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Clinical Trials

Non-Invasive Lung IMPEDANCE-Guided Preemptive Treatment in Chronic Heart Failure Patients: A Randomized Controlled Trial (IMPEDANCE-HF Trial)

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ABSTRACT

Background: Previous investigations have suggested that lung impedance (LI)-guided treatment reduces hospitalizations for acute heart failure (AHF). A single-blind 2-center trial was performed to evaluate this hypothesis (ClinicalTrials.gov-NCT01315223).

Methods: The study population included 256 patients from 2 medical centers with chronic heart failure and left ventricular ejection fraction ≤35% in New York Heart Association class II-IV, who were admitted for AHF within 12 months before recruitment. Patients were randomized to a control group treated by clinical assessment and a monitored group whose therapy was also assisted by LI, and followed for at least 12 months. Noninvasive LI measurements were performed with a new high-sensitivity device. Patients, blinded to their assignment group, were scheduled for monthly visits in the outpatient clinics. The primary efficacy endpoint was AHF hospitalizations; the secondary endpoints were all-cause hospitalizations and mortality.

Results: There were 67 vs 158 AHF hospitalizations during the first year ($P < .001$) and 211 vs 386 AHF hospitalizations ($P < .001$) during the entire follow-up among the monitored patients (48 ± 32 months) and control patients (39 ± 26 months, $P = .01$), respectively. During the follow-up, there were 42 and 59 deaths (hazard ratio 0.52, 95% confidence interval 0.35–0.78, $P = .002$) with 13 and 31 of them resulting from heart failure (hazard ratio 0.30, 95% confidence interval 0.15–0.58 $P < .001$) in the monitored and control groups, respectively. The incidence of noncardiovascular death was similar.

Conclusion: Our results seem to validate the concept that LI-guided preemptive treatment of chronic heart failure patients reduces hospitalizations for AHF as well as the incidence of heart failure, cardiovascular, and all-cause mortality. (*J Cardiac Fail 2016;■■:■■–■■*)

Key Words: Acute heart failure, chronic heart failure, monitoring heart failure, lung impedance.

Patients with chronic heart failure (CHF) discharged after hospitalization for acute heart failure (AHF), frequently require rehospitalization because of additional exacerbations of heart failure (HF). Such occurrence should be prevented because pulmonary congestion precipitating severe AHF inflicts additional myocardial damage, leading eventually to further clinical deterioration, more hospitalizations, and increased mortality.[1] In addition, treatment of HF patients and hospitalizations from AHF also represent a major economic burden on the health care system.[2]

Invasive hemodynamic monitoring of pulmonary arterial pressure using a permanently implanted pressure sensor has been recently reported to decrease hospitalizations for AHF.[3] In the present study, monitoring of pulmonary congestion was

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achieved in CHF patients by using a noninvasive (surface) impedance technique, as described previously.[4–8] Existing impedance techniques use transthoracic impedance for assessment of pulmonary congestion.[9–11] In fact, transthoracic impedance consists of the target net lung impedance (LI) plus the high impedance of the chest walls. The net LI, which is the impedance of interest, composes only a small fraction of the overall transthoracic impedance. Therefore, the use of the latter to monitor pulmonary congestion to initiate preemptive treatment was found to be insufficiently sensitive and did not allow reliable monitoring of lung fluid content in the individual patient.[10] In the current study, we used a monitor based on an algorithm that calculates the chest wall impedance that is the preponderant component of the total transthoracic impedance. Subtraction of the chest wall impedance from the latter yields the net LI.[6–8] The current monitor is endowed with several advantages over existing devices. In the present setup, the electromagnetic energy passes through the chest in the sagittal plane and not in the axial direction, which would distribute the signal through the aorta and not the lung, which is the organ of interest. A scheme of 3 electrodes on each side of the chest allowed additional electrical circuits between electrodes, which enables calculation of the chest wall impedance and its subtraction from thoracic impedance. As we have shown, this approach increased by approximately 25-fold the sensitivity of the device to measure changes in lung fluid content.[4–8] As a result, preemptive treatment of evolving pulmonary congestion could be initiated very early, a therapeutic policy shown to be effective in patients with ST elevation myocardial infarction.[6] The present study was undertaken to assess the hypothesis that LI-guided treatment based on noninvasive assessment of pulmonary congestion may also improve long-term outcome in ambulatory outpatient CHF patients.

Methods

Patients

Before initiation of the main study, LI was measured between 15 and 30 times during a 12-month period in 30 healthy volunteers (30 measurements in 27 subjects, 28 measurements in 2 subjects, and 15 measurements in 1 subject) to determine physiological day-to-day variability. We have found that LI may deviate in normal healthy subjects by ±2.1% on a daily basis. Following this, the study was initiated with patients eligible for participation in the IMPEDANCE-HF (Non-invasive Lung IMPEDANCE-guided Preemptive Treatment in Patients with Chronic Heart Failure) trial if they were older than age 18 years, had left ventricular ejection fraction (LVEF) ≤35% with New York Heart Association (NYHA) functional class II-IV HF, and were within 12 months of hospitalization for AHF. Patients had to be optimally treated for HF according to current guidelines.[12] Exclusion criteria included the implantation of a cardiac resynchronization device within the preceding 3 months and severe or advanced chronic kidney disease (estimated glomerular filtration rate <25 mL/min/1.73 m^2). Patients were randomly assigned by 1:1 ratio to management by clinical assessment with noninvasive LI assessment (monitored group) or without (control group), and were followed for at least 12 months. Randomization was applied by a 16-field table with a block size of 4. The institutional review board of the 2 participating medical centers approved the study protocol, and all patients provided written informed consent.

