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CASE STUDY

Early Intervention with Impedance-guided Heart Failure Management Improves Long-term Outcome: Insights from the IMPEDANCE-HF Trial

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ABSTRACT

Background: Lung-impedance (LI) guided treatment of heart failure (HF) patients was shown to improve clinical outcomes.

Objectives: To perform a post-hoc analysis of the IMPEDANCE-HF extended trial in order to explore the mechanism underlying the improved outcome of the LI-guided compared with conventional therapy of HF patients.

Methods: The study included 290 HF patients with LVEF≤ 45% randomized 1:1 to LI-guided or conventional therapy. The normal LI (NLI), representing the dry lung status, was calculated upon enrollment. The level of pulmonary congestion (LPC) was represented by ΔLIR= [(measured LI/NLI)-1] × 100%.

Results: There were 11473 outpatient visits in the LI-guided group and 10245 visits in the control group during follow-up, or 15.5 and 15.9 visits/patient×year, respectively (p=0.74). The LI-guided patients were on average less congested during follow-up than those in the control group (by 20 %, p<0.01). Multivariate regression analysis showed that the likelihood of hospitalization for HF [hazard ratio (HR): 0.62, 95% confidence interval (CI): 0.52-0.72, p<0.01) and of all-cause mortality (HR: 0.83, 95%CI: 0.70-0.98, p=0.03] were lower in the LI-guided group than in the control group. In the LI-guided group, diuretic up-titration was 2-fold more frequent and at an earlier timepoint and at a 21% lower LPC (p<0.01). In both groups the diuretic response was more prominent when up-titration was done at a lower LPC (p<0.01).

Conclusion LI-guided diuretic titration prompted earlier, and more frequent diuretic dose increase when the LPC was only beginning to increase and this resulted in a greater decongestive response with better clinical outcomes.

Key words: heart failure; heart failure readmission; lung impedance; clinical outcome in heart failure patients; diuretic response.

Abbreviations

LVEF	-	Left Ventricular Ejection Fraction
LUS	-	Lung ultrasound
NYHA	-	New York Heart Association
GDMT	-	Guideline Directed Medical Therapy
BMI	-	Body Mass Index

INTRODUCTION

Hemodynamic monitoring, blood N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, lung ultrasound (LUS), and lung impedance (LI) techniques have been proposed as methods to assess the level of pulmonary congestion (LPC) in patients with heart failure (HF)[1-14]. NT-proBNP-guided treatment of HF patients is controversial. The HOME-HF study has demonstrated that the NT-proBNP values were highly variable during follow-up when tested in the same patient with a dispersion of 39.3%, 57.7%, and 73.6% when measured at 1, 60, and 120 day intervals, respectively[6]. However, using the special filter for averaging NT-proBNP values improved the power of the NT-proBNP level to predict deterioration[6]. We have shown that the LPC as assessed by the LI technique during hospitalization due to worsening HF or at discharge is a strong predictor of HF readmission[13, 14]. The data regarding the association between the LPC at drug up-titration, and clinical outcome are scarce. Platz E et al., found that a 6-month LUS-guided treatment decreased the average LPC of HF patients and reduced the rate of HF readmissions[9]. Heart failure patients recruited to the IMPEDANCE-HF extended trial were treated in the outpatient clinic setting based on either conventional clinical assessment or on LI-guidance therapy[12-14]. Analysis of the study results demonstrated that preemptive LI-guided treatment resulted in better clinical outcomes[12-14].

The aim of the present post-hoc analysis of the IMPEDANCE-HF extended trial was to explore the mechanism underlying the better outcome of the LI-guided patient group and to assess whether earlier LI-guided diuretic up- and down-titration lead to better clinical outcome.

METHODS

The IMPEDANCE-HF extended trial was a randomized (1:1) controlled two-center single-blinded trial. Patients were eligible for participation if they were older than 18 years, had a left ventricular ejection fraction (LVEF)≤ 45% at New York Heart Association (NYHA) functional class II-IV and have been hospitalized for HF within the 12 months prior to recruitment (ClinicalTrials.gov NCT01315223). Exclusion criteria included implantation of a cardiac resynchronization device within 3 months of planned recruitment and estimated glomerular filtration rate <30 mL/min per 1.73 m^2. Study patients were followed monthly in the out-patient clinics of the participating hospitals. Lung impedance values were made available to the treating physicians in the LI-guided patient group but not in the control group where therapeutic decisions were based on clinical assessment. All patients provided written informed consent.

Treatment algorithm

Non-invasive impedance device (CardioSet Company, Tel Aviv, Israel) was used for LI measurement. The normal LI (NLI), representing the dry baseline lung status, was calculated for each patient on study entry according to a previously proposed equation (10). The LPC at any time was calculated with its baseline status serving as reference and computing as ΔLIR = [(measured LI/NLI)-1]×100%. When the pulmonary fluid content exceeds the normal level, the electrical resistance of the lung tissue decreases, and LI values decrease to lower levels than NLI yielding a negative value for ΔLIR. The clinical accuracy of the LPC by ΔLIR was validated by comparison with the chest x-ray (CXR), ($r=0.92$, $p<0.01$ between NYHA-related ΔLIR and CXR) (9).

