DANISH MEDICAL JOURNAL

Original Article

Acute haemodynamic and diuretic effects of intravenous furosemide in acute heart failure

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Dan Med J 2026;73(3):A07250556. doi: 10.61409/A07250556

ABSTRACT

INTRODUCTION. While the diuretic effect of loop diuretics in acute heart failure (AHF) is well established, it remains debated whether furosemide exerts any extrarenal decongestive effects. This study aimed to examine the acute effects of furosemide on pulmonary congestion, diuresis and haemodynamics in patients hospitalised with AHF.

METHODS. We conducted a prospective interventional study including 20 AHF patients, each receiving 80 mg of intravenous furosemide at baseline. Diuresis, perfusion index, echocardiography and pulmonary fluid via remote dielectric sensing (ReDS) were assessed at predefined time points until 360 minutes. The primary endpoint was a change in ReDS within 30 minutes.

RESULTS. The cohort had a mean age of 78 ± 9 years, with 65% diagnosed with heart failure with reduced ejection fraction. Baseline ReDS was 35.3 ± 1.8%. No significant reduction in ReDS was observed at any time point; a non-significant decrease of 1.7% was observed at 20 minutes (p = 0.32). Diuresis reached 134 ± 56 ml by 20 minutes (p = 0.02). Perfusion index declined significantly by 25 minutes (p = 0.03) and remained stable until 120 minutes. No other haemodynamic parameters changed significantly.

CONCLUSIONS. Intravenous furosemide did not acutely reduce pulmonary fluid before diuresis, suggesting no immediate extrarenal effect. Haemodynamic changes occurred only after diuresis, indicating its primary acute action is diuretic, with later responses likely being secondary to volume loss.

FUNDING. None.

TRIAL REGISTRATION. The protocol was registered with clinicaltrials.gov on 29 August 2023 (Identifier: NCT06024889).

Loop diuretics are first-line therapy in acute heart failure (AHF) [1]. In volume redistribution, adding vasodilators may be beneficial [2-4]. However, despite the widespread use of loop diuretics, most studies of their pharmacological effects date back to the 1970s [2, 5-9]. It is theorized that furosemide induces an acute vasodilation, reducing preload and decreasing pulmonary capillary wedge pressure (PCWP) [5, 6, 10]. In 1973, Dikshit et al. reported that the earliest pharmacological effect of furosemide administration was peripheral vasodilation before and independent of a notable urinary output [5]. Other studies, however, report an acute vasoconstriction prior to diuresis [8, 9, 11]. Consequently, the immediate haemodynamic effects of furosemide in AHF remain unresolved.

This knowledge gap is clinically important, as loop diuretics are often the first therapy administered to patients presenting with acute congestion; yet, their hyperacute mechanism of action remains unclear. This study aimed to reexamine the acute haemodynamic effects of intravenous furosemide in contemporary patients with AHF, using modern non-invasive bedside tools to evaluate pulmonary congestion. We specifically assessed whether furosemide reduces congestion within 30 minutes before notable diuresis occurs and whether responses differ between patients with reduced versus preserved left ventricular ejection fraction (LVEF).

Methods

This was a prospective interventional study of 20 AHF patients admitted to the Department of Cardiology at Copenhagen University Hospital Amager-Hvidovre between September 2023 and February 2024. The study was approved by the Scientific Ethical Committee (H-23029822) and the Danish Data Protection Authorities (P-2013-14703). The protocol was registered with clinicaltrials.gov on 29 August 2023 (Identifier: NCT06024889), and a protocol article was published in June 2024 [12].

Study procedure

Patients with AHF were screened for eligibility for inclusion [12]. Patients were included as early as possible after their admission to the Cardiac Ward. The inclusion criteria were 1) adult (≥ 18 years of age), 2) ability to give informed consent, 3) clinical diagnosis of AHF requiring hospitalisation based on the treating physician's assessment and in accordance with European Society of Cardiology guidelines (typical symptoms such as dyspnoea/orthopnoea, physical signs of congestion and objective evidence of cardiac dysfunction), 4) systolic blood pressure ≥ 100 mmHg, 5) oxygen saturation < 94% or need of oxygen as documented in the patient's medical record), 6) confirmed pulmonary congestion on chest X-ray by a cardiologist or by a remote dielectric sensing (ReDS) value > 35 [12]. Patients were excluded 1) if more than 40 mg intravenous furosemide was administered within the past three hours before randomisation, as this washout period was considered sufficient to minimise residual hyperacute vascular effects from previous dosing while maintaining feasibility in the acute setting. A full list of the exclusion criteria is available in the published study protocol [12].

