Circulation: Heart Failure

ADVANCES IN HEART FAILURE

Conceptual Considerations for Device-Based Therapy in Acute Decompensated Heart Failure

DRI_2P_2S

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ABSTRACT: Acute decompensated heart failure remains the most common cause of hospitalization in older adults, and studies of pharmacological therapies have yielded limited progress in improving outcomes for these patients. This has prompted the development of novel device–based interventions, classified mechanistically based on the way in which they intend to improve central hemodynamics, increase renal perfusion, remove salt and water from the body, and result in clinically meaningful degrees of decongestion. In this review, we provide an overview of the pathophysiology of acute decompensated heart failure, current management strategies, and failed pharmacological therapies. We provide an in depth description of seven investigational device classes designed to target one or more of the pathophysiologic derangements in acute decompensated heart failure, denoted by the acronym DRI_2P_2S. Dilators decrease central pressures by increasing venous capacitance through splanchnic nerve modulation. Removers remove excess fluid through peritoneal dialysis, aquaphoresis, or hemodialysis. Inotropes directly modulate the cardiac nerve plexus to enhance ventricular contractility. Interstitial devices enhance volume removal through lymphatic duct decompression. Pushers are novel descending aorta rotary pumps that directly increase renal artery pressure. Pullers reduce central venous pressures or renal venous pressures to increase renal perfusion. Selective intrarenal artery catheters facilitate direct delivery of short acting vasodilator therapy. We also discuss challenges posed in clinical trial design for these novel device–based strategies including optimal patient selection and appropriate end points to establish efficacy.

Key Words: heart failure ■ hospitalization ■ patient selection ■ renal artery ■ splanchnic nerves

The clinical, societal, and financial burdens of acute decompensated heart failure (ADHF) are well established.[1–4] ADHF remains the most common cause of hospitalization in older adults; almost 33% of patients hospitalized with ADHF are rehospitalized within 60 to 90 days of discharge, and nearly 66% die or will be rehospitalized within 1 year.[5,6] Studies with implanted heart pressure monitors show that a period of gradually increasing cardiac filling pressures, which may be upward of 40 days, often precedes overt clinical symptoms such as weight gain and dyspnea that prompt patients to seek urgent, unscheduled attention.[2,7–12] Despite attempts at medical optimization to achieve euvolemia during ADHF admissions, persistently elevated central venous pressure (CVP), pulmonary capillary wedge pressure, and biomarkers of congestion are observed at hospital discharge in up to 80% of patients and up to 55% of patients fail to lose weight during hospitalization. These parameters portend a markedly increased risk of 30-day rehospitalization.[13–20] The high morbidity, mortality, and economic costs of ADHF are explicable, in part, by limitations of loop diuretics and lack of new efficacious medical decongestive therapies. Indeed, a myriad of drug-based interventions for ADHF have failed to enhance the speed or magnitude of in-hospital symptomatic improvement or reduce 30-day postdischarge event rates (Table I in the

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Nonstandard Abbreviations and Acronyms

ADHF	acute decompensated heart failure
SVC	superior vena cava

Data Supplement). This has motivated the development of device-based strategies targeting at least 7 different mechanisms that could potentially alleviate intravascular and extravascular fluid overload.

The main goals of this review are to provide an overview of the pathophysiology of ADHF and focus on 7 classes of mainly investigational device-based therapies, classified by the primary mechanism in which they improve hemodynamics in ADHF, which we denote using the acronym DRI_2P_2S (Table; Figure 1). We also discuss challenges establishing parameters for identifying patients most suitable for these therapies and difficulty selecting clinically meaningful end points in study design.

FAILURE OF MEDICAL THERAPY IN ADHF: AN ODE TO THE KIDNEYS

The pathophysiology of fluid retention in ADHF in patients with advanced disease has been detailed previously (Figure 2A).[21] In brief, reduced circulating blood pressure and cardiac output due to impaired contractility activates baroceptors, stimulates the renin-angiotensin-aldosterone system, and releases nonosmotic vasopressin. These factors increase vascular resistance, including that of the renal artery, and lead to renal sodium and water retention, which expands circulating plasma volumes and increases systemic and pulmonary venous pressures. In addition, splanchnic vasoconstriction promotes a functional shift of blood from the unstressed to the stressed blood volume pool, thereby further increasing venous pressures.[22,23] These mechanisms collectively result in the signs and symptoms of congestion and decompensated heart failure.

Diuretic Response and Resistance

Loop diuretics remain the cornerstone of decongestive therapies for heart failure patients to maintain a euvolemic state, despite the lack of high-quality data demonstrating clinical benefit on cardiovascular outcomes. Intensification of loop diuretics can reverse the course of volume accumulation and obviate hospitalizations.[24] Diuretic response, broadly characterized by the ability to achieve natriuresis, diuresis, and ultimately clinical decongestion following administration of appropriate doses of diuretic, depends on multiple factors. Loop diuretics block the sodium-potassium-chloride co-transporter on the luminal side of the loop of Henle and increase urinary sodium excretion. This process requires active proximal secretion of sodium via protein transporters, which is dependent on renal blood flow. While 25% of filtered sodium is reabsorbed in the thick ascending limb, the remainder of sodium reabsorption in the nephron occurs in the proximal and distal convoluted tubules, limiting the quantity of sodium excreted with loop diuretics and ultimately leading to the production of hypotonic urine.[25]

In ADHF, patients can exhibit reduced responsiveness to diuretics, often referred to as diuretic

Table. DRI_2P_2S Classification of Device-Based Approaches Under Investigation to Treat ADHF

Mechanistic Class	Nickname	Mechanism	Drug Example	Device Example	Phase of Study in ADHF
D	Dilators	Increase venous capacitance	Nitrates	Splanchnic denervation	Pilot human studies completed
R	Removers	Direct removal of sodium and/or water	Diuretics	Aquaphoresis, peritoneal dialysis	Large, randomized studies of aquaphoresis, pilot study of Alfapump completed
I_1	Inotropes	Increase LV contractility, typically combined with vasodilation	Dobutamine, milrinone, levosimendan	Cardiac plexus nerve stimulation	Pilot studies underway
I_2	Interstitial	Accelerate removal of lymph	PDE III inhibitor (olprinone)	Lymphatic duct decompression	Pilot studies underway
P_1	Pushers	Increase renal arterial pressure	Pressors	Suprarenal descending aortic pumps	Pilot studies of Reitan pump completed, studies of aortic and second heart assist not yet underway in humans
P_2	Pullers	Decrease renal venous pressure	Nitrates/diuretics	Suprarenal IVC blood pump, intrarenal vein pump, infrarenal partial obstruction, intermittent SVC occlusion	Proof of concept study for PreCardia completed, first in man study for Doraya is underway
S	Selective	Selective intrarenal artery vasodilator drug delivery	None	Intrarenal delivery catheter of fenoldepam or papaverine	Animal studies completed

ADHF indicates acute decompensated heart failure; IVC, inferior vena ceva; LV, left ventricle; PDE, phosphodiesterase; and SVC, superior vena cava.