Protocol of LI-guided diuretic up titration for patients with increasing LPC

The NLI model was constructed based on data of 222 HF patients admitted 388 times[11]. The LPC at the visit before HF admission and the probability of HF hospitalization during the following 30-day was assessed. We have found that HF hospitalization occurred on average 15.6±12.2 days following the outpatient clinic visit. Only 2 of 388 HF hospitalizations occurred within 30-day at a ΔLIR level in the range of 0 to -18% on the visit before admission. Such a minimal LPC was defined as LPC 0 and did not require adjustment of the diuretic treatment in the LI-guided group during their outpatient visit. Sixty-two of the 388 HF hospitalizations (16%) occurred within 30-day at a ΔLIR range between -18.1 to -24% representing mild LPC (LPC 1). At this LPC, an increase of the diuretic treatment of LI-guided patients was strongly recommended but the final decision was at the

discretion of the treating physicians. The majority of HF admissions [324 of 388 (84%)] occurred in the presence of moderate LPC defined as ΔLIR= -24.1 to -34% (LPC 2), moderate-to-severe LPC (ΔLIR= -34.1 to -44%, LPC 3), or severe LPC (ΔLIR= -44.1 to -70%, LPC 4) as measured on the clinic visit prior to admission. Under these conditions treating physicians were obligated to increase the decongestive treatment in LI-guided group but increasing the doses of the diuretics and the other heart failure medications were at the discretion of the treating physicians.

Protocol of LI-guided diuretic down-titration for patients with decreasing LPC

A reduction of decongestive treatment was recommended if the LPC improved by one or two levels. Moreover, if the LPC of the patient reached LPC 0 a reduction of decongestive treatment was mandatory. In contrast, drug titration strategy in the control group was exclusively based on the clinical assessment of the patients. Doses of non-furosemide diuretics were accounted for in the present study by conversion to the equivalent dose of furosemide. The average doses of guidelines directed medical therapy (GDMT) prescribed during follow up were calculated and compared with GDMT recommended doses[15].

Criteria for HF hospitalization

The cause of hospitalization was determined as HF-related if all of the following criteria were fulfilled: (1) The primary discharge diagnosis in the medical record was acute or worsening HF;

(2) Clinical signs indicating worsening HF such as increased dyspnea, peripheral edema or jugular venous distension were evident; or weight gain (≥1.5 kg) or a change in NYHA class were reported; and (3) Increased pulmonary congestion was present as assessed by chest radiography or by admission serum NT-proBNP level higher than a previous one.

If the cause for admission or death was unclear, adjudication by chart review of the diagnosis was carried out by two independent cardiologists.

Methodology of averaging of measured parameters

Patient gender, group assignment, age, weight, body mass index (BMI), drugs doses and their modifications and ΔLIR were recorded at each outpatient visit. Serum sodium, potassium, hemoglobin, creatinine, troponin and NT-proBNP were measured during these outpatient visits. All variables were available in 72% of the visits. LVEF, diabetes mellitus, and hypertension were recorded at study entry. Quantitative parameters were averaged per year and over the whole follow-up period. In the case of HF hospitalizations, all parameters were documented at admission and at discharge and used for calculation of average values.

Statistical analysis

Continuous variables are presented as mean ± SD if normally distributed according to the Kolmogorov-Smirnov and visual inspection tests or as median and interquartile range if not. Categorical variables were analyzed by the chi-square (Fisher) tests. Multivariate analysis utilized the Andersen-Gill modification of Cox regression analyses is adopted for recurrent events with entrance criterion in the forward selection model when p=0.05 and p=0.15 for removal was used. For computation of the multivariate regression analysis all variables (x_i*) were standardized using mean (m) and standard deviation (SD) for reaching comparability of effect size of the different parameters as follows $x_i^* = (x_i - m)/sd$. A value of $p < .05$ was considered significant. The SPSS 21.0 statistical package, StatSoft Inc. (version 12) and the MedCalc Statistical Software version 14.8.1 were used for statistical analysis.

RESULTS

The 290 HF patients included in the IMPEDANCE-HF extended trial were followed for 57.2±39 months. Of these, 84 were not hospitalized for HF while 206 patients were admitted 766 times for HF exacerbation (0.78 HF admissions/patient×year). One hundred and fifty-five patients died during the follow up period, of which 85 expired due to HF (55%). The demographic, clinical, and laboratory data of the study population are shown in Table 1.

Table 1: Baseline patient characteristics.

Parameters	LI-guided group n=145	Control group n=145
Age, years	68.3±9.9	68.1±10.6
Male, %	86	85
LVEF, median, IQR, %	29 (IQR:25-35)	30 (25-35)
NYHA Class		
II, %	48	49
III, %	32	33
IV, %	20	18
Ischemic etiology, %	75	74
S/P Coronary Artery Bypass Graft, %	22	21
Atrial fibrillation/flutter, %	26	27
Diabetes mellitus, %	52	52
Hypertension, %	75	76
Hyperlipidemia, %	79	80
Chronic lung disease /Bronchial Asthma, %	5	4
Chronic Renal Failure, %	35	34
Smoking, %	40	39
ICD only, %	29	30
CRT-D, %	40	41
ACE-I or ARB, %	96	97
Beta-blockers, %	92	92
MRA, %	74	73
Nitrates, %	42	43
Statin, %	91	90
Aspirin, %	80	80
Digoxin, %	35	36
Diuretics, %	97	96
Furosemide equivalent dose mg/day	103	101
BMI, kg/m2 on entry to the study	29.2±4.1	29.1±4.9
Systolic blood pressure, mm Hg	127±17	126±16
Jugular Vein Distention, JVD*	0.8±0.7	0.8±0.8
Estimated Glomerular filtration rate, ml/min/1.73m2	60.3±18.9	59.9±17.7

Values are mean ±SD or %; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CRT-D, cardiac resynchronization therapy-defibrillator; ICD, implantable cardioverter defibrillator; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; BMI, body mass index; *JVD: 0- no JVD distention more than 2 centimeters above sternal notch, 4- maximal distention, IQR – intra quartiles range; n- the number of events.