Intervention and monitoring

At baseline, we obtained electrocardiograms, chest X-rays and baseline measurements of ReDS, diuresis, perfusion index, echocardiography and vital signs (Supplementary Figure 1). Diuresis was assessed by cumulative urine output collected via a urinary catheter and recorded at prespecified study intervals; the catheter bag was emptied between each timepoint to ensure accurate measurement. ReDS sensors were positioned on the right thorax; through electromagnetic means, a dielectric coefficient was generated, indicating the percentage of fluid content within the lung tissue. [13-15]. Perfusion index was measured using a pulse oximeter adhesive sensor (Masimo SET Radical-7, model M-LNCS Adtx; Masimo Corporation) [16]. Measurements of perfusion index, vital signs, diuresis and ReDS were obtained at baseline (prior to the intervention), every five minutes during the first 30 minutes, every 15 minutes between T30 and T60, and every 30 minutes from T60 to T120. Echocardiography was performed at baseline, T15, T30, T60, T120 and T360 [12] (Supplementary Figure 1).

Outcomes

The primary outcome was a change in pulmonary parenchymal fluid content measured by ReDS 0-30 minutes after administration of 80 mg intravenous furosemide [12]. The secondary outcomes are listed in the protocol article [12].

Statistical power

In a similar experiment, a loop diuretic-induced fall in pulmonary capillary wedge pressure (PCWP) from 20.4 to 14.8 mmHg (30% decrease) was observed [5]. Assuming a correlation between cardiac filling pressures and pulmonary congestion, with a power of 0.80 and a significance level of 0.05, at least 14 subjects needed to included to demonstrate a 30% reduction in lung fluid content relative to baseline with a standard deviation for the change of 18%. To account for missing values, we aimed to include 20 patients.

Statistical analyses

Continuous variables are plotted as histograms to assess normality. Normally distributed data are presented as means with standard deviations, whereas non-normally distributed data are presented as medians with quartiles (Q1-Q3). Categorical variables are shown as counts with percentages, and χ^2 tests were used for difference analyses. Between-phase differences were evaluated using repeated-measures mixed models. In a sub-analysis, we examined continuous measurement with patients divided into heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF). In cases of missing data for the primary outcome, data were imputed using a mixed model. All statistical tests are two-sided, with the significance level set at $p < 0.05$. Analyses were operated using software R, version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS statistical software, version 7.4 (SAS Institute, Cary, NC).

Trial registration: The protocol was registered with clinicaltrials.gov on 29 of August 2023 (Identifier: NCT06024889).

Results

We screened 83 AHF patients and included 20 (24%) (Supplementary Figure 2). A total of 13 (65%) were male, aged 79 ± 9 years and with a LVEF 40 ± 17% (**Table 1**). Baseline systolic blood pressure (sBP) was 129 ± 23 mmHg, heart rate (HR) 81 ± 16 beats/min, SpO_2 95 ± 4% and oxygen supplementation 3.5 l/min. (IQR: 0-10) (Table 1). Seven patients (35%) had HFpEF, and 13 (65%) had HFrEF (Table 1).

TABLE 1 Baseline characteristics.

