A Novel Approach to Monitoring Pulmonary Congestion in Heart Failure: Initial Animal and Clinical Experiences Using Remote Dielectric Sensing Technology

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Despite current therapies and disease management approaches, rates of heart failure (HF) rehospitalization remain high. New tools are needed to assess preclinical (asymptomatic) pulmonary congestion to enable outpatient management. Hence, a novel monitoring system based on noninvasive remote dielectric sensing (ReDS) technology was developed. Validation of the ReDS technology was conducted in preclinical and clinical studies. In a porcine HF model, acute fluid overload followed by administration of diuretics were performed. Changes in ReDS values were correlated to serial computed tomographic (CT) assessments of lung fluid concentrations. In hospitalized decompensated HF patients, changes in ReDS values were correlated to net fluid balance changes. A nearly linear pattern between the changes in ReDS and CT fluid concentration values was observed in 6 discrete experiments (Intraclass correlation=0.95). Results from 24 patients demonstrated a reduction in ReDS values of 17.53%±11% throughout hospitalization, consistent with a reduction in pulmonary congestion. This finding strongly correlated with changes in net fluid balance (Pearson correlation=0.86; 95% confidence interval, 0.68–0.94; R^2=0.74). These findings suggest that ReDS technology accurately quantifies lung fluid concentration and has potential for monitoring HF patients through hospitalization and possibly at home.

Acutely decompensated heart failure (ADHF) is a major public health concern. Aside from being the most common cause of hospitalization in adults older than 65 years, ADHF is associated with high rates of morbidity and mortality and is a tremendous health economic burden.[1–3] Exacerbation of heart failure (HF) is predominantly associated with elevated ventricular filling pressures eventually leading to pulmonary congestion, worsening symptoms of dyspnea, and the need for hospitalization as documented in major American and European registries.[4–7]

Despite the widespread use of numerous telemonitoring approaches to reducing ADHF admissions, the number of admissions is rising in the United States and elsewhere, and the 30-day readmission rate of 25% for HF is the highest among all medical or surgical causes of hospitalization.[8] Further evidence supporting the failure of current HF monitoring approaches comes from recent randomized controlled trials that demonstrate no benefit from electronic telemonitoring of HF using systems that assess changes in patient symptoms, daily weight, vital signs, or intrathoracic impedance.[7,9–11] The ineffectiveness of these approaches was partially explained by the low sensitivity and specificity to HF exacerbation attributed to the monitored parameters. New, more precise tools are needed to assess preclinical (asymptomatic) pulmonary congestion, enable outpatient intervention, and reduce the rate of HF hospitalization. An implantable wireless pulmonary artery pressure monitoring device was shown to have a substantial effect on ADHF patient readmissions and quality of life.[12] While regulatory approval is anticipated for this investigational device, an invasive approach to HF monitoring is unlikely to be indicated in all patients.

In this report we present, for the first time, a novel electromagnetic energy-based technology (remote dielectric sensing [ReDS]) that can accurately quantify changes in lung fluid concentration noninvasively.

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METHODS

ReDS Technology

ReDS technology (Sensible Medical Innovations Ltd, Netanya, Israel) measures the dielectric properties of tissues. Low-power electromagnetic signals are emitted into the body, and the intercepted signals reflect the dielectric properties of tissues that are most affected by their fluid content. Two sensors are attached to the body: one anteriorly on the chest and the other on the back of the patient. Each sensor is a small round device capable of transmitting and intercepting the energy either reflected from or transferred through the pulmonary tissue. The analyzed signal reflects the dielectric properties of the section of the lung between the sensors. The spatial resolution does not allow distinguishing in which compartment of the lung the fluids were