There were 11473 outpatient visits in the LI-guided group and 10245 visits in the control group during follow up (15.5 and 15.9 visit/patient×year, respectively, p=0.74). The average LPC of study groups as assessed by ΔLIR during the whole follow-up period were -18.7±10.6% and -23.4±11.8% in the LI-guided and control groups, respectively (p<0.01). Of 766 HF hospitalizations, 276 (36%) were in the LI-guided and 490 (64%) in the control group (p<0.01). The likelihood of HF hospitalization

was lower in the LI-guided group [Hazard Ratio (HR): 0.62, 95% Confidence Interval (CI): 0.46 to 0.82, p<0.01]. Of 155 all-cause deaths, 62 (40%) occurred in the LI-guided group and 93 (60%) in the control group (p<0.05). The likelihood of all-cause mortality was lower in the LI-guided group (HR: 0.82, 95% CI: 0.72 to 0.94, p<0.01). Eighty-six HF-associated deaths occurred during the study, 25 patients (29%) in the LI-guided and 61 patients (71%) in the control group (p<0.01). The likelihood of HF-associated death was lower in the LI-guided group (HR: 0.69, 95% CI: 0.58 to 0.82, p<0.01). Figure 1 shows the dynamics of LPC in both groups during the follow-up. Within the first 2 years the LPC progressively improved in both groups but more significantly in the LI-guided group (p<0.01). Improvement of LPC continued in the LI-guided patient group after the second year and reached on average the LPC 0 zone. The average LPC in the control group remained at the LPC 1 zone after the improvement during the first 2 years.

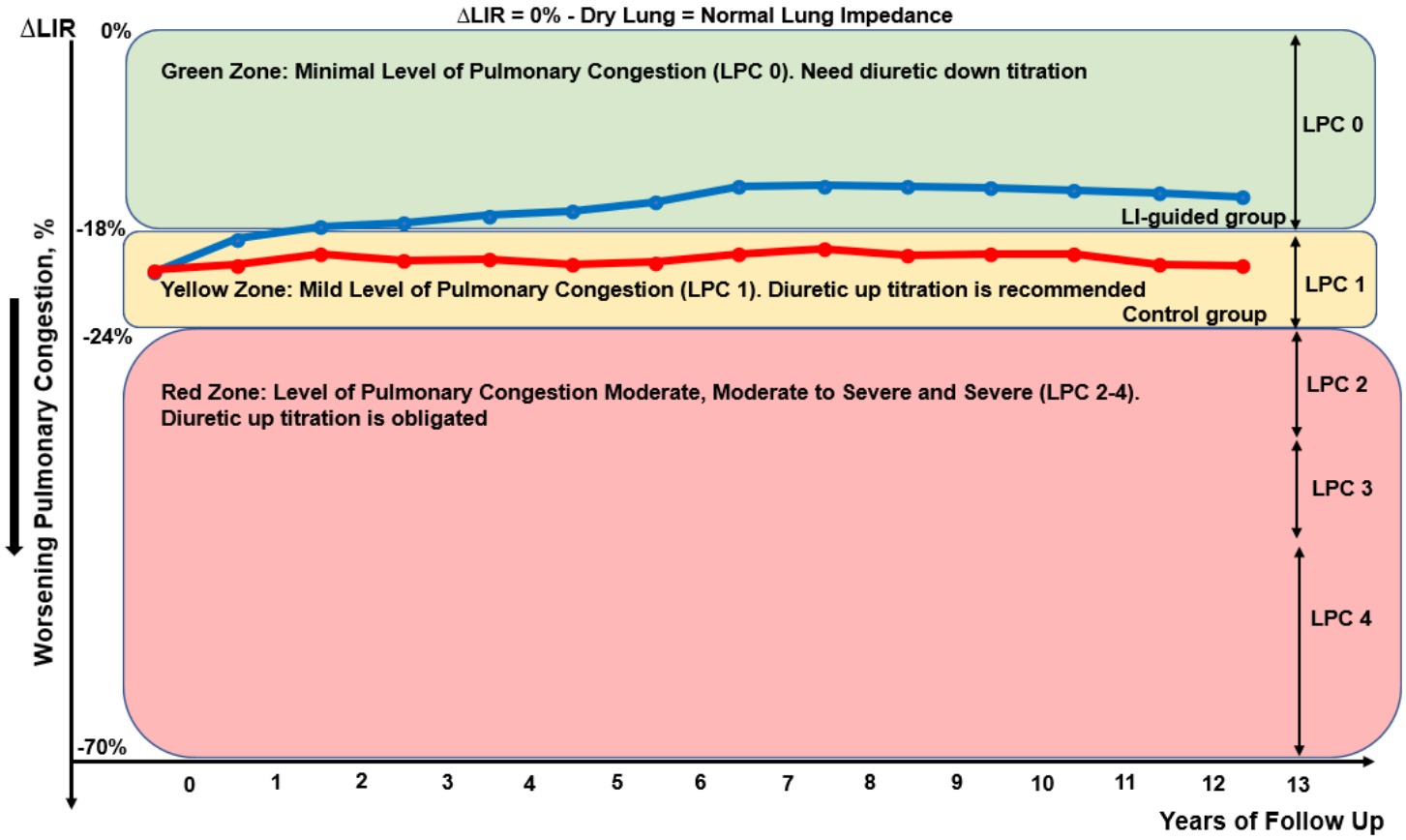

Figure 1: Level of pulmonary congestion during follow up in LI-guided and control groups.
LI, Lung Impedance; LPC, level of pulmonary congestion.

Patients in both groups were divided into five subgroups according to the rate of HF hospitalizations that occurred during follow up. Subgroup 0 included the patients, which were not hospitalized for HF during the follow up. Patients with HF admissions were allocated to subgroups 1-4 according to quartiles (Q1-4) of HF hospitalizations. Figure 2 shows the LPC dynamics of all study patients during follow-up according to the rate of HF hospitalizations subgroup. As expected, patients who required more HF hospitalizations were characterized by higher LPC during follow up and vice versa.