Study Protocol

Patients were scheduled for monthly visits (range 30 ± 5 days) in the hospital outpatient clinic, which included NYHA class assessment; physical examination with blood pressure, heart rate, and oxygen saturation measurement; a 6-minute walk test every 6 months; and chest X-ray (CXR) annually, during each hospital admission and discharge. Patients were requested to assess and report any change in their clinical functional status during the period preceding the clinic visit. A functional scale was ascribed to the change of status as follows: slightly improved (+1), significantly improved (+2), no change at all (0), slightly deteriorated (−1), or significantly deteriorated (−2) in comparison with their capacity during the previous period. Adverse events were also recorded. Medication doses used were calculated as average for each patient for the whole duration of the study and presented as percent of the maximal guideline-recommended dosage. The number of changes of medical regimen in each group was recorded as well.

Lung Impedance Measurements and Presentation

LI was measured at each outpatient clinic visit. A technique to accurately and reproducibly place electrodes as well as a method to determine baseline LI (BLI) in CHF patients with existing pulmonary congestion have been previously presented.[8] This was applied for calculation of BLI based on LI results of the first 3 clinic visits. LI and BLI were used to calculate the lung impedance ratio (ΔLIR) = [(current LI/BLI) − 1] × 100% with negative ΔLIR values representing the degree of LI decrease from BLI (ie, reflecting the extent of pulmonary congestion).

Algorithm of Medical Intervention

Therapy in the monitored group was based on ΔLIR measurement with the following protocol: a ΔLIR decrease between 0 and −18% did not require any change in therapy. This was based on a previous report that no AHF hospitalization occurred if measured ΔLIR decrease was less than −24%,[8] and the premise that intervention at ΔLIR = −18% might preclude further deterioration.

Titration of therapy could be implemented according to physician's discretion to adjust heart rate, blood pressure, and creatinine level or because of side effects. A ΔLIR decrease of more than 18% was an indication to intensify treatment and take other measures as deemed appropriate by treating physician. Modification of the treatment in the control group depended on the physician and was based on clinical assessment only. Each time treatment was altered, in both study

groups, as a result of clinical deterioration, the patients were scheduled for a follow-up visit 1 week later. In case of emergent hospitalization, LI recording was performed during the first 16 hours of admission, at some time during hospitalization, and at discharge. The cause of hospitalization and of death was classified by the investigator as cardiovascular (CV) or non-CV, with the former also determined whether it was due to HF.

Patients were blinded to their group assignment and LI measured by technicians at each visit in both groups was available only to the physicians to be applied in the monitored group. The study was carried out in 2 university hospitals with no external funding. Devices used in the study were manufactured and supplied by RSMM Ltd (Tel Aviv). The present trial was registered with ClinicalTrials.gov (NCT01315223).

Statistical Analysis

Study Sample Size. During the first 18 months of the study, 60 patients who were routinely treated in the hospital HF outpatient clinics were randomized to the monitored group (n = 30) and to the control (n = 30) and followed for a mean duration of 1 year. The incidence of hospitalizations for AHF was 0.8 ± 1 and 1.5 ± 1.7 admissions/patient/y in the monitored and the control groups, respectively. During the same period, 4 patients (13%) died in the monitored group and 8 patients (27%) died in the control group. Sample size calculation based on comparison of the means of admission rate between groups yielded a sample size of 118 patients for each arm to achieve a statistically significant difference between groups with a 90% power and 5% level of significance. Similarly, calculations with regard to mortality yielded a sample size of 136 patients for each arm (272 for the study) to achieve a statistically significant difference between groups with an 80% power and 5% level of significance. Potential dropout was estimated as 10%; therefore, the study population size needed to achieve the primary (hospitalizations for AHF) and secondary (all-cause hospitalizations and death) endpoints of the study was 260 and 300 patients, respectively.

Statistical Methods. Analyses were conducted according to intention-to-treat. Baseline continuous independent characteristics were expressed as mean and standard deviation if distribution were normal according to the Kolmogorov-Smirnov test or median and interquartile range if not a normal distribution. Comparisons between normally distributed continuous independent variables of 2 groups were done by the 2-sample *t* test, and between abnormally distributed independent continuous variables by the Mann-Whitney test. Linear mixed effects regression model was used for calculation of continuous data of ΔLIR when patients were measured at different time points. To compare two independent samples of ordinal values between groups the chi-square test was used. Correlations of ordinal variables were done by Spearman rho test. We used the Cox proportional hazard regression model to compare differences in hospitalizations between groups. Time for each hospitalization was calculated as time from the beginning of follow-up until hospitalization. The Kaplan-Meier survival model was used to evaluate differences in death of different causes between groups during the monitoring period. Difference in number of drug adjustments between groups was evaluated by the Wilcoxon rank-sum test. A value of $P < .05$ was considered significant. The SPSS 21.0 statistical package (SPSS Inc., Chicago, IL) was used.

