Journal of the Society for Cardiovascular Angiography & Interventions 2 (2023) 101210

JSCAI

The official journal of the Society for Cardiovascular Angiography & Interventions

Comprehensive Review

Emerging Device Therapies for Cardiorenal Syndrome

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ABSTRACT

While the existence of cardiorenal perturbations has been known for nearly 2 centuries, only in the past 2 decades has significant progress been made in classifying these alterations and characterizing the pathobiology and hemodynamic signature of cardiorenal syndrome (CRS). Empiric intravenous diuretic therapy with fluid and sodium restriction and selective use of vasoactive agents have remained cornerstones of managing acute heart failure with or without acute CRS; however, recent clinical data has exposed the shortcomings of this approach. The traditional view of CRS has long focused on low cardiac output with resultant renal arterial hypoperfusion as the central hemodynamic derangement but this too, has been challenged by new preclinical and clinical observations. Renal venous congestion/hypertension has since been identified as an important hemodynamic contributor to the development of CRS, resulting in diminished renal perfusion pressure, defined as the difference between arterial driving pressure and renal venous pressure. Novel circulatory renal assist devices for the treatment of acute (type I) CRS are in development and may be divided into 2 broad categories: "pushers" which aim to improve renal arterial perfusion (renal preload) and "pullers" which are designed to reduce renal venous congestion (renal afterload). Numerous devices have shown promise in early-stage clinical studies but none have been approved yet for commercial use in the United States. The value of CRS device therapies will ultimately rest on safety as well as the ability of these devices to effect predictable, meaningful, and durable improvements in renal function along with clinical and hemodynamic markers of congestion.

Introduction

The biological crosstalk that exists between the heart and the kidneys, in both health and illness, has been recognized for nearly 2 centuries.[1] Observations made by Dr Robert Bight in a case series published in 1836, detail postmortem changes to the heart in patients with advanced kidney disease, mirroring common echocardiographic findings seen in patients presenting today with both heart failure and chronic kidney disease: cardiac enlargement and increase in left ventricular mass with wall thinning and chamber dilatation.[2] While knowledge regarding the precise nature of this complex pathophysiological interdependence has continued to grow over many decades following these initial observations, it is only in the recent past that concerted attempts have been made to classify these interactions as a family of disorders we now refer to collectively as cardiorenal syndrome (CRS).[1] Whereas CRS is often thought of in prosaic terms, as a primary hemodynamic insult resulting in renal dysfunction, the current understanding acknowledges that either acute or chronic dysfunction of the heart or the kidneys can result in acute or chronic dysfunction of the other organ system.[3] Furthermore, there is growing recognition of the roles of vascular disease, neurohormonal and biochemical dysregulation, the impact of cytokines and inflammation, and progressive changes in cardiac structure and function as contributory factors.[1,3]

The first formal conceptualization of CRS by the Working Group of the National Heart, Lung, and Blood Institute in 2004 espoused a cardiac-focused view of the condition, wherein increasing circulating volume exacerbated the symptoms of heart failure in its early stages and in its end stages, efforts at decongestion were hindered by the apparent decline in renal function.[1] In 2008, a consensus statement from the Acute Dialysis Quality Initiative proposed the division of CRS into 2 phenotypes based on the primary or inciting cause: cardiorenal versus renocardiac.[4] A subsequent refinement to the classification schema, which is currently utilized and endorsed in the 2019 American Heart Association Scientific Statement on CRS, divides the syndrome into 5 distinct groups on the basis of acuity of illness and order of organ involvement.[1] Clinicians utilizing this classification, detailed in Table 1,[4] should also acknowledge the overlap and fluidity of these categories in patients whose clinical condition may be in evolution.

Patients with type I or type II CRS (acute vs chronic CRS, respectively) may present clinically with heart failure symptoms, manifesting varying degrees of acuity, volume overload, neurohormonal and electrolyte

Abbreviations: AHF, acute heart failure; CRS, cardiorenal syndrome; CVP, central venous pressure; DR, diuretic resistance; IVC, inferior vena cava; PCWP, pulmonary capillary wedge pressure; SVC, superior vena cava; WRF, worsening renal function.

Keywords: cardiorenal syndrome; circulatory devices; heart failure.

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https://doi.org/10.1016/j.jscai.2023.101210
Received 27 September 2023; Received in revised form 3 October 2023; Accepted 4 October 2023

Table 1. Classification of cardiorenal syndrome (CRS) based on the consensus conference of the Acute Dialysis Quality Initiative[4]

Phenotype	Syndrome	Mechanism and presentation
Type 1 CRS	Acute CRS	Acute cardiac insult (acute coronary syndromes/acute myocardial infarction with cardiogenic shock, acute heart failure) resulting in acute kidney injury
Type 2 CRS	Chronic CRS	Chronically impaired heart function leading to kidney injury or dysfunction
Type 3 CRS	Acute renocardiac syndrome	Acutely worsened kidney function with resultant volume overload and metabolic changes leading to cardiac injury and/or dysfunction
Type 4 CRS	Chronic renocardiac syndrome	Chronic kidney disease leading to changes to cardiac structure and function, ventricular remodeling, and eventually, heart failure
Type 5 CRS	Secondary CRS	Systemic medical illnesses such as sepsis, amyloidosis, etc., which simultaneously lead to cardiac and kidney injury and/or dysfunction