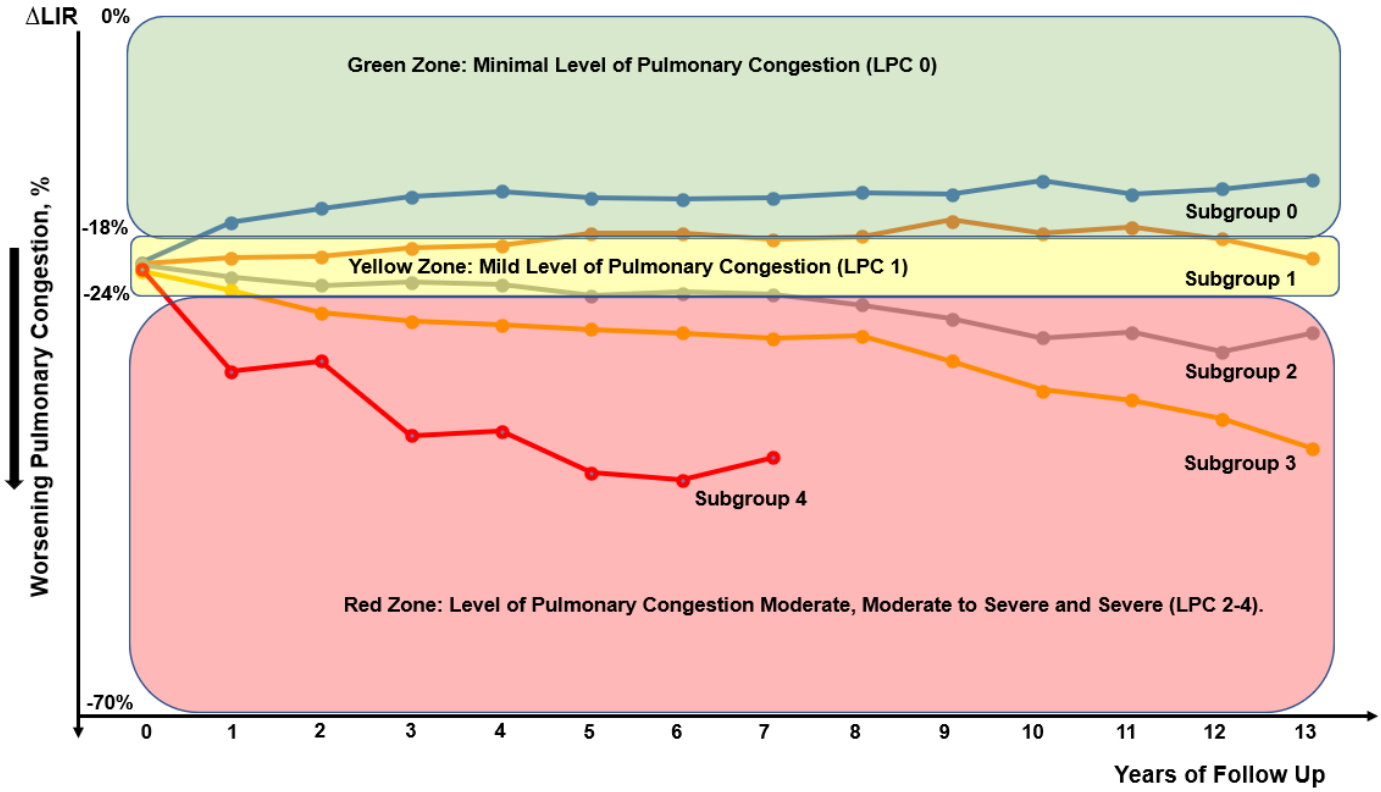

Figure 2: Level of pulmonary congestion during follow up in both groups according to the rate of heart failure hospitalization.
Subgroup 0. No HF hospitalizations during follow up. Average ΔLIR of all years = - 13.9%.
Subgroup 1. Q1: (0.01-0.5)/HF hospitalizations×year. Average ΔLIR of all years = - 18.7%.
Subgroup 2. Q2: (0.51-1.0)/HF hospitalizations×year. Average ΔLIR of all years = - 25.3%.
Subgroup 3. Q3: (1.01-2.33)/HF hospitalizations×year. Average ΔLIR of all years = - 29.4%.
Subgroup 4. Q4: (> 2.33)/HF hospitalizations×year. Average ΔLIR of all years = - 38%.

We evaluated the impact of each measured variable on the clinical outcome. Toward this end, variables were annually averaged, standardized and analyzed by the Anderson-Gill model of regression analysis. The results presented in the supplement (Table 1A-D). We have demonstrated that the annual LPC is the best predictor of HF readmissions according to the size effect and chi-square parameters. According to the univariate analysis, increasing LPC by 1% per year increased the probability of HF admission within this year by 9% (HR: 1.09, 95%CI: 1.07-1.10, p<0.01). Additionally, the LPC as assessed by ΔLIR is the most prominent predictor of all-cause mortality. Increasing LPC by 1% per year increased the probability of all-cause death within this year by 5% (HR: 1.05, 95%CI: 1.04-1.07, p<0.01).