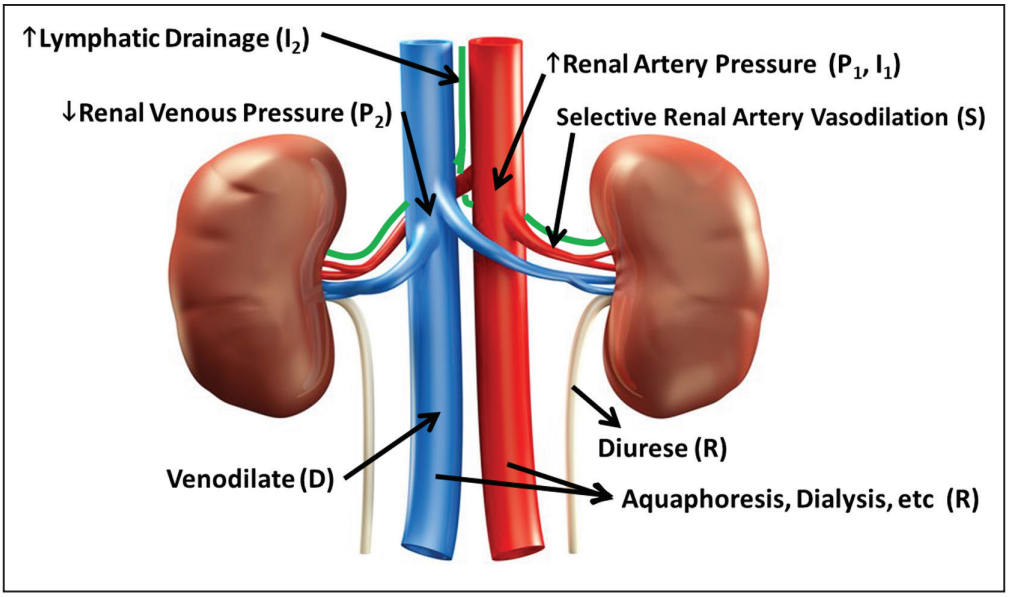

Figure 1. Overview of the mechanisms of DRI_2P_2S.
Dilators (D) increase arterial and venous abdominal capacitance through splanchnic nerve modulation, removers (R) remove excess fluid through peritoneal dialysis or aquaphoresis, catheter-based inotropes (I_1) directly modulate the cardiac nerve plexus, interstitial (I_2) catheters accelerate removal of through lymphatic duct decompression, novel rotary-flow pushers (P_1) in the descending aorta directly increase renal artery pressure, pullers (P_2) reduce central venous pressures and renal venous pressures, and selectives (S) deliver intrarenal vasodilator therapy.

resistance. Several studies have shown that a poor diuretic response is associated with a higher risk of re-hospitalizations and death.[26,27] Diuretic resistance can be caused by several mechanisms (Figure 2B) including impaired absorption of diuretics in the gut, inability of the drug to bind to albumin due to hypoalbuminemia, reduced renal filtration (caused by decreased renal blood flow and/or increased CVP), proximal sodium reabsorption, competitive binding by organic acids to the organic anion transporter, distal sodium reabsorption due to the braking phenomenon, and activation of the renin-angiotensin-aldosterone system.[10,21,28,29] As the intravascular volume expands and venous pressures increase, glomerular filtration rate decreases, reinforcing progressive renal dysfunction, diuretic resistance, and volume accumulation.

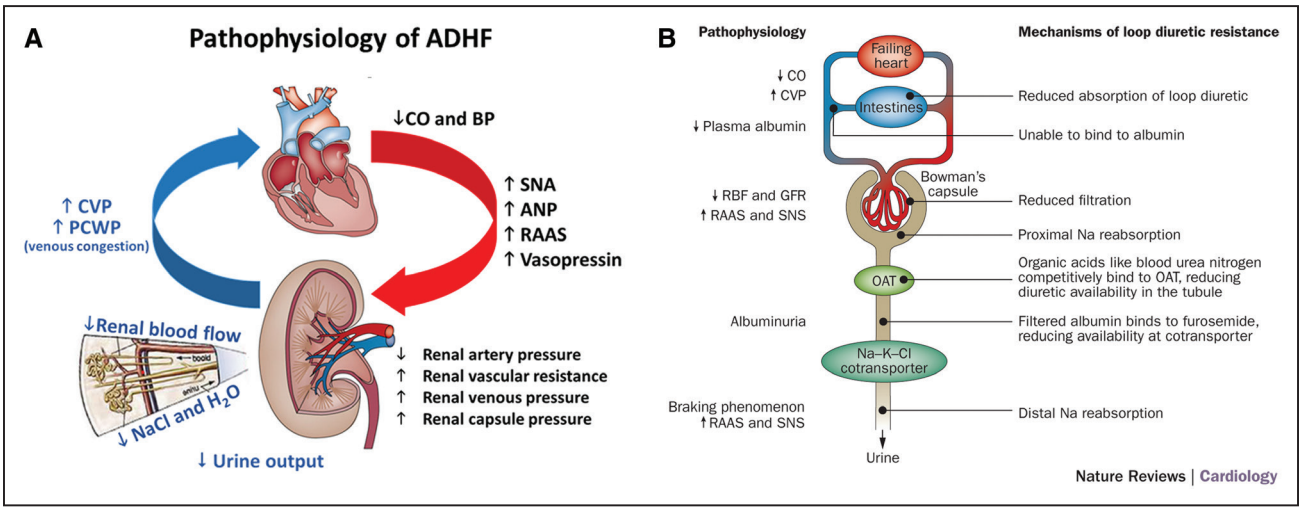

Figure 2. The pathophysiology of fluid retention and mechanisms of diuretic resistance in acute decompensated heart failure (ADHF).
A, Decreased cardiac output and blood pressure lead to activation of the renin-angiotensin-aldosterone axis, nonosmotic vasopressin release, and upregulation of the sympathetic nervous system. These effects lead to decreased renal artery pressure, decreased renal blood flow, and increased sodium and water retention, thereby increasing central pressures. Elevation in renal venous pressures in addition to decreased renal artery perfusion lead to increased renal capsule pressure and further reduction in urine output. **B**, An overview of diuretic resistance in decompensated heart failure. High central pressures lead to intestinal edema and decreased oral diuretic absorption. Decreased renal blood flow leads to reduced filtration and decreased delivery of loop diuretic to the nephron. Proximal or distal sodium reabsorption further limit the ability to achieve affective natriuresis and diuresis. CVP indicates central venous pressure. Reprinted from ter Maaten et al with permission. Copyright© 2015, Springer Nature.