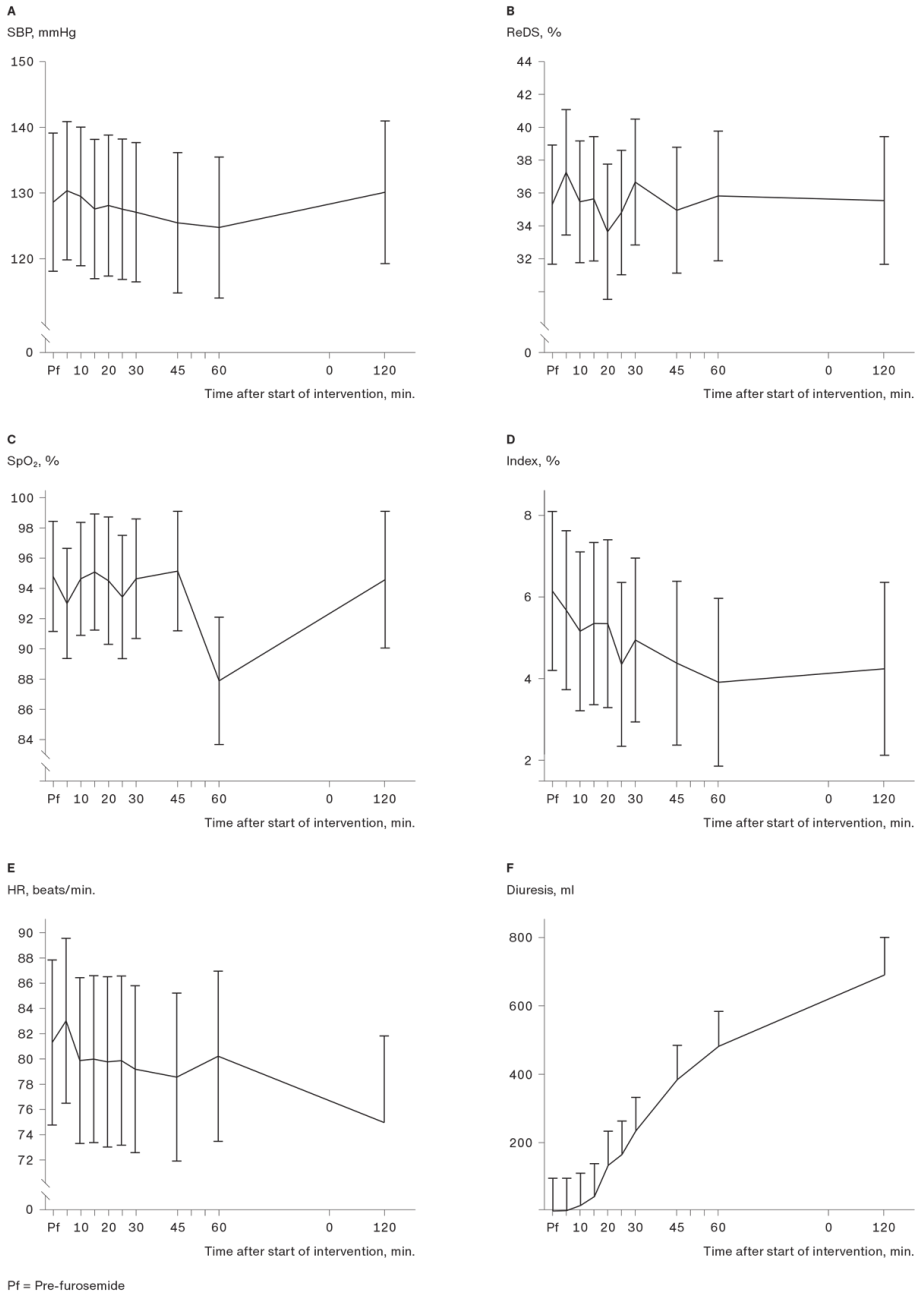
	HFrEF (N_r = 13)	HFpEF (N_p = 7)	Overall (N_o = 20)
Men, n (%)	8 (61.5)	5 (71.4)	13 (65.0)
Age, mean (± SD),	77.6 (± 9.0)	80.2 (± 7.7)	78.4 (± 8.5)
BMI, mean (± SD), kg/m²	24.1 (± 4.8)	27.9 (± 6.1)	25.4 (± 5.5)
LVEF, mean (± SD), %	30.0 (± 12.2)	58.6 (± 4.8)	40.0 (± 17.2)
Vitals			
Systolic blood pressure, mean (± SD), mmHg	126 (± 23.3)	134 (± 21.9)	129 (± 22.6)
Heart rate, median (IQR), beats/min.	77 (61-95)	82 (56-122)	80.5 (56-122)
O_2 saturation, median (IQR), %	94 (90-100)	95 (86-100)	94.5 (86-100)
O_2 supply, median (IQR), l/min.	4 (0-10)	2.5 (0-5)	3.5 (0-10)
Cardiovascular history, n (%)			
Known heart failure	8 (61.5)	0	8 (40.0)
Ischaemic heart disease, N (%)	3 (23.1)	1 (14.3)	4 (20.0)
CABG	1 (7.7)	0	1 (5.0)
PCI	2 (15.4)	1 (14.3)	3 (15.0)
Supraventricular tachycardia	7 (53.8)	4 (57.1)	11 (55.0)
Pacemaker	2 (15.4)	0	2 (10.0)
ICD	3 (23.1)	0	3 (15.0)
Aortic regurgitation	4 (30.8)	2 (28.6)	6 (30.0)
Aortic stenosis	1 (7.7)	1 (14.3)	2 (10.0)
Mitral regurgitation	4 (30.8)	1 (14.3)	5 (25.0)
Comorbidities, n (%)			
Hypertension	7 (53.8)	5 (71.4)	12 (60.0)
Diabetes	3 (23.1)	1 (14.3)	4 (20.0)
Active smoker	4 (30.8)	0	4 (20.0)
Asthma	0	0	0
Chronic kidney disease	2 (15.4)	0	2 (10.0)
Stroke	3 (23.1)	0	3 (15.0)
Cancer	0	1 (14.3)	1 (5.0)