Drug treatment

The dosages of the GDMT, accounted for by their average percent deviation from the maximal recommended dose were similar in both groups upon study entry (Table 2). Prescription rates of GDMT and their percent of maximal recommended dose increased gradually during follow-up in both groups but more in the LI-guided group (p=NS, Table 2). The number of patients treated with >50% of maximal recommended doses of all 3 categories of GDMT increased more in the LI-guided group and at the end of the study was 2.7-fold higher in the LI-guided patients compared with the control patients (p<0.01, Table 2). Medications were adjusted more frequently in the LI-guided group (p<0.01) but the difference was more prominent for diuretic up- and down-titration (p<0.01). Diuretic up titrations were done in the LI-guided group according to protocol and on

average at ΔLIR = -28.6±8.4% (LPC-2). In the control group diuretic up-titrations were done based on clinical assessment and were done on the higher LPC (ΔLIR= -36.2±10.6, LPC 3, p<0.01, Table 2). We have noticed that 94% of all up-titrations in the LI-guided group were done in the absence of patient complaints compared with previous visit. Down-titration, according to the pre-specified protocol, was indicated in the LI-guided group when the LPC improved by a minimum of one level or reached LPC 0. Down-titration in this group was done 892 times at an average ΔLIR = - 19.3±6.6%. In control group down-titration was done 295 times according to clinical assessment on average ΔLIR = -14.4±9.5%, (p<0.01 between groups).

Table 2: Drug treatment. LI, lung impedance; FU, follow up; GDMT, guideline directed medical therapy

Drugs treatment

Parameters	**LI-guided Group**	**Control Group**	**p**
Number of out-hospital visits during FU	11473	10245	=0.34
Number of out-hospital visits/per patient year	15.5	15.9	=0.74
ACE-I /ARB titration			
Rate of ACE-I/ARB at study entry, %	96	97	=0.90
Rate of ACE-I/ARB > 50% GDMT dose at study entry, %	32	34	=0.79
Rate of ACE-I/ARB at the end of 1st year of FU, %	97	99	=0.80
Rate of ACE-I/ARB > 50% GDMT dose at the end of 1st year of FU, %	62	57	=0.68
Rate of ACE-I/ARB > 50% GDMT dose at the end of study, %	76	63	=0.30
B-blockers titration			
Rate of b-blockers at study entry, %	92	92	=1.0
Rate of b-blockers > 50% GDMT dose at study entry, %	47	46	=0.94
Rate of b-blockers at the end of 1st year of FU, %	99	99	=1.0
Rate of b-blockers > 50% GDMT dose at the end of 1st year FU, %	67	59	=0.57
Rate of b-blockers > 50% GDMT dose at the end of study, %	73	61	=0.32
MRA titration			
Rate of MRA at study entry, %	74	73	=0.90
Rate of MRA > 50% GDMT dose at study entry, %	17	18	=0.90
Rate of MRA at the end of 1st year of FU, %	80	79	=0.90
Rate of MRA > 50% GDMT dose at the end of 1st year FU, %	68	64	=0.28
Rate of MRA > 50% GDMT dose at the end of study, %	77	63	=0.26
All 3 groups of GDMT titration			
Rate of 3 groups GDMT at the study entry, %	65	65	=1.0
Rate of 3 groups GDMT > 50% recommended dose at study entry, %	3	3	=1.0
Rate of 3 groups GDMT at the end of 1st year, %	77	77	=0.72
Rate of 3 groups GDMT > 50% recommended dose at the end of 1st year, %	25	15	=0.09
Rate of 3 groups GDMT at study closing, %	85	74	=0.19
Rate of 3 groups GDMT > 50% recommended dose at the end of study, %	48	18	<0.01
Drugs titration and diuretic doses during FU			
Number of ACE-I/ARB adjustment during FU	324	156	<0.01
Number of b-blockers adjustment during FU	385	176	<0.01
Number of MRA adjustment during FU	220	82	<0.01
Number of diuretic up titrations	999	499	<0.01
Level of ΔLIR when diuretics were up titrated, %	-28.6±8.4	-36.2±10.6	<0.01
Number of diuretics down titrations	896	275	<0.01
Level of ΔLIR when diuretics were down titrated, %	-19.3±6.6	-14.4±9.5	<0.01
Average diuretic doses added on up titration visits, mg	24.8±14.3	29.5±16.2	<0.01
Average furosemide dose per patient×day in mg during FU	63±54	118±83	<0.01

ΔLIR, lung impedance ratio. Other abbreviations as in Table 1.

The dose of furosemide added during up-titration in LI-guided group was 25.3±14.3 mg and in the control group it was 29.4±13.7 mg ($p<0.01$).

Diuretic response

Study patients were evaluated in the outpatient clinics monthly according to protocol. Therefore, diuretic response for a 40 mg furosemide up-titration was measured as an LPC improvement within 30-day. Diuretic response was defined as inadequate if the LPC did not improve or the patient was hospitalized for exacerbation of HF within 30-days from the day of up-titration. We have found that the same dose of diuretic on up-titration induced a significantly larger effect if patients were at the LPC 1 and the response decreased progressively if the intervention was done at the higher LPC (LPC 2 to LPC 4, Table 3). This phenomenon was actually observed in both groups, through up-titration was done earlier and at lower LPC in the LI-guided patients and the rate of adequate up-titration was 1.4 times more frequent ($p<0.01$, Table 3). Linear regression analysis yielded a correlation between the diuretic response (DR) to up-titration of 40 mg of furosemide and the ΔLIR-assessed LPC within 30-days, as follows: $DR = 20+0.4\times\Delta LIR$ (Figure 3). This means, that up-titration with 40 mg furosemide on "ideal" LPC 1 induces a 20%, 40% and 60% higher decongestive effect than at the LPC 2, 3 or 4, respectively ($p<0.01$). During the follow up, the average daily dose of diuretics in LI-guided patients was 53% of the dosage used in the control group ($p<0.01$, Table 3).

