Circulation Research

HEART FAILURE COMPENDIUM

Pathophysiology and Therapeutic Approaches to Acute Decompensated Heart Failure

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ABSTRACT: Acute decompensated heart failure (ADHF) is one of the leading admission diagnoses worldwide, yet it is an entity with incompletely understood pathophysiology and limited therapeutic options. Patients admitted for ADHF have high in-hospital morbidity and mortality, as well as frequent rehospitalizations and subsequent cardiovascular death. This devastating clinical course is partly due to suboptimal medical management of ADHF with persistent congestion upon hospital discharge and inadequate predischarge initiation of life-saving guideline-directed therapies. While new drugs for the treatment of chronic HF continue to be approved, there has been no new therapy approved for ADHF in decades. This review will focus on the current limited understanding of ADHF pathophysiology, possible therapeutic targets, and current limitations in expanding available therapies in light of the unmet need among these high-risk patients.

Key Words: diagnosis ■ heart failure ■ hospitalization ■ morbidity ■ mortality ■ therapeutics

Acute decompensated heart failure (ADHF) continues to be an entity with incompletely understood pathophysiology and limited therapeutic options. Although agents for the management of chronic HF continue to expand and the arsenal of guideline-directed medical therapies is robust, the same cannot be said for management of ADHF.[1] This is clinically relevant as acute HF (AHF) events and repeat hospitalizations are associated with a worse prognosis and progressive multiorgan failure.[2] There are over 1 million hospitalizations per year for HF in the United States and Europe with an astounding 24% readmission rate within 30 days and 50% within 6 months.[3–5] Patients with readmission for cardiovascular disease within 90 days of discharge for HF hospitalization have a higher risk of mortality independent of the exact amount of time from discharge.[6] One in 6 patients admitted for HF die within 30 days of hospitalization.[7,8] These grim statistics for ADHF in contrast to the promising future of chronic HF management prompt the need for a better understanding of the distinct entity of ADHF. Additionally, suboptimal medical management of ADHF often results in persistent congestion upon hospital discharge and subsequent increased risk of recurrent hospitalization, morbidity, and mortality.[9]

In light of the stagnating clinical outcomes with ADHF, the American College of Cardiology released an expert consensus decision pathway in 2019 to assist in risk assessment, management, and evaluation of clinical trajectory of patients with ADHF.[10] The highlight of this document lay in the importance of effective decongestion and cardiac function optimization, frequent reevaluation of clinical trajectory and ensuring improvement in symptoms, hemodynamics, and biomarkers, comprehensive evaluation of comorbid contributions, and safe discharge preparation and follow-up. We will use this outline to guide our discussion as it relates to current data for patients with ADHF. This review will focus on the current limited understanding of ADHF pathophysiology, possible therapeutic targets, and current limitations in expanding available therapies in light of the unmet need among these high-risk patients. The discussion will predominantly focus on typical cases of ADHF (not including the relatively rare cases of

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For Disclosures, see page 1481.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ADHF	acute decompensated heart failure
AHF	acute HF
ANP	atrial natriuretic peptide
ARBs	angiotensin receptor blockers
BNP	B-type natriuretic peptides
EF	ejection fraction
GLP-1	glucagon-like peptide 1
HF	heart failure
HFrEF	HF with preserved ejection fraction
HFrEF	HF with reduced ejection fraction
IL	interleukins
MRAs	mineralocorticoid receptor antagonists
NIV	noninvasive ventilation
NPR-A	natriuretic peptide receptor A
SGLT2	sodium-glucose cotransporter 2
TGF-β	transforming growth factor-β
TNF	tumor necrosis factor

cardiogenic shock or requirement of mechanical circulatory support).

DEFINITION AND CLINICAL PRESENTATION

The clinical presentation of symptoms and signs of congestion and poor organ perfusion due to HF requiring urgent, usually intravenous, therapy has been variously called AHF, ADHF, AHF syndrome, and hospitalized HF, as well as other terms. For the purposes of this review, ADHF will be used, recognizing that most patients have a subacute evolution of their symptoms and signs resulting from cardiac and vascular dysfunction due to a variety of etiologies and triggers resulting in decompensated hemodynamics.[11] There are a number of classifications for HF including by ejection fraction (EF; HF with reduced [HFrEF] or preserved EF [HFpEF]) and predominant left versus right ventricular dysfunction.[12]

The subacute or acute dysfunction in ADHF overwhelms compensatory mechanisms resulting in signs and symptoms of left or right (and often both) ventricular increased filling pressures leading to symptoms including dyspnea, exercise intolerance, palpitations, presyncope, peripheral edema, abdominal bloating, early satiety, and fatigue.[13] Pulmonary vascular congestion from left ventricular failure increases right ventricular pressures and results in a cascading effect on multiorgan function. While the most common cause of right HF is left HF, isolated right HF is becoming increasingly recognized and can also result in increased peripheral signs of congestion and end-organ dysfunction. Since many of these patients with right HF have a severe pulmonary disease as the cause of their HF, they can present with significant dyspnea independent of pulmonary congestion.

Physical exam findings include pulmonary crackles in the presence of pulmonary edema and pleural effusions, peripheral edema, ascites, elevated jugular venous distension, abdominojugular or hepatojugular reflux, third heart sound, and worsening mitral or tricuspid regurgitation murmurs. Signs of end-organ dysfunction secondary to congestion include aforementioned pulmonary edema, gastrointestinal edema, hepatocellular damage, and cardiorenal syndrome.[2] Additionally, in the presence of decreased cardiac output, reduced organ perfusion can contribute to end-organ damage. Increased ventricular pressures and neurohormonal compensatory mechanisms to augment chronotropy and inotropy can trigger tachycardia, arrhythmias, and increased myocardial strain and ischemia.

The pathophysiology of ADHF is pleiotropic and dependent on a number of factors including the degree of systolic and diastolic cardiac dysfunction, the relative involvement of the right and left ventricles, the arterial and venous vascular tone, the neurohormonal and inflammatory activation state, and comorbid contributing influences. Further complicating the standardization of ADHF management lies in the difference between the underlying substrate and pathophysiology of chronic HFrEF and HFpEF. The central defect in HFrEF can be readily conceptualized as reduced systolic function with resultant increases in left ventricular filling pressures and diastolic dysfunction producing increased pulmonary venous pressures and congestion, often resulting in right HF and peripheral signs of congestion, associated with decreased cardiac output resulting in end-organ hypoperfusion and dysfunction. However, the pathophysiology of HFpEF is more complicated and poorly understood, thought to be related, in part, to cardiomyocyte hypertrophy and fibrosis, impaired compliance and diastolic filling of the left ventricle, microvascular inflammation, altered adrenergic-adipokine signaling, and peripheral arterial stiffness and vasoconstriction affecting afterload.[14–16] There is a paucity of chronic therapeutic options for patient with HFpEF, which predominantly focus on the management of comorbidities.[17] Additionally, the vast majority of landmark studies and current guideline-directed medical therapy have only been shown to have significant clinical benefit in the chronic HF patient population due to significant logistical limitations related to the acuity and oftentimes clinical severity of patients admitted with ADHF.[12]

ADHF develops in the context of this background pathophysiologic canvas where compensated HF has

attained an intricate balance between preload, afterload, intrinsic inotropy, and neurohormonal signaling (Figure). There is a significant interdependence that, if altered, can result in increased intracardiac filling pressures, venous and arterial congestion and vasoconstriction, and depressed inotropy, ultimately producing ADHF. Additional significant factors include end-organ damage and feedback signaling, pulmonary insults, and specific comorbidities.

Intravascular Congestion

The most common symptoms and signs of ADHF are directly related to intravascular congestion[18] which can result from progressive accumulation of fluid through interdependent mechanisms including sodium retention due to renal dysfunction, dietary indiscretion, or medical nonadherence, by increased left ventricular filling pressures resulting in increased pulmonary and central venous congestion, or by rapid central redistribution of intravascular volume from peripheral or splanchnic venous circulation.[13,19] Progressive intravascular fluid volume expansion or redistribution[20] produces multiple positive feedback interactions that exacerbate the development of ADHF. For example, neurohormonal-induced vascular redistribution into the central venous system can cause increased central venous pressures, which can decrease renal function, increasing salt and fluid retention which further expands intravascular volume and ventricular preload. Given that diastolic dysfunction is typically present in both HFpEF and HFrEF, the additional preload will elevate end-diastolic pressures, increasing ventricular wall stress and myocardial oxygen consumption, further worsening diastolic function. Expanded ventricular volumes can produce or exacerbate functional tricuspid or mitral regurgitation, further increasing venous pressures, which can worsen renal function.