derangements, reflecting the inability of the kidneys to restore sodium and fluid homeostasis along with the overlay of lymphatic congestion.[3,5,6] Type 1 CRS (acute CRS) results from an acute hemodynamic insult such as heart failure decompensation or acute coronary syndrome/acute myocardial infarction with cardiogenic shock resulting in acute kidney injury. Type 2 CRS (chronic CRS) denotes the progressive decline in renal function (chronic kidney disease) as a result of chronic heart failure. Type 3 CRS (acute renocardiac syndrome) reflects acutely worsened kidney function (acute kidney injury) with resultant volume overload and metabolic changes leading to cardiac injury and/or dysfunction. Type 4 CRS (chronic renocardiac syndrome) occurs in the context of chronic kidney disease leading to insidious changes in cardiac structure and function, ventricular remodeling, and eventually, overt heart failure. Type 5 CRS (secondary CRS) refers to systemic medical illnesses such as sepsis, amyloidosis, etc. simultaneously leading to cardiac and kidney injury and/or dysfunction.[1,3,7]

Compounding the clinical picture commonly seen in Types 1 and 2 CRS are issues of inadequate response to decongestive therapies and rising renal biomarkers. With respect to this latter issue, an abrupt rise in serum creatinine $\geq$0.3 mg/dL in the setting of acute heart failure (AHF, interchangeably referred to as acute decompensated heart failure) has traditionally been regarded as "worsening renal function" (WRF), often prompting a decrease or interruption of diuretic dosing or at times, even calling into question the original clinical judgment of volume overload. It should be noted that while meta-analysis data link WRF to increased mortality and hospitalization in HF, the small changes in markers of glomerular filtration seen in AHF patients being aggressively decongested may in fact, reflect hemoconcentration rather than true tubular injury and may not confer negative prognostic value as previously thought, if euvolemia is restored in the process.[3,5,8] Indeed, recent data have confirmed that inadequate decongestion poses a far greater threat to patients than small increases in serum creatinine during diuretic administration.[9,10] Thus, in AHF patients undergoing inpatient decongestion, it is important to interpret renal biomarker fluctuations within the broader context of clinical trajectory, changes in other serum markers of volume status such as hematocrit and B-type natriuretic peptide, etc., and in selected patients, use of invasive hemodynamic profiling.[3]

Despite growing awareness of the treatment considerations detailed above and various national initiatives to reduce the enormous burden of heart failure, the inability to achieve adequate decongestion early (or often, ever) in the majority of hospitalized AHF patients with CRS, remains both a reality and a problem of monumental clinical importance. Acute decompensated heart failure is the leading cause of hospitalization in older patients, resulting in well over 1 million hospitalizations annually in the United States, alone.[11–15] Over 25% of HF admissions are associated with WRF over the course of treatment, representing the type 1 CRS population. The overwhelming majority of these CRS patients (approximately 90%) fail to achieve adequate fluid balance within the first 4 days of initiation of medical therapy and most are discharged in a state of persistent volume overload.[11–14] Following discharge, nearly one-third of hospitalized AHF patients are readmitted within the next 3 months and a significant proportion of AHF patients with or without CRS, succumb within 1 year.[13–15] These observations taken together, serve as both the rationale and mission statement for the development of device-based therapies ("renal assist" devices) for decongestion in CRS.

In this targeted review, we will discuss the key hemodynamic changes associated with CRS (primarily AHF with acute kidney injury and diuretic resistance [DR]), touch briefly upon conventional decongestive strategies and finally highlight those investigational mechanical circulatory support (MCS)/renal assist platforms furthest along in development and clinical validation. Devices targeting volume removal, modulation of venous capacitance, lymphatic drainage, etc. will not be discussed as they are covered elsewhere in this issue.

Hemodynamic alterations in AHF with CRS

The pathophysiology of CRS is considerably more complex than initially understood, invoking not only hemodynamic and neurohormonal derangements but also systemic and vascular inflammation, endothelial dysfunction, venous congestion of the renal, hepatic, and splenic beds, and increased abdominal pressure due to gut edema and ascites.[1,3,7] The classic hemodynamic explanation of CRS in AHF postulates that low cardiac output primarily drives renal arterial hypoperfusion with activation of the sympathetic nervous system and renin-angiotensin-aldosterone (system) axis, resulting in the secretion of arginine vasopressin, sodium retention, and water reabsorption and ultimately, worsening ventricular performance through increased preload and afterload.[1,3,7] This explanation, which focuses on a low-flow cardiac state as the primary trigger for CRS, has been challenged however by a number of recent clinical observations. Firstly, the occurrence of CRS in AHF does not appear to be definitively linked with hypotension or even impaired left ventricular systolic function.[1] In an analysis of the Acute Decompensated Heart Failure National Registry (ADHERE), it was noted that while in-hospital mortality and ICU length of stay were both inversely proportional to left ventricular ejection fraction (LVEF), creatinine rise of $\geq$0.5 mg/dL was more often seen in patients with AHF and preserved LVEF than in those with severely decreased LVEF.[16] In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) Trial, an inverse correlation was found between cardiac index and estimated glomerular filtration rate (eGFR), with higher cardiac indices associated with worse eGFR.[17] Moreover, no associations were observed between higher cardiac index and higher eGFR across any subgroup analyzed.[17] The current understanding of acute CRS hemodynamics has thus, shifted away from a condition driven primarily by "poor forward flow" toward one characterized by a decrease in renal perfusion pressure, defined as the difference between the arterial driving pressure (termed "renal preload") and the renal venous pressure ("renal afterload").[1,3,5,7,14,15] It has long been known that the kidneys form a low resistance circuit which, as a consequence, handle a larger proportion of the cardiac output than other visceral organs.[17–19] Renal blood flow and adequate glomerular filtration rely upon the maintenance of arterial perfusion pressure but to a greater degree, upon unrestricted venous outflow in order to maintain the large resting pressure differential across the vascular beds of an organ that is both encapsulated and inelastic.[7,18–20] In the absence of renal venous hypertension, reduction in afferent arteriolar flow (vis-à-vis reduced cardiac output) can be offset by vasoconstriction of the efferent arterioles, thereby preserving glomerular filtration rate across a relatively wide range of