CABG = coronary artery bypass grafting; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Pulmonary congestion and urinary output

Mean baseline ReDS was 35.3 ± 1.8%, indicating substantial congestion (**Figure 1**). After furosemide, no significant ReDS reduction was observed. From five to 20 minutes, ReDS fell non-significantly from 35.3 ± 2.0% to 33.7 ± 1.6% (p = 0.32) (Figure 1). Mean diuresis rose significantly to 134 ± 56 ml at 20 minutes (p = 0.02) and reached 691 ± 61 ml at 120 minutes (Figure 1).

FIGURE 1 Continuous variables measured at predefined time points: 0-120 minutes. Error bars represent 95% confidence intervals. Data were analysed using repeated-measures mixed-effects models. **A**. Systolic blood pressure (SBP). **B**. Remote dielectric sensing (ReDS). **C**. Peripheral oxygen saturation (SpO_2). **D**. Perfusion index. **E**. Heart rate (HR). **F**. Accumulated diuresis.

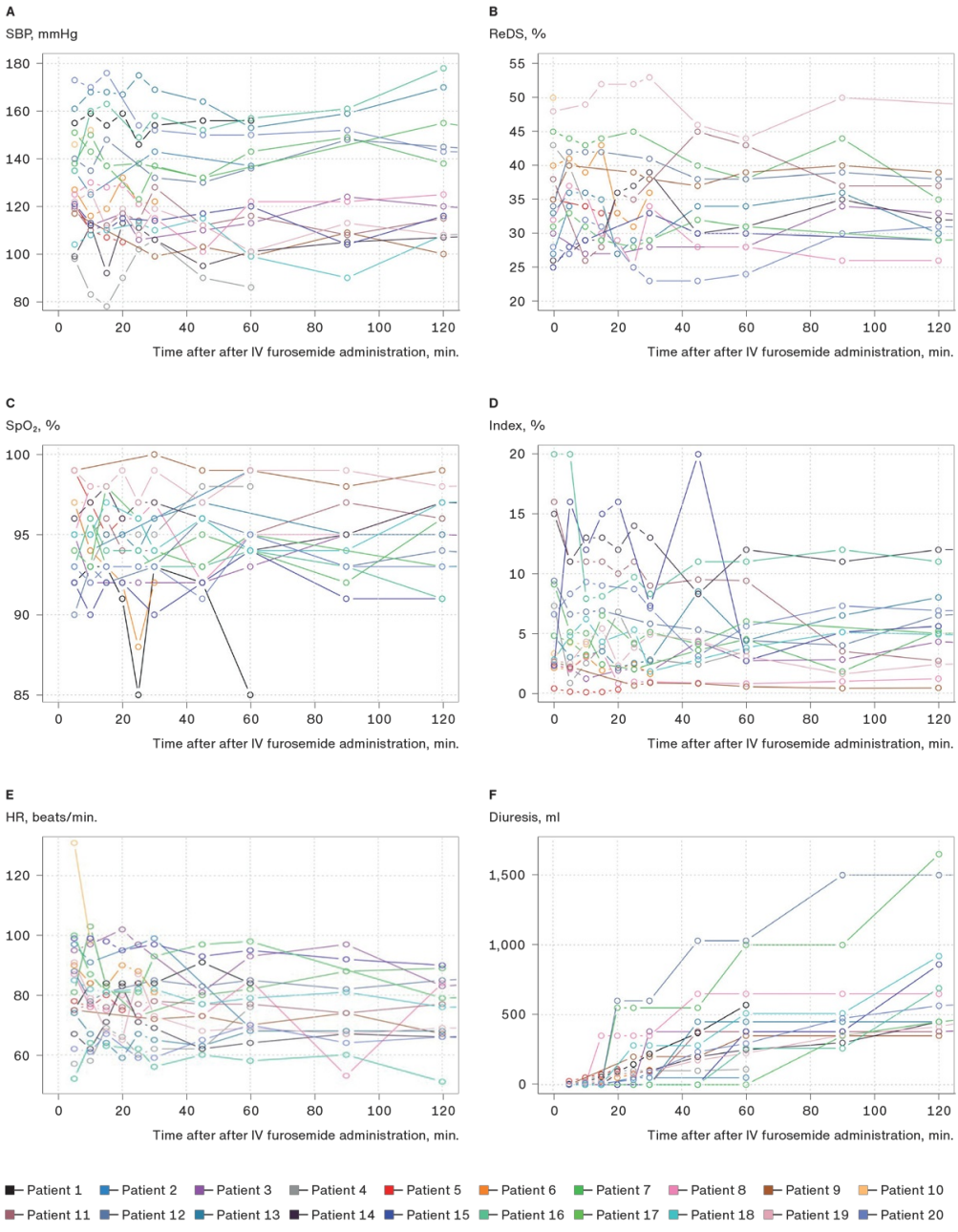


Pf = Pre-furosemide

Haemodynamic measurements and vital parameters

Perfusion index declined significantly from 6.1 ± 1.0 to 4.3 ± 0.8 at 25 minutes ($p = 0.03$), remaining low through 120 minutes (Figure 1). Nine patients started with a perfusion index > 3.5% (**Figure 2**). SpO_2 declined at 60 minutes ($p = 0.01$), notably in one patient. HR declined significantly at 120 minutes ($p < 0.01$) (Figure 