Results

Between January 1, 2005, and June 31, 2014, we screened 312 patients, of whom 256 were randomly assigned to study groups (n = 128 each, Fig. 1). All patients remained in their assigned group until the last patient completed 12 months of follow-up. The demographic, clinical, and laboratory data are presented in Table 1. The mean follow-up was 48 ± 32 months (5221 visits, 511 patient-years follow-up, 10.6 visits/patient-year) in the monitored group, and 39 ± 26 months (4351 visits, 411 patient-years follow up, 10.6 visits/patient-year) in the control group ($P = .01$). The groups were similar with respect to baseline characteristics (Table 1).

Hospitalizations

Rate of hospitalizations and survival analyses are presented in Table 2 and Fig. 2. During the follow-up period, there were overall 528 and 691 hospitalizations in the monitored and control groups, respectively (rate [per patient-year follow-up] 1.03 vs 1.68, hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.59–0.74, $P < .001$). Of these, 274 and 464 hospitalizations were due to CV reasons (rate 0.54 vs 1.13, HR 0.62, 95% CI 0.53–0.72, $P < .001$). It is important to note that the vast majority of hospitalizations, especially those from exacerbation of HF, were patient self-referrals to the emergency department or by the family physician, and only rarely were prompted by the study physician in the clinic. These patients, known to be HF patients, are usually admitted to the medical wards even if their symptoms improve following initial therapy because this is common clinical practice of the emergency department attending physicians.

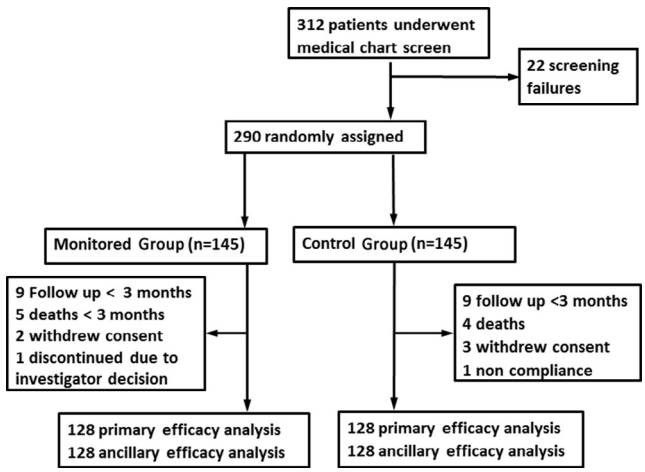

Fig. 1. Trial profile.

Table 1. Baseline Patient Characteristics

Parameter	Monitored Group	Control Group	*P* Value
Age	67.5 ± 11.7	67.7 ± 10.4	.88
% of males	82%	87%	.20
Ejection fraction, median (IQR)	30 (25–30)	30 (25–30)	.716
NYHA II, III, IV	48%, 29%, 23%	47%, 30%, 23%	.92
Ischemic cause	66%	75%	.12
Coronary artery bypass graft	17%	26%	.12
Atrial fibrillation/flutter	27%	25%	.66
Diabetes mellitus	52%	53%	.80
Hypertension	75%	74%	.88
Hyperlipidemia	75%	73%	.77
Chronic renal failure	34%	33%	.89
Smokers	41%	39%	.69
ICD/CRT-D	28 (22%); 17 (13%)	27 (21%); 18 (14%)	.88/.86
Baseline medications (at randomization)			
ACE-I or ARB	96%	96%	.97
Beta-blockers	92%	90%	.66
Mineralocorticoid receptor antagonist	65%	58%	.29
Nitrates	48%	46%	.80
Statin	86%	83%	.59
Aspirin	78%	76%	.76
Digoxin	39%	33%	.35
Coumadin	20%	19%	.91
Plavix	29%	23%	.38
Diuretics	96%	95%	.63
Furosemide equivalent dose (mg/day)	99	95	.60
Physical examination			
BMI, kg/m^2	29.6 ± 4.5	28.7 ± 5.2	.15
Systolic blood pressure (mm Hg)	129.1 ± 21.1	127.4 ± 21.2	.52
Heart rate, beats/min; median (IQR)	70 (65–81)	70 (62–79)	.518
Jugular vein pressure (cm water, Lewis method)	7.4 ± 3.1	7.1 ± 2.8	.31
Peripheral edema grade (grade 0–4) (mean)	0.7	0.8	.29
Laboratory results			
Creatinine (mg/dL)	1.33 ± 0.64	1.32 ± 0.54	.93
Estimate of GFR, mL/min/1.73 m^2	60.5 ± 22.7	57.4 ± 22.2	.28
Glucose (mg/dl), median (IQR)	126 (102–159)	112.5 (96–160)	.15
HBA1c, (%), median (IQR)	6 (6–8)	7 (6–8)	.29
Urea, median (IQR)	38 (26–57)	46.5 (29.7–67.2)	.23
Sodium (mg/L), median (IQR)	139.5 (138–142)	139 (137–141)	.18
Potassium (mg/L), median (IQR)	4 (4–5)	4 (4–5)	.49
NT-proBNP (pg/mL)	2592 ± 3317	2984 ± 3583	.36
ΔLIR (% from baseline values), median (IQR)	–27.3 (–15.8; –36.8)	–27.1 (–14.2; –35.7)	.89
ICD/CRT-D at end of study	41 (32%); 51 (40%)	40 (31%); 53 (41%)	.89/.8

ΔLIR, lung impedance ratio; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRT-D, complete resynchronization therapy-defibrillator; GFR, glomerular filtration rate; HbA1c, glycosylated hemoglobulin; ICD, implantable cardioverter defibrillator; IQR, interquartile range; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New Year Heart Association.