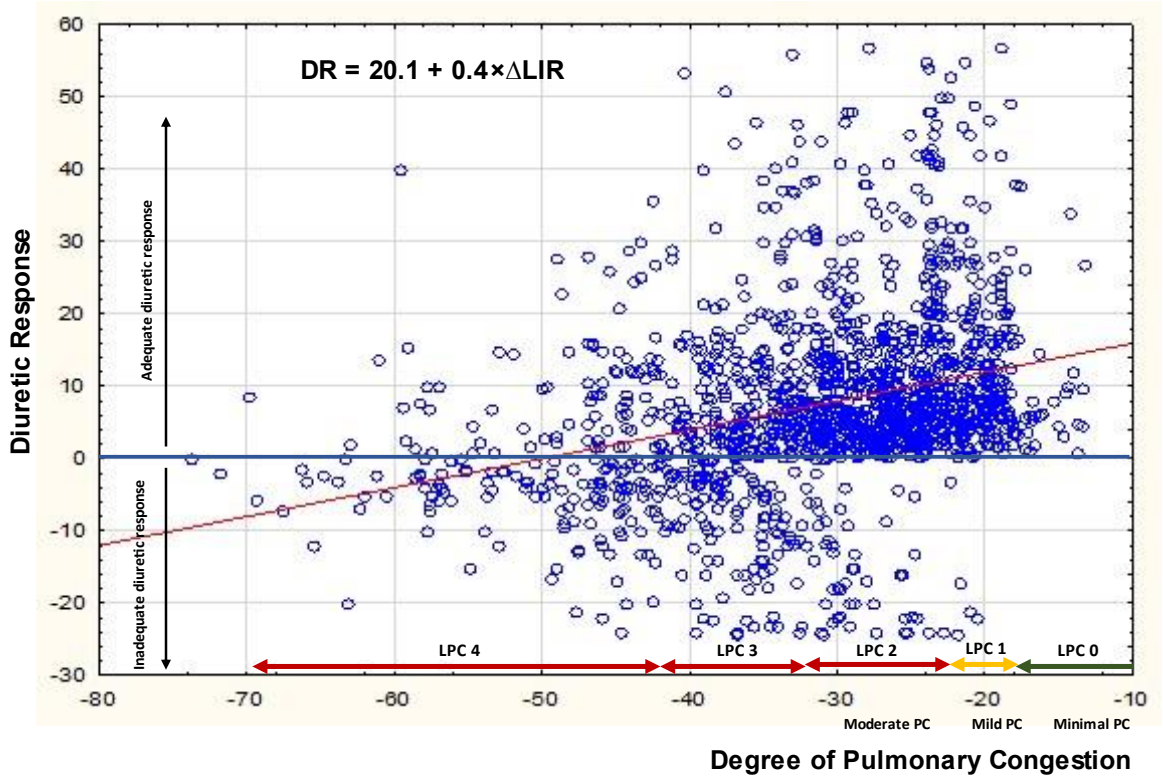

Figure 3: 30-day pulmonary congestion response to furosemide 40 mg up titration. Scattered plot.

Table 3: Diuretic response on different levels of pulmonary congestion. PC, pulmonary congestion.

Diuretic Response			
Parameters	**LI-guided Group**	**Control Group**	**p**
Number of the diuretic up titrations according to the LPC			
Mild PC (LPC 1)	369 (37%)	21 (4%)	<0.01
Moderate PC (LPC 2)	391 (39%)	255 (51%)	<0.01
Moderate-Severe PC (LPC 3)	159 (16%)	142 (29%)	<0.01
Severe PC (LPC 4)	80 (8%)	81 (16%)	<0.01
Number of patients on each level when up titration was done			
Mild PC	117	18	
Moderate PC	113	96	
Moderate-Severe PC	65	64	
Severe PC	35	40	
Average degree of the PC on up titration			
Mild PC	-21.2±2.5	-20.4±8.6	=0.66
Moderate PC	-28.3±4.3	-29.7±3.4	<0.01
Moderate-Severe PC	-38.3±2.7	-38.3±3.3	=0.86
Severe PC	-47.1±3.6	-53.7±7.3	<0.01
30-day PC improvement after diuretic up titration			
Mild PC	13.1±10.5	13.2±17.7	=0.97
Moderate PC	8.4±11.3	6.0±13.3	<0.03
Moderate-Severe PC	3.3±16.2	3.9±15.5	=0.74
Severe PC	-0.5±11.8	-1.0±15.5	<0.01
Patient's current diuretic dose on up titration visit			
Mild PC	66±49	93±37	<0.01
Moderate PC	83±49	108±49	<0.01
Moderate-Severe PC	110±45	133±53	<0.01
Severe PC	137±66	151±52	=0.16
Doses of diuretics added to current treatment on up titration visit			
Mild PC	21±10	24±12	=0.22
Moderate PC	25±13	27±13	=0.06
Moderate-Severe PC	31±17	32±14	=0.36
Severe PC	34±16	38±14	=0.09
Adequate diuretic response			
Rate of the adequate diuretic response	87%	63%	<0.01
PC at heart failure admission			
Level of PC at admission for heart failure	-38.4±7.5%	-42.6±11.7%	<0.01

LPC, level of pulmonary congestion. Other abbreviations as in Table 1,2.
LPC 1: ΔLIR: -18 to -24%; LPC 2: ΔLIR: -24.1 to -34%; LPC 3: ΔLIR: -34.1 to -44%;
LPC 4: ΔLIR: -44.1 to -70%

DISCUSSION

The aim of the current sub-analysis of the IMPEDANCE-HF extended trial was to uncover the mechanisms that underline the clinical improvement observed in the LI-guided group.