hemodynamic conditions. In the case of reduced cardiac output with severely elevated central venous pressure (CVP) however, renal venous hypertension and venous congestion ensue, with a reduction in renal blood flow, eventually exceeding the capacity of compensatory mechanisms, resulting in the loss of filtration ability.[1,18–20] An analysis of the ESCAPE trial found that right atrial pressure was the only hemodynamic measure that correlated with baseline serum creatinine and furthermore, there was no relationship between baseline hemodynamics or hemodynamic changes to WRF.[21] Elevated intra-abdominal pressure caused by visceral edema and ascites, further impedes renal blood flow by extrinsic compression of renal veins and ureters.[22] Renal lymphatic drainage which serves to help decompress the congested renal interstitium in the setting of AHF, may be overwhelmed in the setting of severely elevated CVP, functionally limiting lymphatic flow through the thoracic duct.[23,24] Renal assist devices in development thus seek to favorably alter hemodynamic alterations across 3 broad domains: augmentation of renal arterial perfusion ("pushers" to improve "renal preload"), renal venous decongestion ("pullers" to reduce "renal afterload") and reduction in renal interstitial overload.[5,15,25–27] The former 2 categories of devices are discussed herein.

Acute decongestion strategies in CRS

The first lines of therapy for AHF with volume overload (with or without CRS) are almost always diuretics in escalating doses, continuous IV infusion, or in combinations as dictated by the initial therapeutic response.[1] While diuresis remains critically important for improvement in volume status and improvement in congestive symptoms, there are no data thus far to suggest that diuretics improve HF mortality or rehospitalization.[1,28,29] Loop diuretics such as furosemide, bumetanide, torsemide, and rarely, ethacrynic acid, are most often employed for acute diuresis. While furosemide remains the most common choice of loop diuretic, torsemide and bumetanide are both associated with greater bioavailability than furosemide.[30] Impaired absorption of oral diuretic doses in patients with HF remains an important therapeutic consideration with furosemide manifesting the greatest interpatient and intrapatient variability absorption.[30,31] Increased volume of distribution in hypoalbuminemic AHF patients may also serve as a significant confounder to loop diuretic response.[1]

DR is a commonly encountered phenomenon in hospitalized AHF patients and is defined as a diminished diuretic effect with limited sodium and chloride excretion and inadequate relief of volume overload. The causes of DR are numerous, variable from one patient to another, and beyond the scope of a detailed discussion within this review but it should be recognized that DR has been linked with WRF as well as HF rehospitalizations and death. Commonly implicated factors in DR include variable absorption, pharmacokinetic/pharmacodynamic variables, decremental natriuretic/diuretic response to repeated drug doses (referred to as the "braking phenomenon"), and structural changes to the distal nephron (tubular remodeling) secondary to chronic diuretic usage.[1,3] The use of other types of diuretics such as thiazides, utilizing a different site of action than loop diuretics, has been proposed as a solution for the latter mechanism of DR and is sometimes referred to as "sequential nephron blockade." Other diuretic classes such as potassium-sparing agents and carbonic anhydrase inhibitors may also be considered for adjunctive use on a case-by-case basis. Numerous other guideline-directed medical therapies have shown clinical value across the clinical spectrum of chronic heart failure but play limited roles in acute decongestion. As stated previously however, irrespective of the diuretic strategy employed, the majority of AHF CRS patients admitted with volume overload fail to achieve adequate decongestion early in their hospital course or even by the time of discharge, thus setting the stage for relapse and rehospitalization in a large proportion of patients.[11–14]

Ultrafiltration (UF), also referred to as aquapheresis, involves the direct removal of isotonic fluid from the body by pumping whole venous blood across a semipermeable membrane in the setting of a negative transmembrane pressure gradient. It has been touted as an alternative to aggressive IV diuretic regimens in congested AHF patients or as a means for augmenting decongestion in patients with DR.[1,3,15,32–34] It also carries the theoretical advantage of avoiding the neurohormonal activation observed with chronic and/or repeated diuretic dosing, minimizing electrolyte wasting and greater removal of sodium from the body than with loop diuretics.[32,34] UF can be achieved through central or peripheral venous access and can potentially be initiated outside the intensive care unit. A number of clinical trials have been conducted comparing UF to various diuretic regimens and have come to somewhat disparate conclusions with regard to the clinical value of UF over diuretic protocols and the impact of UF on renal function, leaving clinicians to consider using UF selectively, pending the results of future outcomes studies.[1,3,15,32,34]