In the first year of the study, 67 patients in the monitored group and 158 patients in the control group were hospitalized for AHF (rate 0.52 vs 1.23, HR 0.51, 95% CI 0.38–0.68, $P < .001$). During the entire study period, there were 211 and 386 hospitalizations for AHF (rate 0.41 vs 0.94, HR 0.63, 95% CI 0.53–0.75, $P < .001$) in the study groups. Figure 2 shows the hospitalizations for all causes during the entire follow-up period. There was no difference between groups with respect to non-CV hospitalizations ($P = .82$, Table 2). To check whether the effect of LI monitoring was NYHA class–dependent, we stratified the annual rate of HF hospitalizations of study groups by NYHA class. There were 61/38/29 patients in the monitored group and 60/39/29 patients the control group classified as NYHA II/III/IV, respectively. HF hospitalization rate for monitored vs control patients was 0.36 vs 0.94 (HR 0.47, 95% CI 0.36–0.66, $P < .001$) for NYHA II, 0.74 vs 1.81 (HR 0.74, 95% CI 0.55–0.98, $P = .04$) for NYHA III ,and 1.17 vs 2.16 (HR 0.52, 95% CI 0.37–0.72, $P < .001$) for NYHA IV, respectively.

Hospitalizations for AHF

ΔLIR values at 1 month before, during admission, and after AHF hospitalization show that ΔLIR begins to decline progressively 3 weeks before hospitalization for AHF in both study groups (Fig. 3). During the 2 weeks before AHF hospitalization, ΔLIR decrease became steeper ($P < .001$), with maximal decline in both groups during the last week before hospitalization. Importantly, we have confirmed our previous finding[8] because there were no AHF hospitalizations if ΔLIR decreased by less than 24% from BLI. Therapy during hospitalizations alleviated congestion substantially in both study groups as ΔLIR increased by 21% in the monitored group (from –43.8 ± 9.6% on admission to –34.7 ± 13.2% at

Table 2. Effect of Lung Impedance–Guided Treatment on Efficacy Endpoints

	Monitored Group (n = 128); 511 Y of Follow-up	Control Group (n = 128); 411 Y of Follow-up	HR (95% CI)	*P* Value	NNT
Primary efficacy endpoints					
AHF hospitalizations up to 12 mo	67* (0.52)†	158* (1.23)†	0.51 0.38–0.68	<.0001	1.4
AHF hospitalizations during entire follow-up	211* (0.41)†	386* (0.94)†	0.63 0.53–0.75	<.0001	1.9
Secondary efficacy endpoints					
All hospitalizations during entire follow-up (number, events per patient per year)	528* (1.03)†	691* (1.68)†	0.66 0.59–0.74	<.0001	1.6
Cardiac hospitalization during entire follow-up	274* (0.54)†	464* (1.13)†	0.62 0.53–0.72	<.0001	1.8
Noncardiac hospitalization during entire follow-up	254* (0.50)†	227* (0.55)†	0.96 0.80–1.15	.63	
All-cause mortality during entire follow-up	42* (0.08)†	59* (0.14)†	0.52 0.35–0.78	.002	7.5
Cardiac mortality during entire follow-up	26* (0.05)†	47* (0.11)†	0.41 0.25–0.67	<.0001	6.1
HF mortality during entire follow-up	13* (0.03)†	31* (0.08)†	0.35 0.15–0.58	=.0001	7.1
Non-cardiac mortality during entire follow-up	16* (0.03)†	12* (0.03)†	0.96 0.45–2.04	.92	

*Number of events.
†Events per patient per year.
AHF, acute HF; CI, confidence interval; HF, heart failure; HR, hazard ratio; NNT, number needed to treat.

discharge, $P < .001$), and by 20% in the control group (from −41.2 ± 9.5% at admission to −33.1 ± 12.1% at discharge, $P < .001$, Fig. 3). It is important to note that in 11.4% of monitored patients, ΔLIR upon discharge was in the range of 0 to −18%; in 10.4%, it was between −18.1 to −24%; and in 78.2% of the monitored group, it was between −24.1 and −50%. In the control group, on the other hand, ΔLIR measured at discharge was in the range of 0 to −18% in 8.1% of patients, between −18.1 to −24% in 13.9% of patients, and between −24.1 and −50% in 78% of the patients (P = NS).

During HF hospitalization, LI response to treatment was similar regardless of study group and length of hospital stay was comparable, 4.7 ± 5.9 and 4.7 ± 4.3 days in the monitored and control groups, respectively (P = NS). Within 2 weeks after discharge, an additional increase in ΔLIR ($P < .005$, Fig. 3) was documented, which reflected further amelioration in pulmonary congestion in both groups. Hospitalizations for non-AHF causes occurred in either group with patients significantly less congested than when admitted for AHF ($P < .001$). No difference was observed between patients of both groups in the degree of pulmonary congestion during non-AHF hospitalizations (P = NS).