Although the clinical phenomenon of diuretic resistance is well known to clinicians, precise definition of this phenomenon has been challenging. Nevertheless, the literature reports up to 20% to 50% of hospitalized patients with ADHF have a poor response to IV loop diuretics.[27,30,31] The use of weight loss, hemoconcentration, urine volume output, spot urine sodium, and clinical measures of congestion are proposed measures to determine appropriate diuretic response. In the face of congestion with administration of loop diuretic, a spot urine sodium content of <50 to 70 meq/L after 2 hours and/or urine output of <100 to 150 mL/hour during the first 6 hours is useful to identify patients with diuretic resistance.[32–35] Timely identification of these patients is key to provide escalation of adjuvant diuretic therapies or other advanced decongestive strategies.[36]

PHARMACOTHERAPY IN ADHF: TRIALS AND TRIBULATIONS

A myriad of pharmacological therapies (including adjuvant diuretics, vasodilators, and inotropes) aimed at improving hemodynamics and relieving congestion in ADHF have been tested but, as yet, have not yielded new effective therapeutic strategies, at least in terms of reducing 30-day readmission rates (Table I in the Data Supplement). It is noteworthy that while several of these therapies demonstrate short-term beneficial biochemical, symptomatic, and hemodynamic effects, these successes fail to translate into meaningful clinical outcomes (eg, reduced rates of rehospitalization or mortality).[37–40] As a result, even in the 2019 ACC Expert Consensus Decision Pathway, there has been little advancement in expert consensus for standardized therapy of patients admitted to the hospital with ADHF.[41]

DEVICE-BASED THERAPIES FOR ADHF

The large, unmet need and lack of significant progress in the development of effective pharmacological therapies for ADHF has stimulated interest in a host of investigational device-based therapies. These strategies can be classified mechanistically based on the way in which they intend to improve central hemodynamics, increase renal perfusion, remove salt and water from the body to achieve clinically meaningful degrees of decongestion. We denote these device classes with the acronym DRI_2P_2S: dilators, removers, inotropes, interstitial, pushers, pullers and selective. As summarized in the Table and illustrated in Figure 1, each of these mechanisms has a drug-based precedent and the devices are in various phases of clinical study. In general, in contrast to their drug-based precedents, which may have off-target and secondary mechanisms of action, these devices in principle more specifically target the pathophysiologically deranged mechanism of decompensation and diuretic resistance. In this review, we included investigational devices for ADHF identified by performing a survey of the co-authors and performing extensive searches of PubMed and www.ClinicalTrials.gov. We include devices under investigation for ADHF but did not include devices for the treatment of cardiogenic shock, such as mechanical circulatory support, or durable left ventricular assist devices for the management of chronic heart failure.

Dilators (D)

The veins of the abdomen normally have a high capacity to store and mobilize blood. These vessels contain anywhere from 20% to 50% of the total blood volume and serve as a major blood reservoir and buffer for regulating central and peripheral venous pressures.[22,23,42] In animal models of ADHF, increased sympathetic tone decreases venous capacity via vasoconstriction of the splanchnic vasculature and redistributes volume into the thoracic cavity which increases systemic and pulmonary venous pressures.[43] Functional shifts of blood from the unstressed to the stressed blood volume pool are a primary mechanism of acute and chronic increases in central and peripheral venous pressures.[22,23] Clinically, this pathophysiology is observed in patients presenting with signs and symptoms of congestion without significant weight gain, concepts confirmed by multiple studies with implantable cardiac monitors demonstrating that weight gain often does not occur before increases of filling pressures.[22]

Vasodilators such as nitroprusside and nitroglycerine have potent effects on both arterial and venous tone and can improve symptoms and congestion in ADHF; diuretics also have vasodilatory actions, though to a more limited extent. CVP decreases as blood shifts from the central compartment back to the peripheral splanchnic venous bed. Vasodilators also decrease ventricular afterload, improving cardiac output but at the risk of systemic hypotension.

Catheter-based splanchnic nerve modulation is an investigational therapy aimed at increasing both arterial and venous capacitance in the abdominal cavity (Figure 3).[44] In the Splanchnic HF-1 pilot study of 11 patients, temporary bilateral splanchnic nerve block using lidocaine resulted in ≈8 mm Hg reductions of mean pulmonary artery and capillary wedge pressures, and 0.4 L/min/m^2 increases in cardiac index and improvement of patient-reported symptoms, without causing systemic hypotension.[45,46] Despite acknowledged limitations typical of small scale studies, this study has provided initial proof of concept that reduction of sympathetic tone by this method can regulate central and pulmonary venous pressures. A

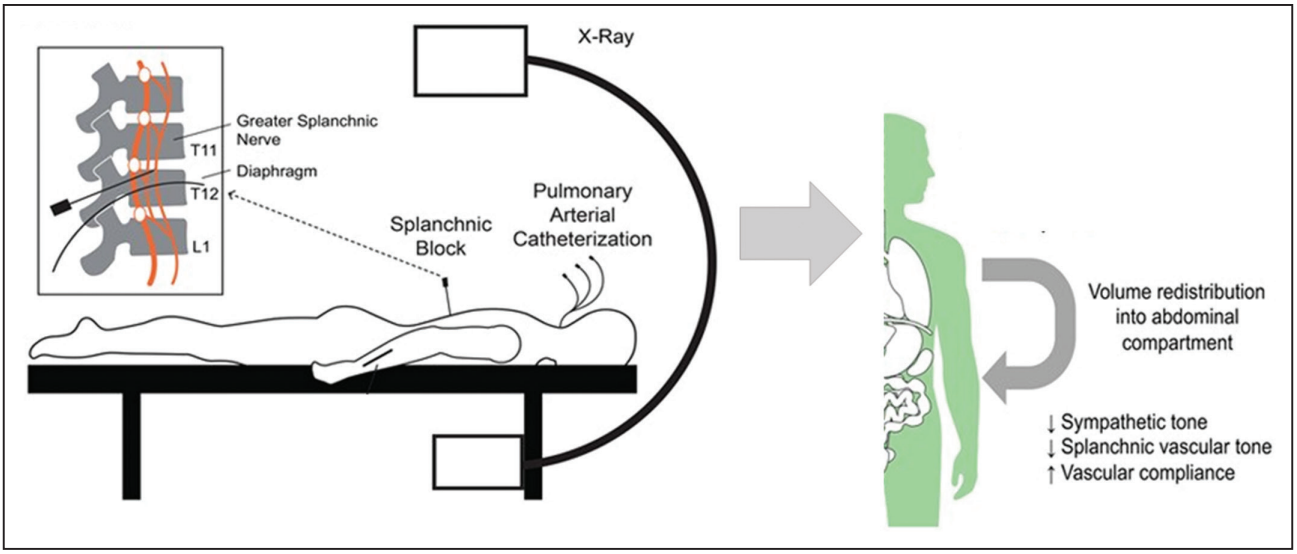

Figure 3. Dilators.
Catheter-based splanchnic nerve modulation increases both arterial and venous capacitance in the abdominal cavity aiming to reduce venous pressures. Reprinted from Fudim et al[45] with permission. Copyright© 2018, Wolters Kluwer Health, Inc.

follow-up study is investigating the impact of temporary splanchnic nerve block on exercise tolerance and invasive hemodynamics during exercise (www.clinicaltrials.gov identifier NCT03453151). While procedures have thus far been performed by direct injections via transcutaneous needle puncture, devices are under development to reach and block the greater splanchnic nerve percutaneously.

