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Validation of radiofrequency determined lung fluid using thoracic CT: Findings in acute decompensated heart failure patients



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ABSTRACT

Background: Noninvasive outpatient monitoring for heart failure (HF) has significant opportunity to reduce patient morbidity and the costs associated with recurrent hospitalization. The purpose of this study was to validate the ability of radiofrequency (RF) to assess lung fluid via a wearable patch device compared to thoracic CT in order to characterize volume overload.

Methods: 120 subjects were studied: 66 acute heart failure (AHF) inpatients and 54 subjects without AHF (Control – 44 healthy and 10 stable HF). All underwent supine thoracic CT scans and supine RF readings from the wearable patch device placed on the left mid-axillary line (age = 74 ± 16 vs. 57 ± 15 yrs.; female = 38 vs. 44%; BMI = 33.2 ± 9.0 vs. 27.3 ± 5.1 , AHF vs. Control respectively). Reflected RF signals and subject-specific anthropometric data were used to calculate the RF-determined lung fluid content. CT Lung fluid was reported as percentage of lung volume. Classification analyses were used to compare RF and CT performance.

Results: AHF presented with higher lung fluid than controls by both CT and RF (CT: $20.1 \pm 4.2\%$ vs. $15.4 \pm 2.4\%$; RF: $20.7 \pm 5.6\%$ vs. $15.6 \pm 3.3\%$; $p < 0.05$ for all). The correlation between lung fluid measured by CT vs. RF was $r = 0.7$ ($p < 0.001$). RF determined lung fluid performed as well as CT in distinguishing AHF from control subjects: Sensitivity: 70% vs. 86%; Specificity: 82% vs. 83%; Positive Predictive Value: 82% vs. 86%; Negative Predictive Value: 69% vs. 83%, CT vs. RF respectively.

Conclusions: Noninvasive nonionizing RF determined lung fluid provides a potential alternative to other measures for diagnosing and monitoring pulmonary fluid overload.

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1. Introduction

Heart Failure (HF) is a major public health concern and significant healthcare burden affecting 5.7 Million people in U.S. and 26 Million worldwide [1–2]. “HF” = Cost of HF care in the U.S. is \$31 Billion annually, and these costs are expected to double by 2030 [2]. Acute HF (AHF) is the second leading cause of hospital admissions in those over 65 years of age [3–4], and 50% of the expenses that Medicare pays for HF patients is related to hospitalizations [5–6]. These hospital admissions cost nearly \$6000/admission in U.S. hospitals [7], and currently 20% of patients admitted for HF are readmitted within 30 days, and 20–50% within six months [8–9].

Abbreviations: AHF, acute heart failure; CT, computed tomography; HF, heart failure; HFAMS, Heart Failure and Arrhythmia Management System; HU, Hounsfield Units; RF, Radiofrequency.

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One proposed approach to reduce admissions and healthcare costs is to improve outpatient monitoring. This may allow for earlier detection, possibly presymptomatic, of looming decompensation and outpatient treatment intensification to reduce the likelihood of rehospitalization.

Current remote monitoring methods aimed to prevent rehospitalization are primarily dependent on patient education and compliance. Remote monitoring for changes in symptoms such as edema, paroxysmal nocturnal dyspnea, orthopnea, or increased fatigue are often present a week before admission, but sometimes too late for outpatient treatment to be effective [10]. Newer systems that record physiologic parameters and report findings directly to healthcare providers, such as the implanted pulmonary pressure monitoring device, have demonstrated a 43% reduction in HF hospitalizations in NYHA III patients [11].

Pulmonary congestion is a primary cause HF of admission/readmission, with almost 70% of AHF patients presenting to clinic wet (congested) and warm [12–14]. To date there is no effective method for measuring and monitoring pulmonary edema in the

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outpatient setting non-invasively, but devices that effectively capture a patient's congestion status have the potential to reduce HF hospitalizations if they are adequately sensitive and specific [11,15–16]. Previous research has demonstrated that the typical HF symptoms present patients when there is already greater than 50% change in thoracic computed tomography (CT) assessed lung fluid. Although CT has been shown to be the best method to quantify changes in lung fluid, cost and radiation exposure limits its ability to be used as a monitoring tool [17].

We evaluated the ability of a radiofrequency (RF) based non-invasive, remote monitoring device (μ CorTM Heart Failure and Arrhythmia Management System (HFAMS), ZOLL, USA) to detect the presence of pulmonary congestion in patients hospitalized for AHF. RF determined lung fluid content was validated by comparing to thoracic CT assessed lung fluid content.

