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CASE REPORT
Heart failure

Cutting the Gordian knot of diuretic resistance using continuous ultrafiltration in a Holt–Oram patient with decompensated heart failure and Eisenmenger syndrome: a case report

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Background Continuous ultrafiltration consists a decongestion method for patients with refractory decompensated heart failure with diuretic resistance as it enables the energetic withdrawal of isotonic fluid under controlled rate according to the patient's vital signs, offering decongestion without exceeding plasma refill rate.

Case summary A 62-year-old male with history of Holt–Oram syndrome with Eisenmenger physiology presented with worsening dyspnoea. Patient initial clinical and laboratory examination, renal vein ultrasound, and echocardiogram were consistent with significant congestion. A combined strategy of intravenous furosemide with early initiation of continuous ultrafiltration at an adjustable rate for 4 days was finally selected. Patient remained haemodynamically stable during the total treatment time and exhibited significant clinical and laboratory improvement. Consecutive renal vein ultrasounds and echocardiograms demonstrated a continuous and steady recession of congestion. During the 4 days of ultrafiltration, total fluid loss was estimated at 42 L. Patient remained asymptomatic without signs of worsened congestion at 1, 3, and 5 months follow-up.

Discussion Our case depicts that continuous ultrafiltration without exceeding plasma refill rate allows an impaired right ventricle to maintain significant preload. This suggests that it might be considered for patients in whom a session of short classic ultrafiltration might have detrimental results regarding cardiac output.

Keywords Continuous ultrafiltration • Heart failure • Congestion • Cardiorenal syndrome • Case report

ESC curriculum 6.4 Acute heart failure • 6.7 Right heart dysfunction • 9.7 Adult congenital heart disease • 9.6 Pulmonary hypertension

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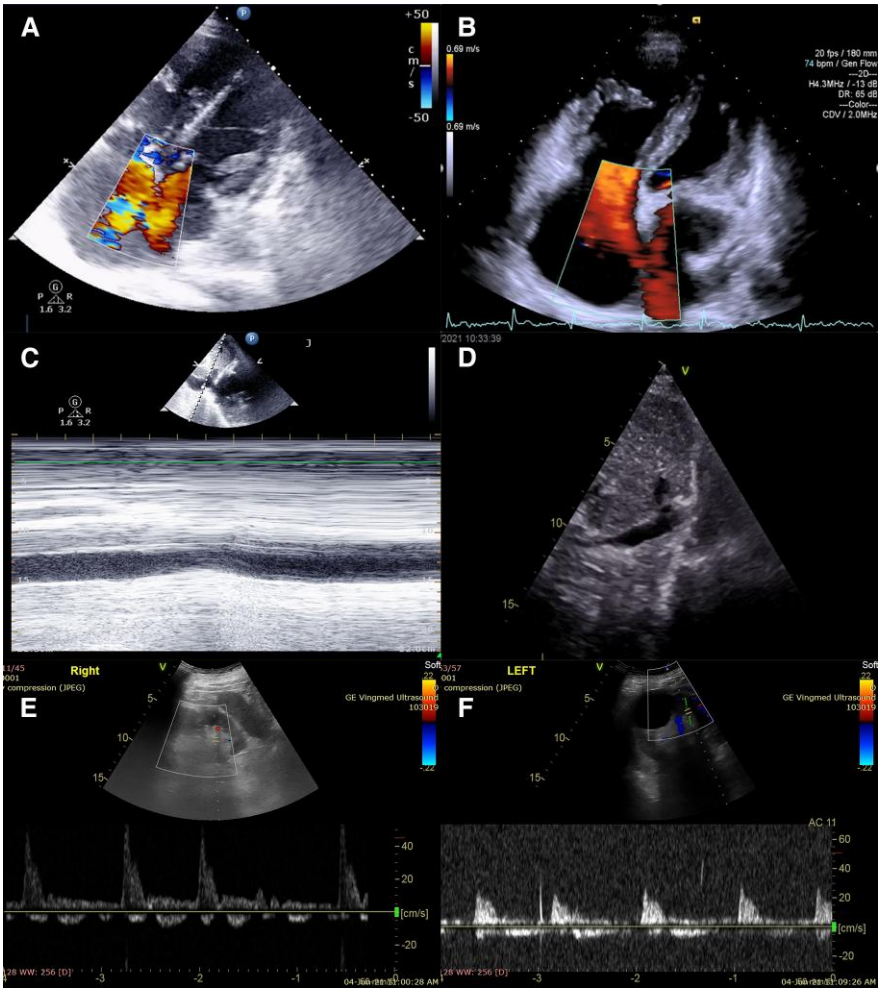
Learning points