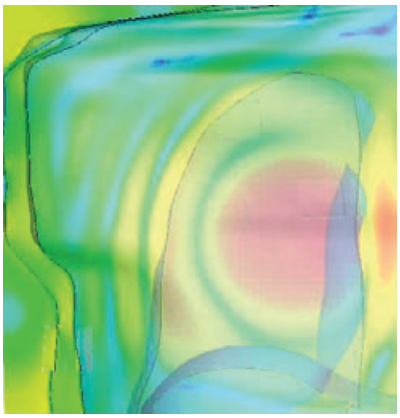

FIGURE 1. An example of region of interest size and location (color-coded red) as calculated by an electromagnetic simulation tool.

accumulated, eg intravascular, interstitial, or alveolar compartments. An illustration of the pathway of the electromagnetic beam and the resultant anatomical region of interest (ROI) is presented in Figure 1.

In brief, the dielectric coefficient of a material is represented by a frequency-dependent complex number describing its interaction with electromagnetic energy including the degrees of absorption, reflection, and retention of the energy. Different tissues are characterized by different dielectric coefficients.[13,14] Since water has a very high dielectric coefficient (approximately 80), dielectric coefficients of tissues are determined predominantly by their fluid content. For example, healthy fat tissue, which is of low fluid content, is characterized by a relatively low dielectric coefficient, while healthy muscle tissue, relatively rich in fluids, is characterized by a higher dielectric coefficient. The dielectric coefficient of pulmonary tissue is determined by the dielectric coefficients of each of its components and their concentration (eg, blood, lung parenchyma, air, and their relative concentrations). Since air has the lowest dielectric coefficient (1), pulmonary tissue is composed of two types of highly contrasting components, making its dielectric coefficient a very sensitive and direct indicator of the volume ratio of fluid to air, ie, fluid concentration. The high sensitivity of this parameter to fluid concentration is the physical basis for the hypothesized high accuracy of the device in detection of pulmonary edema and its progression over time.

The lack of an accurate gold standard reference for quantifying pulmonary congestion rather than pulmonary pressure in humans necessitates that accuracy testing is performed in animals. In particular, computed tomography (CT) is considered the most accurate modality for quantifying lung fluid congestion,[15] but due to its harmful irradiation characteristics, it is not suitable for serial testing in humans. Thus, a two-step approach was used, first establishing the accuracy of ReDS using CT as a gold standard in the preclinical setting and then correlating changes in ReDS values with clinical parameters during treatment of ADHF.

Animal Study

The objective of this study was to assess in an animal model the ability of ReDS to accurately quantify lung fluid content compared with measurements via CT. The Institutional Animal Care and Use Committee (at the Chaim Sheba Medical Center) approved the study.

Six discrete independent experiments of acute fluid overload were performed (female pigs weighing 60–75 kg [65.6±4.0 kg]) 3 weeks after HF was induced using a previously described model of anterior myocardial infarction. The latter was achieved by acute occlusion of the left anterior descending coronary artery by implantation of hyperthrombotic coil (VortX, 18 fibered platinum coil; Boston Scientific, Natick, MA).[16] This model was chosen because it is similar to the human cardiovascular system (eg, reduced fat layers and reasonable resemblance to the dimensions of the human chest). The animals were then given 4 weeks of rehabilitation. Subsequently, the animals were re-anesthetized and subjected to acute volume overload by isotonic saline (2 L over 40 minutes) followed by 30 minutes of rest, an additional overload and stabilization cycle (over 40 and 30 minutes, respectively), and finally administration of diuretics (intravenous furosemide 40 mg) to allow for the assessment of dehydration.