2. Methods

2.1. Participants and informed consent

The study population consisted of patients hospitalized with AHF and non-AHF subjects (Control). Individuals with AHF were recruited from patients admitted to St. Mary's Hospital from May 2018 through March 2019 with a diagnosis of AHF requiring intravenous diuretics and clinical evidence of pulmonary congestion. Control subjects had no evidence of AHF or pulmonary congestion which included both healthy individuals (those with no cardiovascular or pulmonary disease) and subjects with stable HF. Subjects were excluded if they were in cardiogenic shock, were pregnant or planning to become pregnant during their study participation, had a cardiac implantable device in an anatomical location that would lead to placement of the HFAMS sensor directly on top of the implantable device, and/or had any skin condition that would prevent them from wearing the HFAMS adhesive patch (Figs. 1). All known potential participants both AHF and controls were approached and those willing to participate were enrolled in the study such that only a self-selection bias exists. All participants provided written informed consent to participate in the study, which had been approved by the Mayo Clinic Institutional Review Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.2. Experimental overview

All participants completed a single visit. For those with AHF, the study testing was performed as soon as possible after being admitted and averaged 38 h. A thoracic CT scan was performed within a 4 h window before or after measurements were made with HFAMS. The average time between the CT scan and HFAMS measurements was 1 h and 44 min.

2.3. Thoracic computed tomography

Thoracic Computed Tomography (CT) scans were performed on one the available clinical scanners based on clinical availability (Siemens: Definition n = 46; Edge n = 6; Flash n = 10; Sensation 64 n = 4). Scans were obtained with 2.5 mm thick slices and 1.2 mm overlap and reconstructed to 1.25 mm thick slices with a 0.6 mm overlap; the total radiation dose for all scans combined was 25.2 mSv. An initial scout scan was performed to ensure capture of the entire lung volume. Scans were performed by an experienced CT technician. With subjects lying supine, a member of the

study team coached the subject to take a deep breath and hold it before signaling to the technician to begin the scan. In the subsequent quantitative analysis lung tissue was segmented from surrounding tissue and large blood vessels automatically with the use of Matlab built-in active contour algorithms (Mathworks, Natick, Massachusetts). Only pixels within the range of – 1000 Hounsfield Units (HU, corresponding to pure air) to 0 HU (corresponding to pure water) were included in the analysis, with most voxels having a value between these extremes because they contain a combination of air and water. The lung density was calculated from the distribution of CT attenuation within the segmented areas. Mean lung density was then used to calculate fluid content as a percentage using the equation: Fluid content = (mean lung density + 1000)/10, a formula which has been validated and used in previous studies [16,18–20]. This allows for comparison of CT lung fluid and RF lung fluid in the same units of measure i.e., lung fluid expressed as a percentage of the total lung that is wet.

2.4. Heart failure and Arrhythmia management system (HFAMS)

The system consists of an adhesive patch, a removable sensor, and gateway (data transmission device). The sensor is placed in the patch via snap-in clip and positioning tabs (Figs. 1A and 1B). Once the patch and sensor combination is placed on the body in the left anterior axillary position, the sensor noninvasively records ECG, radiofrequency determined thoracic/lung fluid, respiration rate, activity, and posture (Fig. 1C). In order to measure fluid up to one minute radar reading is needed. There is no expert technique required to perform the measurement. The radiofrequency module of the system transmits a modulated wave at pre-defined frequencies through the left thorax, and then receives the reflected signals from the tissues. One minute RF measurements with HFAMS were collected every 5 min over ~ 17 min with participants first in a sitting position, before transitioning to lying in a supine position. Participants were asked to remain relaxed, quiet and as still as possible during data collection. The characteristics of the reflected signal that includes amplitude, phase, and time of arrival of the reflected pulse, in addition to subject-specific anthropometric data, are used to calculate RF-determined lung fluid content. The HFAMS is FDA-cleared for use in the clinic and home settings for patients who require fluid management and/or require monitoring for the detection of non-lethal cardiac arrhythmias.