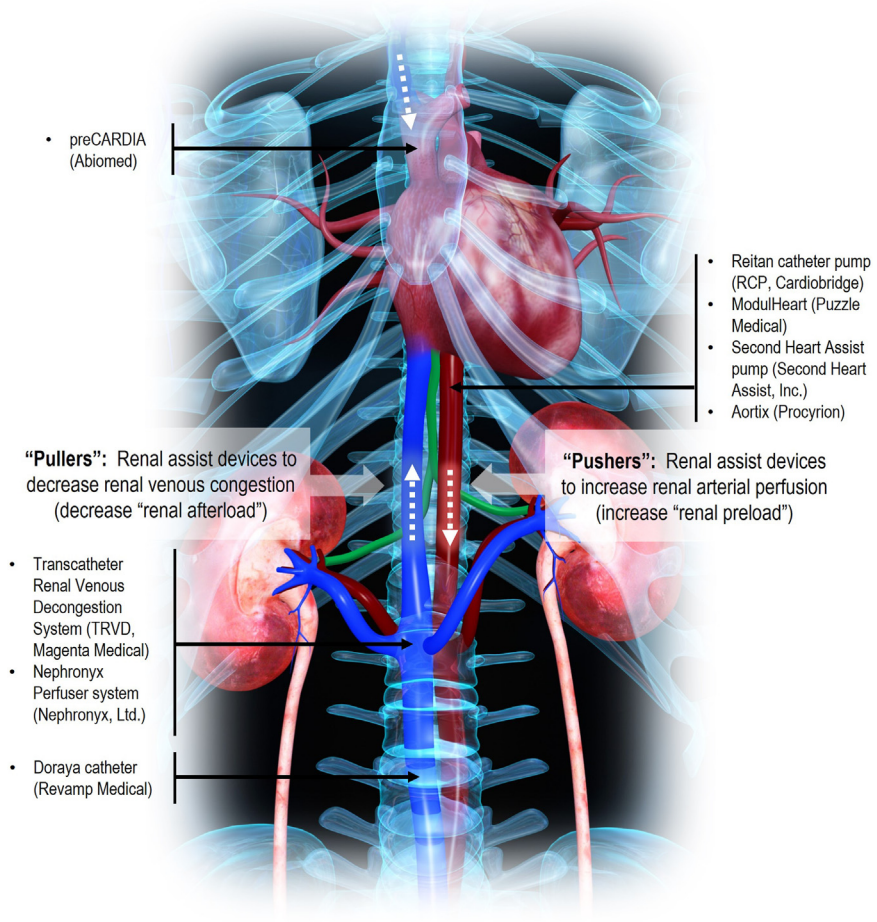
Renal assist devices for the treatment of CRS

Circulatory devices for the treatment of acute (type I) CRS fall into 2 broad categories as stated previously, seeking to restore the normal renal perfusion pressure gradient from one side of the hemodynamic equation or the other.[7,15] "Pushers" are devices that aim to improve renal arterial perfusion (renal preload) independent of vasopressor/inotrope use while "pullers" are designed to reduce renal venous congestion (renal afterload) (Central Illustration). Summaries of the devices discussed in this review are provided in Tables 2 and 3. It should be noted that each device described below is still investigational in the United States at the time of writing, each has only been trialed in small groups of human subjects, and still needs to meet the full burden of clinical evidence in CRS patients. Nevertheless, it is conceptually attractive to consider the use of "pusher" and "puller" strategies either alone or in conjunction with one another and further, to combine mechanistically different device-based therapies in the future management of CRS.

Devices for improving renal arterial perfusion ("pushers")

Procyrion Aortix. The Aortix (Procyrion) device is a novel, percutaneous, temporary MCS device. This miniaturized axial flow pump is currently being investigated for use in patients with decompensated heart failure (DHF) complicated by CRS. The device is implanted in the descending aorta, above the level of the renal arteries, and provides approximately 3.5 L/min of flow at nominal speeds (25,000 rpm).[35] The Aortix device consists of a rotating impeller mounted within an anchoring system, connected to a motor controller by a flexible externalized driveline, and works on the principle of entrainment pumping to increase renal artery blood flow and pressure by approximately 35% and decrease left ventricular (LV) afterload. Images of Aortix, representing the device in the "pusher" category furthest in clinical validation, are provided in Figure 1. The Aortix pump is 6.5 cm long and approximately 6 mm wide, requiring delivery through an 18F delivery sheath, typically placed in the common femoral artery.[35,36] The device is positioned in the descending aorta between the 10th and 12th thoracic vertebrae and unsheathed using passive exposure. After delivery of the device, the delivery sheath is removed and suture-based arteriotomy closure is performed to secure the drive line of the device in the femoral artery. This limits the risk of limb ischemia while the device is in place. At the time of removal, the drive line is used as a rail for serial dilation of a large bore sheath which is used for pump removal. Thereafter, final closure is performed. A detailed description of the placement and removal of the device has already been published.[37]

The first use of the Aortix device was described by Grafton et al who implanted a 54-year-old male with DHF-CRS.[36] The patient had already



Central Illustration.
Categories of renal circulatory assist devices, broadly divided by mechanism of effect: increase in renal arterial perfusion vs decrease in renal venous congestion/hypertension. Sites of implantation for specific investigational devices are noted.

been treated with 6 days of intravenous diuretics including bumetanide 2 mg/h, metolazone, and dobutamine 2 μg/kg/min. After the placement of the Aortix device, diuresis improved from 1325 mL/d to a peak of 7280 mL/d on day 4. In total, there was a net negative fluid loss of >23 L within 6 days. Hemodynamics improved including a 37% reduction in systemic vascular resistance and 35% increase in cardiac

Table 2. Renal assist devices to improve renal arterial perfusion ("pushers") in acute (type 1) cardiorenal syndrome.