2). Diastolic blood pressure showed a transient, non-significant rise at 15 minutes, and mean arterial pressure (MAP) followed a similar short-lived pattern before returning to baseline (Supplementary Figure 5). Pulse pressure remained stable, averaging 55-60 mmHg, with no significant temporal change.

FIGURE 2 Haemodynamic variables and remote dielectric sensing measurements for 20 individual patients during predefined time points 0-120 minutes after intravenous (IV) furosemide administration. **A**. Systolic blood pressure (SBP). **B**. Remote dielectric sensing (ReDS). **C**. Peripheral oxygen saturation (SpO_2). **D**. Perfusion index. **E**. Heart rate (HR). **F**. Accumulated diuresis.



Echocardiographic measurements

Left ventricular filling pressure (LVFP), represented by E/e' declined from a median 11.1 mmHg to 10.4 mmHg at T120 (p = 0.08) (Supplementary Figure 4). The tricuspid regurgitant pressure gradient, representing right ventricular systolic pressure (RVSP), decreased by 5 mmHg from baseline to 60 minutes. Inferior vena cava diameter was unchanged to T30. No significant change in LVEF was observed. Mean and median LVEF remained stable around 35-40% within 120 minutes.

Continuous measurements for patients with heart failure with reduced ejection fraction and heart failure with preserved ejection fraction