It is obvious from this example that there are multiple potential triggers for this cycle which also provide numerous potential opportunities for intervention. As noted in the example above, an additional contributing factor to consider in evaluating congestion causes is concurrent or subsequent valvular disease, particularly mitral regurgitation. Mitral regurgitation results in retrograde blood flow, directly increasing pulmonary pressures and congestion. It is categorized as either primary dysfunction related to structural abnormalities or secondary dysfunction in the setting of left ventricular dysfunction, left ventricular or atrial dilation, and mitral apparatus effects.[21] Moderate and severe mitral regurgitation are well known to worsen clinical outcomes in patients with HFrEF.[22–24]

Therapies to target these pathophysiologic mechanisms include initiation of diuresis and vasodilators to improve the clinical manifestations of intravascular congestion. However, it is often difficult to distinguish the predominant culprit factor to focus on treatment approaches. Invasive evaluation with right heart catheterization may be useful in patients admitted with ADHF to guide aggressive diuresis and indication for initiation of vasodilator therapies.[12] In patients with moderate-to-severe mitral regurgitation during ADHF, the degree of mitral regurgitation should be reevaluated once euvolemia is achieved to assess for indication for further transcatheter or surgical intervention.

Importantly, when clinical congestion has improved, there is often still significant hemodynamic congestion that remains present. If not addressed before discharge, patients admitted with AHF and treated insufficiently with diuretics are more likely to revert to a clinically congested state with recurrent hospitalizations. Hemodynamic congestion can precede clinical congestion by up to weeks with a relative lack of symptoms. The advent of continuous pulmonary artery pressure monitoring has allowed for data analysis that confirmed a correlation between elevated filling pressures and risk of cardiovascular events.[25]

Inotropy

Inotropy is dependent on myocardial contractility produced by the myosin (thick) and actin (thin) filament cross-bridges.[26] The binding strength is augmented by calcium availability, which activates the thin filament, increases cross-bridge formation, and improves contractility. Clinical circumstances affecting inotropy include ischemia, myocarditis, valvular disease, pericardial disease, arrhythmias, toxic cardiomyopathies, and metabolic abnormalities. In systolic dysfunction, there is a direct inotropic derangement while one mechanism of advanced diastolic dysfunction is decreased compliance and end-diastolic volume resulting in reduced stroke volume. Severity and acuity of inotropic dysfunction can result in cardiogenic shock commonly defined as hypotension <90 mm Hg, cardiac index <2.2 L/min per m^2, and signs of end-organ hypoperfusion, including decreased urine output, cool extremities, altered mental status, and serum lactate elevation.[27] While cardiogenic shock, fortunately, constitutes a small percentage of cases with ADHF, decreased systolic function can play an important role in the pathogenesis of ADHF and in appropriately selected patients, it represents an important therapeutic target even in the absence of shock. In addition, it is essential that acute coronary syndromes be diagnosed and treated as a potential underlying or exacerbating cause of the systolic dysfunction.

Venous and Arterial Vasoconstriction

Dynamic alterations in vascular tone are another important component of the pathogenesis of ADHF. As noted above, increases in peripheral and splanchnic venous vasoconstriction can result in marked volume

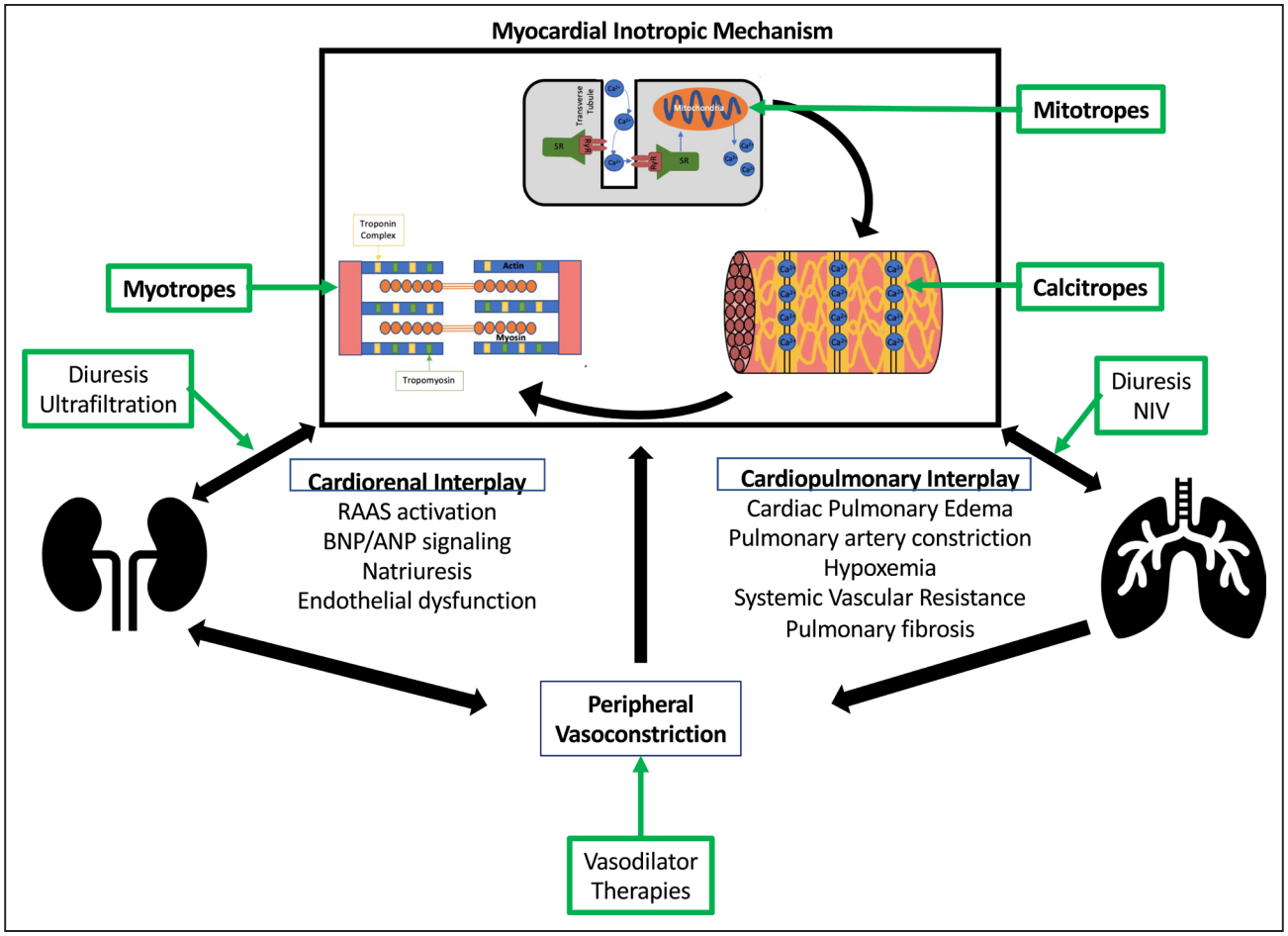

Figure. Complex interdependence of cardiac and multiorgan involvement contributing to acute decompensated heart failure (ADHF) development and medical therapy options.
BNP/ANP indicates B-type/atrial natriuretic peptide; NIV, noninvasive ventilation; and RAAS, renin-angiotensin-aldosterone system.

redistribution to the central venous system. This redistribution and direct central venous vasoconstriction cause significant and rapid increases in central venous pressure which can worsen renal and right ventricular function. Increased pulmonary arterial pressures are also frequently observed in ADHF often due to a combination of elevated left ventricular filling pressures, preexistent pulmonary hypertension, and hypoventilation-related pulmonary artery vasoconstriction. Increases in systemic vascular resistance are predominantly mediated by arteriolar vasoconstriction and result in elevated left ventricular pressures increasing ventricular wall stress, exacerbating myocardial ischemia, and contributing to myocardial injury. The marked sympathetic activation associated with ADHF can exacerbate the arterial vasoconstriction, particularly in the setting of underlying systemic hypertension and endothelial dysfunction. Importantly, as part of a feedback system, in ADHF with decreased cardiac output, decreased baroreceptor activation results in signaling to paradoxically increase peripheral arterial vasoconstriction resulting in detrimental increased afterload. In ADHF, acute and often dramatic increases in afterload due to sympathetic system activation can result in rapidly developing pulmonary congestion or flash pulmonary edema, especially in the setting of diastolic dysfunction and HFpEF.

