

# Impacts of right ventricular function and venous congestion on renal response during depletion in acute heart failure

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## Abstract

**Aims** Venous congestion is a major determinant of worsening renal function (WRF) in acute decompensated heart failure (ADHF), particularly when associated with right ventricular (RV) dysfunction. Whether the individual impacts of hemodynamic variables on renal outcomes in ADHF is modified according to RV function remains unclear. We aimed to determine the association between hemodynamic parameters and early changes in renal function during depletive therapy and explore the association of these changes with clinical outcomes.

**Methods and results** WRF was defined as any increase in creatinine after 24 h of depletive therapy and improvement in renal function (IRF) as any decrease. Assessments were prospectively obtained on admission, 24 h later and at discharge. Out of the 105 patients enrolled, 45% had IRF, and 41% had poor RV. At baseline, patients evolving towards IRF had a lower mean arterial pressure ( $84.7 \pm 13.9$  vs.  $90.9 \pm 15.2$  mmHg), a lower renal perfusion pressure ( $69.4 \pm 16.2$  vs.  $75.4 \pm 15.1$  mmHg), and a poorer RV function (tricuspid annular plane systolic excursion  $16.5 \pm 6.0$  vs.  $18.8 \pm 5.6$  mm) in comparison with those with WRF (all  $P < 0.05$ ). In a multivariate linear regression model, tricuspid annular plane systolic excursion was the dominant parameter correlated with early changes in creatinine when RV was poor ( $\beta = 0.337$ ), whereas mean arterial pressure ( $\beta = -0.334$ ) and cardiac output ( $\beta = -0.298$ ) were the only parameters correlated with renal function in patients with preserved RV function (all  $P < 0.05$ ). RV dysfunction, but not early changes in renal function, was associated with post-discharge clinical events.

**Conclusions** RV dysfunction is a predictor of an early but transient progression to IRF during depletive therapy. RV dysfunction modifies the individual impact of various hemodynamic variables on the early trajectory of renal function in ADHF.

**Keywords** Acute decompensated heart failure; Congestion; Worsening of renal function; Depletive therapy; Right ventricular function

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## Introduction

Venous congestion has been shown to play a major role on changes in renal function in acute decompensated heart failure (ADHF), particularly when associated with right ventricular (RV) dysfunction.<sup>1</sup> Recent data have challenged the assumption that worsening renal function (WRF) was driven by other hemodynamic alterations such as decreased cardiac output (CO).<sup>2,3</sup> WRF, when it occurs, has been associated with a worse outcome, and frequently limits the speed with which patients

are returned to a euvolemic state, and consequently prolongs hospitalization.<sup>4</sup> However, this association with poor outcomes does not seem to be linear,<sup>5</sup> such that improvement in renal function (IRF) in the setting of ADHF has been associated with a more advanced disease<sup>6</sup> and an even worse prognosis.<sup>5,7</sup> Moreover, whether the individual impact of hemodynamic variables on renal outcomes in ADHF is modified according to baseline RV function remains unclear.

RV systolic function is commonly estimated using the tricuspid annular plane systolic excursion (TAPSE), which

reflects longitudinal RV function.<sup>8</sup> TAPSE has been shown to be associated with other markers of RV dysfunction<sup>9</sup> and with poor outcomes in various situations including HF<sup>10</sup> and pulmonary hypertension.<sup>11</sup> However, the accurate assessment of RV systolic function at the bedside in patients managed for ADHF remains challenging. Recently, ultrasound markers of RV-associated venous congestion, including measures of portal congestion<sup>12</sup> along with markers assessing impaired intra renal hemodynamics,<sup>13</sup> have emerged. These markers have been associated with increased right atrial pressure in various settings<sup>14,15</sup> and have been associated with poor outcomes in HF,<sup>13</sup> cardiac surgery,<sup>16</sup> and pulmonary hypertension.<sup>17</sup> However, no comprehensive approach that includes an assessment of renal and portal congestion has been developed yet in ADHF, and no studies have focused on their relationship to the trajectory changes of renal function during the first 24 h during depletive therapy.

This study was thus undertaken to (i) describe patient characteristics, including the ultrasound markers of venous congestion and RV function, according to early (24 h) changes in renal function and how these evolve until hospital discharge; (ii) assess the impacts of these changes on the trajectory of renal function during the first 24 h and whether baseline RV dysfunction modifies these impacts; and (iii) explore the association of early changes in renal function, baseline RV function and post-discharge outcomes.

## Methods

### Patients selection and study design

The study was approved by the institutional review board of the Montreal Heart Institute. Patients without hemodynamic compromise with signs and symptoms of ADHF and New York Heart Association (NYHA) functional Class II–IV symptoms managed with intravenous (IV) diuretics from April 2017 to November 2018 were included in this prospective cohort study. Non-invasive hemodynamic assessments were prospectively obtained at three specific time period: following enrolment on hospital admission, after 24 h of depletive therapy and again at discharge. Portal and renal markers were not made available to the clinician in charge of the patient for decision making.

### Definitions and outcomes

Day-to-day changes in renal function based on changes in serum creatinine values were prospectively collected. The first creatinine value was obtained in the emergency department and was considered as the baseline value. For the specific purpose of this work, IRF was defined as any absolute

decrease in serum creatinine, and WRF as no change or any increase after 24 h of depletive therapy. Estimated glomerular filtration rate (eGFR) at baseline was calculated by the Modified Diet and Renal Disease equation based on serum creatinine at admission and 24 h.<sup>18</sup> The clinical assessment of congestion was based on central venous pressure (CVP). CVP was estimated using jugular vein distension, which was clinically assessed by the treating team. Renal perfusion pressure (PP) was calculated as follows: Renal PP = MAP – CVP, where MAP stands for mean arterial pressure. Left ventricular ejection fraction (LVEF) was assessed using the Simpson's equation as per most recent guidelines.<sup>8,19</sup> RV systolic function was assessed using the TAPSE, and values  $\geq 16.5$  mm defined a preserved RV systolic function.<sup>8,19</sup> CO was estimated using the following formula:  $CO = 3.14 * LVOT-d^2/4 * LVOT-VTI * HR$  [heart rate (HR), left ventricular outflow tract diameter (LVOT-d, mm), LVOT velocity-time integral (LVOT-VTI, cm)]. The simplified Bernoulli equation was used to calculate pulmonary artery systolic pressure using peak tricuspid regurgitation velocity.<sup>8,20</sup> Major clinical outcomes were all-cause deaths alone, all-cause hospitalization alone, and the combination of death and hospitalization from any causes.