The animals were assessed throughout the procedure using both ReDS and serial CT scans. The animals were placed in a prone position on the CT bed, and the ReDS sensors were positioned on the left and right sides of the chest as depicted in Figure 2. As mentioned above, the CT technology was used as the benchmark because of its high sensitivity to changes in lung fluid content. Nevertheless, there is not an automatic method suited for analyzing sequential CT scans for estimating pulmonary congestion over a period of time (probably because of its irrelevancy to clinical practice). Such a method should be agnostic to movement of the animal between the scans. A method for analyzing the CT scans was developed: analysis of an ROI within the lung between the sensors was conducted by tiling 3-dimensional boxes in the first CT image and using automatic tracking methods to find the location of these boxes in each successive scan. Hence, the mean and standard deviation (SD) of the attenuation levels of the lung in Hounsfield units (HU) were computed over time. Raw CT data, recorded in HU, were converted into percentage of fluid concentration using a linear scale based on the knowledge that healthy lung tissue is composed of two dielectric-based distinguished lung elements (within standard CT irradiation frequencies): (1) the blood and parenchyma and (2) air volumes. Transformation from HU to percent fluid concentration was prespecified and not fit to the data post hoc. Specifically, values of percent fluid

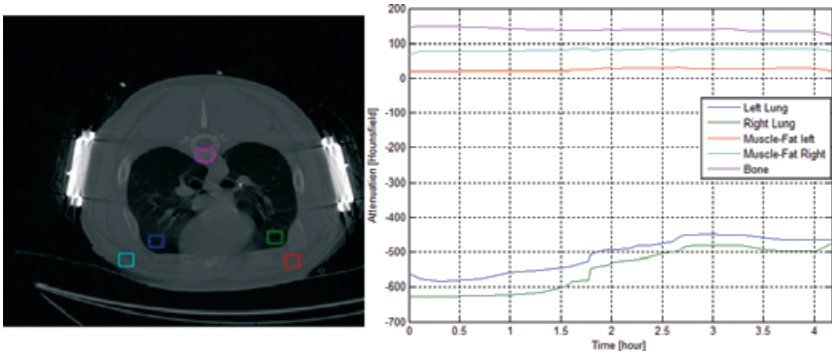

FIGURE 2. Three-dimensional analyzed regions of interest (ROIs) were defined in several areas. The purple, cyan, and red color-coded ROIs are outside the lungs, and the blue and green color-coded regions are within the left and right lungs, respectively. Note that gradual fluid overload is observed on computed tomograpy only in the lungs.

concentration were assigned from 0% to 100% along the range of HU values from −1000 HU (calibrated radiodensity of air) to 0 HU (calibrated radiodensity of water). CT data are at times presented throughout this report in units of percent fluid concentration (eg −800 HU is equivalent to 80% air content, 20% fluid concentration).

Statistical Analysis. Since CT observations were made every several minutes while ReDS observations were made approximately every 4 seconds in each respiration cycle, the two datasets required synchronization for comparison. For each CT observation, the nearest ReDS observation was identified and paired with its synchronous CT counterpart. The paired CT and ReDS values, in units of percent fluid concentration, were the basis for all statistical analyses. In order to enable investigation of the relationship between change in CT and change in ReDS, all pairwise differences within both CT and ReDS were computed. The relationship between CT and ReDS data pairs was assessed using Pearson and Intraclass correlation (ICC) models. For ICC calculations, a single-measure two-way mixed-effect model was used. For all correlations, the 95% confidence interval (CI) was calculated. The relationship between change in CT and change in ReDS was evaluated descriptively by boxplots. A mixed linear model was used to determine that each experimental session was independent. All statistical analyses were carried out using SAS (version 9.2; SAS Institute Inc, Cary, NC).

Clinical Study

The purpose of this first-in-human HF clinical study was to assess the ability of ReDS to correlate with both the clinical course of ADHF, manifesting as pulmonary congestion, and with changing fluid balance status. The institutional review board (Lady Davis Carmel Medical Center) approved this observational study. All participants gave written informed consent prior to enrollment.