The new noninvasive lung impedance-based technique for assessment of patient' LPC was used in the present study. The principal distinction of this technology from previously used noninvasive devices is the algorithm which is capable of differentiating the lung impedance signal from the noise signal of the impedance of the chest walls. Such approach eliminates the noise signal of the chest walls and allows reliable assessment of the small changes in lung fluid content which are so important for preemptive drug up-titration. One of the examples of inability to differentiate lung and chest impedance and, therefore, the inability to record small changes in the LPC during the preclinical stage is the Bio Z impedance cardiography[16]. The gap in the LPC assessed by BioZ device in patients admitted and not admitted for HF within 14 days after evaluation was only 12% while, in our study, the LPC assessed at the same timepoints were -23.2% and -40%, respectively accounting for a difference of 172%.

In this sub-analysis we have shown that (1) the average LPC among the LI-guided patients during follow-up was significantly lower than that in the control group, (2) Up-titration of study drugs, and especially diuretics, was carried out more frequently and at an lower LPC in the LI-guided group, (3) the same dose of diuretic was more effective for pulmonary decongestion if the titration was performed at a lower LPC, (4) down-titration of diuretics was more frequent and done earlier in the LI-guided group, (5) the control patients were treated on average by a 1.9-fold higher daily dose of diuretics during follow-up, (6) treatment according to a guiding variable is an important trigger for to up- as well as to down-titrate drugs in asymptomatic or very mildly symptomatic patients, (7) that LPC assessed by LI is a reliable and accurate parameter for guiding treatment and predicting clinical outcome. Patients included in the IMPEDANCE-HF extended trial were essentially similar to patients of other trials with the same design as evident by the demographic data and the frequency of HF readmissions[3, 17]. It has been repeatedly shown that a large portion of HF patients are discharged from the hospital with a significant level of residual pulmonary congestion[13, 14, 18]. In this sub-analysis, we found that many patients, especially in the control group, persist throughout their daily life with a significant LPC. Higher long-standing LPC in HF patients may lead to additional organ dysfunction and worse outcome[19]. Therefore, reducing the LPC is important for improving clinical outcome. Drug titration according to common practice using clinical assessment or guided by NT-proBNP biomarker is not sufficiently sensitive to improve clinical outcome[20, 21]. We found that in the LI-guided group 94% of diuretic up-titrations were carried out early, before clinical deterioration, at a stage when the clinical status of patients did not seem to mandate diuretic up-titration.

Assessment of LPC by LI is a simple and promising method. We have shown that assessment of LPC by LI was more accurate for clinical prediction of prognosis than by NT-proBNP (12, 13). It seems that the LI-guided treatment leads to better clinical outcome by allowing earlier intervention when a diuretic response is more effective. Additionally, LI assessed by the lung impedance technique is not affected by stress, infection, and renal function and is influenced primarily by the lung fluid content. As the result, the daily variability of LI values in stable patients in this study was less than 3% in comparison with a daily NT-proBNP variability in the range of 30-70% in same patients[6].

The diuretic response at LPC 1 was 1.7, 3.7 and 15 times more pronounced in both groups when compared to a diuretic response at LPC 2, LPC 3 and LPC 4, respectively (Figure 4). Diuretic up-titration in the control group was done only after worsening of the clinical status has occurred. This prompted diuretic up-titration at a higher LPC that resulted in a lesser effect. Such a practice resulted in significantly higher LPC of control group patients during the study and a need of the 14% higher average dose of diuretic increase during up-titration that in the LI-guided group. As the result, they were treated with 1.9 higher doses of furosemide in compare with LI-guided group. We can, therefore, conclude that LI-guided up- and down-titration of the diuretics effectively controls LPC and this, in turn, improves clinical outcome.