Device	Manufacturer	Access and placement	Mechanism(s) of action	Physiologic effect(s)
Aortix	Procyrion, Inc	18F femoral arterial access with axial flow pump unsheathed in descending aorta between T10-12 vertebrae and connected to motor controller unit via drive line externalized through the femoral artery.	Impeller rotation generates high-velocity jets, accelerating native aortic flow through the device outlet and entraining blood flow around the device, creating a transaortic pressure gradient.	When placed above the renal arteries and activated, the axial flow pump generates approximately 3.5 L/min flow, increasing renal arterial perfusion and modestly decreasing cardiac afterload.
Reitan catheter pump (RCP)	Cardiobridge GmbH	The RCP is inserted through a 10F femoral arterial sheath and advanced into the descending aorta, 5-10 cm distal to the origin of the left subclavian with the pump head assembly closed during insertion and removal of the RCP and open during operation.	Pump activation temporarily increases flow in the thoracic and abdominal aorta, creating a 10 mm Hg pressure differential.	Increases renal arterial perfusion and modestly decreases cardiac afterload.
Second Heart Assist pump	Second Heart Assist, Inc	Self-expanding stent-based impeller pump inserted percutaneously via the femoral artery with 2 different device designs/ applications being planned. Access size and dimensions not available.	Axial flow pump providing short-term circulatory support in high-risk PCI and CRS (first catheter-based application) and chronic support for advanced HF patients (second, wireless, powered device with 22 mm nitinol aortic cage).	Increases renal arterial perfusion and decreases cardiac afterload (with est. 4-6 L/ min of support capability intended for larger, wireless implant currently in design).
ModulHeart	Puzzle Medical Devices Inc	22F femoral arterial access for delivery of 3 separate pumps inserted in series on a single driveline and assembled in the descending aorta for operation in combination.	Three axial flow pumps operating in parallel in the descending aorta above the renal arteries provide approximately 4 L/min of flow at 14,000 rpm.	When used in high-risk PCI, the pump decreased CVP and LVEDP with increased cardiac output and renal perfusion and augmented urine output.

All devices listed are currently in clinical investigation and none are available yet for commercial use in the United States at the time of writing.
CRS, cardiorenal syndrome; CVP, central venous pressure; HF, heart failure; LVEDP, left ventricular end-diastolic pressure; PCI, percutaneous coronary intervention.

Table 3. Renal assist devices to decrease central venous and/or renal venous congestion ("pullers") in acute (type 1) cardiorenal syndrome.

Device	Manufacturer	Access and placement	Mechanism(s) of action	Physiologic effect(s)
preCARDIA	Abiomed	14F right internal jugular venous access with occlusion balloon positioned in the SVC, connected to external pump console	Cycled intermittent SVC occlusion with the saline/contrast filled balloon reduces the minority of total venous inflow (approximately 30%) occurring via the SVC	Reduction in central venous congestion is noted with reduction in CVP as well as reduction in PCWP. The observed increase in urine output is presumed secondary to both improved left ventricular systolic performance and renal venous decongestion.
Doraya catheter	Revamp Medical	Passive (nonpowered) renal venous flow regulator which is percutaneously deployed in the IVC below the level of the renal veins using femoral venous access	Deployment of the device below the level of the renal veins creates a small (6 mm Hg) and controllable pressure gradient in the IVC	The small observed drop in CVP translated to a decrease in renal venous pressure with significant increase in diuretic response, urine output and improvement in reported dyspnea.
Magenta Transcatheter Renal Venous Decongestion System (TRVD)	Magenta Medical	Axial flow pump for nonselective placement in the IVC adjacent to the renal veins, via femoral venous access	Axial flow pumping in conjunction with sealing elements above and below the level of the renal veins to isolate the renal segment of IVC, allows for selective venous decompression	Reduction in renal venous pressure appears to promote diuresis, natriuresis, and reduction in CVP in early clinical data.
Nephronyx system (Perfuser)	Nephronyx, Ltd	Passive (nonpowered) device based on a covered stent, advanced via the femoral vein and deployed in the IVC segment adjacent to the renal veins	Renal venous congestion is reportedly reduced by employing the Bernoulli effect and fluid entrainment principles	Renal venous pressure is presumably decreased by improvement in flow. Clinical data are not available.

CVP, central venous pressure; IVC, inferior vena cava; PCWP, pulmonary capillary wedge pressure; SVC, superior vena cava.

output. CVP was reduced from a baseline of 26 mm Hg to 8 mm Hg, along with a decrease in pulmonary capillary wedge pressure (PCWP) from 33 mm Hg to 14 mm Hg. At the 30-day follow-up, the patient experienced a net weight loss of 27 kg with improvement in self-assessed dyspnea scores.[36]