Inclusion criteria were a clinical diagnosis of ADHF presenting with symptoms, clinical signs, and chest x-ray (CXR) findings of pulmonary congestion. Exclusion criteria included known severe pulmonary disease, renal failure, and dominant right HF. Patients were monitored using ReDS technology intermittently throughout hospitalization (4–6 sessions lasting up to 15 minutes each daily). The sensors were removed in between the time of measurements. Patients were measured in their beds. The bed tilt angles were kept the same (±5°) for each patient throughout the entire monitoring period according to the smallest angle (from horizon) in which the patient still felt comfortable. The managing team was blinded to ReDS measurements, and treatment decisions were undertaken without knowledge of this parameter. Routine physical examinations, laboratory analyses, CXR studies, and fluid balance (I/O) were quantified throughout hospitalization. The latter consisted of all oral intake (solid and fluid), esophageal catheter volumes, intravenous infusions, and urine output. Serial samples for N-terminal B-type natriuretic peptide (NT-BNP; Elecsys 1010; Roche Diagnostics, Indianapolis, IN) were collected at enrollment and prior to discharge. Thirty patients were recruited into the study.

In addition, 5 healthy volunteers that did not have heart disease were monitored in a protocol similar to that of the ADHF patient group to be used as negative controls.

Statistical Analysis. Fluid balance observations were made when an I/O event occurred, eg, urination or drink, while ReDS was measured at predetermined intervals 4 to 6 times a day. Hence, the two datasets required synchronization for comparison. For each ReDS observation, the spline interpolated I/O observation was paired with the ReDS observation. The paired I/O and ReDS values were the basis for all statistical analyses between these two parameters. The relationship between I/O and ReDS data pairs was assessed using a Pearson correlation along with its

95% CI and R^2. Since it was not possible to combine data across patients for computation of the Pearson correlation and R^2, the overall η^2 was calculated instead. Paired Student *t* test was used when comparing initial and predischarge NT-BNP levels. The ability to differentiate between the patient group and the reference group based on ReDS trend evaluation was examined using Student *t* test. All data are presented as mean±SD. Statistical analyses were carried out using SAS version 9.2.

RESULTS

Animal Study

Mean ejection fraction at the beginning of each experiment in the HF animals was 43%±10.4%. All induced fluid overload events and the transition events from fluid overload to normal or diuresis-induced dehydration were clearly detected by a change of ReDS trend direction within a maximum of 20 seconds.

Comparison of ReDS Findings With CT. CT imaging capabilities and the described attenuation-based analysis method enabled detection of changes of fluid concentration in the lungs and provided a reference for performance comparison between the two modalities. Figure 2 demonstrates that fluid buildup was identified and quantified on CT only in ROIs within the lungs as a result of the fluid overload. An example is presented where ROIs outside of the lungs present positive attenuation values close to zero [H] (calibrated for water), which do not change throughout the study (negative control) as a consequence of the induced fluid overload, while in contrast the ROIs within the lung present attenuation values near −600 [H] (mixture with air calibrated to −1000 [H]), which become less negative (trend) as fluid is accumulated, replacing air as a result of the fluid overload. The correlation coefficients between CT and ReDS measurements are summarized in Table I and a representative example is provided in Figure 3. In this model of acute volume overload, all animals behaved similarly (ie, no differences were observed in response to either overload or diuresis between animals). The relationship between change in CT and change in ReDS across all experiments was evaluated descriptively by boxplots—a nearly linear pattern between the change in ReDS and CT is shown in Figure 4, indicating a high correlation between change in CT (ΔCT) and change in ReDS (ΔReDS).

