Brief Report

Treatment of Diuretic Resistance with a Novel Percutaneous Blood Flow Regulator: Concept and Initial Experience

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ABSTRACT

Diuretic resistance in acute heart failure is a common clinical problem, and it is associated with adverse outcomes. Effective therapies are still lacking. The Doraya catheter, a temporary intravenous flow regulator placed in the inferior vena cava below the level of the renal veins, is a novel device designed to target renal and cardiac congestion, thereby improving diuretic response. A first-in-man clinical study is currently ongoing. (*J Cardiac Fail 2019;25:932−934*)

Key Words: Acute heart failure, diuretic resistance, device therapy.

Signs and symptoms of fluid retention are the main reasons for admission of patients with acute heart failure (AHF), and nearly 90% of patients are treated with intravenous diuretics.[1−3] Failure to respond adequately to diuretic therapy is a common clinical problem, which has a prevalence of up to 33%.[4−7] Recent studies have shown a correlation between diuretic resistance and adverse outcome, independent of underlying glomerular filtration rate (GFR).[4−7]

Treatment of diuretic resistance in AHF usually involves combining several types of diuretics or ultrafiltration.[8,9] Until now, these strategies have not proven to be beneficial and might result in worsening renal function (WRF).[10] When facing a significant rise in serum creatinine, many clinicians taper or temporarily withhold diuretics because previous studies have described a correlation between WRF and adverse outcomes.[11,12] However, residual congestion now appears to be a more important determinant of prognosis than transient rises in serum creatinine.[13] Thus, a treatment that effectively targets volume overload and diuretic resistance while preserving renal function could potentially modify the prognosis of patients with AHF.

The Doraya catheter (Revamp Medical, Netania, Israel) is a temporary intravenous flow regulator that is percutaneously positioned in the inferior vena cava below the level of the renal veins (Fig. 1). By adjusting the opening of the distal frame, a partial obstruction of venous flow is created, resulting in reduced cardiac preload and venous congestion. Theoretically, this will set into motion a cascade of hemodynamic effects. The first effect is the unloading of the renal venous system. Venous congestion is a strong determinant of WRF through transmission of increased venous pressure to renal veins and kidneys, leading to hypoxia of the renal parenchym and reduced renal perfusion pressure.[14,15] The risk of WRF is lower when sufficient reduction of central venous pressure (CVP) ($\leq$ 8 mmHg) has been achieved.[14] The second effect is the unloading of the left ventricle, resulting in reduced intraventricular filling pressure and hence reduced wall stress, according to the Laplace law, and afterload. This will shift the Frank Starling curve up and leftward, which increases stroke volume and improves cardiac performance.

A first-in-human clinical study (NCT03234647) is currently ongoing; it assesses the feasibility, safety and hemodynamic effects of treatment with the Doraya catheter in people with AHF.[16] Patients with signs and symptoms of fluid overload, insufficient response to diuretic treatment (based on failure to reduce weight or to increase urine output within 24 hours, as used in ASCEND-HF[7]), elevated N-terminal pro-brain natriuretic peptide, evidence of cardiac etiology, and elevated CVP (> 12 mmHg) are eligible

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Manuscript received June 16, 2019; revised manuscript received August 18, 2019; revised manuscript accepted August 22, 2019.

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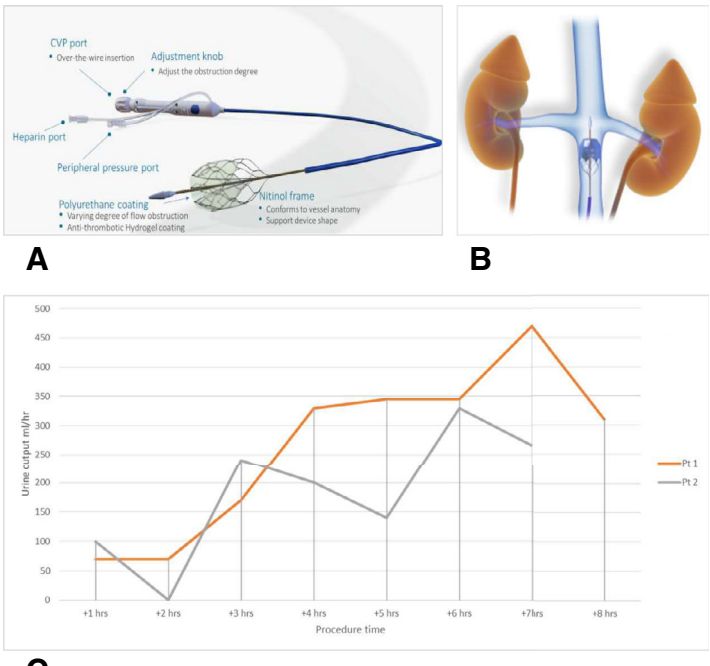
1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2019.08.017



