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Protocol Article

The acute effects of furosemide in acute heart failure assessed by remote dielectric sensing. A protocol

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ABSTRACT

INTRODUCTION. Intravenous loop diuretics have been a key component in treating pulmonary oedema since the 1960s and have a Class 1 recommendation in the 2021 guidelines for acute heart failure (AHF). While the diuretic effect of loop diuretics is well established, it remains unclear how furosemide influences pulmonary congestion and cardiac filling pressures in the hyperacute phase before significant diuresis occurs.

METHODS. This was a prospective study of adult patients with AHF and objective signs of pulmonary congestion admitted to the cardiac ward. Remote dielectric sensing (ReDS) will directly measure lung fluid content, and cardiac filling pressures will be assessed by echocardiography with Doppler and strain analysis.

CONCLUSIONS. This study will examine if furosemide leads to a hyperacute reduction in pulmonary congestion assessed by ReDS independent of diuretic effects in patients with AHF. We hypothesise that the haemodynamic effect of furosemide shown on pulmonary congestion may explain the subjective instant relief in patients with AHF receiving furosemide.

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TRIAL REGISTRATION. This protocol was approved by the Scientific Ethical Committee, H-23029822, and the Danish Data Protection Agency P-2013-14703. The protocol was registered with ClinicalTrial.org on 29 August 2023 (Identifier: NCT06024889).

Acute heart failure (AHF) is a leading cause of hospitalisations in elderly patients, accounting for more than one million cases annually in the USA, with comparable numbers in Europe [1]. AHF may manifest as an acute decompensation of chronic heart failure or as new-onset heart failure, with symptoms including dyspnoea, fatigue, orthopnoea and peripheral oedema [2]. Acute cardiogenic pulmonary congestion and oedema (in the following referred to simply as “pulmonary congestion”) is a cardinal sign of AHF [2]. The pathophysiology of pulmonary congestion is not fully understood. However, it was suggested that decreased stroke volume with compensatory increased systemic vascular resistance (left ventricular afterload) may lead to a further reduction in stroke volume, backward failure, increased left atrial pressures and, finally, pulmonary congestion and oedema [3, 4].

Loop diuretics remain a fundamental pharmacological therapy to remove excess fluid and improve symptoms in AHF [2]. The European Society of Cardiology guidelines from 2021 recommend using diuretics and intravenous vasodilators [2] despite sparse evidence from randomised trials to support these strategies [5]. The effects of vasodilation and loop diuretics have not been studied individually and have been compared only in a few controlled clinical trials [6] (Supplementary Table 1). The lack of evidence has led to treatment disorientation in clinical practice [6, 7]. Although both approaches may be correct because of the heterogeneity of AHF patients, physiological targets guiding a stratified treatment approach would benefit clinicians and patients.

One of the primary challenges for clinicians is assessing congestion in patients with AHF, as some patients present with volume redistribution (central volume shift) rather than volume overload [8]. Intravenous vasodilators such as nitrates may be preferred in the acute setting where volume redistribution is the primary driver of congestion. However, where the diuretic response to furosemide is well known, an acute vasodilatory effect has been reported in some studies [9]. In 1973, Dikshit et al. reported that the earliest and most important haemodynamic changes after furosemide injection reflect vascular rather than diuretic mechanisms [9]. In the study, Dikshit et al. examined 20 patients with AHF post-myocardial infarction and found a significant acute reduction in capillary wedge pressure (PCWP) before a significant urinary output. Previous studies have found a similar correlation between decreased PCWP before significant diuresis [10] and lung fluid demonstrated by chest computed tomography (CT) [11]. Better knowledge of the acute haemodynamic effects could have direct clinical implications for the emergency management of AHF with pulmonary congestion.

This study aims to examine the acute effect of furosemide on reducing pulmonary congestion before significant diuresis occurs using comprehensive echocardiography and remote dielectric sensing (ReDS) technology. In this study, we will investigate the acute effect of furosemide on reducing pulmonary congestion before significant diuresis occurs, using comprehensive echocardiography and the ReDS technology.