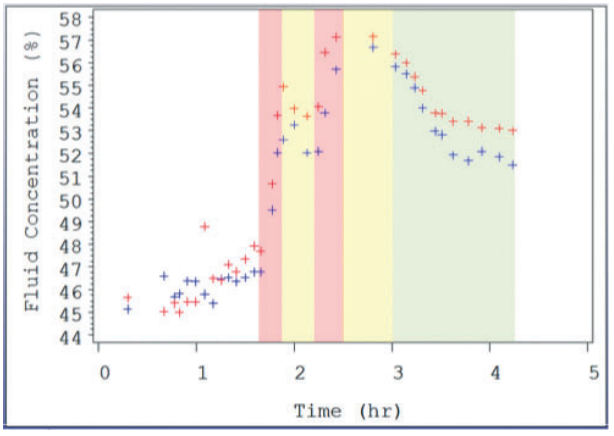

FIGURE 3. Computed tomographic (blue) and remote dielectric sensing (ReDS) (red) tracings of acute overload (two cycles) and diuresis in a single experimental session. Baseline values do not start at zero as lung fluid concentration includes intravascular as well as parenchymal fluids. The various experimental phases are indicated on the ReDS tracing. All data are presented as percentage of fluid concentration. In this example, Pearson and intraclass correlation coefficients (CCs) were 96% and 97%, respectively.

Clinical Study

Of the 30 enrolled HF patients, 6 were excluded from analyses because of inaccurate I/O follow-up (difference between I/O follow-up and weight change during hospitalization period >2 kg), leaving a total of 24 patients included in this study and reported herein. Patient demographics and baseline data are summarized in Table II. Throughout hospitalization, all patients demonstrated clinical improvement. Average±SD hospital length of stay was 6.1±2.8 days. NT-BNP levels at admission were 6754±7108 pg/mL and at discharge were 2730±2576 pg/mL exhibiting a statistically significant difference of $P<.05$. No device-related adverse events were noted throughout this

TABLE I. Correlation Between ReDS and CT

Animal	No.	Pearson Correlation	Lower 95% Confidence Limit	Upper 95% Confidence Limit	ICC	Lower 95% Confidence Limit	Upper 95% Confidence Limit
1	28	0.97	0.93	0.98	0.97	0.93	0.98
2	32	0.90	0.80	0.95	0.90	0.80	0.95
3	15	0.99	0.95	1.00	0.96	0.87	0.99
4	34	0.98	0.95	0.99	0.96	0.92	0.98
5	32	0.98	0.96	0.99	0.95	0.90	0.97
6	38	0.99	0.98	0.99	0.90	0.82	0.95
Total	179	0.95	0.94	0.96	0.95	0.93	0.96

Correlation coefficients (Pearson and Intraclass) were calculated for each animal. No. indicates the number of data points used for statistical analysis in each animal (number of computed tomography [CT] scans). The bottom row (labeled "Total") includes data from all animals in one regression model and indicates minimal variation in CT-remote dielectric sensing (ReDS) correlation as a function of animal or experimental session.

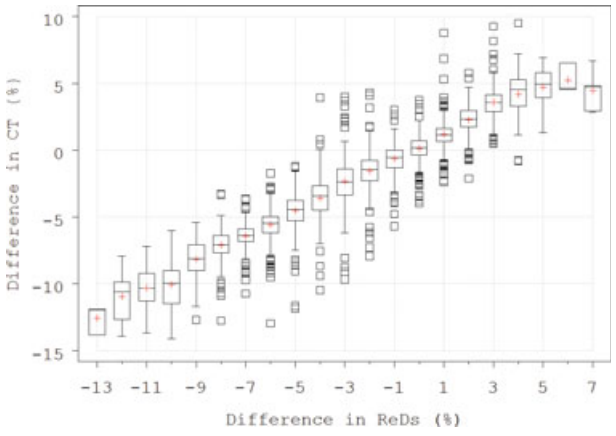

FIGURE 4. Relationship between Δcomputed tomographic (CT) and Δremote dielectric sensing (ReDS). Delta (Δ) is defined as a change in value between every two measurements in all animals. For a given ΔReDS, the distribution of values of ΔCT that occurred is plotted. The top and bottom of each box in the boxplot represent the 75th percentile and 25th percentile, respectively, while the middle band represents the 50th percentile (median) and the cross ("+") the mean. The whiskers of each box extend out an additional 1.5 interquartile range from the end of the box, with outliers indicated by individual squares.