Removers (R)

As noted, loop diuretics are the mainstay of medical therapy but associated with a high incidence of diuretic resistance, and a number of novel drugs have failed to improve upon their efficacy or result in the avoidance of diuretic resistance. However, removing excess fluid from patients with ADHF is still essential for treating the volume overloaded (congested) patient with ADHF. Ultrafiltration (Figure 4), either by aquaphoresis or peritoneal dialysis, has been investigated as a method for direct sodium and water removal while avoiding significant intravascular volume depletion. With both strategies, fluid that is isotonic and isonatremic to plasma is slowly removed, leading to both total body sodium and water loss while maintaining stable hemodynamics and preserving renal perfusion. Peritoneal dialysis has the additional advantage of reducing intraabdominal pressure and potentially alleviating compressive forces which compromise kidney function. In contrast to loop diuretics, which remove primarily hypotonic urine, cause large volume shifts, and lead to relative renal hypoperfusion, ultrafiltration slowly removes isotonic fluid. Additionally, ultrafiltration does not decrease sodium delivery to the macula densa and thus mechanistically avoids the neurohomornal activation and accompanying sodium and water reabsorption precipitated by loop diuretics. In both the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD)[47] and Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF)[48] trials, decongestion with aquaphoresis resulted in increased net fluid loss and led to a reduction in HF readmissions compared with loop diuretics. In the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF)[49] study, ultrafiltration led to hemodynamic improvement but was not beneficial for patients who had already developed renal impairment and was associated with an increased number of adverse events.[50] The discrepancies in these study results suggest that ultrafiltration may be useful before the development of renal impairment in ADHF. However, important differences between the studies should be mentioned including a significantly lower rate of ultrafiltration and more aggressive pharmacological protocol in CARESS-HF compared with the UNLOAD and AVOID-HF studies, potentially leaving open the question of whether patients with renal impairment would also benefit, had there been no differences in the rate of ultrafiltration or medical therapy.

The use of peritoneal dialysis in the setting of refractory heart failure has long been described, and small studies have reported improvement in symptoms, quality of life, and neurohormonal activation in patients with refractory congestion despite high- dose loop diuretics.[51] In a prospective observational study of 159 outpatients with refractory heart failure, peritoneal dialysis was associated with improvement in New York Heart Association class and decreased HF hospitalizations.[52] Direct sodium removal using a sodium-free osmotic solution compared with standard peritoneal dialysis solution in a phase 1 study of end stage renal disease patients on

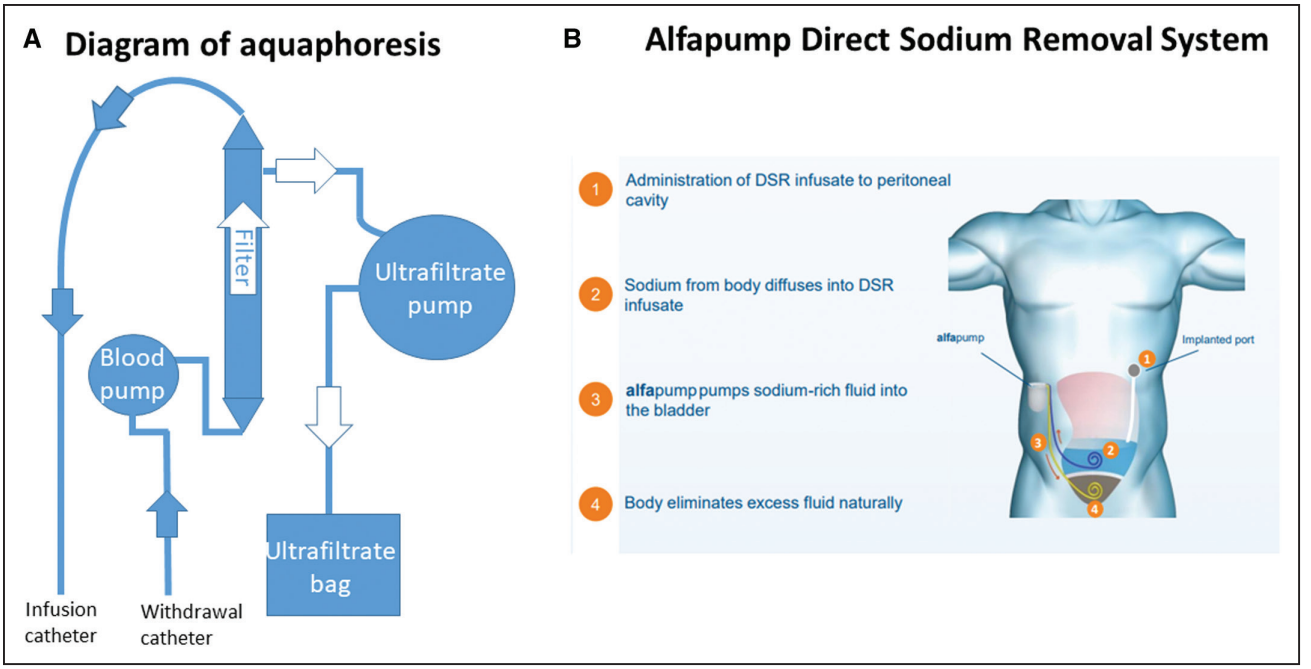

Figure 4. Removers.
A, Ultrafiltration gently removes isotonic and isonatremic excess fluid. **B**, The alfapump system uses a zero sodium peritoneal dialysate to facilitate removal of sodium-rich fluid. A catheter connected from the peritoneal cavity into the bladder allows natural excretion of dialysate fluid. DSR indicates direct sodium removal.

peritoneal dialysis lead to substantially higher sodium removal (4.5 versus 1.0 grams).[53] In a pilot study, the newly developed Alfapump direct sodium removal system (Figure 4B) was shown to be safe and improved net sodium and volume loss using direct sodium removal compared with standard peritoneal dialysis in patients with ADHF.[54] This system also has potential use for long-term fluid management in patients with heart failure with compromised renal function developing diuretic resistance via a pump implanted in the peritoneum and effluent draining directly into the bladder.

A new strategy for volume removal is being investigated with The Reprive system, an automated fluid management system that allows more accurate control of a target fluid balance by measuring urine output and replacing excess removed volume with normal saline. The appearance of the device is similar to that of other compact aquaphoresis systems with the exception of a urine collection and measurement bag and a secondary pump for reinfusion of normal saline. The Reprive system is designed to work in conjunction with loop diuretics to maintain intravascular fluid volume, cardiac output, and renal perfusion and thus avoid upregulation of the renin-angiotensin-aldosterone system and the associated sodium and fluid retention. In 2 first in man studies, TARGET-1 and TARGET-2,[55] which combined included 19 patients with ADHF, the study met its goal of achieving net fluid output of 200 mL/hour (2400 mL/24 hours). Specifically, urine output during the 24-hour treatment period averaged 6284 mL, compared with an average of 1966 mL during the 24 hours before treatment. Urine sodium concentration increased by ~8 mmol/L during treatment, and median sodium excretion was 9.7 mmol/hour during therapy. Additionally, there was an associated ~3 mmHg reduction in CVP and improvement in patient reported symptoms. The therapy was safe, without adverse effects on systemic blood pressure. These results await further confirmation in larger patient cohorts with ADHF.

Inotropes (I_1)

Inotropes such as dobutamine, milrinone, dopamine, and levosimendan are frequently used in patients with ADHF showing inadequate response to diuretics. Side effects include tachycardia, hypotension, and arrhythmias. In addition, studies have broadly failed to show long-term benefit on patient outcomes (Table I in the Data Supplement).