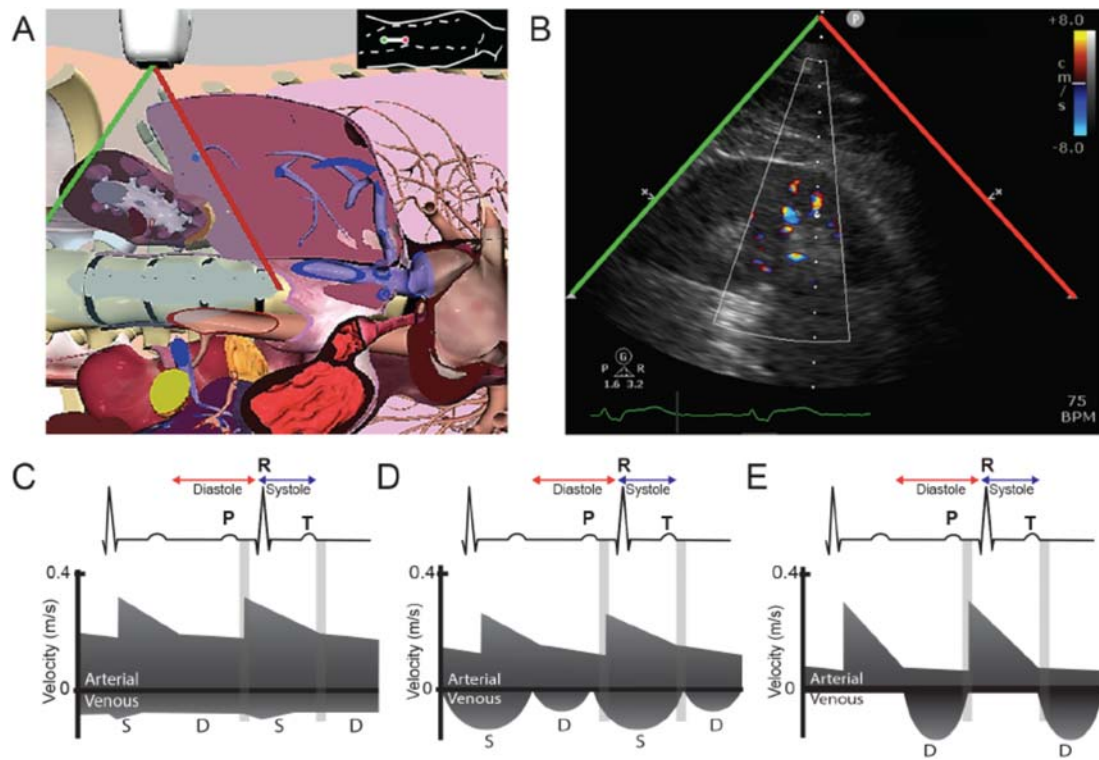
### Ultrasound assessment of portal and renal Doppler flow

Ultrasound assessment of portal venous flow was performed at the bedside as previously published and was based on the calculation of portal vein pulsatility index (PVPI).<sup>21</sup> Abnormal or discontinuous portal flow was defined for values of PVPI  $> 50\%$ .<sup>14,15,21,22</sup> Intrarenal venous flow (IRVF) using renal Doppler ultrasonography at the level of renal parenchymal veins was used for profiling intrarenal hemodynamics as presented in *Figure 1* and was obtained as previously published.<sup>13,23</sup> Abnormal or discontinuous IRVF patterns have been related to increased interstitial pressures within the kidney in the setting of increased venous congestion.<sup>23</sup>

### Statistical analysis

Results are presented using counts and percentages for categorical variables and mean  $\pm$  standard deviation (SD) or median [interquartile range (IQR)] for continuous variables, where appropriate. The groups (IRF vs. WRF, and poor vs. preserved RV function) were compared using  $\chi^2$  and Fisher's exact test (for categorical variables), Student's *t*-tests, and Mann–Whitney *U* tests (for continuous variables), as appropriate. Paired samples *t*-test and paired samples Wilcoxon test were used for paired data, as appropriate. To determine the associations between changes in creatinine between 24 h and baseline, and various hemodynamic variables, a stepwise

**Figure 1** Intrarenal venous flow (IRVF) assessment using abdominal ultrasound. (A) Probe placement in the posterior axillary position using the Vimedix simulator (with permission of CAE Healthcare, St-Laurent, Canada). (B) Longitudinal view of the right kidney with colour Doppler identifying interlobar vessels. (C–E) IRVF patterns: Normal pattern, venous flow in continuous during the cardiac cycle (C), Abnormal patterns: Discontinuous biphasic venous flow (D) and Discontinuous monophasic venous flow (E, venous flow is exclusively diastolic in this pattern). (Reprinted with permission from Taylor and Francis Group, LLC, a division of Informa plc).



linear regression model was used and included the following hemodynamic parameters: delta MAP (change between 24 h and baseline), delta CVP (change between 24 h and baseline), delta CO (change between 24 h and baseline), and TAPSE. Finally, the Kaplan–Meier method was used to draw the stratified composite event-free rates (hospitalization or death), and the log-rank test was used to compare the survival curves according to early changes in renal function (WRF vs. IRF) and to RV systolic function at baseline (poor vs. preserved). All analyses were conducted using SPSS version 24 (IBM, Armonk, NY) and  $P$ -values  $<0.05$  were considered to be statistically significant.

## Results

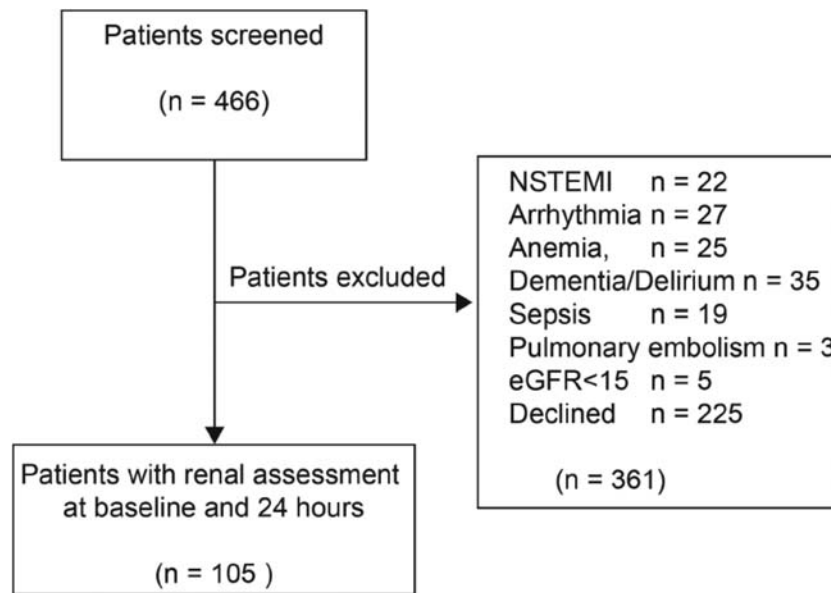
### Patients population

Recruitment process is demonstrated in *Figure 2* and baseline characteristics in *Table 1*. PVPI was considered interpretable in all patients on hospital admission, at 24 h, and at discharge, and IRVF was considered interpretable