The Aortix device has since been studied in an 18-patient pilot feasibility study the results of which were recently reported.[38] Patients were on average, 60 years old with a median LVEF of 22.5%. Most patients (61%) were already on inotropes and had received IV diuretics (~720 mg of furosemide per day). The Aortix device was implanted in about 46 minutes and explanted in about 15 minutes. On average, CVP decreased by 39% and PCWP by 33%. The mean peak net fluid loss was 3.6 ± 1.8 L/d. While more evidence is needed to further elucidate the risks and benefits of the Aortix MCS device, plans are underway to start the pivotal Diuretics Alone vs Aortix Endovascular Device for AHF (DRAIN-HF) trial (NCT05677100). A planned total of 268 subjects will be

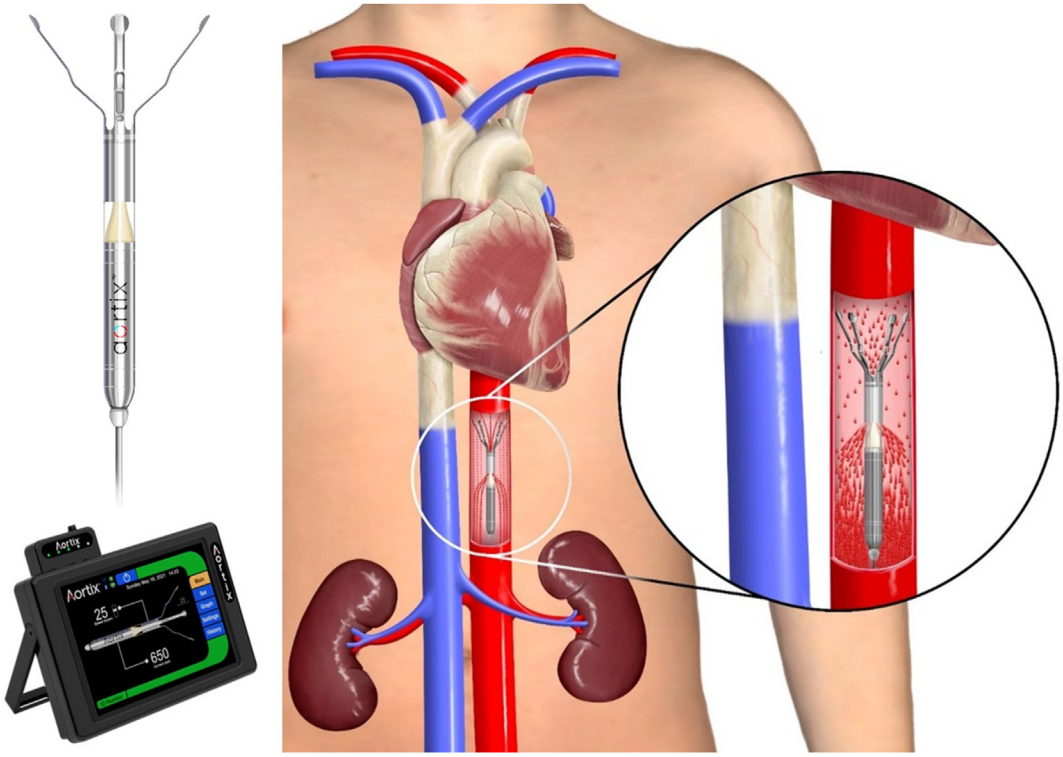


Figure 1.
The Procyrion Aortix Device. The Procyrion Aortix device is an 18F axial flow pump that is deployed in the descending aorta, positioned above the level of the renal arteries, self-centering via atraumatic nitinol struts and delivering 3.5 L/min at nominal speed (25,000 rpm). After deployment, a 6F power lead exits the femoral arteriotomy and connects to the Aortix Control System (ACS) which comprises a controller and cradle and provides hemodynamic support for CRS for up to 7 days. Once activated, a portion of native blood flow enters the pump inlet and is accelerated into high-velocity jets which exit the pump, entraining native blood flow that passes around the pump body resulting in increased total blood flow velocity. Aortix has been demonstrated to decrease cardiac afterload, increase cardiac output, improve renal arterial perfusion, and increase urine output.

randomized in a 1:1 fashion to either Aortix along with medical therapy to medical therapy alone. The primary effectiveness end point is a combined composite end point of a clinically significant reduction in net fluid loss over 7 days and freedom from mortality or heart failure rehospitalization/therapy escalation from the baseline visit to the 30-day follow-up visit.

Reitan Catheter Pump. The Reitan Catheter Pump (RCP, Cardiobridge GmbH) is a percutaneous expandable pump inserted via the femoral artery, designed to reduce cardiac afterload and increase renal arterial perfusion in patients with CRS.[39–41] The current generation of the RCP comprises a foldable, rotating propeller which is 15 mm in diameter and is contained within a collapsible 10F cage. The RCP is inserted through a 10F femoral arterial sheath and advanced into the descending aorta, 5 to 10 cm distal to the origin of the left subclavian with the pump head assembly closed during insertion and removal of the RCP and open during operation wherein it achieves a 10 mm Hg pressure differential.[41] The pump was evaluated in a small prospective observational study of 20 patients admitted with DHF and low LVEF (<30%), reduced cardiac index (<2.1 L/min/m^2), and requiring inotropic or MCS.[39] Patients in this study underwent RCP support for a mean of 18.3 hours during which time significant increases were noted in cardiac index (from 1.84 L/min/m^2 to 2.41 L/min/m^2) and urine output (from 71 mL/h to 227 mL/h) and decrease in serum creatinine (188 μmol/L to 161 μmol/L) with no significant vascular complications or hemolysis noted.[39] Plans for commercialization in the United States remain unclear at the time of writing.