Survival

All-cause mortality during the follow-up period included 42 patients (33%) in the monitored group and 59 patients (46%) in the control group (rate 0.08 vs 0.14 per patient-year follow-up, HR 0.52, 95% CI 0.35–0.78, $P = .002$, Table 2). CV death occurred in 26 (20%) and 47 patients (37%) (rate 0.05 vs 0.11, HR 0.41, 95% CI 0.25–0.67, $P < .001$) in the monitored and control group, respectively. During the entire study period, there were 13 deaths (10%) from HF in the monitored and 31 HF deaths (24%) in the control groups (rate 0.03 vs 0.08, HR 0.35, 95% CI 0.15–0.58, $P = .001$, Fig. 2D–F). There was no significant difference in the incidence of non-CV deaths (Table 2).

ΔLIR Dynamics During Follow-Up

Patients of both groups were equally congested upon entry to the study (P = NS, Fig. 4). During the first year of follow-up, the level of congestion significantly improved in both groups ($P < .001$), but the improvement was more pronounced in the monitored compared with the control group ($P < .001$, Fig. 4). Within the 8-year follow-up period, the levels of pulmonary congestion, as represented by average per-year values of ΔLIR, were lower in the monitored group in comparison with these values in the control group ($P < .001$, Fig. 4).

NYHA, ΔLIR, and the Radiological Score

NYHA was assessed and ΔLIR calculated at each visit (5221 visits in the monitored and 4361 in control groups). During follow-up, 999 and 1122 CXRs were performed in the monitored and control groups, respectively; of these, 929 and 1048 were of sufficient quality for analysis. Mean NYHA class for the whole follow-up period was 2.0 and 2.4 in the monitored and control groups, respectively ($P < .001$). Average ΔLIR values per year of follow-up are presented in Fig. 4. The mean radiological score for the whole follow-up period (from 0 [normal CXR] to 10 [for full-blown pulmonary edema]) was 3.2 and 3.5 for monitored and control patients, respectively ($P = .002$). Statistically significant correlations at corresponding visits were found between ΔLIR values and CXRs ($r = –0.93$ and $r = –0.93$, $P < .001$), between ΔLIR and NYHA ($r = –0.87$ and $r = –0.63$, $P < .001$), and between CXR