We hypothesise that intravenously administered (IV) furosemide induces a hyperacute (within 30 minutes) lowering of cardiac filling pressure and pulmonary congestion before significant diuresis occurs.

Methods

This study is conducted using a prospective interventional design at the Department of Cardiology, Hvidovre Hospital, Denmark. The study population consists of patients admitted to the Department of Cardiology with AHF who meet the inclusion criteria (**Table 1**). The study was initiated in September 2023 and is registered with ClinicalTrials.gov (Identifier: NCT06024889).

TABLE 1 Eligibility criteria.

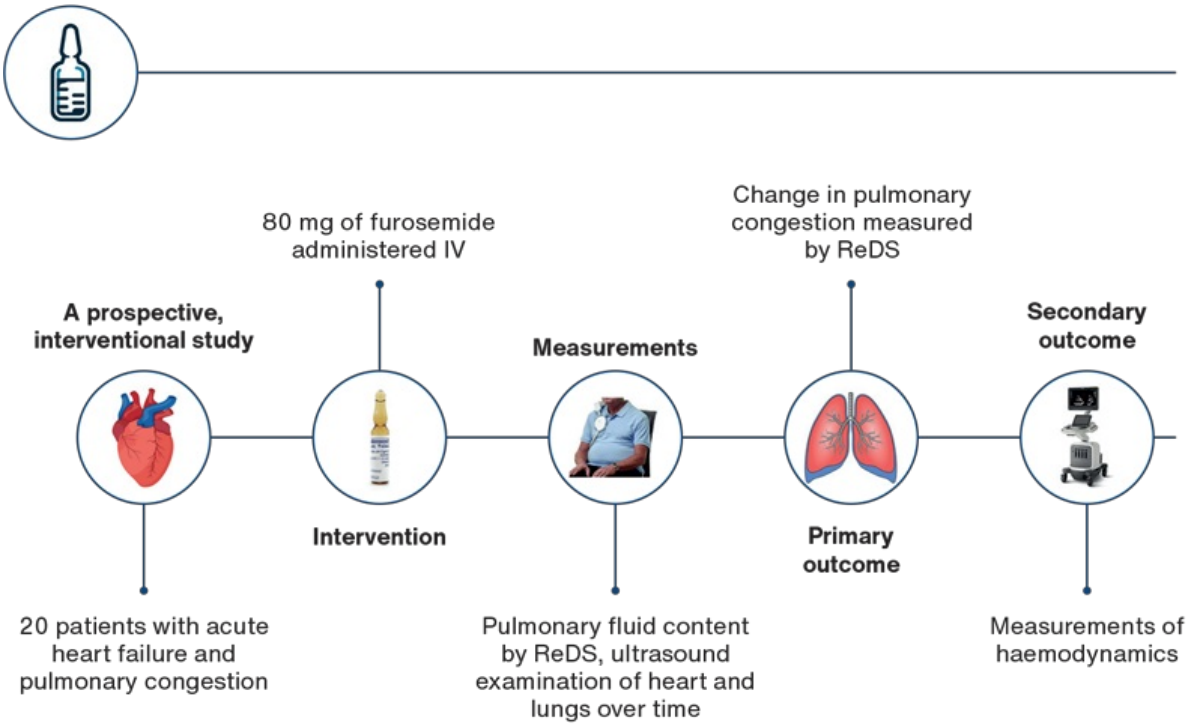
Criterion	ReDS-specific exclusion
Inclusion criteria	
Age ≥ 18 yrs	
The ability to give informed consent	
Clinical diagnosis of acute heart failure requiring hospitalisation	
Systolic blood pressure ≥ 100 mmHg	
O_2 saturation < 94% or need of O_2 supplement	
Confirmed pulmonary congestion on chest X-ray by cardiologist or ReDS > 35%	
Exclusion criteria	
Administration of > 40 mg IV furosemide within the past 3 hrs before randomisation, including prehospital administration	
Ongoing ventricular taky- or bradyarrhythmias or supraventricular arrhythmias with heart rate > 180 beats/min. or < 40 beats/min.	
Known chronic obstructive lung disease	
Patients who are unable to sit upright	
Pacemaker or ICD on the right side	√
Known congenital heart malformations or intrathoracic mass that would affect the right lung anatomy, e.g., dextrocardia, lung carcinoma	√
Wounds, burns, healing tissue, skin infection or recent skin graft or flap where the sensors should be attached to the skin	√
Height < 155 cm or > 200 cm	√
BMI < 18 kg/m² or > 38 kg/m²	√