Second Heart Assist pumps. The Second Heart Assist (Second Heart Assist, Inc) temporary circulatory assist pumps are devices in early-stage development and are reportedly targeting 3 different applications via 2 separate designs, built on iterative modifications to the root pump technology.[27] The first platform is a short-term, catheter-based device for application in high-risk PCI and CRS (target support time of 12-72 hours). The second design is a wireless, powered device with a 22 mm nitinol cage, intended for chronic use in patients with advanced heart failure as a bridge to destination. This device is intended to generate 4 to 6 L/min of flow to augment native cardiac output. At the present time, there is no published clinical data available.[28,42]

Puzzle Medical ModulHeart. The ModulHeart device (Puzzle Medical Devices Inc) is a novel design for a temporary, percutaneous circulatory support device comprising 3 separate endovascular pumps inserted in series on a single driveline/delivery system, via 22F femoral arterial access, then assembled in parallel on a dedicated self-expanding nitinol anchor in the descending aorta and operated in unison.[43] The objective of this unique, modular design is to provide higher flow rates than could be afforded by a single pump element, but at lower rotational speeds per individual pump (4 L/min at 14,000 rpm), which in theory could translate to reduced shear-induced trauma to cellular elements of the blood and von Willebrand factor. In the first-in-human experience with the pump, 4 patients underwent successful high-risk PCI with ModulHeart device support.[43] Mean delivery and removal time of the pump was 8 minutes and 7 minutes, respectively with an average time on support of 49 minutes. The investigators reported a 25% increase in cardiac index, 37% decrease in CVP, and 78% decrease in left ventricular end-diastolic pressure. Urine output reportedly increased 9-fold after 15 minutes of pump support and no adverse events.

Devices for decreasing venous congestion ("pullers")

preCARDIA. The preCARDIA system (Abiomed) is a novel catheter-mounted balloon for intermittent superior vena cava (SVC) occlusion which when deployed in patients with acute DHF, affects a rapid reduction in cardiac filling pressures without any apparent adverse effects on blood pressure or cardiac output.[44] The therapy is predicated on observations that central venous congestion can not only increase pulmonary venous pressures but also impact LV filling and capacity due to LV-RV interactions and right to left shift in the interventricular septum. Whereas the majority of central venous return occurs via the inferior vena cava (IVC) and thus IVC occlusion is not well tolerated hemodynamically, transient SVC occlusion is both well-tolerated and associated with favorable effects on cardiac preload and central venous congestion. The preCARDIA system consists of a catheter-mounted SVC occlusion balloon which is inserted via 14F right internal jugular venous access and a pump console. After baseline hemodynamic assessment and performance of an SVC venogram, the preCARDIA device is cycled intermittently via the pump console.[45] Images of the preCARDIA system, representing the entry to the "puller" category furthest in clinical validation, are provided in Figure 2.

The VENUS-HF EFS (VENUS-Heart Failure Early Feasibility Study) tested the safety and feasibility of using the preCARDIA system for decongestion in patients with acute DHF.[45] The system was safely used for 12-24 hours in 30 AHF patients meeting prespecified hemodynamic criteria with no device- or procedure-related complications and no neurologic sequelae noted. Hemodynamic parameters of interest were all significantly improved with 34% reduction in right atrial pressure and 27% reduction in PCWP. Fluid balance was also rapidly improved during the period of device-based decongestion with urine output increased by 130% and net fluid balance increased by 156%, as compared with the pretreatment period.[45]

Doraya catheter. While the majority of AHF/CRS decongestion devices in development employ some form of active pumping technology, the Doraya catheter (Revamp Medical) is a passive renal flow regulator that is percutaneously deployed in the IVC below the level of the renal veins, creating a temporary and controllable pressure gradient in the IVC.[46] The first-in-human Study of the Doraya Catheter for the Treatment of AHF Patients (NCT03234647) enrolled 9 AHF patients with clinical evidence of volume overload, diuretic resistance, and elevated CVP and deployed the Doraya catheter for up to 12 hours from femoral venous access.[47] The device remained in place for an average of 8.5 hours with no device-related complications and 1 vascular access site bleed which resolved without incident. During the treatment period, the catheter created a small (mean reduction of 6 mm Hg) but significant reduction in CVP above the level of the device with no difference in pressure below the device as compared with baseline and no significant changes to systolic blood pressure. Additionally, the rate of diuresis nearly tripled during the period of device deployment with an average peak urine output rate during deployment of 294 ± 139 mL/h.[47]

Magenta Transcatheter Renal Venous Decongestion System. The Transcatheter Renal Venous Decongestion (TRVD) System (Magenta Medical) was originally designed as miniaturized, self-expanding, axial flow pumps placed directly into the renal veins, with the ability to independently control flow in each vein. Proof of concept and early clinical data suggested improvements in diuresis, natriuresis, renal venous pressure, and CVP.[48] The system was subsequently simplified to an axial flow pump for nonselective placement in the IVC, coupled with sealing elements above and below the level of the renal veins to isolate the renal segment of IVC for selective decompression.[49] No further information is available at the present time regarding the progress of the redesigned system.