TABLE II . Patient Demographics

Variable	AHF Patients (n=30)
Demographics	
Sex (male)	22 (73)
Age, y	73.3±11.4
Body mass index, kg/m^2	30.3±6.2
Heart failure history	
NYHA class III/IV[a]	(18/12)
Left ventricular ejection fraction	37.6±15.4
Medical history	
Coronary artery disease	21 (70)
Diabetes mellitus	22 (73)
Laboratory and physical findings[a]	
Creatinine level, mg/dL	1.59±0.45
Urea level, mg/dL	76.8±35.7
Sodium level, mEq/L	136.7±3.4
NT-proBNP level, pg/mL	6754±7100 [4000–7980]
NT-proBNP delta, pg/mL	−2730±2570 [−2520 to 5390]
Systolic blood pressure, mm Hg	138±36
Baseline medications[a]	
Angiotensin receptor blockers/ angiotensin-converting enzyme inhibitors	21 (70)
β-Blockers	22 (73)
Aldospirone	6 (20)
Statins	16 (53)

Abbreviations: AHF, acute heart failure; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association. Data are presented as mean±standard deviation or (median [interquartile range] or number (percentage of patients).
[a]At admission.

study. Correlation between I/O fluid status balance and ReDS quantification of discrete lung fluid concentration was observed in all patients and is shown in

TABLE III. I/O-ReDS Correlations

No.	Pearson CC	Lower 95%	Upper 95%	R^2
1	0.95	0.76	0.99	0.91
2	0.9	0.79	0.95	0.81
3	0.9	0.52	0.98	0.8
4	0.72	0.52	0.84	0.52
5	0.75	0.57	0.93	0.56
6	0.7	0.6	0.78	0.51
7	0.81	0.59	0.92	0.59
8	0.97	0.94	0.99	0.95
9	0.93	0.86	0.97	0.87
10	0.79	0.61	0.92	0.55
11	0.87	0.66	0.95	0.75
12	0.82	0.61	0.92	0.67
13	0.94	0.69	0.99	0.88
14	0.89	0.67	0.97	0.79
15	0.77	0.51	0.91	0.6
16	0.96	0.89	0.98	0.91
17	0.68	0.43	0.83	0.46
18	0.9	0.68	0.97	0.81
19	0.97	0.92	0.99	0.94
20	0.97	0.9	0.99	0.95
21	0.85	0.53	0.96	0.72
22	0.85	0.71	0.94	0.71
23	0.79	0.7	0.87	0.73
24	0.91	0.69	0.98	0.83
Mean	0.86	0.68	0.94	0.74
SD	0.09	0.14	0.06	0.15
SE	0.02	0.03	0.01	0.03
Count	24.00	24.00	24.00	24.00

Abbreviations: SE, standard error; SD, standard deviation. I/O-remote dielectric sensing (ReDS) Pearson correlations and R^2 values calculated. The 95% confidence interval values in the bottom row provide the confidence interval for the mean Pearson correlation coefficient (CC).

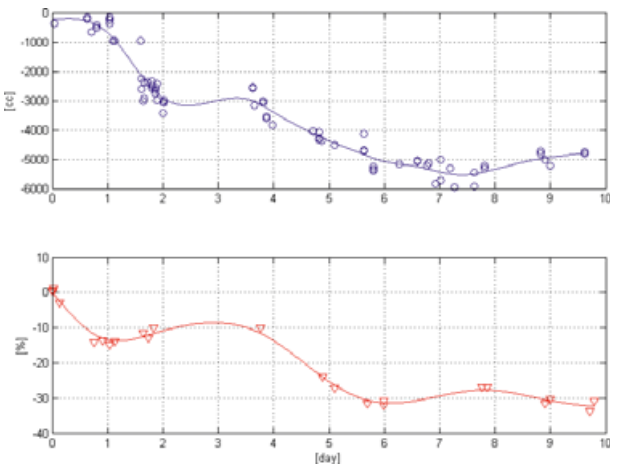

FIGURE 5. Remote dielectric sensing correlation with fluid balance throughout the entire hospitalization period of a patient with acute decompensated heart failure (Pearson coefficient coefficient [CC] =0.92, R^2=0.85).

