Peak action at 60 min	
Torsemide	10–20 milligrams IV	Diuresis starts within 10 min	Same as above
		Peak action in 1–2 h	

Abbreviations: IVP = IV push; NTG = nitroglycerin; ↓ = decreased. *Used with permission from Collins SP, Storrow AB[72]

Table 5. Selected Acute Heart Failure Vasodilator Clinical Trials

Trial And Intervention	Year	N	Systolic Blood Pressure Criteria	Enrolment	Dyspnea as endpoint
VERITAS [75, 76] Tezosentan v Placebo	2007	1448 (1453)*	EXCL: < 100mmHg or < 120mmHg in patients receiving a vasodilator	After admission (within 24 hours	Yes (Primary)
OPTIME-CHF[77] Milrinone v Placebo	2002	951	EXCL/INCL: < 80 or > 150mmHg	After admission (within 48 hours of hospitalization)	Yes** (Secondary)
VMAC[68] Nesiritide v Nitrates v Placebo	2002	489	EXCL: < 90mmHg	After admission (no specific time window except need for hospitalization and IV therapy)	Yes (Co-primary with PCWP)
EVEREST[78] Tolvaptan v Placebo	2007	Trial A = 2048, Trial B = 2085	EXCL: < 90mmHg	After admission (within 48 hours of hospitalization)	Yes (Secondary)
SURVIVE[79] Levosimendan v Dobutamine	2007	1327	EXCL: systolic blood pressure < 85mmHg	After admission (no definite window of enrolment)	Yes (Secondary)
REVIVE-II[80] Levosimendan v Placebo	2005 (2013)	600	EXCL ≤ 90mmHg	After admission (no definite window of enrolment)	Yes (Secondary)
Pre-RELAX-AHF[81] Serelaxin (4 doses) Placebo	2009	234	INCL: >125mmHg	Within 16 h of presentation, including time spent in the emergency department	Yes (Part of primary treatment targets)
PROTECT[82] Rolofylline v Placebo	2010	2033	INCL: ≥ 95mmHg	Within 24 hours hospital presentation, including time spent in the emergency department	Yes (part of composite)
ASCEND-HF[67] Nesiritide v Placebo	2011	7141	EXCL: < 100mmHg or < 110mmHg if on IV nitrates	Within 24 hours of first IV AHF therapy	Yes (primary)
COMPOSE-EARLY[83] Cinanciguat (3 doses) v Placebo	2012	160 planned (halted early)	INCL: ≥ 120mmHg	Within 12 hours of admission	Yes (primary)
RELAX-AHF 1[61] Relaxin v Placebo	2012	1161	INCL: > 125mmHg	< 16 hours from presentation	Yes (primary)

ATOMIC AHF Omecamtiv mecarbil (3 sequential dose escalation) v Placebo	2013 (presentation)	600	INCL: > 90mmHg		Yes (primary)
DOSE-AHF[59] Differing dosing strategies of diuretics	2011	308	EXCL: < 90mmHg	Within 24 hours presentation	Yes (secondary)
PRONTO Clevidipine v Standard therapy vasodilators	2012	104	INCL: ≥160 mmHg		Yes (secondary)
ROSE-AHF[84] Dopamine v Nesiritide (both low dose)	2013	360	EXCL: < 90mmHg	Within 24 hours of presentation	Yes (secondary)
Trials below are either currently enrolling or their results have yet to be reported					
TRUE AHF Ularitide v Placebo	Enrollment completed June 2015	2152	INCL: ≥116 and < 180 mmHg	Within 12 hours of presentation	No
BLAST-AHF[73] TRV 027 v Placebo	Enrolling	620 (increased from 500)	INCL: ≥ 120 and ≤ 200 mmHg	Within 16 hours of presentation	Yes (composite)
RELAX-AHF 2 Relaxin v Placebo	Enrolling	6800 planned (event driven)	INCL: ≥ 125mmHg	Within 16 hours of presentation or first IV loop diuretic dose	Yes (composite secondary)

*VERITAS was discontinued before full enrolment due to improbability of achieving significant treatment effect. The n listed is the planned enrolment. VAS = visual analog scale, NA = not available (information generated from abstract only)

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