Neurohormonal Signaling and Circulating Biomarkers

The dysregulation and feedback signaling involving the renin-angiotensin-aldosterone system can cause detrimental hemodynamic changes and release circulating proteins that serve as clinical biomarkers in ADHF.[28] Renin is an enzyme released by the kidneys and signals the activation of angiotensinogen to angiotensin I. ACE (Angiotensin-converting enzyme) is released by vascular endothelium to cleave angiotensin I into active angiotensin II. Angiotensin II signals vasoconstriction both directly on vascular endothelium and via release of vasopressin and norepinephrine, resulting in increased systemic vascular resistance. It also activates renal sodium transporters to increase glomerular sodium reabsorption and signals for aldosterone release from the adrenal glands. Aldosterone acts directly on the kidneys to further increase glomerular sodium and water reabsorption.

The renin-angiotensin-aldosterone system is activated by signs of low renal perfusion or increased sympathetic nervous system activation. The overall activation results in increased vasoconstriction and volume retention resulting in paradoxical worsening of ADHF. Multiple other vasoconstrictor pathways are stimulated in ADHF, including endothelin-1, one of the most potent vasoconstrictors that is release by vascular endothelial cells causing peripheral vascular smooth muscle contraction with increased expression associated with systemic hypertension as well as chronic HF.[29,30]

With ventricular chamber dilation from increased volume or increased pressure, myocardial cells release BNP (B-type natriuretic peptides) that signal for vasodilation, decreased renin activity, and subsequent diuresis. BNP is produced by the ventricles in an inactive form known as preproBNP which undergoes enzymatic cleavage to proBNP and further broken down to active BNP and inactive N-terminal-proBNP. BNP is the active form that signals inhibition of the renin-angiotensin-aldosterone system, endothelin activity, and the sympathetic nervous system. Compared with BNP, NT-proBNP is a more stable marker of intravascular congestion and left ventricular dysfunction due to its longer half-life and its plasma concentrations are unaffected by neprilysin inhibition with sacubitril.

ANP (Atrial natriuretic peptide) is release by atrial myocardial cells in response to atrial dilation but is also signaled by sympathetic activity via β-adrenergic activation. Both ANP and BNP bind to NPR-A (natriuretic peptide receptor A) which is highly expressed in the kidney and vascular endothelium. When NPR-A, and to a lesser extent NPR-B, is bound it activates guanylyl cyclase and signals cyclic guanosine monophosphate production. Cyclic guanosine monophosphate is the primary signaling molecule for natriuretic peptides to increase vasodilation and diuresis while inhibiting mitogenesis, inflammation, and tissue hypertrophy. Natriuretic peptides are cleaved and inactivated by neprilysin, a circulating endopeptidase, as well as insulin-degrading enzymes. Additionally, neprilysin has been found to break down and inactivate angiotensin II.[31]

Because of their direct roles in ADHF, natriuretic peptides and other proteins specific to the cardiovascular system have been frequently used as biomarkers with a number being evaluated for utility as therapeutic targets. Major guideline committees, including the American College of Cardiology Foundation/American Heart Association and European Society of Cardiology, have included specific recommendations for commonly used biomarkers, such as BNP, NT-proBNP, and troponin.[12,32] The role of circulating biomarkers as it relates to clinical trials have served dual roles in clinical trials. First, natriuretic peptides are a marker of increased risk for rehospitalization and cardiovascular death in patients admitted for ADHF and thus can serve as enriching the enrolled patient population for potentially modifiable clinical events.[33] However, it is well established that a number of subgroups of patients with HF may not present with typical BNP or NT-proBNP elevation during episodes of HF, resulting in limited enrollment in studies that require elevated levels for inclusion.[12,34] Second, given this prognostic value of natriuretic peptides and putative role as a marker of disease progression, many clinical trials have used a decrease in natriuretic peptides as a surrogate for clinical efficacy.[35]

Multiple studies have demonstrated the prognostic significance of troponin as a marker of myocardial injury in patients admitted for ADHF.[36–40] As with natriuretic peptides, baseline troponin levels could be used to enrich the patient population for potentially modifiable events in trials of ADHF therapies. The change in troponin during the early phase of admission has also been shown to be prognostic, suggesting the possibility that therapies may be able to target the acute myocardial injury in ADHF and possibly improve intermediate-term clinical outcomes.[40]

Novel biomarkers that are being validated with ongoing studies include ST2 and galectin-3, markers of myocardial injury and stretch that have prognostic utility in ADHF. ST2 is part of the IL-1 class of involved in inflammatory signaling. Elevated levels of ST2 also indicate the presence of adverse cardiac remodeling and fibrosis.[41,42] In ADHF, it has reliably correlated with vascular congestion and particularly with New York Heart Association class, with increased 1-year cardiovascular mortality observed in patients with higher serum levels.[42,43] Another emerging biomarker is galectin-3, a lectin molecule with antiapoptotic activity found to promote cardiac fibroblast activity resulting in left ventricular dysfunction.[44–46] Although the mechanistic roles of ST2 and galectin-3 remain incompletely defined, they provide improved prognostic assessment of patients by monitoring serum levels in combination with BNP during hospitalizations.[12,47]

ROLE OF INFLAMMATION

A number of cytokines are known to be involved in the pathophysiology of HF, including TNF (tumor necrosis factor), TGF-β (transforming growth factor-β), and IL (interleukins)-6 and IL-1.[48,49] These cytokine cascades independently can cause endothelial dysfunction, pulmonary edema, and left ventricular dysfunction and are thought to contribute, in part, to these presentations in clinical HF. Better understanding of the significance of inflammatory mediators in the pathophysiology of ADHF can also allow for more targeted therapeutic approaches. While the triggers of these inflammatory cytokine cascades may be secondary to the neurohormonal activation and oxidated stresses associated with ADHF, there is also evidence for elevated bacterial or endotoxin translocation in ADHF, perhaps associated with gut edema

or relative hypoperfusion.[50] Elevated levels of high-sensitivity C-reactive protein have also been noted in ADHF, supportive of increased inflammatory state.[51] In a study assessing biomarkers across a range of EFs of patients admitted for ADHF, inflammatory biomarkers were elevated in patients with reduced, mid-range, and preserved EFs, and markers of inflammation had predictive value for cardiovascular outcomes in the patients with HF with mid-range EF and HFpEF.[52] These findings suggest that therapies direct to reducing inflammatory signaling might have a role in the treatment of ADHF.

COMORBIDITIES

Comorbidities are critical considerations when discussing ADHF as they serve as both risk factors as well as complications that worsen prognosis during and after hospitalizations for ADHF.[53–55] The European Society of Cardiology collected data from multiple large AHF trials, and cardiovascular comorbidities were observed in patients admitted for HF included hypertension (70% of patients), coronary artery disease (50%–60%), and atrial fibrillation (30%–40%).[56] Noncardiac comorbidities included diabetes (40%), renal dysfunction (20%–30%), chronic obstructive pulmonary disease (20%–30%), and anemia (15%–30%). Cardiac comorbidities in ADHF often need immediate intervention, such as acute coronary syndromes, hypertensive urgency/emergency, and clinically significant atrial or ventricular arrhythmias.