The cardiac plexus contains both sympathetic and parasympathetic cardiac nerves, which modulate heart rate, myocardial contraction, and relaxation. Intravascular electrical stimulation of the cardiac plexus has been shown to increase ventricular contractility without increasing heart rate in animal models[56,57] and in human subjects with heart failure. In recent proof of concept and feasibility studies, stimulation of the nerves in the right pulmonary artery (Figure 5) for 1 hour was safe and resulted in >20% increase in contractility and a 13% increase in mean arterial pressure without an

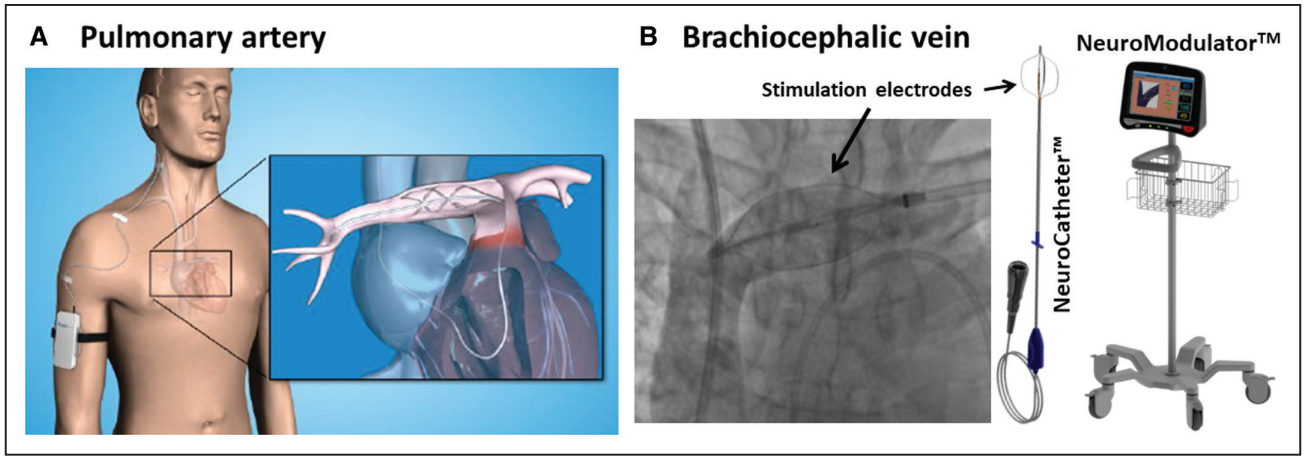

Figure 5. Inotropes.
A, Direct cardiac plexus stimulation modulates both the sympathetic and parasympathetic nervous system aiming to increase ventricular contractility and mean arterial pressure without increasing heart rate. **B**, Similarly, simultaneous transvenous electrical stimulation of the right vagus nerve and postganglionic sympathetic nerves also increases contractility, with minimal effect on heart rate and potentially decreases systemic vascular resistance.

increase in heart rate (Cardionomic, Inc). Similarly, the NeuroTronik cardiac autonomic nerve system placed in the left brachiocephalic vein aims to stimulate both cardiac branches of the vagus nerve and postganglionic cardiac sympathetic nerves as they pass to the cardiac plexus with the goal of an increase in contractility with little impact on heart rate and potentially with a decrease in systemic vascular resistance. In a recent single arm pilot study in patients admitted with ADHF, placement of the cardiac autonomic nerve system led to a significant increase in cardiac index, decrease in systemic vascular resistance, and decrease in wedge pressure with little change in blood pressure or heart rate.[58] Ongoing pilot studies are underway with these technologies to further test the efficacy and safety of neural stimulation over longer periods of time (www.clinicaltrials.gov identifiers: NCT03169803, NCT03542123).

Interstitial (I_2)

The lymphatic system is responsible for maintaining normal extravascular fluid volume by providing a route of return for fluid entering the interstitium from the vasculature (Figure 6). Under normal conditions, ≈80% of lymph flows through the left thoracic duct and is returned to the venous system near the junction of the left subclavian and internal jugular veins. Early clinical studies showed that in chronic compensated heart failure, thoracic duct flow is similar to normal, nonheart failure patients (≈1 mL/minute). In states of decompensation, whether it be acute or acute on chronic, thoracic duct flow increases (on average to ≈8 mL/minute).[59] However, while flow is increased, the flow capacity of the lymphatic system is overwhelmed by the increase capillary filtration leading to tissue edema; that is, there is a relative deficiency in lymphatic flow.

Regarding lymph production, elevated venous pressure increases fluid and protein flux across the wall of the microcirculation vessels with the flux also determined by vascular wall permeability. The permeability of the microcirculation, in turn, is determined by properties of a small pore glycocalyx matrix, membrane-bound water transport channels (aquaporin), large diameter intercellular clefts between endothelial cells (sinusoidal cells in the liver and spleen), and a large pore plasma protein transport system. Several of these factors, along with extravascular oncotic pressure and intravascular hydrostatic pressure, differ significantly among different organs, which contributes to the fact that different organs are more or less susceptible to development of congestion.

Concomitant with the increased fluid flux into the interstitium, return of lymph back to the venous system is impeded. The main mechanisms of return of lymph to the venous system involves active rhythmic contractions of lymphatic vessels whose pumping efficiency is enhanced by lymphatic valves[60,61] and by a negative pressure gradient from tissue interstitial space to CVP. Normally, at venous pressures of 0 to 5 mmHg, lymph flows freely, but the pumping of the lymph through the thoracic duct cannot overcome elevated CVP characteristic of ADHF.

Surgical external lymphatic drainage as a method of volume removal in ADHF was first described in 1969.[59] In this study, the lymphatic circulation was vented via the externalized cervical thoracic duct and led to decreased CVP and diminished edema within hours. A surgical approach has also been described for patients with a lymphatic complication of Fontan circulation, by which the innominate vein is anastomosed to the left atrial appendage, a lower pressure structure in the Fontan circuit.[62] Preclinical studies have also explored the possibility that