ICD = implantable cardioverter defibrillator; IV = intravenously administered; ReDS = remote dielectric sensing.

ReDS noninvasively assesses lung fluid content using electromagnetic waves via two sensors across the thoracic cavity [12] (Supplementary Figure 2). Perfusion index (PI) assesses the pulsatile strength at a specific monitoring site (e.g. the hand, finger or foot). It is calculated using pulse oximetry by expressing the pulsatile signal [13]. The O2matic is a novel device that delivers automated oxygen administration by a closed-loop system that continuously measures the patient's peripheral oxygen saturation by pulse oximetry and automatically titrates oxygen flows [14].

Patients admitted to the cardiac ward who received intravenous (IV) furosemide will be screened for participation. After informed consent, the following examinations will be performed: vital signs, diuresis echocardiography with Doppler and strain analysis, PI and ReDS measurements (**Figure 1**). An O2matic machine will be placed on the patients, and the time furosemide is administered will be considered study time zero (T0). All patients will receive 80 mg of furosemide intravenously (**Table 2**). Follow-up will be performed 360 minutes (T360) after furosemide administration (**Figure 2**).

FIGURE 1 Haemodynamics of furosemide. Acute effects of furosemide on pulmonary congestion in acute decompensated heart failure.



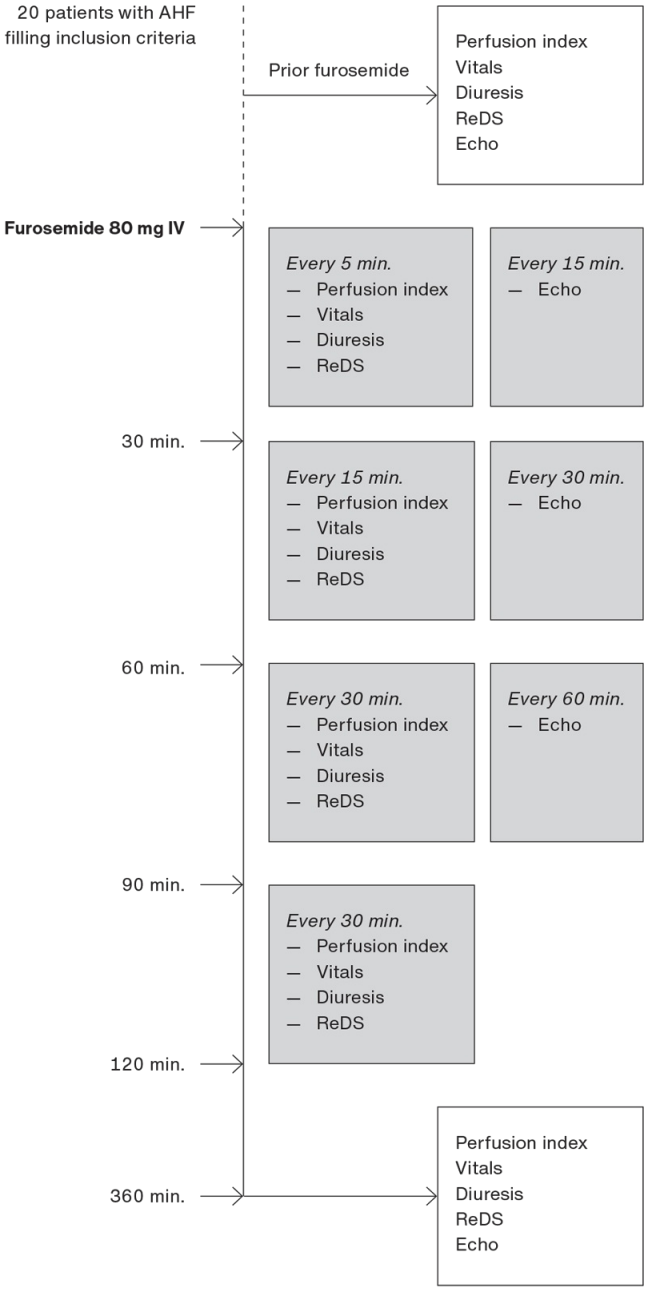
IV = intravenously; ReDS = remote dielectric sensing.