Less straightforward is the role of noncardiac comorbidities and the appropriate timing for their interventions. Chronically, diabetes is associated with risk of rehospitalizations and increased cardiovascular morbidity and mortality; acutely hyperglycemia and glycemic variability during cardiac hospitalizations are associated with worse outcomes, however, data are still conflicted regarding benefit or increased risk of tight glycemic control.[57–59] Hyperglycemia increases endothelial dysfunction, oxidative stress, resultant myocardial fibrosis, decreased sarcolemmal calcium transportation, as well as affects myocardial metabolism, which may affect cardiac function during ADHF hospitalizations, although a unifying underlying mechanism is not fully elucidated.[60]

Renal dysfunction also has a strong correlation with poor clinical outcomes as well as its implications on therapeutic limitations.[61,62] Independent of the level of renal injury compared with baseline, these patients when treated with HF are consistently underdosed or undertreated in regard to ACE inhibitors, ARBs (angiotensin receptor blockers), and MRAs (mineralocorticoid receptor antagonists) as well as diuretic use either for concern for worsening renal function or limited by loop diuretic resistance.[63–65]

The frequent confounding presence of chronic obstructive pulmonary disease results in challenging differentiation of the cause of common symptoms, including dyspnea, palpitations, and occasionally chest discomfort.[66] Additionally, patients with known chronic obstructive pulmonary disease admitted with ADHF are less likely to be prescribed β-blocker therapies and have underutilization of ACE inhibitors and mineralocorticoid receptor antagonists due to common medical misconceptions.[64,67–69] The relationship between ADHF and chronic obstructive pulmonary disease lies in the acute ventilatory and hemodynamic changes superimposed on both chronic pulmonary and cardiac fibrosis and dysfunction in addition to endothelial effects of acute vasoconstriction and hypoxia.[70]

Anemia can be seen in up to 50% of patients hospitalized with ADHF and 30% of patients with CHF compared with <10% in the general population.[71–73] The cause of anemia can be multifactorial, however, most significant in ADHF is iron deficiency anemia which results in decreased red blood cell oxygen-carrying capacity, leading to mitochondrial dysfunction, abnormal sarcomere structure, and eventually left ventricular systolic dysfunction.[74–76] Importantly, the presence of iron deficiency with or without anemia is considered clinically significant and intervention with intravenous iron during the presenting hospitalization should be considered.[77]

END-ORGAN DAMAGE

End-organ damage from ADHF can occur via 2 main hemodynamic mechanisms: elevated venous and ventricular filling pressures resulting in congestion and hypoperfusion due to either decreased cardiac output or local hemodynamic regulation. Increased inflammation and oxidative stress may exacerbate these hemodynamic effects. The common organs affected by congestion, including the lungs, kidneys, liver, and gut. Pulmonary congestion results in increased hydrostatic forces across leaky pulmonary capillaries leading to pulmonary edema and, in many cases, pleural effusions.[78] Recurrent cardiopulmonary insults cause alveolar stiffness and pulmonary fibrosis, further worsening alveolar gas diffusion and eventually resulting in pulmonary hypertension (WHO Group II) and restrictive ventilation.[79,80]

Cardiorenal interplay is critical in the pathophysiology and management of ADHF. The renal system has direct control over preload management by signaling for increased or decreased urine output based on a number of complex pathways, including the renin-angiotensin-aldosterone system, which regulates neurohormonal pathways that additionally control autonomic nervous system activation and vascular endothelium as mentioned above. This system is affected in the setting of acute renal injury, which may occur as ADHF sequelae or as a precipitating factor. Cardiorenal syndrome is formally classified into 5 subtypes with the most relevant pathophysiology being a combination result of poor cardiac output with poor renal perfusion and central venous congestion with increased afterload on the kidneys.[81,82]

Most studies have suggested that increased central venous pressure is a much more critical factor than reduced cardiac output, and some studies have demonstrated that worsening renal function is only predictive of poor cardiovascular outcomes when accompanied by persistent congestion.[83–87]

Hepatic congestion is a common sequela of severe cardiac dysfunction and in the setting of ADHF can cause critical hepatic dysfunction. Although relatively common during admissions for ADHF, elevated liver enzymes are independently poor prognostic markers.[88] Additionally, severe hepatic dysfunction can cause independent complications, including coagulopathies and biliary cholestasis. Hypoperfusion as an cause of hepatic dysfunction in ADHF is less common due to the dual circulatory system of the liver. However, it can be seen with severe cardiac dysfunction as indicated by the term shock liver.[89] During ADHF with increased sympathetic activity, splanchnic arterioles and veins are signaled to constrict to divert blood flow to critical organs, such as the heart and brain, contributing to hypoperfusion of the splanchnic system.[90] The gastrointestinal system also experiences negative consequences of increased vascular congestion usually more relevant in the chronic period resulting in gut edema and resultant decreased absorption affecting nutrition and medication absorption and bioavailability,[91] although as noted above, alterations in gut permeability may contribute to the increased inflammatory state in ADHF. This is an important consideration during evaluation for cause of acute decompensations in patients admitted with ADHF.

Hypoperfusion from poor cardiac output and increased vascular congestion can negatively affect all organs in the body. The heart may sustain injury in ADHF due to elevated ventricular pressures and wall stress, increased sympathetic inotropic and chronotropic stimulation, and increased afterload due to vasoconstriction, all of which may cause supply demand mismatch and myocardial ischemia or injury, especially with preexisting coronary disease. This myocardial injury is reflected clinically in the increased troponin levels in the absence of acute coronary syndrome in patients with ADHF.[92] Cerebral hypoperfusion is an important marker of critical cardiac dysfunction that can present as altered mental status, somnolence, and obtundation. Noninvasive measures to evaluate central hypoperfusion have been studied with the hope to validate transcranial doppler sonography during episodes of ADHF.[93] Early detection of cerebral hypoperfusion can guide decision-making, including indication for inotropic support. Recurrent insults are likely to result in chronic cerebral dysfunction and may lead to early dementia.[94]

THERAPEUTIC OPTIONS

Despite scores of years of research and development, the main pharmacological therapies for ADHF remain diuretics, vasodilators, and calcitropes (inotropes that improve cardiac function by altering myocardial calcium transients).[26] Intravenous loop diuretics are the primary therapy in most patients admitted with ADHF and as noted above, improve symptoms predominantly by decreasing venous congestion and volume overload. While early studies with vasodilators suggested improvements in symptoms, a recent large trial evaluating early intensive and sustained vasodilator strategy compared with usual care (predominantly intravenous diuretics) demonstrated no difference in all-cause mortality or rehospitalization for ADHF.[95] Additionally, there was no difference in measures of symptom relief, weight loss, or reduction in NT-proBNP. Data supporting current calcitropic therapies in patients with ADHF have been equally disappointing with commonly used agents, including dobutamine, dopamine, milrinone, and epinephrine, being associated with increase short-term mortality, arrhythmia, and end-organ damage without significant improvement in cardiovascular morbidity and mortality.[96–106] Low-dose dopamine, which is proposed to work via either renal vasodilation or increased perfusion, has not been shown to improve renal function in multiple trials, although a post hoc subgroup analysis suggests that it may increase urine volume and weight reduction in patients with HFrEF.[107] Although these findings are discouraging, it is important to acknowledge the contributing limitations and obstacles that are present with clinical trials focused on ADHF.

Inclusion criteria for ADHF studies tend to rely on clinical diagnoses with variable inclusion of biomarker confirmation (about 39% in the past decade) which, as mentioned above, has significant limitations that can result in significant inappropriate inclusions and exclusions.[108] Clinical end points to determine clinical success of drugs vary from symptom relief to biomarkers or echocardiographic markers of improvement, to hospitalization length of stay, rehospitalization rates, and mortality. It is unclear if studies that demonstrate symptomatic relief carry significantly lower power as symptom recurrence is the most common reason for rehospitalization and morbidity.[109] Last, there is a conflict in evaluating the chronic effects of acute management of patients with ADHF wherein some studies may not demonstrate short-term utility (the common focus in these trials) but may hold long-term benefits that are overlooked. These considerations are depicted in Table with the major ADHF landmark trials for aforementioned agents to reiterate the problematic nature of the current ADHF literature.