in 86 patients at baseline, 88 patients at 24 h, and 89 at discharge. The 105 patients were predominantly male (74.3%) aged  $74.0 \pm 11.3$  years, and presented in NYHA functional Class III (66.7%). At the time of hospital admission, CVP  $15.7 \pm 4.3$  cm H<sub>2</sub>O, MAP was  $88.2 \pm 14.9$  mmHg, renal PP  $72.7 \pm 15.8$  mmHg, and CO  $4.7 \pm 1.6$  L/min. Baseline mean LVEF was  $41.5 \pm 16.3\%$ . RV dysfunction was frequent with poor RV systolic function in 41% of patients and mean TAPSE  $17.8 \pm 5.9$  mm. Overall, 65.7% of patients had discontinuous portal flow, and 62.8% had discontinuous IRVF on hospital admission. At baseline, creatinine was  $129.1 \pm 48.2$   $\mu$ mol/L, eGFR  $63.2 \pm 29.9$  mL/min/1.73m<sup>2</sup> and N terminal pro brain natriuretic peptide was 4474.0 pg/L (IQR 2463.0–7351.5).

### Baseline characteristics according to early changes in renal function

Overall, 45% of patients evolved towards an IRF after 24 h of depletive therapy. Although CVP was similar at baseline in both groups ( $P > 0.05$ ), patients with an early IRF had a lower MAP ( $84.7 \pm 13.9$  vs.  $90.9 \pm 15.2$  mm Hg,  $P = 0.032$ ), a lower

**Figure 2** Selection process. eGFR, estimated glomerular filtration rate.

renal PP ( $69.4 \pm 16.2$  vs.  $75.4 \pm 15.1$  mmHg,  $P = 0.056$ ), and tended to have a lower CO ( $4.4 \pm 1.5$  vs.  $5.0 \pm 1.6$  L/min,  $P = 0.070$ ) when compared with patients that progressed to WRF. Patients presenting with an early IRF had a poorer RV systolic function (TAPSE  $16.5 \pm 6.0$  vs.  $18.8 \pm 5.6$  mm,  $P = 0.043$ ) in comparison with those with WRF. At baseline, there was no significant difference between groups in terms of markers of portal or renal congestion (both  $P > 0.05$ ), although patients with IRF had poorer renal function (creatinine  $140.5 \pm 51.9$  vs.  $119.8 \pm 43.3$   $\mu\text{mol/L}$ ,  $P = 0.031$ ) on hospital admission as compared with those presenting a WRF. Notably, patients with IRF were receiving more MRAs (49% vs. 29%,  $P = 0.032$ ), but similar beta blockers, loop diuretics, and ACEi/ARB/ARNI (all  $P > 0.05$ ) pre-admission (Table 1, Figure 3).

### Baseline characteristics according to RV systolic function

Overall, 41% of patients ( $N = 43$ ) had poor RV systolic function at baseline as previously defined. There were no significant differences in terms of other hemodynamic parameters (MAP, CO, and LVEF) or renal function at baseline according to baseline RV status (all  $P > 0.05$ ). When compared with patients with preserved RV systolic function, patients with poor RV function were severely symptomatic at the time of hospital admission (81.4% vs. 56.5% were in NYHA Class III,  $P = 0.024$ ), they had higher CVP ( $17.4 \pm 3.9$  vs.  $14.6 \pm 4.3$ ,  $P = 0.001$ ) and lower renal PP ( $68.3 \pm 13.7$  vs.  $75.7 \pm 16.6$ ,

$P = 0.014$ ). In addition, patients with poor RV systolic function displayed significantly more features of portal and renal congestion when compared with those with preserved RV, with 83.7% vs. 53.2% having discontinuous portal flow and 78.4% vs. 51.0% having discontinuous IRVF, respectively, both  $P < 0.05$  (Table 1).

### Characteristics of patients after 24 h of depletion

After 24 h of depletive therapy, and despite similar doses of IV furosemide ( $130.2 \pm 76.9$  vs.  $116.2 \pm 82.7$  mg IV furosemide equivalent,  $P = 0.372$ ) and urine output during the first 24 h ( $1813.9 \pm 774.2$  vs.  $2053.8 \pm 819.8$ ,  $P = 0.127$ ), patients with IRF had more evidence of persistent venous congestion either assessed clinically (CVP,  $12.0 \pm 4.3$  vs.  $10.2 \pm 3.9$  cm H<sub>2</sub>O,  $P = 0.021$ ) or using ultrasound markers of portal (discontinuous portal flow 46.8% vs. 25.9%,  $P = 0.021$ ) and renal (discontinuous IRVF 61.5% vs. 36.7%,  $P = 0.018$ ) congestion when compared with patients with WRF. Baseline differences in renal function (creatinine,  $131.0 \pm 50.1$  vs.  $127.9 \pm 44.3$   $\mu\text{mol/L}$ ,  $P = 0.743$ ) and in MAP ( $85.8 \pm 13.9$  vs.  $87.1 \pm 12.0$  mmHg,  $P = 0.594$ ) had disappeared according to whether patients progressed towards an early IRF vs. WRF (Table 2).