2.5. Statistical analysis

The SPSS statistical software package (v25; SPSS, Chicago, IL), GraphPad Prism (V8.0, GraphPad Software, San Diego, CA), and RStudio (Version 1.2.1335; RStudio, Inc, Boston, MA) was used for all analyses. All data are presented as mean \pm SD. Comparisons of demographic variables and fluid content (%) between AHF and

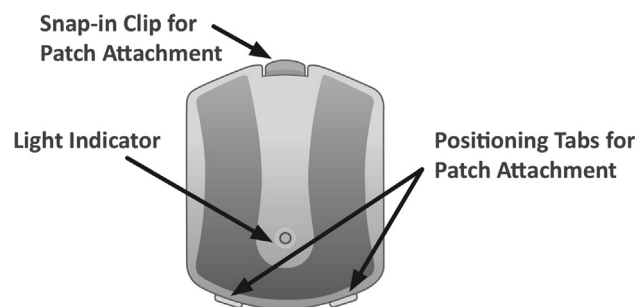


Fig. 1a. Sensor's front view.

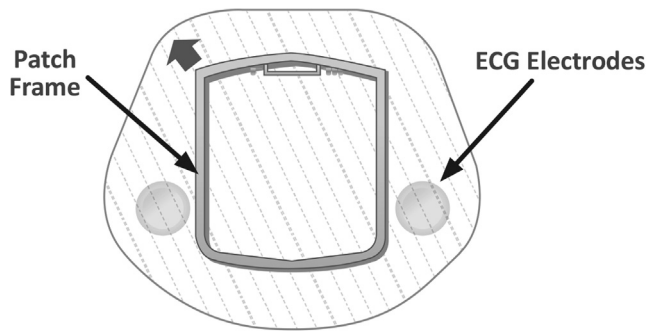


Fig. 1b. Adhesive patch.

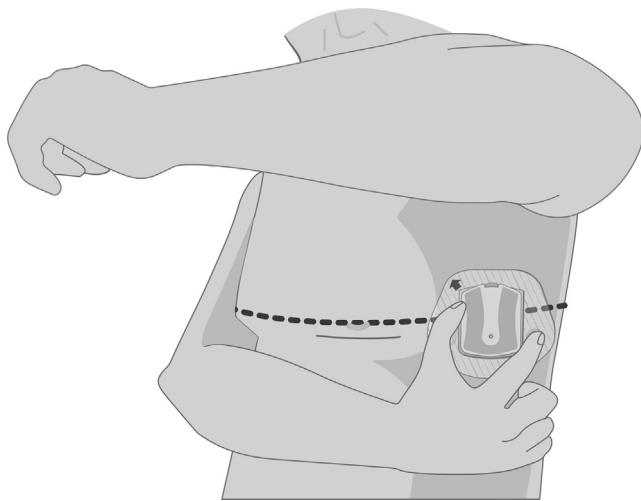


Fig. 1c. Placement of the sensor and patch in the left anterior axillary.

control groups were assessed using two-sided independent samples t-tests with a two-sided p-value of 0.05 used to determine significance. The correlation between CT and RF determined lung fluid was calculated using Pearson's correlation coefficient. To compare the agreement between the two measurement methods for fluid content the Bland-Altman test was used.

To evaluate the performance of CT and RF determined lung fluid in classifying AHF and Control, the following definitions were used:

1. True Positive: Number of AHF subjects correctly classified as AHF
2. False Positive: Number of Control subjects incorrectly classified as AHF
3. True Negative: Number of Control subjects correctly classified as Control
4. False Negative: Number of AHF subjects incorrectly classified as Control
5. Sensitivity: Percentage of AHF subjects classified correctly as AHF
6. Specificity: Percentage of Control subjects classified correctly as Control
7. Positive Predictive Value (PPV): Percentage of subjects classified as AHF having a AHF diagnosis
8. Negative Predictive Value (NPV): Percentage of subjects classified as Control not having a AHF diagnosis
9. Positive Likelihood Ratio (LR +): Sensitivity/(100-Specificity)

The best threshold for CT and RF lung fluid content was determined by maximizing the Youden Index [21], defined as sensitivity + specificity – 100.