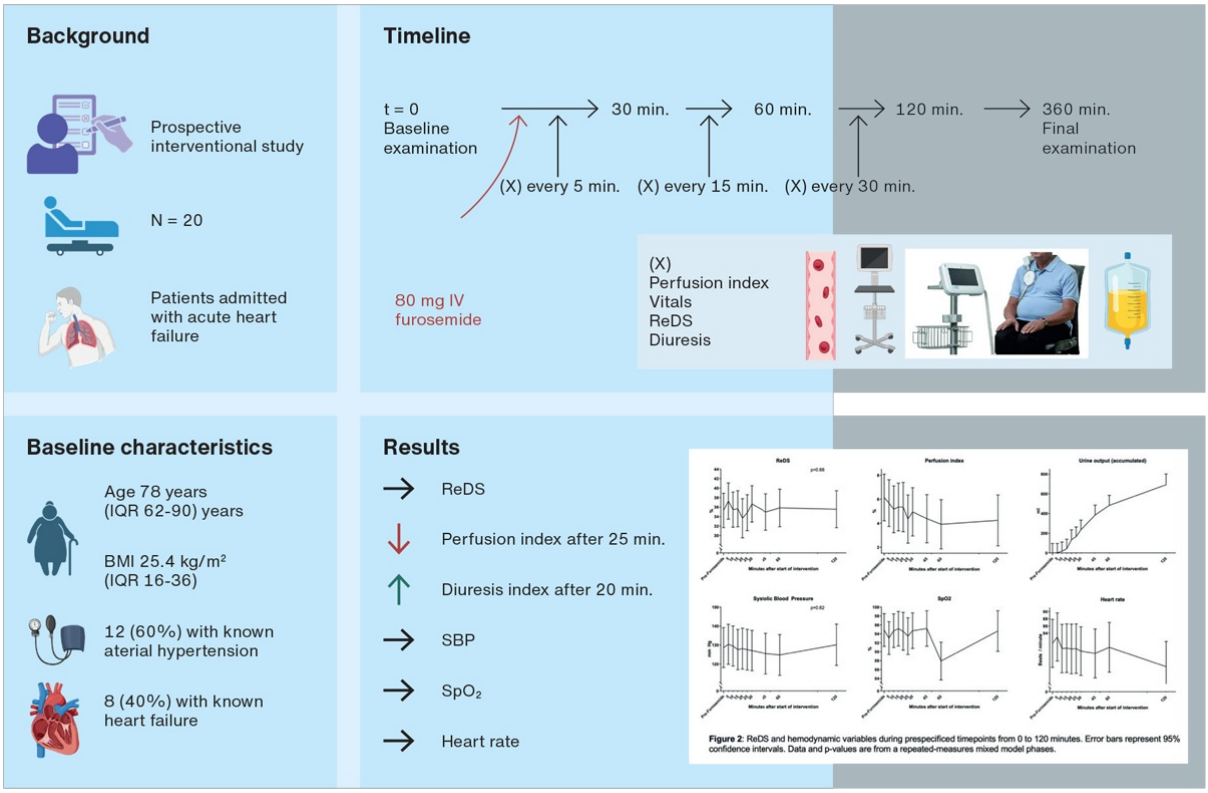
In subgroup analysis, HFpEF patients showed a non-significant ReDS increase (from 35.9% to 38.7%), whereas HFrEF patients showed a decrease (from 35.6% to 32.3%). The perfusion index declined over time in both groups (Supplementary Figure 3).

Discussion

This study explored the early haemodynamic effects of intravenous furosemide in AHF. We found no significant reduction in pulmonary congestion by ReDS before diuresis, challenging the hypothesis of rapid extrarenal effects.

Using ReDS, we assessed pulmonary fluid [13, 14]. Values remained > 35%, indicating persistent congestion. Previous studies from the 1970s showed a rapid decline in PCWP following furosemide administration before diuresis [6, 7, 11]. In 1973, Dikshit et al. examined 20 patients with acute myocardial infarction and AHF using continuous invasive measurements and found that peripheral vasodilation occurred rapidly and before a significant urinary output, indicating a furosemide-induced vasodilatory effect independent of diuresis [5]. In contrast, our findings showed no significant decline in pulmonary parenchymal fluid before the diuretic response. However, although we found no acute reductions in pulmonary parenchymal fluid, we cannot exclude that pulmonary vascular pressure may have been reduced acutely; moreover possibly the pulmonary parenchymal fluid would be reduced if monitored for longer. Even though the primary analyses did not demonstrate significant early reductions in pulmonary fluid content by ReDS, we observed a significant perfusion index decrease at 25 minutes after significant diuresis accompanied by a downward trend in both LVFP and RVSP. Previous studies have proposed that furosemide activates the sympathetic and the renin&angiotensin-aldosterone systems (RAAS), thus leading to vasoconstriction [8, 9, 11, 17]. In 1983, Nelson et al. reported increased LV filling pressure in pump failure, attributed to sympathetic and RAAS activation, which increases systemic vascular resistance [8]. In our study, we observed a significant peripheral vasoconstriction at 25 minutes, as evidenced by a decline in the perfusion index (**Figure 3**). The vasoconstrictive effect of intravenous furosemide may be explained by a direct activation of the RAAS or by a secondary response to reduced lower vascular volume due to diuresis [7, 8, 11, 17, 18]. This raises the question of whether the peripheral response could be independent of diuresis, a consequence of diuresis, or a combination of both.