- Increased renal vein pressure and stimulation of the sympathetic nervous system and renin-angiotensin system have been suggested as mechanisms of diuretic resistance in the context of decompensated heart failure.
- Ultrafiltration is proposed as the last resort for decongestion after the failure of high doses of intravenous diuretics combined with vasoactive drugs, however, it is limited by haemodynamic instability.
- Continuous ultrafiltration offers significant decongestion with a minimum impact on cardiac output and thus haemodynamic status and tissue perfusion.

Introduction

Congestion and diuretic resistance play a central role in patients with acutely decompensated heart failure (ADHF) as they have been related to increased morbidity and higher readmission rates.[1] Ultrafiltration (UF) presents as an alternative method when the intravenous diuretics and combination of diuretics strategies fail.[2] However, in preload dependent situations, this method might exert detrimental haemodynamic consequences. In such cases, continuous ultrafiltration has been proposed as an effective alternative enabling fluid removal at significant amounts without exceeding plasma refill rate.[3] Here, we present our experience of continuous ultrafiltration in a patient with Holt–Oram syndrome and Eisenmenger physiology presenting with ADHF.

Summary figure



Baseline echocardiography depicting bidirectional shunt through the ASD due to increased diastolic pressure in the right atrium (*A*). The shunt was left to right after the decongestion therapy leading to an increase of the arterial blood oxygen saturation (*B*). IVC diameter and respiratory variation were improved due to the decrease of right atrial pressure (*C*, *D*). Renal venous pressure decrease was documented with Doppler ultrasound as the pattern was improved from monophasic before the ultrafiltration therapy to biphasic after the first ultrafiltration session (*E*) and finally continuous before discharge (*F*).

Case presentation

A 62-year-old male with frequent hospitalizations due to ADHF presented at the emergency department with worsening dyspnoea at mild exertion, orthopnoea and peripheral oedema, while he had gained 20 kg during the last two months. Patient had a prior medical history of Holt–Oram syndrome, type 2 diabetes mellitus, atrial flutter, and chronic obstructive pulmonary disease under oxygen therapy. Holt–Oram was diagnosed at the age of 58, when malformation of extremities, low height, and the presence of an atrial septal defect (ASD) were noticed during medical assessment. At that time, he had already developed Eisenmenger physiology, right heart failure, and severe pulmonary hypertension. Regarding his medication, he reported taking daily oral furosemide 80 mg, eplerenone 50 mg, dapagliflozin 10 mg, dabigatran 300 mg, valsartan 160 mg, metformin 1000 mg, macitentan 10 mg, and digoxin 0.25 mg three times per week. He did not report use of tobacco, alcohol, or any illicit drug.

Initial physical assessment showed blood pressure 110/75 mmHg, heart rate of 80 b.p.m., and oxygen saturation of 75% on ambient air. Clinical examination revealed dilated jugular veins, ascites, and oedema anasarca. Heart auscultation revealed a split S2 and a systolic ejection murmur whereas lung auscultation revealed diffuse wheezing and basal coarse crackles.

Chest radiograph showed an enlarged cardiac silhouette with signs of congestion and pulmonary hypertension (see Supplementary material online, *Figure S1*). Electrocardiogram showed atrial flutter at 85 b.p.m. and right bundle branch block. Initial renal vein ultrasound demonstrated a monophasic pattern of renal vein flow with a single flow phase in diastole. Baseline echocardiogram showed left ventricle with normal dimensions and wall thickness and preserved ejection fraction, with systolic and diastolic D-shape movement of intraventricular septum, whereas right cavities were notably enlarged with a systolic tissue Doppler velocity of right ventricle equal of 5 cm/s. Doppler study revealed an ASD with bidirectional flow. Inferior vena cava (IVC) was dilated without respiratory variation, and systolic pulmonary pressure (PASP) was estimated at 100 mmHg (*Summary Figure A*, *C*, and *E*; Supplementary material online, *Videos S1–S3*).

Due to the prominent congestion, as well as decreased urine volume and urine sodium despite intravenous furosemide, initiation of continuous ultrafiltration was decided combined with intravenous furosemide at a daily dosage of 160 mg, maintained during the total treatment time. Patient underwent two 48 h sessions of ultrafiltration at a continuous rate of 200 mL/h. He remained haemodynamically stable during the total treatment time and exhibited significant clinical improvement. Renal function, after the initial expected deterioration, showed a steady improvement.