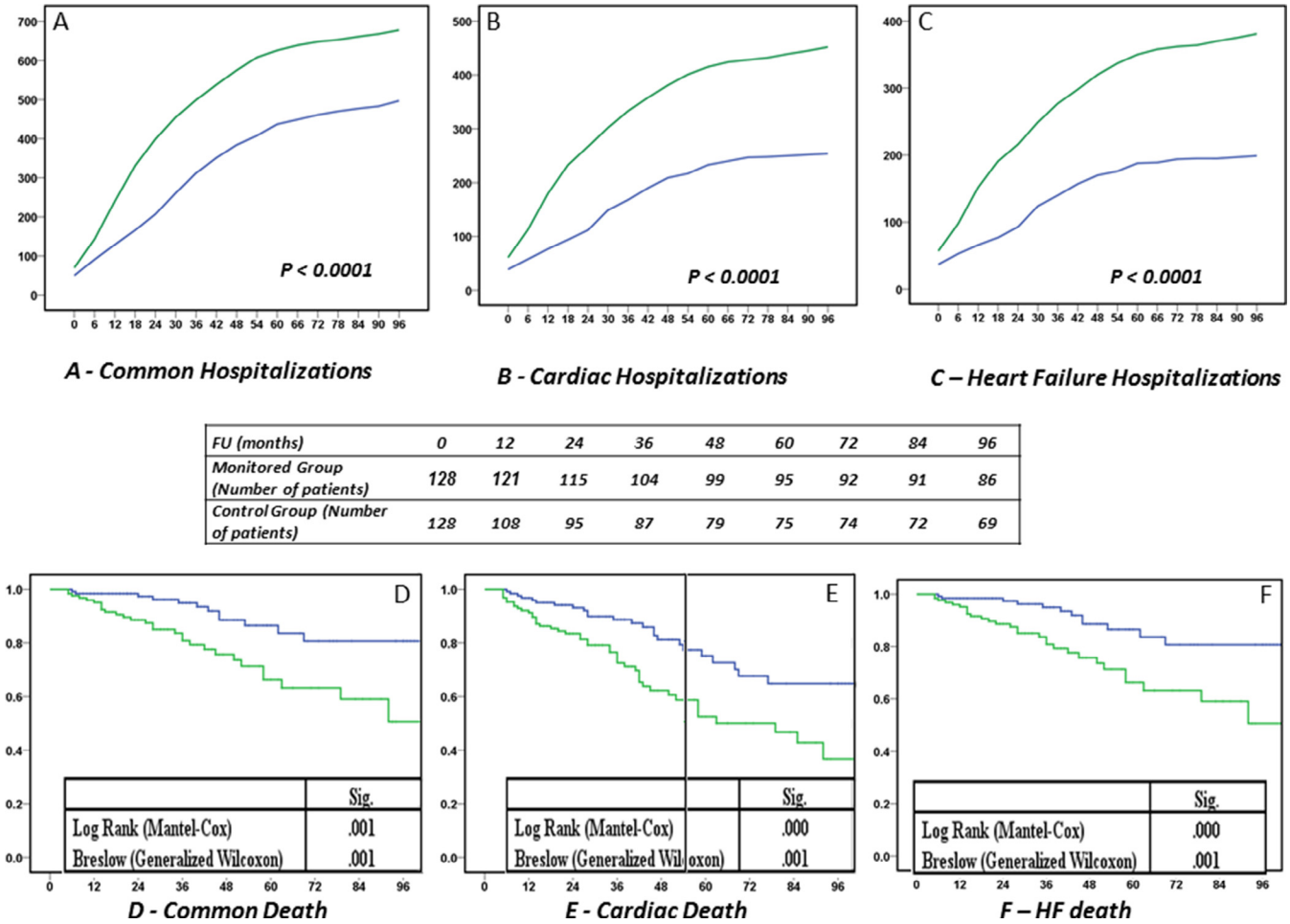

Fig. 2. Cumulative rate of hospitalizations and survival analyses during the follow-up (FU) period. (A–C) Cox proportional hazard regression model to compare differences in hospitalizations between groups was used. (D–F) Kaplan-Meier survival model was used to evaluate differences in death of different causes between groups during the monitoring period.

and NYHA (r = 0.82 and 0.43, $P < .001$) in both the monitored and the control groups, respectively.

Medical Therapy

Details of treatment entry to the study are shown in Table 1. The dosage of medical therapy and an indication of the frequency of dose modification are presented in Table 3. Treatment was changed during follow-up more often in the monitored group than in the control group ($P < .001$). Of note is that in the monitored group the diuretic dosage was increased in 68% and reduced in 32% of all dose changes, whereas in the control group it was increased in 91% and decreased only in 9% of dose titrations ($P < .01$). Of 490 dose titrations in the monitored group (32%) with down-titration of the diuretic dose, 488 times these were in response to improvement in measured LI, whereas in only 2 cases this was done because of overdiuresis. Of the 46 cases of dose reductions in the control group (9%), the diuretic doses were reduced in 29 cases reduced because of clinical improvement and in 17 because of overdiuresis ($P < .001$).

Change in the Clinical Status

Monitored patients tended to report more improvement on the 5-point scale for assessment of functional status than patients in the control group (0.22 vs 0.07, $P < .001$).

Discussion

The present data demonstrate that the use of a noninvasive high-sensitivity LI monitor to titrate medical treatment in CHF patients with reduced LVEF and NYHA functional class II-IV followed in the outpatient clinic significantly reduced the incidence of AHF hospitalization. Within the first year of follow-up, there was a 57% decrease in AHF hospitalizations in the monitored group in comparison with the control group (number needed to treat [NNT] 1.4). The same effect was maintained during the following years, with a 55% decreased rate of AHF hospitalization/patient-year (NNT 1.9). The benefit of LI-guided treatment was realized in all patients regardless of their functional NYHA class. NNT values for AHF hospitalizations obtained in the present study (NNT

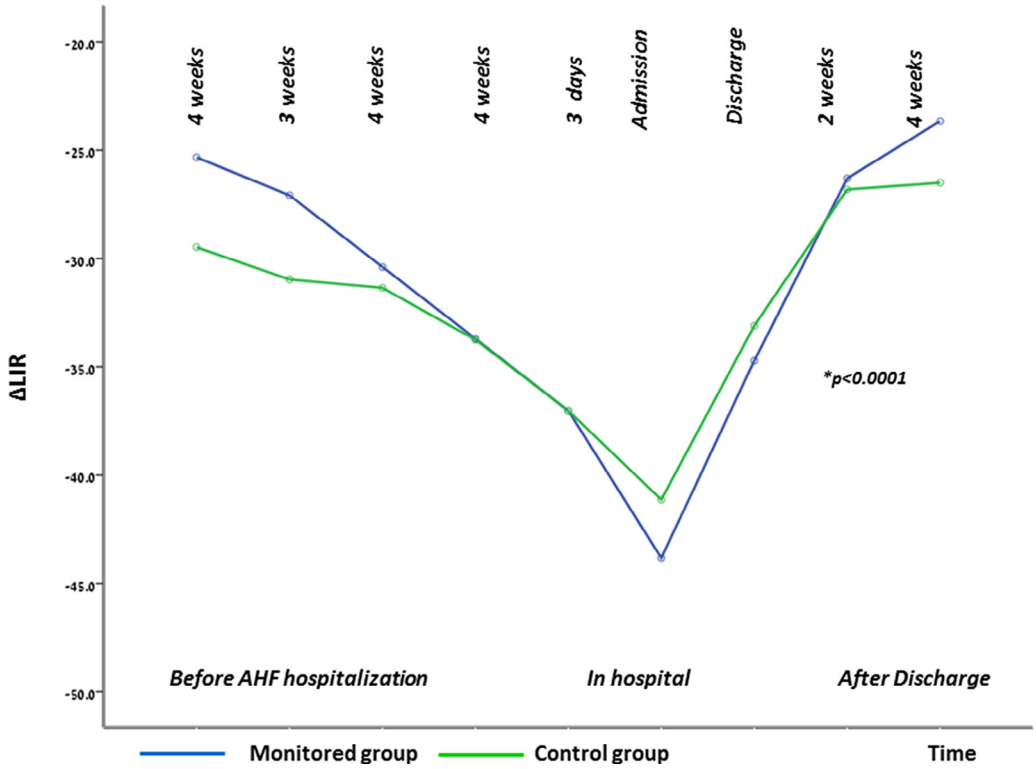

Fig. 3. Dynamics of lung impedance ratio (ΔLIR) before, during, and after hospital admission for acute heart failure (AHF). A linear mixed effects regression model was used to evaluate differences between ΔLIR into and between groups. ΔLIR = [(current lung impedance/baseline lung impedance) - 1]