Patients with poor RV systolic function also trended to more frequently unresolved congestion after 24 h of depletion with higher CVP ( $12.8 \pm 4.1$  vs.  $9.7 \pm 3.7$ ,  $P < 0.001$ ) and more portal (58.1% vs. 19.4%,  $P < 0.001$ ) and renal congestion (67.6% vs. 33.3%,  $P = 0.001$ ), and to poorer response

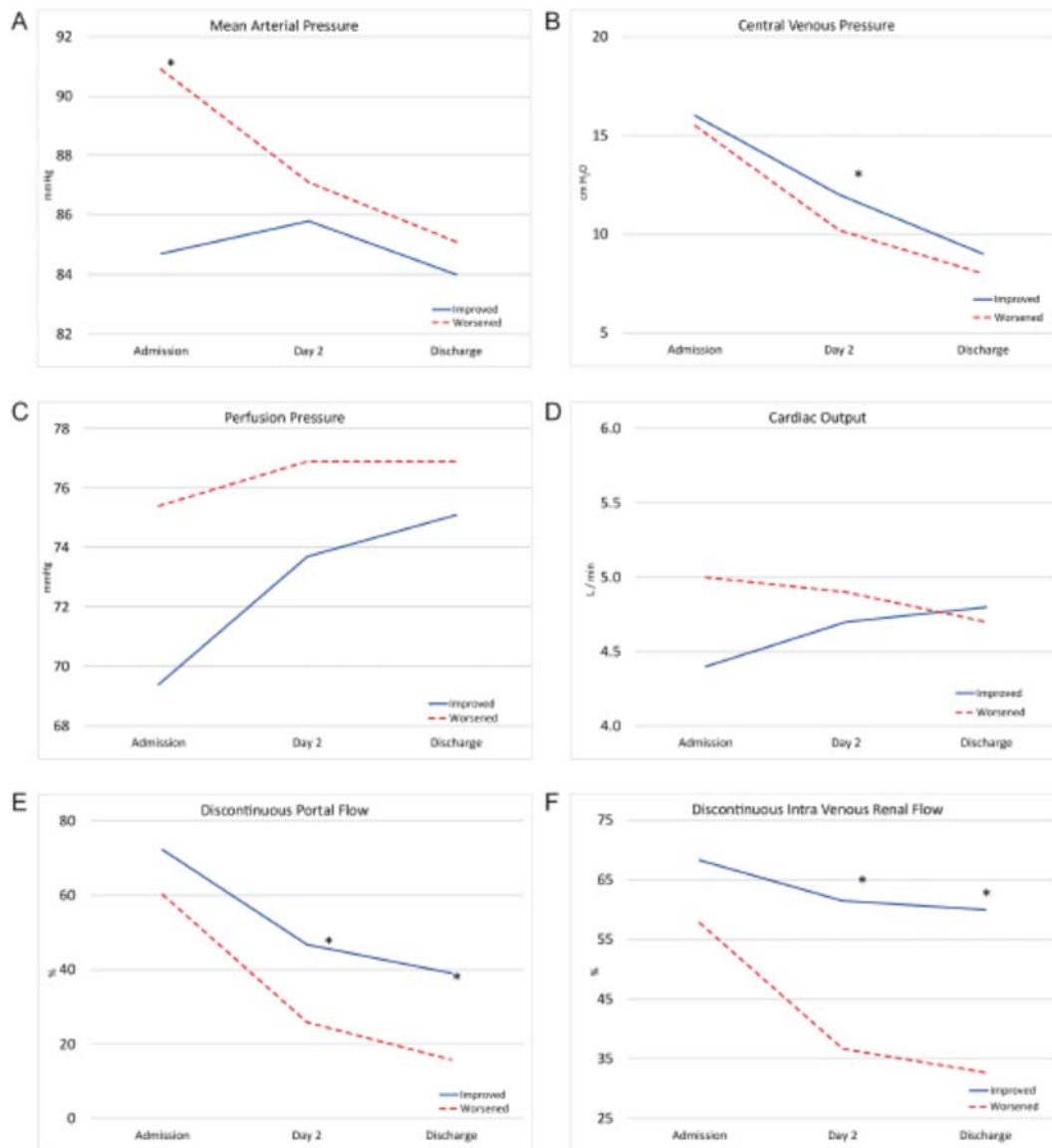
**Table 1** Baseline characteristics according to early changes in renal function and to baseline RV systolic function