FIGURE 3 Graphical abstract summarising the acute haemodynamic and diuretic effects of intravenous furosemide in patients with acute heart failure.



IV = intravenous; ReDS = remote dielectric sensing; sBP = systolic blood pressure; SpO_2 = peripheral oxygen saturation.

Alternatively, a reduced perfusion index might indicate vasodilation [5, 18]. In line with this, MAP showed a modest increase within the first 15 minutes, whereas pulse pressure remained largely unchanged. Our cohort demonstrated a stable sBP and a decrease in HR, an opposite response to what would typically be expected with sympathetic nervous system activation [19]. The observed decrease in HR could indicate volume redistribution rather than sympathetic activation. This observation aligns with findings by Dikshit et al., who reported a rapid peripheral vascular change preceding significant urinary output, pointing to a vasodilatory effect of furosemide independent of its diuretic action [5]. The underlying mechanisms of this vasodilation remain speculative but may involve a reduction in preload, subsequent adjustment of sympathetic tone or even prostaglandin synthesis indirectly stimulated by furosemide [10].

In exploratory analyses, patients with HFpEF showed an early increase in ReDS and a concomitant decrease in perfusion index within 30 minutes, suggesting acute vasoconstriction and a transient elevation in PCWP. This aligns with prior evidence that HFpEF is characterised by volume redistribution rather than fluid accumulation [2, 3, 17, 19], implying that intravenous vasodilators may be more effective than loop diuretics in this subgroup.

Nevertheless, our findings do question whether furosemide induces acute extra-renal effects in patients with AHF and pulmonary congestion. This is of clinical interest for two reasons:

Not all patients with acute pulmonary congestion or oedema are volume overloaded [2, 19]. If there is no or only a minimal acute extrarenal effect of intravenous furosemide in AHF, this patient group may be better treated with vasodilators, and furosemide may only induce volume depletion.

In the hyperacute setting of AHF, loop diuretics cannot stand alone as acute treatment, since the peripheral vasodilatory effects may not adequately lower sBP, and their diuretic effects are slower to take effect [5, 8]. This

effect could support combining loop diuretics with vasodilators in the acute setting to counteract the vasoconstrictive response and improve overall perfusion. Also in this case, rapid injection of vasodilators such as isosorbide dinitrate may be the drug of choice [4, 20].

Strength and limitations

The strength of this prospective interventional study is the detailed clinical and ReDS measurements at multiple time points, which provide insight into the haemodynamic effect of intravenous furosemide. Limitations include its single-centre design, small sample size, ReDS-specific exclusion and reliance on non-invasive surrogates. Regarding echocardiography, wall motion scoring showed no significant LVEF change; strain was not feasible due to image quality, limiting sensitivity to subtle systolic changes. Furthermore, the observational design, in conjunction with the absence of blinding, randomisation and a control group, introduces a potential risk of bias.

Conclusions

Administration of 80 mg intravenous furosemide in patients with AHF did not elicit an immediate haemodynamic response, as no reduction in pulmonary parenchymal fluid was observed before diuresis. Haemodynamic changes, such as a decrease in perfusion index, occurred only after significant diuretic output had been established. This delayed response suggests that the observed vascular changes are more likely secondary to volume depletion rather than a direct, rapid extrarenal effect of furosemide. Thus, furosemide appears to exert its primary acute action via diuresis and not through immediate haemodynamic modulation.

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Accepted 20 November 2025

Published 19 February 2026

Conflicts of interest ES reports financial support from or interest in BMS. NBF reports financial support from or interest in Masimo. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. These are available together with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2026;73(3):A07250556

doi 10.61409/A07250556

Supplementary material a07250556-supplementary.pdf

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