1.4 and 1.9) were better than NNT = 8 achieved in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Patients (CHAMPION) trial.[3] The CHAMPION study has demonstrated, similar to current findings, a significant improvement in AHF

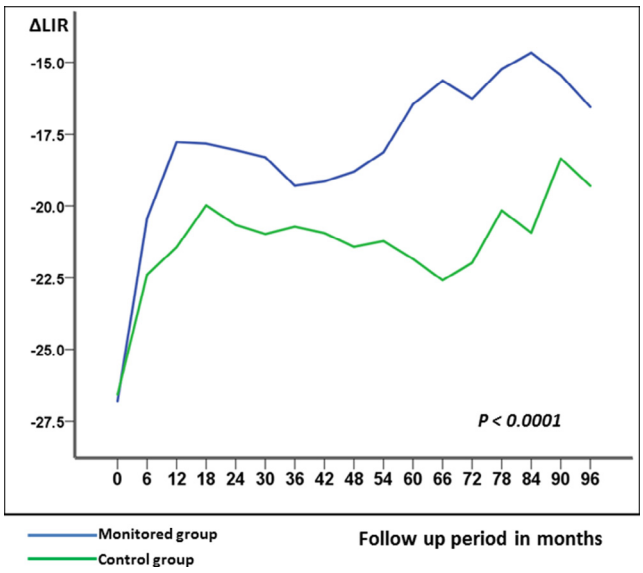

Fig. 4. Difference in pulmonary congestion between groups during follow-up period. A linear mixed effects regression model was used to evaluate differences between ΔLIR into and between groups. ΔLIR, lung impedance ratio. ΔLIR = [(current lung impedance/baseline lung impedance)-1].

hospitalizations and absence effect on the rate of non-CV hospitalizations.

Using LI as a guide for titration of medical therapy has brought about a decrease during the entire study period in all-cause mortality (NNT 7.5), in CV deaths (NNT 6.1) and in mortality because of HF (NNT 7.1). The main improvement in all-cause and CV survival was achieved because mortality due to HF decreased. Important to note that even after excluding HF death, a nonsignificant 36% reduction in CV death was observed. These findings contrast with the CHAMPION trial that has demonstrated only a tendency toward decreased HF mortality in the monitored group.[3] We also found that patients in the LI-guided group were less congested throughout the entire follow-up period as reflected in changes in ΔLIR, NYHA class, and the radiological score. The correlations between ΔLIR and the radiological score in both groups were stronger than the correlation between ΔLIR or the radiological score and the NYHA class. An excellent correlation between ΔLIR and the radiological score was observed suggesting, as shown previously, that these markers are sensitive and equally effective indicators of fluid status.[7] There was also a significant correlation, although weaker, between NYHA, as reported by patient and either ΔLIR or the radiological score demonstrating that NYHA is insufficiently sensitive to guide therapy. This finding underlines that the assessment of patient status with regard to congestion by the device is probably more accurate than the clinical assessment of the NYHA class based mostly on patient self-assessment.

Table 3. Drug Modifications During Entire Follow-up

Medications	Monitored Group	Control Group	*P*	Monitoring /Control Group Ratio of Drug Adjustment
Beta-blockers	0.74*	0.74*	NS	
ACE-I/ARB	0.79*	0.83*	NS	
Rate of changes in medical therapy				
Total	3166 (6.2)†	1244 (3.0)†	<.05	2.1 times
Diuretics	1530 (48%)‡	515 (42%)‡	<.05	
Diuretics	1530 (3.0)†	515 (1.3)†	<.05	2.3 times
Beta-blockers	792 (25%)‡	303 (24%)‡	<.05	
Beta-blockers	792 (1.6)†	303 (0.7)†	<.05	2.3 times
ACE-I/ARB	410 (13%)‡	142 (11%)‡	<.05	
ACE-I/ARB	410 (0.8)†	142 (0.3)†	<.05	2.7 times
Nitrates	166 (5%)‡	78 (6%)‡	<.05	
Nitrates	166 (0.3)†	78 (0.2)†	<.05	1.5 times
MRA	154 (5%)‡	144 (12%)‡	NS	
MRA	154 (0.3)†	144 (0.4)†	NS	0.9 times
Digoxin	114 (4%)‡	62 (5%)‡	<.05	
Digoxin	114 (0.2)†	62 (0.15)†	<.05	1.5 times

*Drug dosage was presented as percentage of maximal guideline-recommended dosage and calculated as average for the entire follow-up period.
†Rate of medicine modifications/patient-year.
‡Absolute number of drug modifications and percent modifications from total.
MRA, mineralocorticoid receptor antagonist; NS, not significant. Other abbreviations as in Tables 1 and 2.