Variables	All patients (N = 105)	IRF: Improvement in renal function at 24 h (N = 47)	WRF: Deterioration or no change in renal function at 24 h <sup>a</sup> (N = 58)	P	Poor RV function at baseline (N = 43)	Preserved RV function at baseline (N = 62)	P
<b>Clinical characteristics:</b>							
Age (years)	74.0 ± 11.3	75.2 ± 11.6	73.1 ± 11.1	0.348	74.2 ± 9.5	73.9 ± 12.5	0.880
Male sex, % (No)	74.3% (N = 78)	72.3% (N = 34)	75.9% (N = 44)	0.425	79.1% (N = 34)	71.0% (N = 44)	0.241
Diabetes, % (No)	49.5% (N = 52)	46.8% (N = 22)	51.7% (N = 30)	0.380	48.8% (N = 21)	50.0% (N = 31)	0.532
Hypertension, % (No)	76.2% (N = 80)	74.5% (N = 35)	77.6% (N = 45)	0.442	74.4% (N = 32)	77.4% (N = 48)	0.449
De novo HF, % (No)	26.7% (N = 28)	19.1% (N = 9)	32.8% (N = 19)	0.088	18.6% (N = 8)	32.3% (N = 20)	0.090
Atrial Fibrillation, % (No)	69.5% (N = 73)	80.9% (N = 38)	60.3% (N = 35)	0.019	76.7% (N = 33)	64.5% (N = 40)	0.130
<b>Symptoms:</b>							
NYHA class, % (No)				0.756			0.024
2	20.0% (N = 21)	17.0% (N = 8)	22.4% (N = 13)		9.3% (N = 4)	27.4% (N = 17)	
3	66.7% (N = 70)	68.1% (N = 32)	65.5% (N = 38)		81.4% (N = 35)	56.5% (N = 35)	
4	13.3% (N = 14)	14.9% (N = 7)	12.1% (N = 7)		9.3% (N = 4)	16.1% (N = 10)	
<b>Clinical assessment:</b>							
CVP, (cm H <sub>2</sub> O)	15.7 ± 4.3	16.0 ± 4.3	15.5 ± 4.4	0.541	17.4 ± 3.9	14.6 ± 4.3	0.001
MAP (mmHg)	88.2 ± 14.9	84.7 ± 13.9	90.9 ± 15.2	0.032	85.6 ± 13.0	89.9 ± 16.0	0.129
PP (mmHg)	72.7 ± 15.8	69.4 ± 16.2	75.4 ± 15.1	0.056	68.3 ± 13.7	75.7 ± 16.6	0.014
CO (L/min)	4.7 ± 1.6	4.4 ± 1.5	5.0 ± 1.6	0.070	4.5 ± 1.7	4.9 ± 1.6	0.226
LVEF (%)	41.5 ± 16.3	38.8 ± 16.6	43.7 ± 16.0	0.132	38.7 ± 16.5	43.4 ± 16.1	0.148
TAPSE (mm)	17.8 ± 5.9	16.5 ± 6.0	18.8 ± 5.6	0.043	12.2 ± 2.8	21.6 ± 4.1	<0.001
	41.0%	48.9%	34.5% (N = 20)	0.097	—	—	—
Poor RV systolic function, % (No)	(N = 43)	(N = 23)	(N = 20)				
PASP (mmHg)	53.9 ± 14.9	55.3 ± 16.0	52.8 ± 14.2	0.464	57.5 ± 11.7	51.5 ± 16.4	0.054
Discontinuous portal flow, % (No)	65.7% (N = 69)	72.3% (N = 34)	60.3% (N = 35)	0.140	83.7% (N = 36)	53.2% (N = 33)	0.001
PVPI (%)	59.2 ± 26.6	64.6 ± 28.9	54.9 ± 23.9	0.070	70.8 ± 25.7	51.2 ± 24.3	<0.001
Discontinuous IRVF, % (No)	62.8% (n = 54)	68.3% (N = 28)	57.8% (N = 26)	0.217	78.4% (N = 29)	51.0% (N = 25)	0.008
<b>Laboratory findings:</b>							
Creatinine (μmol/L)	129.1 ± 48.2	140.5 ± 51.9	119.8 ± 43.3	0.031	134.5 ± 42.5	125.3 ± 51.8	0.324
eGFR, mL/min/1.73 m <sup>2</sup>	63.2 ± 29.9	56.3 ± 28.4	68.7 ± 30.1	0.032	60.9 ± 33.3	64.7 ± 27.4	0.537
WRF at 24 h, % (No)	—	—	—	—	46.5% (N = 20)	61.3% (N = 38)	0.097
	4474.0	4638.0	4215.0	0.151	4474.0	4468.0	0.386
NT-proBNP, pg/L	(2463.0–7351.5)	(2355.0–8758.0)	(2690.5–7200.0)		(2418.0–8282.0)	(2475.7–6789.7)	
<b>Pre-hospital medication:</b>							
Loop Diuretics, % (No)	65.7% (N = 69)	74.5% (N = 35)	58.6% (N = 34)	0.067	74.4% (N = 32)	59.7% (N = 37)	0.087
Dose of loop diuretics (mg/day)	41.5 ± 50.1	49.1 ± 53.6	35.3 ± 46.7	0.070	45.8 ± 48.4	38.5 ± 51.5	0.464
MRA, % (No)	38.1% (N = 40)	48.9% (N = 23)	29.3% (N = 17)	0.032	46.5% (N = 20)	32.3% (N = 20)	0.101
ACE-I, ARBs, ARNI, % (No)	54.3% (N = 57)	53.2% (N = 25)	55.2% (N = 32)	0.498	44.2% (N = 19)	61.3% (N = 38)	0.063
Beta-blockers, % (No)	79.0% (N = 83)	87.2% (N = 41)	72.4% (N = 42)	0.052	88.4% (N = 38)	72.6% (N = 45)	0.041

Abbreviations: ACEi, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index in kg/m<sup>2</sup>; CVP, central venous pressure; eGFR, estimated glomerular filtration rate in mL/min/1.73 m<sup>2</sup>; calculated by the Modified Diet and Renal Disease equation; Discontinuous portal flow is defined by PVPI ≥50%; NT-proBNP, N terminal pro-brain natriuretic peptide in pg/L; IRVF, intrarenal venous flow; LVEF, left ventricular ejection fraction in %; MRA, mineralocorticoid receptor antagonist; MAP, mean arterial pressure; PASP, pulmonary artery systolic pressure in mmHg; PVPI, portal vein pulsatility index in %; TAPSE, tricuspid annular plane excursion in mm. Results are presented using counts and percentages for categorical variables and mean ± standard deviation for continuous variables. For NT-proBNP, results are presented as median [interquartile range (IQR)].

<sup>a</sup>N = 2 patients had unchanged creatinine at 24 h.

**Figure 3** (A–F) Changes in hemodynamic parameters (at baseline, 24 h and at discharge) according to changes in renal function after 24 h of depletive therapy. Red: worsening renal function (WRF) at 24 h and blue: improvement in renal function (IRF) at 24 h. \* refers to statistical significance.



to depletive therapy with lower urine output ( $1675.8 \pm 480.3$  vs.  $2134.1 \pm 926.4$ ,  $P = 0.001$ ) when compared with those with preserved RV systolic (Table 2).

### Characteristics of patients at hospital discharge

At the time of hospital discharge, patients with an early IRF vs. WRF had received similar total furosemide doses (480 (IQR 300–1120) vs. 450 (IQR 270–740) mg), had similar body weight loss ( $-3.9 \text{ kg} \pm 3.3$  vs.  $-4.3 \text{ kg} \pm 4.6$ ), and length of stay, ( $7.9 \pm 6.5$  vs.  $8.0 \pm 7.7$  days), all  $P > 0.05$ .

Hemodynamic (MAP, renal PP, CO) and renal (creatinine  $138.5 \pm 62.1$  vs.  $135.9 \pm 55.7 \mu\text{mol/L}$ ) status between patients with an early IRF vs. WRF were again no longer significant (all  $P > 0.05$ ). As at 24 h, patients with an early IRF demonstrated a trend to a higher CVP ( $9.0 \pm 3.2$  vs.  $8.0 \pm 2.8$  mmHg,  $P = 0.086$ ) and evidence of more frequent altered portal (discontinuous portal flow 39.1% vs. 15.8%,  $P = 0.007$ ) and renal (discontinuous IRVF 60.0% vs. 32.7%,  $P = 0.009$ ) flow when compared with those with an early WRF (Table S1).