Characteristics	Patient 1	Patient 2
Age (yrs)	62	81
LVEF (%)	15	20
NTproBNP (ng/L)	8897	6421
eGFR (ml/min)	27	31
SBP (mmHg)	100	120
Mean urine output (ml/hr):		
*Baseline**	90	91
During treatment	264	182
RAP		
Baseline	23	17
End	10	13
PCWP		
Baseline	33	29
End	18	21
mPAP		
Baseline	58	35
End	46	33
Sodium excretion (mmol/L)		
Baseline	79	78
End	115	78
Duration of treatment (hrs)	10	7

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Fig. 1. (**A**) The Doraya catheter. (**B**) Figure demonstrating the location of the device in the inferior vena cava, below the origin of the renal veins. (**C**) Evolution of urine output in mL/hour for patient 1 and patient 2 during treatment with the Doraya catheter. Time point 0 corresponds to the initiation of diuretic treatment. (**D**) Patient characteristics. CVP, central venous pressure; eGFR, estimated glomerular filtration rate; mPAP, mean pulmonary artery pressure; NTproBNP, N-terminal pro-brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SBP, systolic blood pressure.

*Baseline urine output reflects the mean urine output on the day before study treatment.

for inclusion. According to the study's protocol, the device can be used for up to 24 hours.

We have treated 2 patients successfully by using the Doraya catheter. The first patient was a 62-year-old man with severe ischemic cardiomyopathy and a left ventricular ejection fraction of 15%, admitted with dyspnea and edema. His ambulatory diuretic treatment consisted of bumetanide 5 mg and spironolactone 25 mg daily. Upon admission, he presented with weight gain of 7 kg, prominent jugular vein distention, peripheral pitting edema, and pleural effusion. Compared to his latest outpatient visit, a nearly 10-fold increase in N-terminal pro-brain natriuretic peptide value (from 968 to 8897 ng/L) with a slightly worse estimated GFR (eGFR from 35 to 27 mL/min/1.73m^2) was noted. Despite a doubling of the diuretic dose (bumetanide 10 mg) and association of an intravenous inodilator (levosimendan), diuretic response remained poor, with limited weight loss and urine output and persistent signs of congestion. Baseline hemodynamics are presented in Fig. 1. Compared to the day before study treatment, urine output increased from 90 mL/hour to 264 mL/hour with an unchanged dose of diuretics (Fig. 1). At the end of the treatment, intracardiac filling pressures were significantly decreased (Fig. 1).

The second patient was a 81-year-old man with ischemic cardiomyopathy, who presented with dyspnea at rest, ascites and edema. His ambulatory treatment did not include a loop diuretic. The left ventricular ejection fraction was 20%, N-terminal pro-brain natriuretic peptide (NTproBNP 6421 ng/L) and eGFR 31 mL/min/1.73m^2. Treatment by a continuous infusion of loop diuretics (bumetanide 4 mg) was initiated, but there was poor response. During study treatment, urine output increased from 91 mL/hour to 182 mL/hour (Fig. 1). After 7 hours, CVP had dropped from 17 to 13 mmHg, mean pulmonary artery pressure from 35 to 33 mmHg and pulmonary capillary wedge pressure from 29 to 21 mmHg. In both patients, no adverse events were observed, and systemic blood pressure remained stable.

Based on this early experience, treatment with the Doraya catheter appears to be safe and can help to overcome diuretic resistance. The ongoing first-in-human study will further explore the safety profile and provide insights into hemodynamic and mechanistic effects.

Declaration of Competing Interest

The OLV hospital is a participating center in the first-in-human study, First in Human Study of the Doraya Catheter for the Treatment of AHF patients.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.08.017.

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