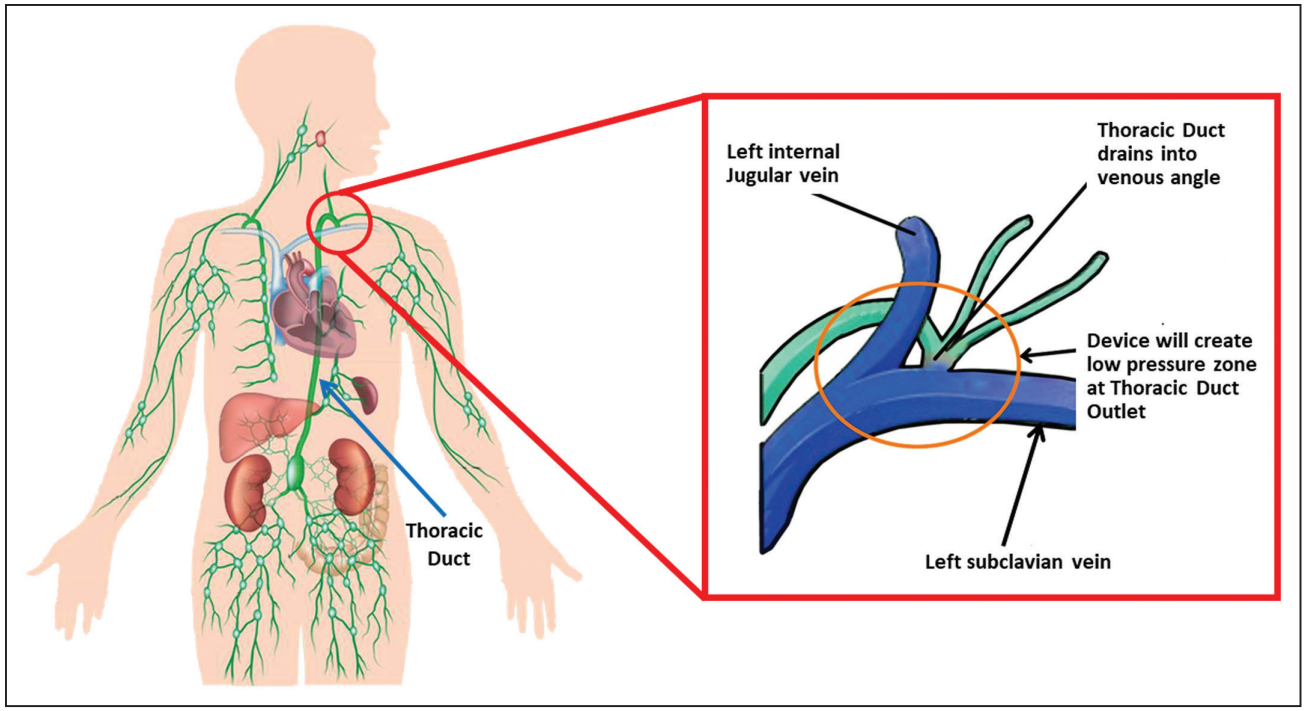

Figure 6. Interstitial.
Overview of lymphatic anatomy emphasizing the dominant role of the thoracic duct (TD) in draining abdominal organs and left lung, with less important role of the right thoracic duct. The WhiteSwell system utilizes transcatheter decompression of the thoracic duct by creating a low pressure zone at the thoracic duct outlet (near the junction of the left internal jugular and subclavian veins) to facilitate lymphatic drainage and subclavian veins to facilitate lymphatic drainage.

certain pharmacological agents (eg, the phosphodiesterase III inhibitor olprinone[38]) may enhance lymphatic contractility and thereby facilitate flow through the duct in the face of increased afterload.

Accordingly, reduction of the load opposing flow through the thoracic duct offers another approach to reducing organ congestion. A transcatheter method to decompress the thoracic duct has been developed for this purpose. The WhiteSwell system (Figure 6) utilizes a catheter-based system designed to isolate and create a low-pressure region where the thoracic duct drains into the venous system, most often at the junction between the subclavian and internal jugular veins. This low-pressure region is intended to facilitate lymphatic drainage, thus potentially decongesting the interstitial space in the lungs, liver, kidney, gut, and other vital organs. In addition to direct effects, decongestion of the kidney can theoretically reduce renal interstitial and capsule pressure and, like relief of intraabdominal pressure with drainage of ascites, improve renal function. Pilot studies with the WhiteSwell system have been initiated.

Pushers (P_1)

Hypotension leading to decreased renal perfusion is a common reason for decreased urine output and decreased effectiveness of diuretics in ADHF. Vasopressors can increase systemic blood pressure but can also paradoxically constrict renal arteries and arterioles, which may blunt any increase in renal perfusion.

Novel intravascular rotary flow pumps positioned in the descending aorta have been designed to directly increase renal artery pressure and renal perfusion, hence the term Pushers (Figure 7A through 7C). These devices include the Reitan catheter pump (RCP, a 10F collapsible device with a rotational propeller), the Procyrion Aortix pump (an 18F axial flow pump), and the Second Heart Assist pump (an aortic stent-based pump). Both the Reitan and Second Heart Assist systems employ a propeller-like design, while the Aortix is a micro-axial flow pump. These devices, deployed in the suprarenal descending thoracic aorta, displace blood and create a negative pressure head above the pump and reduce left ventricular afterload, thereby potentially increasing cardiac output. Preclinical testing showed that in contrast to thoracic positioning, abdominal positioning of the newest generation Aortix device reduces left ventricular afterload and increases cardiac output at low speeds. At higher speeds, an increase in mean pulmonary artery pressure was observed, suggesting an increase in venous return.[63] In a small prospective study of the Reitan pump in 18 patients with ADHF, average cardiac index increased by 0.6 L/min/m^2 (P=0.04) at 24 hours with an associated increase of estimated glomerular filtration from 38 to 46 mL/min/1.73 m^2. Furthermore, there was a marked increase in diuresis without escalating doses of diuretics

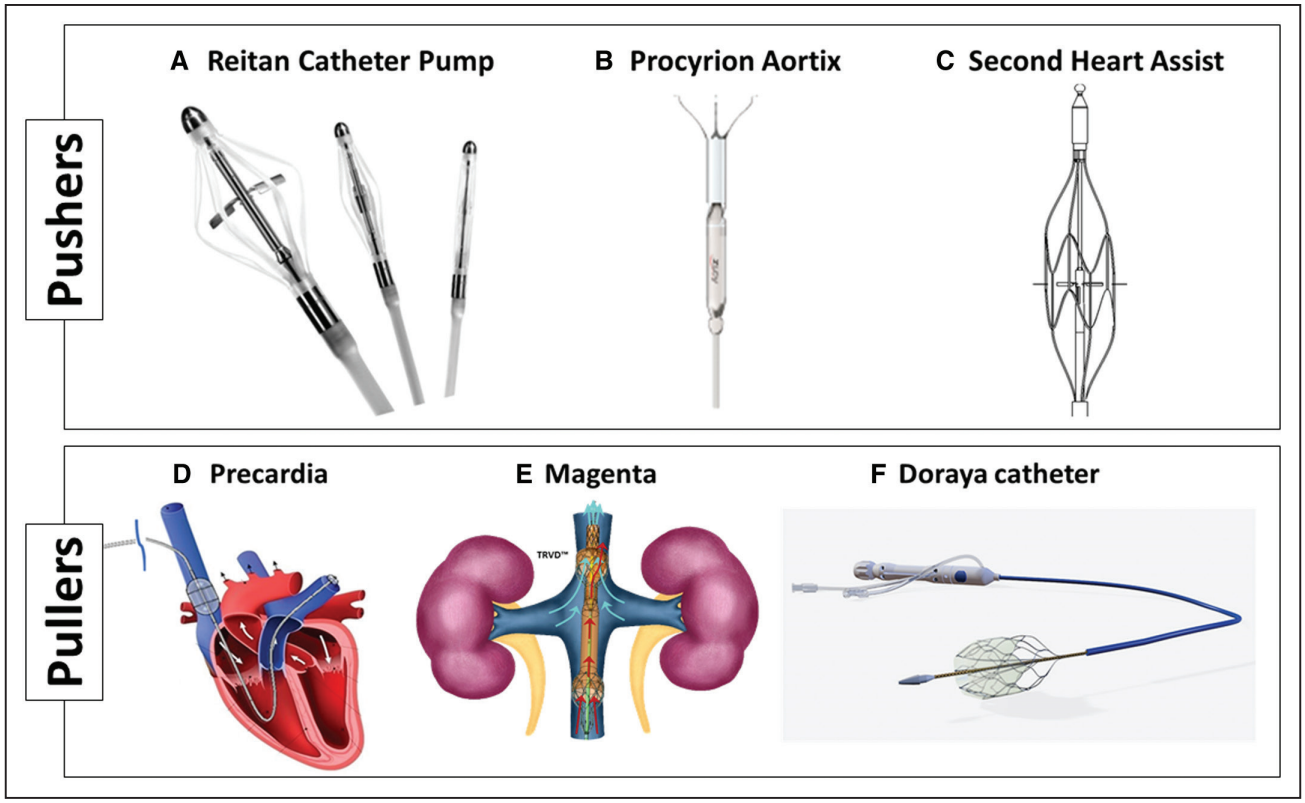

Figure 7. Pushers and Pullers.
Pushers (**Top**): Continuous flow pumps positioned in the suprarenal descending aorta intending to improve renal perfusion. **A**, The Reitan catheter pump is a 10F collapsible device with a rotational propeller. **B**, The Aortix pump (Procyrion) is an 18F axial flow pump. **C**, Second Heart Assist is an aortic stent base pump. Pullers (**Bottom**): Devices designed to reduce central and renal venous pressures aiming to increase urine output. **D**, The Precardia device reduces central venous pressures through intermittent superior vena cava occlusion. **E**, Transcatheter renal venous decongestion system (Magenta) is an axial flow pump that facilitates flow from the renal veins and separates the upper and lower segments of the inferior vena cava, creating a renal venous compartment. **F**, Doraya is positioned in the inferior vena cava below the renal veins and intermittently leads to partial and adjustable obstruction of venous flow, decreasing renal venous pressure.