Patients with a poor RV systolic function also displayed features of a less effective venous congestion despite a trend

**Table 2** Characteristics at 24 h according to early changes in renal function and to baseline RV systolic function

Variables	All patients (N = 105)	IRF: Improvement in renal function at 24 h (N = 47)	WRF: Deterioration or no change in renal function at 24 h <sup>a</sup> (N = 58)	P	Poor RV function at baseline (N = 43)	Preserved RV function at baseline (N = 62)	P
<b>Clinical characteristics:</b>							
Dose of IV diuretics/24 h (mg)	122.4 ± 80.1	130.2 ± 76.9	116.2 ± 82.7	0.372	120.4 ± 83.5	123.8 ± 78.4	0.834
Urine output/24 h (mL)	1946.4 ± 804.9	1813.9 ± 774.2	2053.8 ± 819.8	0.127	1675.8 ± 480.3	2134.1 ± 926.4	0.001
<b>Clinical assessment:</b>							
CVP (cm H <sub>2</sub> O)	11.0 ± 4.1	12.0 ± 4.3	10.2 ± 3.9	0.021	12.8 ± 4.1	9.7 ± 3.7	<0.001
MAP (mmHg)	86.5 ± 12.9	85.8 ± 13.9	87.1 ± 12.0	0.594	84.0 ± 13.7	88.3 ± 12.1	0.101
PP (mmHg)	75.5 ± 13.9	73.7 ± 15.7	76.9 ± 12.2	0.266	71.1 ± 15.4	78.5 ± 12.0	0.010
<b>Ultrasound assessments:</b>							
CO (L/min)	4.8 ± 1.4	4.7 ± 1.5	4.9 ± 1.3	0.407	4.6 ± 1.4	4.9 ± 1.4	0.227
LVEF (%)	43.2 ± 16.6	41.9 ± 17.3	44.2 ± 16.1	0.489	41.3 ± 17.7	46.1 ± 15.8	0.346
TAPSE (mm)	17.9 ± 5.9	16.9 ± 6.0	18.7 ± 5.8	0.124	13.1 ± 3.7	21.2 ± 4.8	<0.001
PASP (mmHg)	46.6 ± 14.7	49.5 ± 16.8	44.3 ± 12.5	0.117	47.1 ± 13.1	46.1 ± 15.8	0.763
Discontinuous portal flow, % (No)	35.2% (N = 37)	46.8% (N = 22)	25.9% (N = 15)	0.021	58.1% (N = 25)	19.4% (N = 12)	<0.001
PVPI, %	42.6 ± 28.1	48.0 ± 28.8	38.2 ± 27.0	0.080	57.0 ± 31.6	32.6 ± 20.4	<0.001
Discontinuous IRVF, % (No)	47.7% (N = 42)	61.5% (N = 24)	36.7% (N = 18)	0.018	67.6% (N = 25)	33.3% (N = 17)	0.001
<b>Laboratory findings:</b>							
Creatinine (μmol/L)	129.3 ± 46.8	131.0 ± 50.1	127.9 ± 44.3	0.743	133.2 ± 41.6	126.6 ± 50.2	0.469
eGFR (mL/min/1.73 m <sup>2</sup> )	63.1 ± 28.8	61.1 ± 30.5	64.8 ± 27.5	0.528	60.8 ± 31.3	64.8 ± 27.1	0.501
<b>Mediation at 24 h:</b>							
MRA, % (No)	66.7% (N = 70)	68.1% (N = 32)	65.5% (N = 38)	0.473	69.8% (N = 30)	64.5% (N = 40)	0.364
ACE-I, ARBs, ARNI, % (No)	54.3% (N = 57)	51.1% (N = 24)	56.9% (N = 33)	0.345	44.2% (N = 19)	61.3% (N = 38)	0.063
Beta-blockers, % (No)	82.9% (N = 87)	80.9% (N = 38)	84.5% (N = 49)	0.407	86.0% (N = 37)	80.6% (N = 50)	0.327

Abbreviations: ACEi, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index in kg/m<sup>2</sup>; CVP, central venous pressure; eGFR, estimated glomerular filtration rate in mL/min/1.73 m<sup>2</sup>; calculated by the Modified Diet and Renal Disease equation; Discontinuous portal flow is defined by PVPI >50%; NT-proBNP, N terminal pro-brain natriuretic peptide in pg/L; IRVF, intra renal venous flow; LVEF, left ventricular ejection fraction in %; MRA, mineralocorticoid receptor antagonist; MAP, mean arterial pressure; PASP, pulmonary artery systolic pressure in mmHg; PVPI, portal vein pulsatility index in %; TAPSE, tricuspid annular plane excursion in mm.

Results are presented using counts and percentages for categorical variables and mean ± standard deviation for continuous variables. For NT-proBNP, results are presented as median [interquartile range (IQR)].

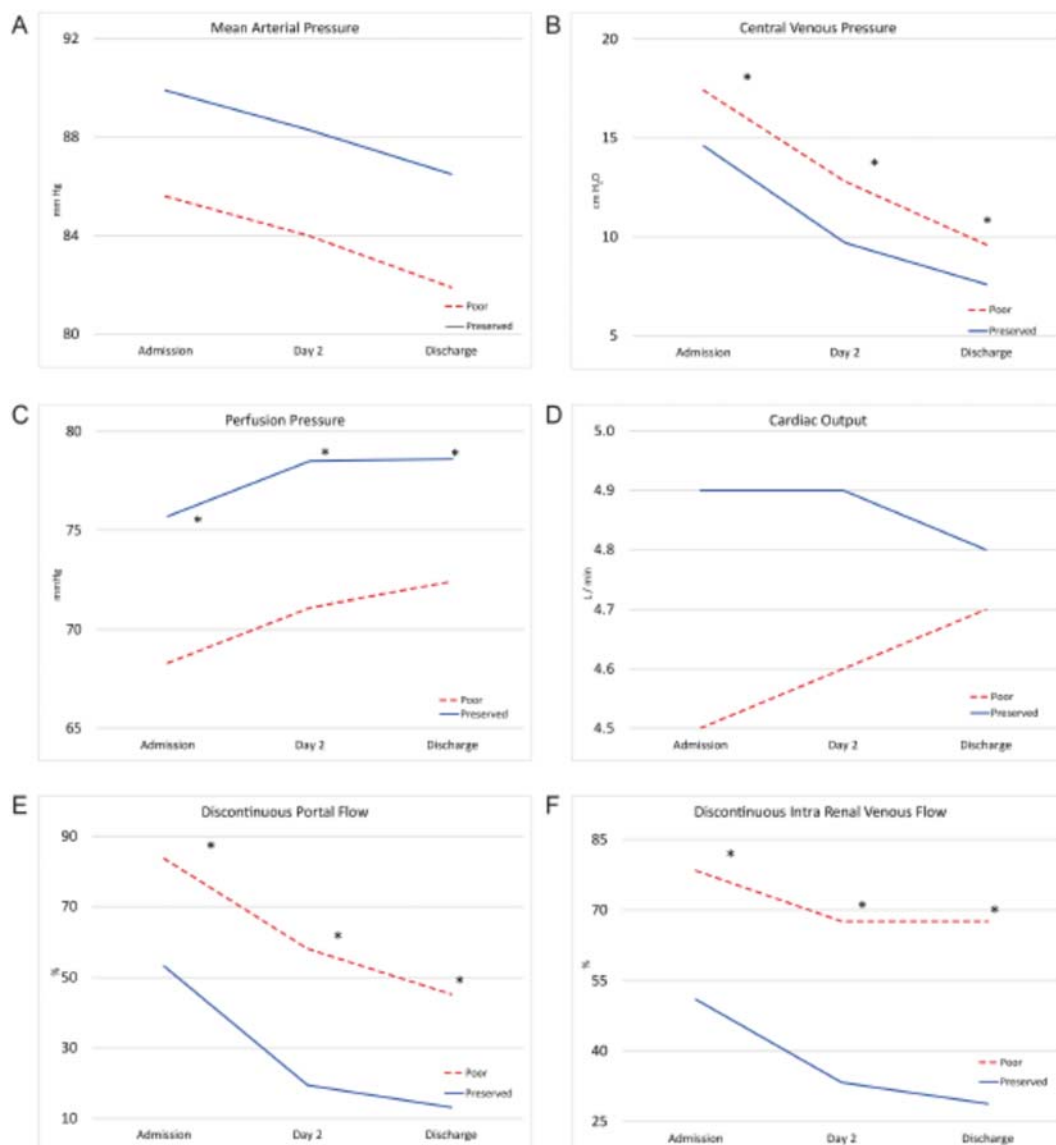
<sup>a</sup>N = 2 patients had unchanged creatinine at 24 h