Table III. Average±standard error Pearson correlation was 0.86±0.02 (95% CI, 0.81–0.91) with an R^2 of 0.74. Using a single regression model for all patients, η^2 value was 0.66. Figure 5 depicts progression over

hospitalization of both fluid balance and ReDS measurements. The correlation observed was high (patient 2: Pearson correlation coefficient, 0.9; $P<.001$). The difference in ReDS values from admission to discharge was 17.53%±11%, exhibiting a statistical difference of $P<.05$.

As negative human controls, 4 men and 1 woman aged 57±15 years with a body mass index of 26.3±2.4 kg/m^2 were also studied. Throughout a monitoring period of 3.8±0.4 days in these healthy individuals, only minimal variation in ReDS values was observed (−1.1%±1.4%). This differed significantly ($P<.01$) from the changes in ReDS values observed throughout hospitalization of the ADHF patient group. In summary, ReDS did not detect changes in healthy volunteers whose lung fluid concentration was not expected to change during the period of monitoring.

DISCUSSION

The present report describes a novel approach to quantification of lung fluid concentration using ReDS technology. In an animal model, comparison with CT as the "gold standard" in a controlled model of HF in pigs demonstrated that ReDS technology is accurate in detecting changes in lung fluid concentration as demonstrated by the high ICC and Pearson correlation coefficients of 0.95. The fast response of ReDS demonstrated by reverse trends caused by induced events defined by the protocol within short intervals of seconds reflects the high sensitivity of the method in detecting small changes in pulmonary congestion.

In the clinical HF study, ReDS assessment of lung fluid concentrations in ADHF patients demonstrated a strong correlation between ReDS measurements and fluid balance status during diuresis. Of note, ReDS measurements corresponded to the clinical course of improvement throughout hospitalization as readings prior to discharge (solely a clinical decision) were improved significantly compared with ReDS reading at admission. Finally, assessments in normal patients studied over several days demonstrated no changes in lung fluid, as expected, serving as a negative control to volume loading and diuresis in the animals and diuresis in the ADHF patients.

Taken together, these findings support the potential clinical utility of ReDS monitoring in the management of HF patients. Detecting pulmonary congestion before significant clinical (symptomatic) worsening of HF could possibly lead to a decrease in hospitalization rates. If hospitalized, the use of ReDS technology could possibly guide therapy (eg, the rate and extent of diuresis and the use of other medications such as vasodilators) and assist in avoiding the premature discharge of patients who remain substantially "wet"[9] or allowing the discharge of such patients with ongoing outpatient diuresis monitored remotely using the ReDS technology. Finally, in the case of chronic HF, ReDS technology may allow optimization of pharmacologic therapy, such as diuretics, vasodilators, and neurohormonal antagonists, to prevent hospitalizations. Of course, further study will be required to support these potential uses of ReDS technology.

LIMITATIONS AND FUTURE DIRECTIONS

The goals of this report are to describe ReDS technology and present our current experience in animals and in humans that support further studies evaluating the diagnostic accuracy and clinical utility of the ReDS system. In this regard, the preclinical accuracy study is limited by the relatively small cohort of animals and the clinical study was strictly observational, so that the usefulness of ReDS measurements in guiding therapy and improving outcomes could not be determined.

CONCLUSIONS

In the current paper we present for the first time a novel, noninvasive electromagnetic monitoring system for quantification of pulmonary congestion. The findings in the animal model as well as our clinical experience with ADHF patients and healthy patients suggest that this technology can detect small changes in lung water or pulmonary congestion. This may assist in both monitoring and managing HF patients and may offer the treating teams several important advantages over current existing modalities.

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