Considering these limited therapeutic options, a number of novel therapies have been developed to address various pathophysiologic targets. With continued interest in filling the therapeutic gaps in the management of patients with ADHF, there are currently many trials underway testing new guideline-directed chronic medical therapy drugs specifically in AHF. However, it is concerning that there is still little distinction between the varying

Table. Selected Clinical Trials for AHF Therapies

Trial	Treatment arms	Population	Results
Vasodilator trials			
VMAC (2002),[179] N=489	Nesiritide (from 24 h up to 7 d) vs placebo (only during first 3 h) vs NTG (from 24 h up to 7 d)	Dyspnea at rest; ≥2 signs of HF within 72 h; CXR with pulmonary edema	Change in PCWP, at 3 h (1°): nesiritide > NTG >, placebo (P<0.001); at 24: nesiritide > NTG (P<0.04)
			Self-evaluation of dyspnea at 3 h, Likert (1°): nesiritide vs placebo, P=0.03; nesiritide vs NTG, NS; at 24 h: NTG vs nesiritide, NS.
			Self-evaluation of global clinical status, at 3 h: P=NS; at 24 h: P=NS.
ASCEND-HF (2011),[3] N=7141	Nesiritide (from 24 h up to 7 d) vs placebo	Hospitalized for ADHF, dyspnea at rest or with minimal activity, ≥1 sign and ≥1 objective measure of ADHF, randomized within 24 h of first IV treatment for ADHF	Self-reported dyspnea moderately or markedly better: NS
			Death or rehospitalization for HF at 30 d: NS
TRUE-AHF (2017),[111] N=2157	Ularitide vs placebo	Men or women, aged 18–85 y; Unplanned hospitalization or ED visit for ADHF; Dyspnea at rest, worsened within the past week; Evidence of HF on CXR; BNP >500 pg/mL or NT-proBNP >2000 pg/mL; Persistence of dyspnea at rest despite ≥ 40 mg of IV furosemide (or equivalent); SBP ≥116 mm Hg and ≤180 mm Hg; Start of study drug infusion within 12 h after initial clinical assessment	1° end points, CV death: NS
			1° end points, hierarchical clinical composite at 48 h: NS
			2° end points: All NS except change in NT-proBNP at 48 h: 47% decrease with ularitide (P<0.001); Change in serum creatinine during first 72 h: Increased with ularitide (P=0.005)
			Adverse events: hypotension: placebo, 10.1% vs ularitide, 22.4%. No difference in renal events.
VERITAS (2007),[115] N=1435	Tezosentan (for 24–72 h) vs placebo	Presenting within 24 h; Persistent dyspnea; Respiratory rate ≥24 bpm; At least 2 of elevated BNP/NT-proBNP, clinical pulmonary edema, CXR with congestion, LV systolic dysfunction	Change in dyspnea AUC, 24 h (1°): NS
			Death or worsening HF, 7 d: NS
EVEREST (2007),[180,181] N=4133	Tolvaptan vs placebo, for at least 60 d	Randomized within 48 h; NYHA III–IV symptoms; LVEF ≤40%; Signs of volume expansion	Composite of changes in global clinical status and body weight, 7 d (1°): P<0.001, for tolvaptan superiority; no difference in clinical status; Change in body weight, 1 d: P<0.001.
			All-cause mortality (1°): superiority P=0.68
			CV death or HF hospitalization (1°): NS
TACTICS-HF (2016),[182] N=257	Tolvaptan vs placebo	AHF within 24 h of presentation	Dyspnea relief by Likert scale: NS. Tolvaptan resulted in greater weight loss and net fluid loss compared with placebo, but tolvaptan-treated patients were more likely to experience worsening renal function during treatment.
		Elevated natriuretic peptides + 1 additional sign or symptom of congestion	
		Serum sodium ≤140 mmol/L	
SECRET of CHF (2017),[183] N=250	Tolvaptan vs placebo	AHF within 36 h of presentation; Active dyspnea; eGFR <60 mL/min per 1.73 m^2 or hyponatremia or diuretic resistance	Dyspnea reduction at day 1 (1°): NS
			Dyspnea reduction at day 3: P=0.01; Weight loss at days 1 and 3: P<0.01
PROTECT (2010),[184] N=2033	Rolofylline vs placebo for up to 3 d	Randomized within 24 h, Persistent dyspnea at rest or with minimal activity, estimated CrCl 20–80 mL/min, BNP ≥500 pg/mL or NT-proBNP ≥2000 pg/mL, IV loop diuretic therapy	Clinical composite (1°): NS
RELAX-AHF (2013),[117] N=1161	Serelaxin vs placebo for 48 h	Patients with dyspnea at rest or on minimal exertion, congestion on chest x-ray, BNP ≥350 ng/L (or NT-proBNP ≥1400 ng/L), eGFR 30–75 mL/min per 1.73 m^2, and SBP>125 mm Hg	Change in dyspnea by VAS AUC to day 5 (1°): P=0.007.
			Proportion of patients with moderately or markedly improved dyspnea by Likert scale at all 3 early time points (6, 12, 24 h; 1°): NS
			Days alive out of hospital up to day 60: NS
			180-day mortality: placebo 65 deaths vs serelaxin 42, HR 0.63 (95% CI, 0.43–0.93), P=0.02
RELAX-AHF-2 (2019),[33] N=6545	Serelaxin vs placebo	Patients with dyspnea at rest or on minimal exertion, congestion on chest x-ray, BNP ≥500 ng/L (or NT-proBNP ≥2000 ng/L), eGFR 25–75 mL/min per 1.73 m^2, SBP>125 mm Hg; start of study drug within 16 h; received ≥40 mg IV furosemide before screening	CV death at 180 d (1°): NS
			Worsening HF through day 5 (1°): NS
			Secondary end points: NS
Other trials			
3CPO (2008),[157] N=1069	NIPPV vs CPAP vs oxygen therapy (O_2)	Clinical diagnosis of cardiogenic pulmonary edema; CXR with pulmonary edema; Respiratory rate >20 bpm; Arterial pH <7.35	All-cause mortality, 7 d (1°): NIPPV + CPAP vs O_2, NS
			Composite death or intubation, 7 d (1°): NIPPV + CPAP, NS
			NIPPV+CPAP better than O_2: Change in arterial pH, 1 h (P<0.001); Dyspnea score, 1 h (P=0.008)

(*Continued*)

Table. Continued

Trial	Treatment arms	Population	Results
DOSE (2011),[142] N=308	Low- vs high-dose furosemide	Randomized within 24 h; ≥1 sign & ≥1 symptom of HF, history of chronic HF treated with furosemide 80–240 mg/d (or equivalent) for at least 1 mo	Global assessment of symptoms (1°): Bolus vs continuous infusion, NS; Low dose vs high dose, *P*=0.06
	Continuous vs intermittent intravenous bolus		
	1:1:1:1 2×2 factorial design		Mean change in SCr (1°): Bolus vs continuous infusion, NS; Low dose vs high dose, NS.
Calcitrope trials			
OPTIME-HF (2002),[104] N=951	Milrinone vs placebo, for 48–72 h	Presenting within 48 h; Known systolic HF; LVEF ≤40%. Excluded if clinically required inotropes.	Days with CV hospitalization or dead in 60 d (1°): NS
			Failure of therapy due to AE within 48 h: Milrinone 20.6% vs placebo 9.2% (*P*<0.001).
			Excess sustained hypotension (*P*=0.004), new atrial fibrillation/flutter (*P*<0.001), VT/VF (*P*=0.06).
REVIVE 1&2 (2013),[120] N=600	Levosimendan (for 24 h) vs placebo	Dyspneic at rest; LVEF ≤35%; SBP >90 mm Hg; HR <120 bpm	Clinical composite end point, 5 d (1°): *P*=0.015
			More frequent hypotension and cardiac arrhythmias, during the infusion period; numerically higher risk of death, 90 d (REVIVE 1&2: levosimendan, 49 deaths/350 patients; vs placebo, 40/350, *P*=0.29)
SURVIVE (2007),[185] N=1327	Levosimendan (for 24 h) vs dobutamine (for ≥24 h)	LVEF ≤30%; Requiring IV inotropic support; At least one of following: dyspnea at rest, oliguria, PCWP ≥18 mm Hg or CI ≤2.2 L/min per m²	All-cause mortality, 180 d (1°): NS
			Change in BNP from baseline to 24 h: *P*<0.001.
			No change in dyspnea at 24 h, days alive out of hospital at 180 d, all-cause mortality at 31 d, CV mortality at 180 d.
DAD-HF (2010),[186] N=60	Dopamine 5 µg/kg per minute plus low-dose furosemide (5 mg/h continuous infusion) vs high-dose furosemide (20 mg/h continuous infusion	Hospitalized for ADHF with evidence of volume overload and eGFR ≥30 mL/min per 1.73 m²	SCr increase >0.3 mg/dL within 24 h (1°): 6.7% low-dose dopamine/low-dose furosemide vs 30% high-dose furosemide, *P*=0.042
			>20% decrease in eGFR within 24 h (1°): 10% low-dose dopamine/low-dose furosemide vs 33.3% high-dose furosemide, *P*=0.057
DAD-HF II (2014),[102] N=161	8-h continuous infusions of (1) high-dose furosemide (n=50, 20 mg/h), (2) low-dose furosemide and low-dose dopamine (n=56), or (3) low-dose furosemide (n=55, 5 mg/h).	Dyspnea on minimal exertion or rest dyspnea; Oxygen saturation <90% on admission arterial blood gas; One or more of the following: (1) signs of congestion, (2) interstitial congestion or pleural effusion on chest x-ray, and (3) elevated serum BNP levels	No significant differences in 60-d and 1-y all-cause mortality and hospitalization for HF), dyspnea relief (Borg index), worsening renal function, and length of stay
ROSE (2013),[103] N=360	Dopamine (2 µg/kg per minute) vs nesiritide vs pooled placebo group	AHF	Compared with placebo:
		Renal dysfunction (eGFR 15–60 mL/min per 1.73 m²)	Dopamine: No significant effect on 72-h cumulative urine volume or on the change in cystatin C level; Increased tachycardia
		Randomized within 24 h of admission.	Nesiritide: No significant effect on 72-h cumulative urine volume or on the change in cystatin C level; Increased hypotension
Myotrope trials			
ATOMIC-AHF (2016),[126] N=606	3 sequential cohorts (≈200 patients per cohort): Omecamtiv mecarbil vs placebo	LVEF ≤40%; Dyspnea at rest or with minimal exertion; Elevated natriuretic peptides; Randomized within 24 h of initial IV diuretic.	Dyspnea relief: No significant difference compared with pooled placebo (1°); Increased dyspnea relief in high-dose cohort at 24 h (placebo, 37% vs OM, 51%; *P*=0.034) and through 5 d (*P*=0.038)