towards higher doses of total furosemide (520.0 (320.0–1200.0) vs. 410.0 (240.0–740.0),  $P = 0.081$ ) and a longer length of stay ( $10.0 \pm 8.4$  vs.  $6.5 \pm 5.8$ ,  $P = 0.023$ ) in comparison with patients with preserved RV systolic function. As such, patients with RV systolic dysfunction had a higher CVP ( $9.6 \pm 3.4$  vs.  $7.6 \pm 2.4$ ,  $P = 0.002$ ) and more features of portal (45.2% vs. 13.1%,  $P < 0.001$ ) and renal congestion (67.6% vs. 28.8%,  $P < 0.001$ ) at hospital discharge when compared with those with preserved RV function (Table S1).

Changes in the hemodynamic and ultrasound markers of renal and portal congestion according to early changes in renal function (IRF vs. WRF) and RV function at

baseline (poor vs. preserved RV function) are demonstrated in Figures 3 and 4, respectively. In patients that presented an early IRF vs. WRF, change in MAP and in CO tended to inversely track with changes in renal function, such that by 24 h and again at discharge, baseline differences between groups were no longer significant (Figure 3). However, evidence of altered portal and renal venous flow remained significantly higher in patients who had an early IRF vs. WRF at 24 h and during the hospital course (Figure 3), also evidenced in patients with poor RV function when compared with those with preserved RV (Figure 4).

**Figure 4** (A–F) Changes in hemodynamic parameters (at baseline, 24 hours and at discharge) according to baseline right ventricular (RV) function. Red: poor RV function, and blue: preserved RV function. \* refers to statistical significance.





## Associations between RV systolic function, venous congestion and early changes in renal function

A stepwise linear regression model was performed to explore the associations between absolute changes in creatinine between 24 h and baseline and the hemodynamic variables previously listed. Overall, and although correlations were weak, delta MAP ( $\beta = -0.262$ ,  $P = 0.009$ ), delta CO ( $\beta = -0.230$ ,  $P = 0.021$ ), and TAPSE ( $\beta = 0.203$ ,  $P = 0.042$ ) were the variables correlated with early changes in creatinine. Amongst patients with a preserved RV systolic function, delta MAP ( $\beta = -0.334$ ,  $P = 0.010$ ) and delta CO ( $\beta = -0.298$ ,  $P = 0.020$ ) remained significantly associated with changes in renal function, whereas in patients with a poor RV systolic function, only TAPSE ( $\beta = 0.337$ ,  $P = 0.044$ ) was significantly associated with changes in creatinine (Table 3).

## Associations with outcomes

At hospital discharge, there were no differences in terms of HF medication according to whether patients had an early IRF vs. WRF (all  $P > 0.05$ ). Overall, 28.6% of patients died and 68.6% were readmitted for any cause at a median follow-up of 188 days (50–423). There were no differences in terms of all-cause mortality (34.0 vs. 24.1% in IRF vs. WRF patients, respectively, log-rank 0.270), all-cause hospitalization (74.5 vs. 63.8%, respectively, log-rank 0.353), and all-cause deaths or hospitalizations at last follow-up (83.0 vs. 70.7%, respectively, log-rank 0.318) according to early changes in renal function (Table S1, Figure S1).

**Table 3** Linear regression model for the prediction of changes in renal function after 24 h of depletive therapy amongst the whole population ( $N = 105$ ), patients with preserved RV function ( $N = 62$ ), and patients with poor RV function ( $N = 43$ )

Population	Variables	Regression coefficient ( $\beta$ )	$P$
Model 1—All patients	Delta MAP	-0.262	0.009
	Delta CO	-0.230	0.021
	TAPSE	0.203	0.042
Model 2—Preserved RV function	Delta TAM	-0.334	0.010
	Delta CO	-0.298	0.020
Model 3—Poor RV function	TAPSE	0.337	0.044

The association was assessed using linear regression. Univariable then multivariable with variables selected using stepwise forward selection. All the following hemodynamic parameters were included in the models: delta MAP (change between 24 h and baseline), delta CVP (change between 24 h and baseline), delta CO (change between 24 h and baseline), and TAPSE. Adjusted  $R^2 = 0.146$  for Model 1, adjusted  $R^2 = 0.170$  for Model 2, and adjusted  $R^2 = 0.088$  for Model 3. Abbreviations: CO, cardiac output; CVP, central venous pressure; MAP, mean arterial pressure; RV, right ventricle; TAPSE, tricuspid annular plane excursion in mm.

Patients with a poor RV systolic function tended to receive less ACEi/ARBs/ARNI at discharge in comparison with those with preserved RV function (45.2% vs. 62.9%,  $P = 0.057$ ), but there were no significant differences in terms of other HF medication. Patients with poor RV function demonstrated significantly poorer outcomes with higher rates of all-cause mortality (44.2% vs. 17.7%, log-rank = 0.010) but no significant differences in terms of all-cause hospitalizations (log-rank = 0.717) or combined deaths and hospitalizations at last follow-up (log-rank = 0.347) (Table S1, Figure S1).