Nephronyx Perfuser. Another passive flow diversion device in early-stage validation is the Perfuser (Nephronyx, Ltd). The nonpowered device is a self-expanding covered stent that is advanced via the femoral vein to the segment of IVC adjacent to the renal veins and deployed, aiming to decrease renal venous congestion by employing

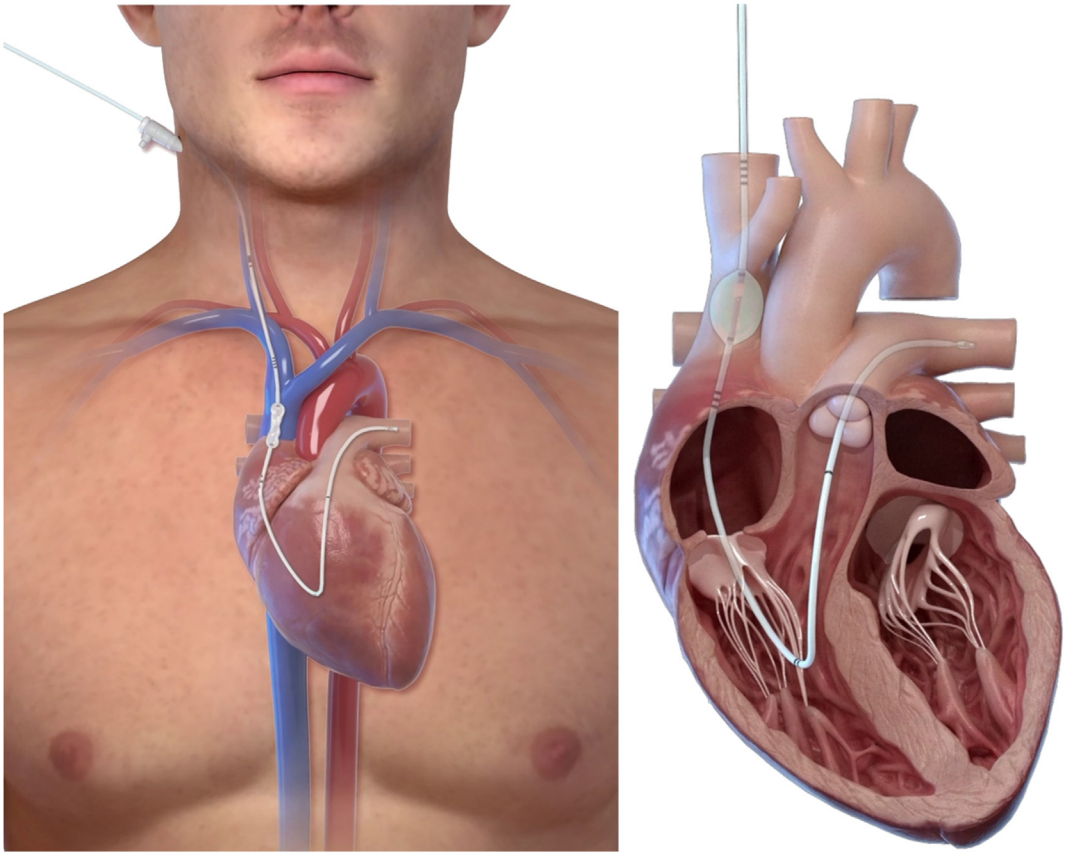


Figure 2.
The Abiomed preCARDIA system. The Abiomed preCARDIA system consists of a catheter-mounted superior vena cava (SVC) occlusion balloon which is inserted via 14F right internal jugular venous access and a pump console. After baseline hemodynamic assessment and performance of an SVC venogram, the preCARDIA device is cycled intermittently via the pump console, with complete occlusion of the SVC thereby reducing central venous inflow, with reductions in both central venous pressure and pulmonary capillary wedge pressure as well as an increase in urine output. An integrated pulmonary artery catheter allows for continuous monitoring of cardiac pressures and sampling of mixed venous saturation, throughout the period of treatment.

the Bernoulli effect and fluid entrainment principles. A small, single-arm clinical trial (The Safety and Performance Evaluation of the Nephronyx System for the Treatment of Patients With ADHF, NCT05759806) is currently underway with a target completion date in late 2023.[5,50]

Conclusions

Numerous investigational device therapies for the management of AHF with CRS have emerged over the past few years. Many have reported encouraging early-stage clinical results demonstrating that they are, at the very least, safe and capable of favorably altering hemodynamics and fluid balance in the short term. It remains unknown however whether the observed hemodynamic gains and decongestion will continue after device removal and if they translate to more meaningful improvements in clinical outcomes such as length of hospital stay, long-term cardiac and renal function, rehospitalization, and mortality. Uncertain also is the optimal duration of renal assist, the potential of combining various device therapies, and the role of device-based decongestion in patients with heart failure with preserved ejection fraction and CRS. While there are currently many more questions than definitive answers, it can be confidently stated that we are likely witnessing the start of a paradigm shift in the management of acute CRS.

Peer review statement

Associate Editor Sandeep Nathan had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Guest Editor Philippe Généreux.

Declaration of competing interest

Sandeep Nathan reports serving as a consultant to AstraZeneca, Getinge, Janssen, Merit Medical, Penumbra, Shockwave, Terumo, and Zoll and in data monitoring roles for Procyrion and Magenta Medical. Mir B. Basir reports serving as a consultant to Abbott Vascular, Abiomed, Boston Scientific, Cardiovascular Systems, Inc, Chiesi, Saranas, and Zoll.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial or non-for-profit sectors.

Ethics statement and patient consent

This review paper did not involve human or animal subjects, thus ethical approval was not required.

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