Patient demonstrated a continuous and steady recession of congestion. His mean daily urine output was 3 L, whereas the total ultrafiltrate was 15 L. Total fluid loss was estimated at 42 L (including 27 L of urine). Treatment results were reflected in a reduction of total body weight by 24 kg. A follow-up echocardiogram at Day 7 showed mainly left to right flow and less right to left compared to the baseline study. Renal vein ultrasound revealed a biphasic pattern with a tendency to the continuous form (*Summary Figure B*, *D*, and *F*).

He was discharged asymptomatic, with minor ankle oedema, blood pressure of 120/80 mmHg, oxygen saturation of 90% on ambient air, and with the following prescribed regime (daily dosage): pantoprazole 40 mg, torsemide 60 mg, eplerenone 50 mg, dapagliflozin 10 mg, bisoprolol 5 mg, dabigatran 300 mg, valsartan 160 mg, allopurinol 100 mg, and digoxin 0.25 mg three times a week.

Patient remained asymptomatic during the 6 months of follow-up, showing substantial improvement in his functional capacity, allowing for a reduction in torsemide dose at 20 mg per day. His main laboratory parameters at admission, exit, and follow-up visits are depicted at *Table 1*, whereas *Figure 1* highlights the course of specific clinical and laboratory parameters of interest.

Discussion

One of the proposed mechanisms of diuretic resistance in the context of ADHF is the increased renal vein pressure that decreases arteriovenous pressure gradient, with a parallel increase in the interstitial pressure within the kidney, thereby decreasing renal blood flow, ultrafiltration pressure, and glomerular filtration rate.[4] Congestion also worsens diuretic resistance by decreasing intestinal absorption, and because of a stimulation of the sympathetic nervous system and renin-angiotensin system. Moreover, worsened liver function in patients with right heart failure and congestion leads to hypoalbuminaemia that can increase resistance to furosemide.[5]

Intravenous loop diuretics at high doses and combination of different diuretics often aid in overcoming the obstacle of resistance.[5] In case of hypoperfusion, the use of vasoactive drugs should be also considered. Ultrafiltration comes as the last resort but its use is limited due the potential further haemodynamic instability if ultrafiltration rate significantly exceeds the plasma refill rate in preload dependent HF patients.

Table 1 Baseline, discharge, and follow-up laboratory parameters

	Reference	Baseline	Discharge	1 month	3 months	5 months
Haematocrit, %	37–52	37.8	40.9	47.8	48.6	46
Haemoglobin, g/dL	12–18	11.3	12.5	15	15.8	14.3
International normalized ratio		1.7	1.4	1.8	1.7	1.6
Alanine aminotransferase, IU/L	5–34	10	21	n/a	18	17
Aspartate aminotransferase, IU/L	0–55	6	13	n/a	14	15
Total bilirubin, mg/dL	0.2–1.2	1.46	1.1	0.9	1.1	1.0
Creatinine, mg/dL	0.57–1.11	1.3	1.5	1.7	1.7	1.4
Urea, mg/dL	15–43	103	103	137	115	96
Pro BNP, pg/mL	<125	5739	1608	1536	1271	n/a
Na, mEq/L	136–145	139	137	133	135	136
K, mEq/L	3.5–5.1	4	4.8	4.1	4.4	4.5

n/a, non-available; BNP, brain natriuretic peptide.

Figure 1 Graphs show the progression of various clinical and laboratory variables during the hospitalization.