The main reason for AHF hospitalization is lung fluid overload.[13,14] Therefore, the idea to detect lung fluid overload noninvasively at an early stage is attractive. There are 2 main approaches to achieve this goal. The first approach is hemodynamic monitoring. A treatment strategy based on invasive monitoring of pulmonary artery pressure was recently found to be successful in preventing AHF hospitalizations, though it achieved only a nonsignificant reduction in mortality.[3] The first disadvantage of this strategy is that pulmonary artery pressure correlates with the wedge pressure,[15] but is not identical. The effect of transpulmonary pressure gradient on the pulmonary artery pressure cannot be assessed accurately, since it is influenced by many factors, sometimes unrelated to heart disease.[16–18] The second problem is that the technique is invasive and expensive and cannot be applied on a routine basis. The second approach to monitoring of CHF patients is to use invasive or noninvasive impedance techniques. Invasive methods based on pacemaker implantation have been found to be imprecise and barely effective with regard to the goal of decreasing the need for AHF hospitalizations.[19] The main reason for this apparent lack of efficacy is the difficulty to detect small changes in net LI against a background of the high electrode tip to tissue impedance.[20] Other noninvasive impedance techniques for HF monitoring, such as radar technology, are under investigation. In the current study, we have used a device that used a novel algorithm that markedly improved its sensitivity to detect small changes in LI. As a consequence, fluid accumulation in the lung could be sensed at an earlier stage, long before the appearance of clinical signs of HF.[6] The results of the present study confirm our previous findings that ΔLIR decreases continuously as lung fluid content gradually increases. As ΔLIR decreases between 0 and −18%, patients are still comfortable and usually need no additional diuretic therapy, which could result in overdiuresis. A larger decrease in ΔLIR of −18 to −24% justifies increasing diuretic therapy to preclude progression of congestion and hospitalization. Present results show that about 80% of patients hospitalized for HF exacerbation are discharged with residual pulmonary congestion (ΔLIR < −24%). This finding highlights the need to follow these patients carefully after their discharge and also explains why a certain portion of patients are rehospitalized within 30 days of discharge. Early therapy of evolving lung fluid overload at the initial stage is of paramount importance if hospitalization for AHF is to be prevented. Such an early therapeutic intervention also improves survival in the long run. Hence, the present trial was undertaken to prove the hypothesis that early preemptive treatment based on noninvasive LI measurements can reduce AHF hospitalizations (primary endpoint) and improve survival (secondary endpoint). The primary endpoint was achieved within the first year of the trial and this beneficial effect was maintained throughout the entire study period. Secondary endpoints (death) were achieved only after several years of follow-up. The effects of LI monitoring manifesting as less AHF hospitalizations and better survival are the result, we suggest, of better and especially earlier LI-triggered therapy of pulmonary congestion. Throughout the trial, we found significantly lower measures of pulmonary congestion by all parameters used in this study: ΔLIR, NYHA class, and the radiological score in the monitored group compared with the control group. This finding is in line with the lower pulmonary artery pressures measured and clinical improvement observed in monitored patients included in the CHAMPION study.[3]

LI-guided treatment involved more frequent adjustments of medical therapy in the monitored group (by 2.2 times per year of patient follow-up). This result is in keeping with the findings reported in the CHAMPION trial. In both groups, we have noticed a significant increase in pulmonary congestion as early as 2 weeks before AHF hospitalizations with a

very sharp deterioration in the last week before admission, and more during the last 3 days before admission. The deterioration in the monitored group was even sharper and led to more extensive pulmonary congestion at admission compared with the control group. Treatment intensification administered in the ambulatory setup in both study groups during the last 3 days before AHF hospitalization did not prevent admission. This means, in all probability, that at this stage of evolving severe pulmonary congestion only intensive intravenous diuretic therapy may preclude admission. No difference in the length of hospital stay between groups was observed, a finding that diverges with the results of the CHAMPION study. It is important to emphasize that 32% of changes in diuretic treatment represented a decrease of diuretic therapy in the monitored group in comparison with only 9% diuretic dose reductions in the control group ($P < .01$). This suggests that LI-guided treatment may be a reliable tool to control diuretic dosage. The use of the impedance monitor was safe with no side effects reported.

Limitations

Only patients with low LVEF were included in the trial. Therefore, the results cannot be directly extended to CHF patients with preserved left ventricular function. Hence, we recently embarked on a randomized trial with a similar design to that of the IMPEDANCE-HF trial for patients with HF with preserved EF (NCT02661841). An additional limitation was the exclusion of CHF patients with chronic kidney disease with glomerular filtration rate <25 mL/min/1.73 m^2. These patients are difficult to treat even when their pulmonary overload status is known and were therefore excluded. The strength of this trial is the inclusion of low LVEF CHF patients at different NYHA stages and the prolonged follow-up postdischarge after recruitment. This allowed the demonstration of the long-term effect of monitoring and treatment titration. The study was of a single blinded design that potentially could affect decision to hospitalize patients. However, we tried to improve blinding by first clinically assessing patients by physicians and only after this initial evaluation, treatment was determined based on LI when available.

Conclusions

The IMPEDANCE-HF is the first trial demonstrating that LI-guided preemptive therapy of nascent or worsening pulmonary congestion using noninvasive measures, prevents hospitalizations for AHF in CHF patients with reduced LVEF, and reduces all-cause CV and HF mortality in these patients. LI monitoring should be considered in patients with CHF with reduced LV function to improve outcomes.

Disclosures

M.S. is a cofounder and member of the board of directors of the RSMM Company, which manufactured the devices used in the trial and supplied the devices for the study.

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