3. Results

One hundred and thirty nine subjects were recruited of which 120 had a complete data with lung fluid assessed with CT and HFAMS and form the basis of this report. Sixty six subjects had been admitted to the hospital for AHF with signs of pulmonary congestion. Most AHF patients had an x-ray taken when in the ED or upon admission (92%). X-ray findings demonstrated pulmonary edema or pulmonary vascular congestion in 34 AHF patients (52%). Lung fluid assessment with CT and HFAMS was performed within 38 ± 45 hrs (median 23 hrs) of being admitted. The control group consisted of 44 healthy individuals with no history of cardiac or pulmonary disease and 10 subjects who have been previously diagnosed with heart failure, but were stable with no signs of pulmonary congestion. The control subjects were younger, and leaner than those with AHF (Table 1, $p < 0.05$). The ten stable HF control individuals were anthropometrically similar to the AHF individuals except for being slightly taller and younger ($p < 0.05$). The AHF group was predominantly NYHA functional class III and IV, whereas the stable HF individuals were class I and II. Further, the individuals with stable HF patients had been living with heart failure for almost twice long as those individuals with AHF. For 18 of the AHF subjects, HF was diagnosed for the first time with the current hospital admission. Comorbidities for the HF subjects included hypertension, hyperlipidemia, diabetes, COPD, chronic kidney disease, sleep apnea, and a history of smoking. The frequency of these comorbidities was similar between the AHF and stable HF subjects. In the healthy subjects there were some with a smoking history, hypertension, diabetes, hyperlipidemia, and sleep apnea.

3.1. CT lung fluid

Assessment of fluid content based on the region of the lung showed that the correlation between full lung versus right and left lungs was 0.99 ($p < 0.01$) and 0.98 ($p < 0.01$), respectively. Similarly, the correlation between the right and left lung fluid content was 0.95 ($p < 0.01$). Because of the high correlation in fluid content between the different regions of the lung and RF fluid assessment performed on the left side of the body, the fluid content of the left lung was used in subsequent analysis. Fluid content in the left lung was not different between stable HF participants and healthy individuals ($15.4 \pm 2.4\%$ vs. $15.4 \pm 2.4\%$, $p = 0.90$). In contrast, left lung fluid content was significantly higher in the AHF group was $20.1 \pm 4.2\%$ when compared to the control group it was $15.4 \pm 2.4\%$ ($p < 0.05$).

3.2. HFAMS RF fluid assessment

The HFAMS RF measured fluid content in the sitting and supine body positions showed a correlation of 0.96 ($p < 0.01$) between the two positions (Fig. 2) suggesting the short duration in the supine position did not cause sufficient shifts in fluid distribution. Due to the strong correlation in fluid content between the two body positions, only the supine position RF fluid content was utilized to compare to the fluid content measured with CT so that position was identical for both methods.

RF measured fluid content in the AHF group was $20.7 \pm 5.6\%$ compared to $15.6 \pm 3.3\%$ in the Control group ($p < 0.05$). Fluid content in the left lung was not different between stable HF participants and healthy individuals ($17.0 \pm 1.8\%$ vs. $16.3 \pm 1.5\%$, $p = 0.16$). The correlation between fluid content measured by CT vs. RF measured fluid content was $r = 0.7$, $p < 0.001$ (Fig. 3). Bland-Altman assessment of the agreement between CT and RF measured fluid content demonstrated a bias of $-0.55 \pm 2.99\%$, with

Table 1
Subject Population.

	Control			
	All	Healthy	Stable HF	AHF
n	54	44	10	66
Gender female	24 (44%)	23 (52%)	1 (10%)	25 (38%)
Age (years)	57 ± 15	55 ± 15	65 ± 13	74 ± 16*†
Height (cm)	173 ± 11	172 ± 12	176 ± 10	169 ± 10†
Weight (kg)	82 ± 19	79 ± 19	93 ± 15	95 ± 29*
BMI (kg/m²)	27.3 ± 5.1	26.7 ± 5.1	29.9 ± 4.6	33.2 ± 9.0
HF Etiology				
Ischemic	4	0	4	36
Non-ischemic	5	0	5	27
Mixed	1	0	1	2
Valvular	0	0	0	1
NYHA Functional Class				
I	9	0	9	0
II	1	0	1	2
III	0	0	0	12
IV	0	0	0	52
Years with HF	9 ± 5	0	9 ± 5	4 ± 5
No. Hospitalizations in last 3 mths	0	0	0	0.7 ± 0.9
Comorbidities				
Hypertension	15	6	9	57
Diabetes	6	3	3	33
COPD	0	0	0	26
Smoking History	10	5	5	40
Hyperlipidemia	16	8	8	54
Sleep Apnea	8	3	5	42
CKD	1	0	1	34

CKD = chronic kidney disease. * p < 0.05 vs. All †p < 0.05 vs. Stable HF.