ADHF indicates acute decompensated heart failure; AHF, acute heart failure; AUC, Area under the curve; BNP, B-type natriuretic peptide; CPAP, continuous positive airway pressure; CrCl, creatinine clearance; CV, cardiovascular; CXR, chest x-ray; eGFR, estimated glomerular filtration rate; HF, heart failure; LOS, length of stay; LV, left ventricle; LVEF, left ventricular ejection fraction; NIPPV, noninvasive positive pressure ventilation; NTG, nitroglycerin; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; VAS, visual analogue scale; VT/VF, ventricular tachycardia/ ventricular fibrillation; and WHF, worsening heart failure.

phenotypes that account for ADHF presentations. It is also important to acknowledge that the potentially promising findings in some of the early, small studies discussed below may follow the unfortunate pattern of many preceding development programs and elude validation in larger clinical trials.

OPTIMIZING VASCULAR RESISTANCE: NOVEL VASODILATORY THERAPIES

The most promising therapeutic target in ADHF outside of decongestion with diuresis is the vasodilatory pathway, and a number of large clinical outcome trials enrolling

patients with ADHF and both HFrEF and HFpEF have been performed with drugs that produce vasodilation as a dominant pharmacological effect.

The natriuretic peptides have been investigated as a potential therapy for ADHF for over 30 years. All of these peptides signal through a set of natriuretic peptide receptors and the guanosine cyclase/cyclic guanosine monophosphate pathway to exert their downstream effects. Nesiritide is an exogenous recombinant BNP developed in increase vasodilation and augment natriuresis in patients with ADHF. Although small studies demonstrated improved diuresis and hemodynamics, multiple larger studies have not seen clinically significant improvement in clinical outcomes, renal function, effective diuresis, or weight loss.[3,103] A number of other natriuretic peptide analogs tested in ADHF cohorts have not had promising outcomes. In a cohort study of 45,595 Japanese patients treated with either intravenous carperitide (human ANP) or nitrates, patients treated with carperitide had higher in-hospital mortality, prolonged length of stay, and greater hospital costs.[110] Nonetheless, is it currently widely used in ADHF in Japan. An ANP analog, ularitide, was investigated in the TRUE-AHF trial (Trial of Ularitide Efficacy and Safety in Acute Heart Failure), enrolling 2157 patients with AHF. Ularitide did not improve a short-term clinical composite end point or cardiovascular mortality.[111] Cenderitide, a chimeric CD-NP (c-terminus dendroaspis natriuretic peptide) that interacts with both NRP-A and NRP-B receptors, has also been studied as a therapy for patients with ADHF, although it is unclear whether it will advance to larger clinical trials.[112]

Using a similar signaling pathway, the soluble guanylate cyclase activators and stimulators have been used in pulmonary hypertension (riociguat), but the cinaciguat development program for ADHF was discontinued due to increased hypotension.[113] The early vericiguat trials also had increased hypotension, although vericiguat decreased HF hospitalizations in patients with chronic HF and reduced EF in the VICTORIA trial (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction),[114] some of whom were enrolled after stabilization during an admission for ADHF. Studies are yet to be performed in patients hospitalized with ADHF.

Endothelin-1 is one of the most potent endogenous vasoconstrictor hormones, which also causes fibrosis, inflammation, and hypertrophy. Multiple endothelin receptor antagonists have been developed, and many have been approved for the treatment of pulmonary hypertension. Tezosentan is an intravenous mixed endothelin receptor antagonist specifically developed as a therapy for ADHF, however, it did not demonstrate improvement in symptoms nor cardiovascular morbidity or mortality in the VERITAS trial (Value of Endothelin Receptor Inhibition with Tezosentan in Acute Heart Failure Study).[115]

Tolvaptan inhibits vasopressin, which would normally be activated as a physiological response to hypotension, decreased atrial filling, renal hyperosmolarity, sympathetic stimulation, or angiotensin II activity and has been shown to be markedly elevated in ADHF. Vasopressin acts directly on the kidney to signal fluid reabsorption and vascular endothelial cells to signal vasoconstriction to increase arterial pressure. Tolvaptan has been thoroughly tested with hopes of preventing loop diuretic resistance and has demonstrated functionality in amplifying weight loss and diuresis in addition to diuretic therapy in patients with ADHF in multiple trials but did not demonstrate significant benefit in renal function or overall mortality.[116]

Serelaxin is a vasodilatory agent, a recombinant form of human relaxin-2 which has vasodilatory, antifibrotic, and anti-inflammatory effects on the cardiovascular and renal systems and demonstrated end-organ protective effects in animal models. The Phase 3, RELAX-AHF (RELAXin in Acute Heart Failure) trial enrolled 1161 patients within 16 hours of admission for ADHF and had promising findings including lower incidence of worsening HF and significantly decreased cardiovascular mortality in patients admitted with ADHF, as well as evidence of renal, hepatic, and cardiac end-organ protection.[40,117] Cardiovascular death was not a prespecified efficacy end point in the RELAX-AHF trial, so the RELAX-AHF-2 trial was conducted. Unfortunately, the 6545 patient RELAX-AHF-2 trial did not confirm a decreased cardiovascular mortality at 6 months in patients treated with serelaxin compared with placebo.[33] Interestingly, in both RELAX-AHF and RELAX-AHF-2, a myocardial protective effect was evident, as assessed by serial troponin release over 2 to 5 days during the initial ADHF hospitalization; a unique effect that has not been observed with any other vasodilating agent.

A number of innovative, device-based approaches to ADHF are being developed. One of these techniques includes splanchnic nerve block which in small pilot studies of 11 patients admitted with ADHF resulted in significantly improved hemodynamics and symptoms.[118] While far from demonstrating clinical utility, such approaches provide insight into future therapeutic directions.

OPTIMIZING INOTROPY: NOVEL CALCITROPE THERAPIES

Levosimendan is a calcitrope that inhibits phosphodiesterase III and amplifies troponin C activity resulting in increased calcium sensitivity to augment contractility.[26,119] It also has a potent peripheral vasodilatory effect due to activation of K_{ATPase} channels. In the REVIVE (Randomized EValuation of Intravenous leVosimedan Efficacy) I and II trials, it was found to reduce HF symptoms but increased early mortality, did not improve morbidity or mortality, and had increased adverse cardiac events, including atrial and ventricular arrhythmias and hypotension.[120] Its utility in the management of ADHF is currently controversial as some smaller studies have demonstrated benefit while larger trials bordered on detrimental results with levosimendan.