Continuous ultrafiltration, on the other hand, exerts a minimum impact on haemodynamic status as the low and continuous ultrafiltration rate contributes to the maintenance of the necessary preload and thus cardiac output.[3,6] Despite the haemodynamic advantages of the method, there are several limitations. It consists a time-demanding treatment with a considerable cost and the need of anticoagulation. Application of the method by experienced personnel is warranted to reduce the odds of adverse events including bleeding, pneumothorax, catheter-related bacteraemia, and infective endocarditis. In RAPID-CHF trial, 40 patients were evaluated and ultrafiltration resulted to higher weight loss than diuretic therapy. In the UNLOAD trial, ultrafiltration was associated with a significantly greater fluid removal, fewer hospitalizations for HF, and lower readmission rate than diuretic therapy in 200 patients.[7] In the CARRESS-HF trial, 188 patients with ADHF and cardiorenal syndrome were assigned to either pharmacologic treatment or ultrafiltration. The main findings were a similar weight loss with fewer complications in the pharmacologic treatment group.[8] The AVOID-HF trial was a multicentre randomized trial comparing continuous UF with adjustable intravenous loop diuretics. UF group had fewer hospitalizations at 30 days, at the cost, however, of an increased rate for total and serious product-related adverse events leading to the premature termination. Of note, the absence of blinding could have affected patient management after discharge.[9] A real world retrospective 10-year study that included 335 consecutive patients has shown superiority on the readmission rates for the ultrafiltration, which could be attributed to the adjustable ultrafiltration rate and personalized ultrafiltration protocol.[10]

This case demonstrated the first to our knowledge patient with Holt–Oram syndrome and Eisenmenger physiology who underwent continuous ultrafiltration with impressive response and sustained long-term results. These patients tend to be underrepresented in clinical trials. Data regarding the use of UF in patients with congenital heart disease are missing. However, it should be noted that despite the prominent right heart failure, our patient had an advantage due to the Eisenmenger physiology. In particular, UF in usual patients with cardiorenal syndrome poses the risk that fluid removal rate might exceed

plasma refill time, significantly reducing preload and ultimately resulting into decreased cardiac output and consequently hypoperfusion. The latter would enhance the vicious cycle of diuretic resistance. On the contrary, in patients with ASDs and Eisenmenger physiology, the presence of right-to-left shunt contributes to the maintenance of adequate cardiac output by preventing the decrease in preload. On the other hand, continuous UF in Eisenmenger patients can lead to a relative reduction in right ventricular pressure and decrease the amount of right-to-left shunt, thus improving oxygen saturation. Torsemide was selected per protocol over furosemide at discharge due to theoretical pharmacological advantages (natriuretic effect, bioavailability, half-time) as well as the suggested less neurohormonal axis activation and its potential antifibrotic effects.[11]

Our case depicts that continuous ultrafiltration may exert a minimum impact on haemodynamic status and tissue perfusion by allowing an impaired right ventricle to maintain a significant preload. Physicians addressing the clinical scenario of refractory ADHF in patients prone to haemodynamic instability, such as those with impaired right heart function, should avoid rapid decongestion using classic UF protocols and prefer bedside continuous UF.

Lead author biography

Dr Yannis Dimitroglou completed his medical training at the University of Thessaly, Larissa, Greece. He is a resident of Cardiology in the First Cardiology Department of the National and Kapodistrian University of Athens, where he is also working on his PhD regarding cardiovascular imaging in patients with liver cirrhosis. He has special interest in the fields of cardiovascular imaging and heart failure.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Data availability

The data underlying this article are available in the article and in its online Supplementary material.

References

1. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. The use of diuretics in heart failure with congestion—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:137–155.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 2013;**62**:e147–e239.
3. Costanzo MR. Ultrafiltration in acute heart failure. *Card Fail Rev* 2019;**5**:9–18.
4. Eder M, Griffin M, Fleming J, Gleason O, Meegan G, Ivey-Miranda J, et al. Venous congestion, not cardiac index is associated with diuretic resistance. *J Card Fail* 2020;**26**:S30–S31.
5. Wilcox CS, Testani JM, Pitt B. Pathophysiology of diuretic resistance and its implications for the management of chronic heart failure. *Hypertension* 2020;**76**:1045–1054.
6. Chrysohoou C, Mantzouranis E, Dimitroglou Y, Mavroudis A, Tsioufis K. Fluid and salt balance and the role of nutrition in heart failure. *Nutrients* 2022;**14**:1386.
7. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007;**49**:675–683.
8. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med* 2012;**367**:2296–2304.
9. Costanzo MR, Negoianu D, Jaski BE, Bart BA, Heywood JT, Anand IS, et al. Aquapheresis versus intravenous diuretics and hospitalizations for heart failure. *JACC Heart Fail* 2016;**4**:95–105.
10. Watson RA, Haas D, Hummel M, Barrella P. Ten year experience with ultrafiltration for the management of acute decompensated heart failure. *J Card Fail* 2020;**26**:S56.
11. Greene SJ, Mentz RJ. Potential advantages of torsemide in patients with heart failure: more than just a 'water pill'?. *Eur J Heart Fail* 2018;**20**:471–473.