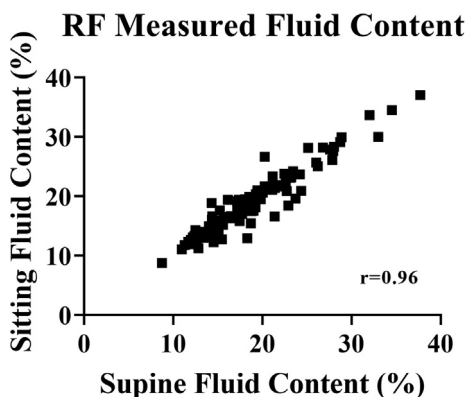


Fig. 2. Comparison of RF measured fluid content based on body position.

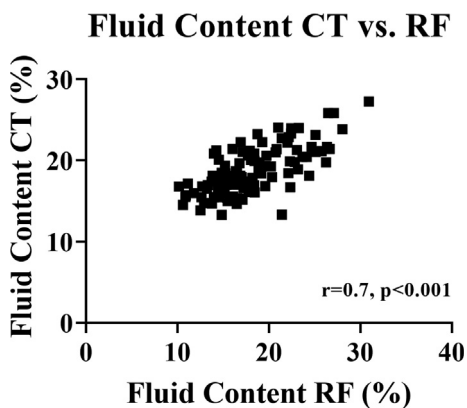


Fig. 3. Correlation between CT and HFAMS measured fluid content.

the 95% CI on the limits of agreement being -6.41 to 5.32. The CT and RF measured fluid content threshold with the best Youden Index for classifying AHF vs Control was 17.5%. Both CT measured FC and RF measured fluid content had a sensitivity of at least 70%, specificity greater than 80%, PPV of 82 and 86%, NPV of 69 and 83%, and a positive likelihood ratio of 3.8 and 5.2 in classifying AHF and Control group subjects, CT and RF respectively (Table 2).

4. Discussion

This investigation evaluated RF lung fluid content measured by HFAMS as compared to the measurements from chest CT. In line with the CT assessment of lung fluid, RF determined lung fluid demonstrated higher fluid content in the AHF patients than control subjects. Lung fluid content measured non-invasively by HFAMS demonstrated similar sensitivity and specificity as thoracic CT in discriminating AHF patients from control individuals. These results validate the ability to assess lung fluid using noninvasive radiofrequency waves.

Congestion (pulmonary and/or peripheral) is a key characteristic of the majority (~70%) of acute decompensated HF admissions [12]. Furthermore, patients discharged with residual congestion have increased 60 day rehospitalization rates and 1 year mortality [12]. When decreased left ventricular function leads to increases in pulmonary artery pressures this causes an increase flux of fluid from intra- to extravascular space based on Starling’s law of fluid filtration, which can eventually overwhelm the body’s ability to clear it and lead to fluid accumulation, i.e. pulmonary congestion [15]. Invasive devices that monitor pulmonary artery pressure, such as with the CardioMEMS device, demonstrated that increases in filling pressure occur more than 20 days prior to clinical evidence of decompensation [22] and has provided evidence that if one can detect changes earlier in the time course preceding a heart failure event it is possible to reduce hospital admissions and readmissions [11]. However, the ability to detect and monitor changes in lung fluid non-invasively, reproducibly and inexpensively is needed [17].

Table 2
Classification analysis of AHF from FC measured by CT and HFAMS.

AHF vs Control	Threshold	True Positive (n)	False Positive (n)	False Negative (n)	True Negative (n)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Positive Likelihood Ratio
CT Left Lung	>17.5	46	10	20	44	70	81	82	69	3.7
HFAMS	>17.5	57	9	9	45	86	83	86	83	5.2

There are non-invasive modalities utilized to assess lung fluid and confirm a diagnosis of AHF in practice, but none meet all of the needs mentioned above for outpatient monitoring of fluid status. X-ray is routinely used to assess edema clinically because of its low cost, ease of use, and reproducibility. However, X-ray can only qualitatively assess fluid. CT assessment has shown that fluid remains elevated in HF patients compared to healthy controls when symptoms and X-ray signs have subsided [16,23], thus limiting the ability to discern a euvoletic target. CT itself is impractical due to its expense and radiation dose. B-type natriuretic peptide (BNP) and N-terminal-proBNP values, lung ultrasound assessments and bioimpedance vector analysis, although good at confirming the presence fluid overload [24–28], are unfeasible for serial outpatient monitoring as they require professional interventions. These noninvasive methods are better suited to evaluating the level of congestion in HF patients.