or inotropes. While the Aortix pump has not yet been studied in the ADHF population, short-term use of the pump during high-risk percutaneous coronary intervention in patients with impaired renal function provided 3.5 L/min of support and led to significant improvements in renal function, suggesting a renal protective effect.[64] Studies of Second Heart Assist in the clinical setting have yet to be reported.

Pullers (P_2)

Elevated CVP impairs renal function in the setting of any cardiovascular disease,[65] including decompensated heart failure.[66,67] As discussed above, pharmacological means of reducing CVP include diuretics and vasodilators (venodilators, in particular), at the risk of causing systemic hypotension. Devices that directly reduce CVP are included in the Pullers class. These devices reduce renal afterload thereby enahcing renal blood flow, increasing urine output, increasing sodium excretion, and improving diuretic responsiveness. These new device-based strategies include intermittent superior vena cava (SVC) occlusion pumps, suprarenal inferior vena cava (IVC) pumps, and partial infra-renal vein fixed obstruction catheters (Figure 7D through 7F).

The preCARDIA system includes a pump console and a catheter (Figure 7D) that is introduced through the internal jugular vein and positioned into the pulmonary artery much like a standard pulmonary artery catheter. A balloon located on the shaft of the catheter is positioned in the SVC superior to the junction with the right atrium. In a preclinical model of heart failure, 12 to 18 hours of intermittent SVC occlusion failed to induce any neurological or vascular injury.[68] In a recent proof of concept clinical study, temporary occlusion of the SVC during right heart catheterization in 8 patients admitted with ADHF significantly decreased CVP and pulmonary capillary wedge pressure without compromising arterial blood pressure or cardiac output. SVC obstruction was well tolerated without neurological safety concerns in this pilot trial.[68] Preservation of cardiac output and blood pressure in the face of reduced pulmonary capillary wedge pressure is postulated to be due to the fact that at the high filling pressures present in ADHF, the overloaded heart is operating on the plateau of the Frank-Starling and that reductions of filling pressure achievable by this approach

do not compromise these parameters. The net effect of the preCARDIA catheter is a reduction in CVP and sustained mean arterial pressure, thereby creating a favorable environment for enhanced renal perfusion.

The transcatheter renal venous decongestion system (Magenta Medical) is a catheter-based axial flow pump system with self-expanding proximal and distal sodium excretion cages (Figure 7E). An incorporated channel connecting the proximal and distal cages allows flow from the lower to the upper portion of the IVC while also creating a renal venous compartment comprised of the renal veins and the segment of IVC into which they drain, thus uncoupling renal venous pressure from CVP. When activated, the pump draws blood from the renal veins, reducing renal venous pressure with the intention of providing the benefits detailed above. Furthermore, the channel connecting the 2 isolation cages increases resistance to blood flow from the lower to upper IVC, thus potentially decreasing right and left ventricular filling pressures.

The Doraya catheter is a temporary fixed intravenous flow regulator positioned in the IVC below the level of the renal veins (Figure 7F) that leads partially restricts venous flow to decrease renal vein pressure. A report on the use of the Doraya catheter in 2 patients demonstrated an increase in urine output in patients with initial poor diuretic response following placement of the catheter.[69] A first in man clinical study is currently ongoing to assess feasibility, safety, and hemodynamic effects in patients with ADHF.[70]

Selective (S)

Direct intrarenal delivery of short-acting vasodilator pharmacotherapies allows selective improvement in renal arterial perfusion without leading to systemic hypotension and hemodynamic consequences. Mechanistically, selective delivery of renal artery vasodilators improves renal artery blood flow, increases urine output, and increases sodium excretion. In preclinical animal studies of ADHF, intrarenal delivery of papaverine, a short-acting vasodilator with effects on sodium reabsorption in the macula densa, lead to augmented renal blood flow and urine output, without causing systemic hypotension associated with peripheral drug administration.[71] Although initially developed for patients with ADHF, in a small study of patients undergoing high-risk percutaneous coronary intervention with renal impairment at risk for contrast-induced nephropathy, intrarenal delivery of fenoldopam (a dopamine 1 receptor agonist) with a specially designed Benephit catheter (Angiodynamics, Latham, NY; Figure I in the Data Supplement), was found to improve renal function by the time of hospital discharge.[72] This was followed by a larger single arm study which showed that use of the Benephit catheter to deliver fenoldopam resulted in a 78% relative reduction of the incidence of contrast-induced nephropathy.[73] The clinical benefits of this approach in patients admitted with ADHF needs to be tested.

CHALLENGES FACED IN STUDIES OF DEVICE-BASED THERAPIES FOR ADHF

While the details of future studies will depend highly on device particulars, there are several common key strategic, clinical, regulatory, and reimbursement questions applicable to the devices reviewed in this paper. These questions include the following: (1) criteria for selecting patients appropriate for invasive device-based therapies, (2) hemodynamic and/or physiological metrics to assess short-term effectiveness to justify larger pivotal studies, and (3) primary clinical end points to ensure regulatory approval and reimbursement. Given the complexity of the nuanced study design and implementation of ADHF device trials, we would argue for the necessity of a consortium to establish appropriate and consistent timing of intervention, enrollment criteria, and clinically meaningful end points for these device-based therapies.

Patient Selection

Recognizing that ADHF is a complex syndrome with various underlying contributing factors and variable clinical presentations, development of study inclusion and exclusion criteria aim to be specific enough to enroll a fairly well-defined patient cohort without being overly restrictive so as to mire enrollment or limit the generalizability of study findings. Regarding patient selection, one strategy is that patients included in such studies should be refractory to medical therapy to justify the risk of adverse events that are typically associated with invasive devices. Alternatively, some investigators have reasoned that device-based therapies should be initiated as early as pharmacotherapy or even be considered as first-line therapy to prevent in-hospital worsening of heart failure and renal function, for more rapid improvement of patient symptoms, for a reduction in hospital length of stay, and to optimize the likelihood of improved patient outcomes. Many device-specific considerations factor into which approach is chosen, including device safety, efficacy, ease of deployment, and ease of patient management while on device. Regardless, appropriate definitions of persistent congestion and diuretic resistance are required. Unfortunately, there is no universally accepted definitions of either.