TABLE 2 Primary and secondary outcomes.

Primary outcome
The primary outcome is a change in pulmonary parenchymal fluid content measured by ReDS at multiple time points T0-T30 after 80 mg IV furosemide
Secondary outcomes
Cumulative diuresis for 120 min.
Heart rate, blood pressure, peripheral oxygen saturation and respiratory rate after 30 min.
Change in O_2 needed to keep peripheral O_2 saturation at 93-95%
Change in global longitudinal strain from baseline to 30 min.
Change in right ventricular global longitudinal strain from baseline to 30 min.
Change in v. cava inferior diameter from baseline to 30 min.
Change in right ventricular systolic pressure from baseline to 30 min.
E/é ratio from baseline to 30 min.
Change in right ventricular E/é from baseline to 30 min.
Change in right ventricular S' from baseline to 30 min.

E/é ratio = ratio of early mitral filling velocity to early diastolic mitral annular velocity; IV = intravenously administered; ReDS = remote dielectric sensing; S' = systolic wave prime.

FIGURE 2 Study overview.



AHF = acute heart failure; echo = echocardiography; IV = intravenously administered; ReDS = remote dielectric sensing; vitals = vital signs.

Research staff will record patient data during their hospital stay. The data collection will be performed using an electronic data capture system integrated with the scientific database RedCap.

Patients will be included after written informed consent. Research in pulmonary congestion is ethically challenging since patients may be acutely affected by dyspnoea. Despite this challenge, research on this patient population to improve outcomes is needed, as recommended by the Declaration of Helsinki.

The ethical justifications for performing this trial are:

1. Knowledge of the acute haemodynamic effects of furosemide in acute heart failure is limited.

2. The disease studied is frequent, meaning that it is a frequent cause of hospital admission and is associated with an unacceptably high mortality rate.

3. The trial interventions are expected to be of minimal risk to the research participant and fall within current treatment guidelines, common clinical practice and local protocols.

4. Increased knowledge of the therapeutic potential of the intervention would expand scientific knowledge of the condition of the individual while increasing knowledge for treating future patients with AHF without exposing the patients to significant risk.

In a similar experiment, a loop-diuretic-induced decrease in left ventricular filling pressure (LVFP) was observed from 20.4 to 14.8 mmHg (corresponding to a 30% decrease) [9]. 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 must be included to demonstrate a 30% reduction in lung fluid content relative to baseline with a standard deviation (SD) for the change of 18%. We included 20 subjects to account for any missing data on the primary outcome.

Categorical variables will be presented as numbers (frequencies) and compared with the χ^2- or Fisher's exact test as appropriate. In contrast, continuous variables will be given as mean ± SD if normally distributed, and as median (25th percentile-75th percentile) if non-normally distributed and compared with the T-test. In continuous data, non-normally distributed logarithmic transformations will be applied to approximate normal distribution as appropriate. Haemodynamic and pulmonary congestion-related variables are evaluated using repeated-measurements mixed models, timepoint and the interaction term as fixed effects. Spearman's rho (r) correlation coefficients are used to estimate correlations between variables. Skewed data are transformed through log transformation before analysis. The statistical analyses are performed using R. All tests are two-tailed, and a p-value of less than 0.05 is considered statistically significant.