The current non-invasive outpatient methods for assessing pre-clinical edema and congestion, either in use or being evaluated, lack sensitivity and specificity [29]. Physiological symptoms such as weight gain, dyspnea, bioimpedance vector analysis, and vital signs are currently assessed in the outpatient setting and become apparent <10 days prior to an impending decompensation [22]. This has prevented them from being useful in outpatient treatment and potential prevention of a hospital admission. Additionally, recent studies have demonstrated that tele-monitoring of symptoms does not reduce admission rates either [30–32]. As such these outpatient monitoring methods are not sensitive enough as the changes they assess do not occur early enough in the days before a looming hospital admission to allow outpatient action to be effective.

In contrast, more recent evaluation of non-invasive means of measuring lung fluid such as the one reported in this study and those reported previously show promise [20]. These devices allow for daily tracking of changes in fluid content to identify patient-specific thresholds for the tolerable amount of residual fluid. While not the primary goal of this investigation, it is interesting to note that in the small group studied, that stable patients with a history of pulmonary congestion demonstrated CT and RF fluid content values similar to non-heart failure patients. Such technology may be used through daily tracking of fluid changes to potentially identify increases in pulmonary congestion early enough in the initial phase of destabilization so that changes to outpatient therapy are effective at preventing hospitalization. Potentially, their use during the course of a hospital stay could identify a patient's specific target for lung fluid homeostasis and optimal fluid distribution. HFAMS may be the first tool available in clinical practice that is a non-invasive and sensitive means to monitor changes in lung fluid to provide ambulatory HF decompensation monitoring which would allow for daily temporal tracking and identification of pulmonary congestion trajectories. In addition to the risk of developing congestion, heart failure patients are predisposed to developing arrhythmias. Early detection of the type of arrhythmia and level of pulmonary congestion using the HFAMS can help clinicians determine the appropriate management strategy. Of equal importance, clinicians will have the ability to determine if arrhythmias preceded any increase in pulmonary congestion, or occurred subsequent to an increase in congestion. These temporal relations have

been a challenge in the past. Overall, noninvasively determined RF lung fluid content could allow clinicians to manage HF patients in outpatient setting and monitor response to for titrating decongestion therapies in an in-hospital setting.

5. Limitations

Although thoracic CT is considered one of the gold standards for measuring lung fluid, it is not a perfect measurement technique [17]. Most imaging methods, other than positron emission tomography, do not measure extravascular lung water but rather provide an estimate of total lung fluid content (vascular and extravascular fluid). The exact location of the lung fluid, whether it is in the bronchial, pulmonary circulation, or extravascular space, is hard to identify [15,23]. This requires an assumption that blood volume in the lung is constant [17]. One might hypothesize that some of these types of lung fluid are less dynamic than others, so any change reflected in total lung fluid may then serve as a useful marker for worsening heart failure. Lung fluid will also change with changes in body position, potentially confounding the results. This study controlled for this effect by consistency in lung position to ensure thoracic CT was a sensitive and specific reference for lung fluid content. It should be noted that the RF technology described in the current study cannot, at this time, be used to determine total body water overload or purely right sided heart failure peripheral edema as the device only looks measures at the lung fields. Furthermore, it is unclear if RF can detect intravascular congestion. Understanding a particular patient's baseline pre-symptomatic level of pulmonary congestion, however, will require individualized attention as some patients may have symptoms at 17% lung water, and others will not have symptoms until 21%, for example.

6. Conclusion

The present study provides evidence that noninvasive, nonionizing RF can determine the presence of and quantify lung fluid. Thus, it provides a potential alternative to other measures as a remote monitoring tool for diagnosing and monitoring for pulmonary fluid overload that is well suited for outpatient/home use or a clinical setting over the course of a hospital admission. Additionally, inpatient use of RF may identify personalized lung fluid balance targets. Further studies will guide the clinical utility of HFAMS and similar devices in HF patient management, and include evaluation of its reproducibility, ability to detect preclinical lung fluid accumulation or help identify lung fluid homeostasis and optimal fluid distribution target for each HF patient in order to reduce hospital admissions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

BDJ and PS conceived and designed the experiments. PS, BDC, and RJW performed the experiments. PS, RJW, BDJ and CMW analyzed and interpreted the results. CMW drafted the paper and all authors contributed to revising and approving this final version.

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