Nitroxyl donors were developed to increase cardiac contractility while also providing vasodilation. These agents,

such as cimlanod, act by signaling for post-translational modifications of target proteins, including SERCA2a, phospholamban, ryanodine receptors, and myofilament proteins in cardiomyocytes.[121] These modifications increase calcium transients and sarcomere calcium sensitivity thereby augmenting myocardial contractility and relaxation. Nitroxyl also has peripheral vasodilatory effects without inducing tachycardia. The STAND-UP AHF (Study Assessing Nitroxyl Donor Upon Presentation with Acute Heart Failure) study demonstrated multiple markers of improved end-organ decongestion with cimlanod, although without a clear increase in urine output or decreased weight.[121]

Istaroxime is a novel drug with a dual mechanism of action involving the inhibition of the sarcolemmal Na^+/K^+ pump and augmentation of the SERCA2a pump activity. These effects are mediated by the displacement of phospholamban from SERCA2a resulting in enhanced calcium reuptake by the sarcoplasmic reticulum, independently of intracellular cyclic AMP concentrations. In an early study, a 6-hour infusion of istaroxime in patients with worsening HF and HFrEF improved both systolic and diastolic left ventricular function with a mild increase in systolic blood pressure.[122,123] These findings were confirmed in another study in patients with ADHF and HFrEF with a 24-hour infusion of istaroxime.[124] The potential to increase cardiac function while augmenting systolic blood pressure represents a unique and clinically useful profile if confirmed in larger clinical trials.

OPTIMIZING INOTROPY: NOVEL MYOTROPE THERAPIES

Omecamtiv mecarbil is a cardiac myotrope that improves cardiac function by augmenting the number of myosin heads interacting with the actin filaments during the power-stroke resulting in increased contractility without increases in the calcium transient or myocardial oxygen demand.[26,125] Multiple Phase 1 and 2 trials demonstrated increased ventricular function with both intravenous and oral omecamtiv mecarbil. In the ATOMIC-AHF trial (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure), 606 patients admitted with ADHF and HFrEF were randomized to intravenous omecamtiv mecarbil or placebo in an ascending cohort design.[126] Patients in the highest omecamtiv mecarbil dose cohort experienced significantly increased dyspnea relief compared with those treated with placebo. Importantly, in all of the trials with omecamtiv mecarbil, including the 8256 patient GALACTIC-HF trial with almost 15 000 patient-years of follow-up with oral omecamtiv mecarbil, the adverse, serious adverse, arrhythmic, and ischemic events of omecamtiv mecarbil were similar to placebo, and there were no adverse effects on blood pressure, heart rate, renal function, or potassium homeostasis.[127] Also of note, 2084 patients in GALACTIC-HF (the Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) were enrolled as inpatients with even a larger treatment effect in the inpatients with higher baseline NT-proBNP.

NOVEL MITOTROPE THERAPIES

Cardiac mitotropes increase cardiac function by improving myocardial energetics and include multiple agents under investigation.[26] Perhexiline prevents fatty acid transport into the mitochondria via blockade of carnitine palmitoyl transferase and seems to improve myocardial ATP production. It has been studied in chronic HF and found to improve VO_2 max, left ventricular EF, and HF symptoms.[128] Trimetazidine inhibits thiolase thereby preventing mitochondrial oxidation of fatty acids to similarly shift cellular metabolism to glucose utilization. Small studies have demonstrated clinically significant improvement in EF and cardiac output in patients with HFrEF treated with trimetazidine.[129] Both agents need to be validated in larger randomized controlled trials.

Elampretide is a mitochondrial membrane protective agent that decreases reactive oxygen species with promising effects on cellular energetics and resultant cardioprotective effects in ischemia and reperfusion injury in animal models.[130] In small clinical trials, elamipretide has been associated with reversed mitochondrial dysfunction and improved left ventricular volumes.[131,132] A Phase 2 trial demonstrated safety in patients managed for HFrEF in the outpatient setting but did not show improved volumes with the intervention arms.[133] Larger, more extensive studies are needed to determine long-term benefits and clinical implications of elampretide therapy in ADHF.

Ranolazine is a mitotrope that is approved as an antianginal therapy. It causes inhibition of the late sodium current responsible for sodium influx during left ventricular repolarization, as well as acting as a partial fatty oxidase inhibitor.[134] No large clinical studies exist evaluating the effects in humans with HF, however, subgroup analyses of the 6560 patient MERLIN (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes) trial demonstrated improved composite cardiovascular death, myocardial infarction, and recurrent ischemia specifically in patients with HF and elevated BNP.[135] More data are necessary in a larger cohort to investigate the potential clinical utility of ranolazine in ADHF.

More recently, a dramatically effective, novel approach to mitotropic therapy in ADHF has emerged. SGLT2 (Sodium-glucose cotransporter 2) inhibitors inactivate the SGLT2 receptor of the proximal convoluted tubule preventing glucose reabsorption resulting in glucosuria and sodium excretion associated with increased natriuresis, decreased blood pressure, renal protection, and improved myocardial energetics.[136] Given that the beneficial clinical effects of these agents are independent of the presence of diabetes and appear to be disproportionate to their diuretic effects, one of the primary emerging mechanisms is the improvement in myocardial energetics, potentially through increased ketone

body substrate utilization.[137,138] In a pilot study, 80 patients admitted for AHF suggested an improvement in net fluid loss and the combined end point of in-hospital worsening HF, hospital readmission, or death within 60 days but did not demonstrate significant differences in the primary outcomes (dyspnea, diuretic response in weight loss, NT-proBNP reduction, or length of hospital stay).[139] The Phase 3 EMPULSE trial (EMPagliflozin in patients hospitalized for acUte heart faiLure who have been StabilizEd) is evaluating the clinical benefit and safety of the SGLT2 inhibitor, empagliflozin, in ≈500 patients with or without diabetes hospitalized for AHF (both de novo and decompensated).[140] The results of the SGLT2 inhibitor trials have markedly increased interest in the role of ketone bodies as therapy for ADHF.[141]

OPTIMIZING VOLUME STATUS—APPROACH TO VASCULAR CONGESTION

The therapeutic approach to diuresis in ADHF has remained relatively unchanged with intravenous agents or consideration for continuous renal replacement therapy. The DOSE trial (Diuretic Optimization Strategies Evaluation) evaluated the efficacy of high dose compared with low dose and bolus compared with continuous infusion of intravenous diuretics in a factorial design enrolling 308 patients admitted with ADHF.[142] The trial demonstrated no difference in the patient's global assessment of symptoms or change in renal function between any of the strategies. Loop diuretics are organic anions that act on the ascending Loop of Henle to inhibit reabsorption of sodium via the $Na^+/K^+/Cl^-$ cotransporter thereby increasing water excretion.[143,144] Worsening renal function results in increased endogenous anions that compete with loop diuretic binding of $Na^+/K^+/Cl^-$ cotransporters contributing to loop diuretic resistance. Additionally, chronic loop diuretic use can cause hypertrophy and hyperplasia of the epithelial cells of the distal convoluted tubule and increased sodium and, therefore, water reabsorption. Loop diuretic resistance is associated with all-cause mortality, sudden death, and death secondary to cardiac failure.[65] Medical management includes initiation of intravenous loop diuretics with bolus dosing which can rapidly improve pulmonary artery pressure. Benzothiazide diuretics augment loop diuretic effectiveness by preventing distal sodium reabsorption at the distal convoluted tubule but are less potent when used as monotherapy.[145] In the ROSE trial (Renal Optimization Strategies Evaluation), the efficacy of low-dose dopamine (renal dose) and nesiritide were evaluated in 360 patients hospitalized for ADHF with renal dysfunction.[103] Neither dopamine nor nesiritide increased cumulative urine volume nor change in renal function as assessed by cystatin C, although both strategies were associated with increased adverse events compared with placebo. When medical diuretics are unsuccessful, continuous renal replacement therapy represents a necessary therapy, although studies have demonstrated that these patients have a higher in-hospital mortality and poor long-term prognosis possibly related to myocardial stunning as demonstrated on transthoracic echocardiography with global longitudinal strain.[140]