## Discussion

This work suggests the following: (i) At baseline, patients with ADHF that will evolve towards an early IRF under depletive therapy have more altered hemodynamic, renal and RV status but similar venous congestion in comparison with those that will present a WRF. (ii) After 24 h of depletive therapy, all the baseline differences between patients with IRF vs. WRF had disappeared, the only remaining being less effective decongestion in patients with IRF. (iii) In a stepwise linear regression model, hemodynamic variables associated with the early renal trajectory appear to vary according to whether RV function is preserved or not at baseline, such that the degree of RV systolic function became the dominant determinant of changes in renal function after 24 h of depletion in the subgroup of patients with poor RV function. (iv) That early in-hospital renal trajectory did not have a major impact on outcomes as compared with the presence of RV systolic dysfunction.

## Changes in hemodynamic variables and renal outcomes in ADHF

Venous congestion has been considered as a major determinant of renal outcomes in HF,<sup>1,24</sup> and studies have shown that early IRF may be partly due to decongestion of the kidney.<sup>24</sup> In this study, there were no significant differences in clinical and ultrasound markers of volume overload at baseline between patients whether they had an improvement or worsening in their renal function after 24 h of depletion. However, patients with IRF more frequently had evidence of persistent renal and portal congestion at discharge despite similar diuresis and resolution of signs of venous congestion. In the present work, patients with IRF had more advanced disease, poorer hemodynamics and significantly poorer RV function on hospital admission in comparison with patients with early WRF. These results are consistent with those of others that have shown that patients with WRF have less advanced heart failure,<sup>5,7</sup> less RV

dysfunction,<sup>6</sup> and a better CO<sup>6</sup> than patients that maintain or improve renal function during depletive therapy. The present study extends these findings to more clearly define the admission hemodynamic, cardiac, portal, and renal characteristics of patients with IRF or WRF and contrasts their early and late in-hospital courses. Previous studies have hypothesized that patients with IRF may have deteriorated their renal function prior to admission due to the adverse effects of volume overload leading to venous congestion.<sup>5</sup> This study supports this hypothesis, and, although speculative, our results may suggest that reduced MAP, and to a certain extent reduced CO and renal PP, may have contributed to this pre-admission renal deterioration and that the reversal of these abnormalities may have contributed to the early IRF in these patients.

### Trajectory of renal function and RV function in ADHF

Patients from this study who evolved towards an IRF after 24 h of depletion had poorer RV systolic function at baseline. This would suggest that RV dysfunction may have contributed to a variable susceptibility to the deleterious effects of volume overload, with more impaired hemodynamics and a more altered renal function on hospital admission in these patients in comparison with those who progressed to WRF. While patients with a preserved RV function appear to demonstrate an expected response to depletion (WRF associated with effective decongestion), those with IRF experience a transient IRF and a less effective decongestion during their hospital course. Taken together, these results may suggest that various hemodynamic determinants may have an impact of whether renal function improves or deteriorates during the first 24 h of depletive therapy in ADHF and that the individual impact of each determinant may change according to RV function and to the response to depletion. The role of the RV in determining the early renal response to decongestive therapy has already been reported,<sup>6</sup> but this is the first time that an association with both portal and renal congestion was documented in ADHF.

### Associations with outcomes

Although renal impairment has been traditionally associated with a wide range of poor outcomes in HF,<sup>4</sup> recent data suggest that changes in cardiac status along with the context accompanying renal dysfunction, rather than renal dysfunction itself, could be the real driver of a poor prognosis.<sup>25–27</sup> A previous study of a large cohort of patients with ADHF found that patients with in-hospital IRF had a worse prognosis as compared with other patients,<sup>28</sup> while another found a worse prognosis if WRF was

persistent post-discharge.<sup>29</sup> Another large study of patients with ADHF found a non-statistically significant increase in death in patients with IRF,<sup>5</sup> while yet another large study found no difference in outcomes regardless of in-hospital renal trajectory.<sup>30</sup> Considering that patients with IRF also have more advanced cardiac disease, a relationship with worse outcomes would be expected, but has been difficult to document, perhaps due to the overall risk and complexity of these patients. Furthermore, that baseline differences in cardiac, systemic, and renal variables had disappeared by 24 h of diuresis in this work was surprising and may help explain the lack of significant difference in outcomes according to in-hospital renal trajectory.

### Limitations

Our study has several limitations. The cohort is small and from a single centre, which limits the strength of our conclusions, particularly in terms of assessing the potential differential response of patients according to HF with preserved or reduced LVEF. Furthermore, the important number of patients declining the study may represent a potential selection bias. RV systolic dysfunction was characterized using a unique ultrasound parameter (TAPSE) and analysed as present or absent, which may limit the accuracy of identifying the nuances of RV dysfunction. Ultrasound assessment of intrarenal venous flow was interpretable in a little over 80% of the whole cohort, which limited our ability to evaluate its accuracy in this context. Hemodynamic parameters were all assessed non-invasively, and such monitoring may imply a certain degree of uncertainty. This being said, this is the largest cohort of patients with ADHF undergoing decongestive therapy in which hemodynamics and both intrarenal and portal hemodynamics were prospectively assessed at various time points and correlated with changes in renal function.

### Conclusions

Early IRF in ADHF under depletive therapy is demonstrated in patients with more advanced disease and poorer RV systolic function at baseline and appears to be associated with a less effective decongestion during the hospital course. The presence of an RV dysfunction is shown to modify the individual impact of various hemodynamic variables on the early trajectory of renal function in this setting. In this relatively small cohort, RV status at admission, but not in-hospital renal trajectory, has shown to be associated with post-discharge outcomes.

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## Conflict of interest

None declared.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1:** Event-free survival from all-cause deaths or hospitalization according to changes in renal function

after 24 hours of depletion (A-C) et to RV function at baseline (D-F). **Panel A:** Event-free survival from all-cause deaths or hospitalization according to changes in renal function after 24 hours of depletion, Log-rank 0.318. **Panel B:** Event-free survival from all-cause deaths according to changes in renal function after 24 hours of depletion, Log-rank 0.270. **Panel C:** Event-free survival from all-cause hospitalization according to changes in renal function after 24 hours of depletion, Log-rank 0.353. **Panel D:** Event-free survival from all-cause deaths or hospitalization according to baseline RV systolic function, Log-rank 0.347. **Panel E:** Event-free survival from all-cause deaths according to baseline RV systolic function, Log-rank 0.010. **Panel F:** Event-free survival from all-cause hospitalization according to baseline RV systolic function, Log-rank 0.717.

**Table S1:** Characteristics at discharge according to early changes in renal function and to baseline RV systolic function

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