Trial registration: This protocol was approved by the Scientific Ethical Committee, H-23029822 and the Danish Data Protection Agency P-2013-14703. The protocol was registered with ClinicalTrial.org on 29 August 2023 (Identifier: NCT06024889)

Discussion

This study will examine if furosemide induces a hyperacute lowering of cardiac filling pressure and pulmonary congestion, assessed by echocardiography and ReDS measurements before significant diuresis occurs. Examining the hyperacute haemodynamic effect of furosemide in individuals with AHF may provide valuable insights into the physiology behind the instant symptomatic relief triggered by furosemide in pulmonary congestion.

When administering intravenous furosemide, diuresis occurs after 30-120 minutes and may thus be less helpful in the acute setting of respiratory failure [9, 15]. The mechanism explaining how furosemide influences pulmonary congestion in the hyperacute phase before diuresis occurs remains unclear. This raises the question of whether direct vasodilators such as nitrates should be preferred in the emergency setting [9]. In 1973, Dikshit et al. reported that the earliest haemodynamic changes after furosemide injection reflect vascular rather than diuretic mechanisms [9]. After administering furosemide, they examined 20 patients with continuous right atrial, pulmonary artery and PCWP measurements using a triple-lumen pulmonary artery catheter. They observed a significant reduction in PCWP before a significant renal output occurred. In 1987, Schmieder et al. found that even in patients undergoing haemodialysis, intravenous furosemide decreases LV preload by venous dilation [16]; and in 1992, Ramires et al. examined eight patients with pulmonary oedema and observed a

significant decrease in PCWP after intravenous furosemide, probably due to redistribution of fluid [17]. These findings indicate that furosemide exerts an acute effect by reducing preload and PCWP before a significant diuresis occurs.

In contrast, Kraus et al. demonstrated that left ventricular preload as reflected by PCWP paradoxically increases in the first 20 minutes after furosemide administration [18], and Francis et al. documented a similar increase in PCWP within the initial 20 minutes of furosemide administration [19]. They observed increased activation of the neurohumoral axis [19]. Francis et al. underlined that Dikshit et al. may not have observed this trend, as patients with post-myocardial infarction may not have had pump failure long enough to disturb the neurohumoral axis. These studies have not been replicated in contemporary heart failure patients but are now possible owing to advanced echocardiography and ReDS.

In our study, the haemodynamic profile of furosemide will be studied by multiple non-invasive measurements [12, 20]. ReDS was originally used to detect pulmonary congestion in patients [5]. Directly measured pulmonary fluid content may provide insight into the mechanism of furosemide and the instant symptomatic relief in patients with AHF receiving furosemide. To our knowledge, this study will be the first to investigate the effect of furosemide on pulmonary congestion using ReDS. Furthermore, the haemodynamics and the impact on cardiac function will be assessed with modern advanced echocardiography. Combining repeated ReDS measurements with sequential echocardiographic measurements will provide a comprehensive haemodynamic profile of the 20 patients with AHF.

Conclusions

This study will examine if furosemide leads to a hyperacute reduction in pulmonary congestion assessed by ReDS independently of diuretic effects in patients with AHF. We hypothesise that the haemodynamic effect of furosemide shown on pulmonary congestion may explain the subjective instant relief in patients with AHF receiving furosemide.

The strength of this prospective interventional study is the detailed clinical, echocardiographic and ReDS measurements at multiple time points, yielding detailed insights into the haemodynamic effect of intravenous furosemide. The limitation of this study is the small sample size of only 20 patients, which may limit the generalisability of our findings. We have based our sample size on a previous study that showed a calculated 30% decrease in LVFP This is a relative change; therefore, this study is underpowered to detect small pressure changes. Additionally, the absence of blinding, a control group and randomisation increases the risk of bias.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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