OTHER MEDICAL THERAPIES

The noncardiac comorbidities discussed above often require intervention before discharge during ADHF hospitalizations. Similar to guideline-directed medical therapy for HF, an important consideration is an importance of initiating therapies before discharge, given the relatively poor outpatient initiation rate. As noted above, the SGLT2 inhibitors are being actively investigated as therapies for ADHF, but importantly, the SGLT2 inhibitors have been demonstrated to decrease HF hospitalizations and cardiovascular death in chronic HFrEF patients both with and without diabetes in multiple trials.[147–150] A recent trial randomized 1222 clinically stable patients with type 2 diabetes who were recently hospitalized for ADHF to sotagliflozin or placebo.[151] Initiation of the SGLT2 inhibitor before or shortly after discharge resulted in significantly decreased hospitalizations and urgent visits for HF. These studies have shown safety in initiation of SGLT2 inhibitor during hospitalizations and prescription of these agents should not be delayed to an outpatient setting. Other agents known to benefit HF patients, such as metformin and GLP-1 (glucagon-like peptide 1) agonists, are often held in the inpatient setting to avoid hypoglycemia and lactic acidosis, but reinitiation should not be forgotten before discharge because of long-term benefits including improved remodeling, improved myocardial glucose utilization, and cardiac fibrosis.[152]

Moderate-to-severe anemia (hemoglobin <12 g/dL in men or <11 g/dL in women) is an independent predictor of death in patients with AHF, although it is unclear whether anemia is a marker of poor clinical outcomes or a risk factor.[153] A number of trials have supported the beneficial effects of iron replacement therapy with intravenous ferric carboxymaltose in patients with chronic HFrEF and iron deficiency, independent of the presence of anemia.[154,155] The suspected mechanism of benefit is related to micronutrient optimization as iron is critical for oxygen transportation, mitochondrial function, myocardial metabolism, and oxidative stress management.[156] The effect of ferric carboxymaltose in 1132 patients hospitalized for ADHF with EF ≤50% and iron deficiency was investigated in the AFFIRM-AHF trial (Ferric Carboxymaltose in Iron-Deficient Patients Discharged After Acute Heart Failure) where this therapy decreased the risk of HF hospitalizations within up to 52 weeks.[77] Although it is unclear whether iron replacement therapy is effective in directly treating ADHF, it clearly reduces subsequent clinical events.

Noninvasive ventilation (NIV) has multiple indications in ADHF. The 3CPO trial (three interventions in Cardiogenic Pulmonary Oedema) randomized 1069 patients with acute

cardiogenic pulmonary edema to standard oxygen therapy, continuous positive airway pressure, or noninvasive intermittent positive pressure ventilation.[157] Although there was no difference in 7-day mortality between the treatment groups, patients treated with NIV had greater dyspnea relief and other improved metabolic markers. This trial and others provide the basis for the utility of NIV in patients with ADHF.[157-159] Beyond reaching euvolemia, patients with ADHF should be evaluated for obstructive sleep apnea and optimization of concurrent to initiate and optimize NIV and improve ventilation. Physiologically, NIV can cause decreased preload and afterload and reduced intrapulmonary shunting, although it is unclear if there are short- or long-term survival benefits. It should be used with caution in patients with isolated right ventricular dysfunction.

Given the role of oxidative stress in the pathophysiology of ADHF, many studies have looked into the utility of oxygen supplementation therapy independent of presence of hypoxia. It is suspected that supplemental oxygen therapy in normoxemic patients results in increased reactive oxygen species and paradoxical oxidative stress as a result of hyperoxia-mediated coronary and systemic vasoconstriction.[160] In the AVOID trial (Air Versus Oxygen In Myocardial Infarction), supplemental oxygen resulted in increased myocardial injury and infarct size in patients admitted with ST-segment–elevation myocardial infarction.[161] In HF cohorts, hyperoxia secondary to oxygen supplementation in normoxemia was associated with impaired diastolic function, increased left ventricular filling pressures, and increased systemic vascular resistance resulting in decreased cardiac output.[162,163]

EVALUATION OF DISCHARGE READINESS

Considering the unacceptably high rates of mortality following hospitalization for ADHF and worse prognosis with recurrent hospitalizations, it is critical to find a standard approach to evaluating these patients before discharge to decrease rehospitalizations.[164] Rehospitalization is often related to inadequate decongestion during index hospitalization with poor appreciation of continued hemodynamic congestion in the absence of overt clinical congestion. The following tools can assist in appropriately evaluating patients before discharge.

Noninvasive provocative exams, such as orthostatic vitals and Valsalva effects on blood pressure, can evaluate persistent hemodynamic congestion.[18] Ultrasound evaluation of intravascular congestion via inferior vena cava measurements, pulmonary venous and hepatic venous flow, and outflow velocity-time integrals can provide objective estimates of hemodynamics. Bioimpedence measures fluid content and cardiac outflow and velocities to estimate cardiac output and filling pressures,[165–167] and in one study, it decreased invasive pulmonary artery catheter placement in patients being managed for cardiogenic shock.[168] Despite promising data, few studies have been completed in the ADHF population to guide the use of noninvasive assessment tools during hospitalizations.

Monitoring natriuretic peptide levels as an assessment of readiness of discharge or predicting rehospitalization has produced variable results. Multiple studies have associated BNP decline with better postdischarge outcomes and persistently elevated BNP levels with poor prognosis.[169–171] In the REDHOT (Rapid Emergency Department Heart failure Outpatients Trial), patients with baseline elevated BNP who had repeat level <200 pg/mL before discharge were associated with very low 90-day mortality (2%) which supports its utility for determining pretest probability of continued vascular congestion and poor prognosis at time of discharge.[172] The inconsistent findings among a number of studies indicate that rather than using BNP as a direct therapeutic target, it can help predict postdischarge outcomes with reassurance in patients who have a decline and/or BNP level <200 pg/mL (higher specificity). Currently, there are no reliable acute biomarkers for therapeutic targets during hospitalization for ADHF.

It is important to acknowledge specific clinical factors that tend to be associated with worse outcomes in patients with rehospitalizations for ADHF. This includes hyponatremia, worsening renal function, hypotension (particularly intolerant of GDMT [guideline-directed medical therapy]), anemia, persistently elevated BNP, and ventricular dyssynchrony.[173] Although these may not be therapeutic targets, presence of any of these factors at time of discharge should prompt planning for close follow-up within a couple of weeks to avoid risk of rehospitalization during the vulnerable phase as described by Greene et al.[174] The increased utility of telemedicine during the coronavirus pandemic can serve as reassurance that it will continue to be a useful tool to increase early-discharge follow-up and monitoring for concerning signs or symptoms of progressive congestion. Shared decision-making should be approached regarding indication and utility of chronic hemodynamic monitoring with pulmonary artery implantable devices such as CardioMEMS.[25,175,176] Multidisciplinary teams, including pharmacists, social work, and physical therapy to name a few, can improve long-term outcomes in this patient population by avoiding rehospitalizations secondary to poor health care literacy, medication noncompliance, psychosocial factors, and progressive deconditioning.[177]

Although this article did not focus on chronic therapeutic options, it is essential to highlight the importance of optimizing guideline-directed medical therapy before discharge. It is critical to acknowledge the abysmal prescription rates in the outpatient setting for appropriate and life-saving agents, including ACE inhibitors, ARBs, ARNIs (Angiotensin Receptor Neprilysin Inhibitors), β-blockers, and MRAs.[64,178] Additionally, with growing literature supporting improved outcomes and decreased rates of rehospitalizations, initiation of SGLT2 inhibitor, and iron repletion should be considered before discharge.

CONCLUSIONS

Although management options for CHF continue to expand and improve outcomes, the same advances have not been achieved among patients with ADHF. ADHF is a distinct entity with a multifaceted pathophysiology that has yet to be clearly elucidated and, therefore, not effectively managed. A better understanding of the condition on a cellular and molecular level would allow targeting of crucial therapies, including vasodilators, agents that improve cardiac function such as myotropes and mitotropes, and possibly therapeutics to address the inflammatory and other pathways. Additionally, significant work needs to be completed to better understand the role of active management of comorbidities during ADHF hospitalizations. Multidisciplinary teams both in-hospital and postdischarge can be key to decrease risk of rehospitalization. Effective clinical evaluation of patients with ADHF is also limited, with few validated biomarkers and noninvasive evaluation tools currently available. Overall, a multipronged attack on the morbidity and mortality of ADHF is critical and has been underappreciated for far too long.

ARTICLE INFORMATION

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