The gold standard for the detection of congestion in heart failure remains assessment of central venous and pulmonary venous pressures by right heart pulmonary artery catheterization. While reliance on pulmonary artery catheterization data for inclusion of patients into small feasibility and mechanistic studies may be helpful and, in some cases ideal, this is impractical in larger-scale trials. At the same time, it must be acknowledged that the diagnostic accuracy of congestion in routine clinical practice has relatively poor sensitivity and specificity.[74,75] Consequently, a large number of clinical signs

and symptoms, laboratory tests, imaging and other non-clinical tests, either separately or more commonly combined into composite scores, have been used to identify patients with persistent congestion[76] as summarized in Table II in the Data Supplement. A potential limitation of composite scores is that patients can be enrolled having significantly different congestion profiles. While this reflects the reality of the diversity of the population of patient with ADHF, it has the potential to result in the enrollment of patients having different primary mechanisms of ADHF that may respond differently to a given therapy. Indeed, the pathophysiology driving the clinical decompensation may involve highly diverse mechanisms. While dyspnea and elevated filling pressures are a final common pathway, those changes could be the result of renal sodium and water retention (itself driven by multiple mechanisms) or may be secondary to sympathetically mediated volume shifts.[22] Accordingly, the parameters selected for a study's inclusion and exclusion criteria should be chosen according to the mechanism of the particular device being studied and the hypothesized mechanism of refractory ADHF in the particular patient.

As noted, candidates for device-based therapies for ADHF must not only have persistent congestion, it can be argued that they should also demonstrate a significant risk for or at least some degree of diuretic resistance. Various indexes of physiological and clinical assessments of congestion in response to specified doses of intravenous diuretics have been used for this purpose as summarized in Table III in the Data Supplement. In some cases, physiological indexes have included parameters such as urine output, sodium excretion, and weight loss in response to standardized doses of loop diuretic,[26] the presence or lack of hemoconcentration, changes of natriuretic peptides, serum sodium, or serum creatinine and IVC size and collapsibility. Similarly, clinical indexes of diuretic resistance (or at least inadequate response to diuretics) have included persistent peripheral edema, pulmonary edema, pleural effusion, elevated jugular venous pressure, and composites of these parameters (eg, the composite congestion score). Typically, study inclusion is allowed based on satisfying at least one of these criteria. In some cases, however, the criteria for defining diuretic resistance and persistent congestion are dealt with by a single composite index; for example, a clinical congestion score >2 after having received ≥80 mg furosemide for 3 to 5 days. Nevertheless, as discussed above for defining residual congestion, there are similar limitations of permitting study entry based on different indexes of diuretic resistance.

Finally, it should be noted that DRI_2P_2S-class devices may find applications not only for patients with ADHF, but also in other settings such as cardiogenic shock and pulmonary hypertension. These are all conditions where the presence of congestion plays a prominent role in clinical signs and prognosis. As such, studies need to be designed in respect to specific target populations.

Study Design and End Point Considerations

Early feasibility pilot studies of device-based therapies for ADHF typically focus on relatively objective end points indicative of physiological effects such as changes in hemodynamics, urine output or chemical composition, or changes in biochemical factors and biomarkers. Symptom-focused end points such as clinical signs and symptoms of congestion (Table II in the Data Supplement) are often included as secondary or exploratory analyses. Initial pilot studies typically employ a single-arm, treatment only design in which patients serve as their own control. In such cases, it is critical that background medical therapy (especially diuretic doses) remains constant during a sufficiently long baseline phase to provide appropriate comparators for measurements made during the treatment phase. Given the limitations of single-arm studies, it is sometimes advisable to perform a pilot randomized study to more definitively define the magnitude and variability of the response before launching a pivotal study. Regardless, when considering how biochemical, hemodynamic, or other findings in early feasibility studies translate into clinical symptom relief and outcome improvements, it is important to note that virtually every pharmacological intervention listed in Table I in the Data Supplement eventually shown to be clinically ineffective was preceded by earlier phase studies showing favorable effects.

Regarding study conduct, pivotal studies of pharmacological therapies are typically double blind. While this is always preferable, this can be much more challenging for studies of device-based studies. Given the typical invasive nature of devices, it cannot always be justified to perform sham interventions or to insert nonfunctional sham devices. When unblinded studies are performed, extra attention is required for choosing end points and attempting to reduce bias on the part of patients and investigators.

Pivotal trials of pharmacological agents have, for regulatory purposes, been required to demonstrate an effect on symptoms and/or outcomes. The most common symptomatic end point has been some measure of dyspnea. A challenge in all studies has been that the comparator therapy (commonly referred to as standard-of-care) involving intravenous diuretics, is effective, and thus placebo group patients improve. The intervention group thus must affect dyspnea more quickly or completely, which usually has not been demonstrated. Physiological measures such as filling pressures or biomarkers reflecting congestion such as natriuretic peptides have not been allowed into primary end point construction since, in and of themselves, do not necessarily reflect clinical benefit to patients.

Studies of devices in patients with ADHF have been executed under somewhat different regulatory guidance, and composite end points have been allowed that have included physiological measures such as wedge pressure, changes of which have a highly plausible relation with changes in symptoms of congestion such as dyspnea and outcome.[12,77] A relevant example is the composite of pulmonary capillary wedge pressure at 72 to 96 hours and days alive out of hospital off mechanical support over 35 days that was used in a trial of a continuous aortic flow augmentation device.[78]

An additional consideration when designing device trials for decompensated heart failure is the timing of intervention. To enroll patients when they are highly volume overloaded and have not had significant improvement with diuretics, drug trials often attempt to enroll patients early in the hospital course. Based on the hypothesis that myocardial stress very early in the course of a decompensated heart failure hospitalization is associated with myocyte damage (evidenced by troponin release) is in turn related to unfavorable downstream outcomes, the Trial of Ularitide Efficacy and Safety in Acute Heart Failure (TRUE-AHF) trial was designed to capture patients very early in their course to treat with the vasodilator ularitide and hopefully mitigate some of that damage. The treatment or placebo infusion was initiated at only 6 hours after initial clinical evaluation,[79] which is remarkable for a trial. However, given the interventional nature of device-based trials, it could be argued that patients should demonstrate diuretic resistance with a trial of medical therapy for some minimal period (eg, 24 hours) before enrollment.

Consideration for using composite end points is particularly important in the planning of device trials, where the feasibility of accruing the large number of patients required to demonstrate mortality-morbidity benefits (generally numbering between 2000 to 6000 patients) is poor. Thus, the development and use of novel composite end points and statistical methodologies is of increasing interest in the design of ADHF device trials.

SUMMARY

There is a critical unmet need for new therapies to address the burden associated with ADHF hospitalizations. Since it is known that many patients are incompletely decongested at the time of hospital discharge, there is significant opportunity for intervention. We reviewed 7 mechanistic classes of therapeutic devices for ADHF, each with the potential to improve renal perfusion and/or directly enhance decongestion. Each device reviewed is in early stage of development, with some still in preclinical phases. Initial studies will be important to clarify each device's mechanism of action which will help refine criteria for optimal patient selection and set expectations for the magnitude of its effect. Subsequent pivotal studies will need to demonstrate sufficient clinical effectiveness and safety to justify the use of invasive, potentially costly, strategies in this complex patient population. Based on the current tempo of device development, a significant number of clinical trials can be expected in the near term. It is therefore imperative that physicians have a broad perspective on the range of devices in development for this challenging patient population.

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