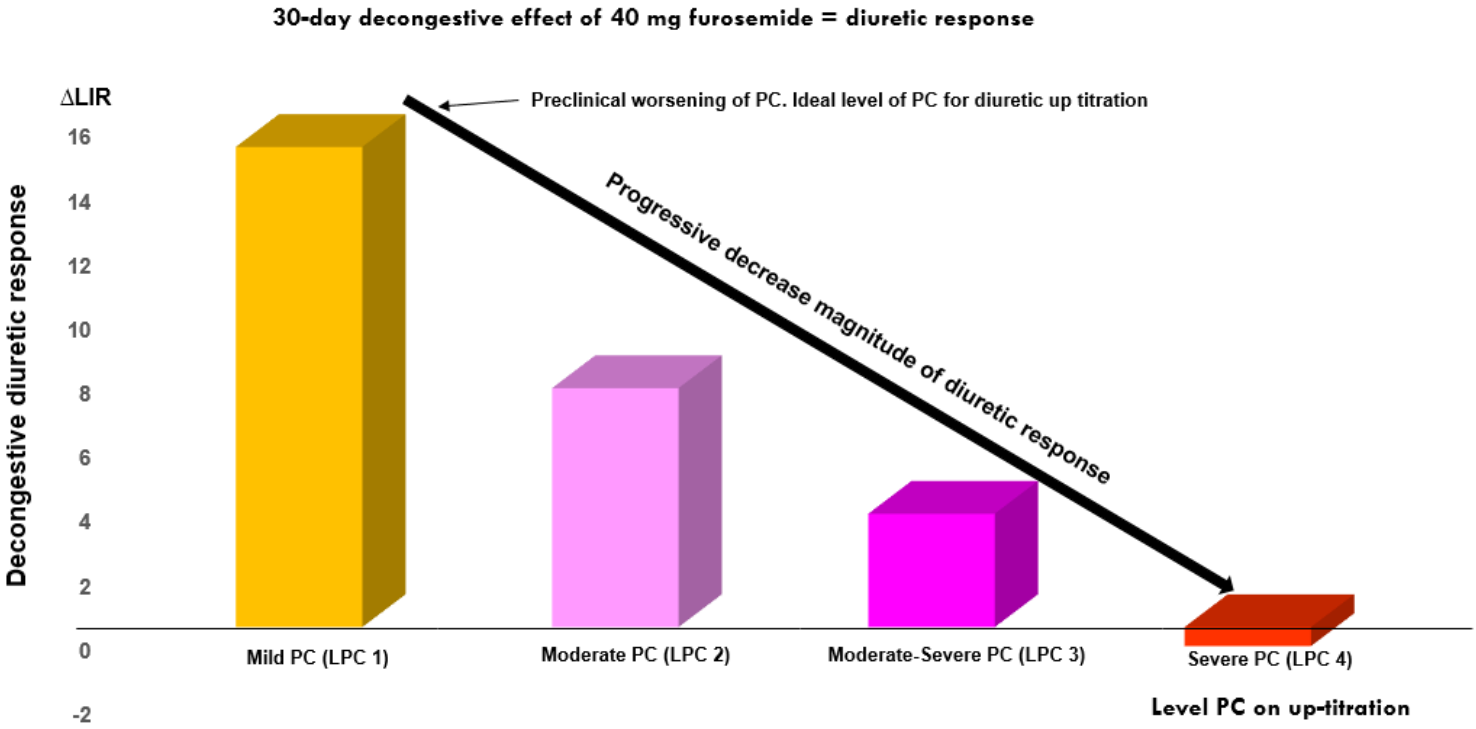

Figure 4: Central illustration. 30-day decongestive effect of 40 mg furosemide. ΔLIR, lung impedance ratio; PC, pulmonary congestion. LPC, level of pulmonary congestion

The doses of the GDMT used for HF patients in our study was disappointingly low especially at the beginning, though better than US general practice as reported in the GUIDE-IT trial[21, 22] and CHAMP-HF registry for HF patients with reduced LVEF[23]. However, the dosage of GDMT increased significantly during the study especially in LI-guided group. LI-guided treatment represented an incentive not only for diuretic titration but also for GDMT increase. The low rates of GDMT administration especially in the control group follows a pattern seen in many other studies[20, 21] and is likely explained by physician and patient related factors. Therefore, LI, may aid in guiding treatment as a trigger for early up- and down titration of therapy to improve clinical outcome.

LIMITATIONS

The present study was a single-blinded, two-center trial designed to assess the impact of LI guidance on the long-term management of patients with clinically significant HF treated in the hospital and followed-up in the outpatient clinic. Therefore, there may have been a potential bias in the decision of readmission in the LI-guided group. Medication changes were made solely based on clinical decisions guided by the protocol. There was no involvement of the study investigator or coordinators in therapeutic decisions.

CONCLUSIONS

Assessment of PC by the LI technique appears to be an effective tool for LI-guided drug titrations. LI-guided diuretic up-titration at the early stage of PC, led to the prevention of HF hospitalizations, all-cause and HF associated death. The main explanation for the efficacy of early up-titration is that patient diuretic response at lower degrees of PC is more pronounced than its effect when reaching the advanced stages of the PC.

PERSPECTIVES

Competency in Medical Knowledge and Patient Care: Important tool for improving heart failure patient's outcome is following to GDMT. In this study we delineated the mechanism by which early preemptive treatment based on monitoring pulmonary congestion by the lung impedance technique improves clinical outcome. The magnitude of the clinical improvement based on pulmonary congestion guiding drug titration may be compare with the impact of once of the classes of GDMT.

TRANSLATIONAL OUTLOOK

This study was prospective, randomized, two-centers, single blinded of 290 heart failure patients with mean follow up of 57 months. Additional research is needed to prove (1) efficacy of lung impedance guided treatment to improve clinical outcome especially in era of the new effective medications for heart failure. Additional study regarding the timing of discharge of patients after heart failure hospitalization as guided by level of pre-discharge pulmonary congestion is needed.

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Statement of Ethics

Study has been performed with the approval of the ethics committees of 2 participated hospitals (Hillel Yaffe Medical Center – 0002-13 HYMC and Soroka Medical Center – 0284-13 SOR, in Israel). Study registration number is: ClinicalTrials.gov NCT01315223. All participants signed informed consent, which is in compliance with the Helsinki Declaration.

Conflict of interest

MKS is member of the board of directors of the CardioSet Startup Company, the manufacturer and supplier of the devices used in the trial. Other Co-authors have no conflict of interests in respect of this study.

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Author contribution

MKS and SM contributed to the conception, study design, analysis, interpretation of data and final approval, while all other authors were involved in the interpretation of data and final approval.

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Supplementary Materials

Supplement Table 1A. Univariate analysis of standardized variables. HF hospitalizations					
Variables	**ES**	**χ^2**	**HR**	**95%CI**	**P**
Lung Impedance guided group/Control group	-0.02	0.6	0.98	0.93-1.03	0.43
Male/Female	-0.39	23.5	0.67	0.57-0.79	<0.01
Age	-0.18	6.2	0.84	0.73-0.96	=0.01
Mean year Body Mass Index	0.14	6.0	1.16	1.03-1.30	<0.02
Body Mass Index at entry to the study	-0.22	3.7	0.80	0.64-1.01	=0.06
Left Ventricular Ejection Fraction at study entry	-0.18	5.5	0.84	0.72-0.97	=0.02
Diabetes Mellitus	-0.01	0.01	0.99	0.86-1.14	=0.91
Hypertension	-0.23	10.4	0.80	0.69-0.92	<0.01
Mean year degree of PC according ΔLIR	-1.07	681	0.34	0.32-0.37	<0.01
Mean year degree of PC according NT-proBNP	0.52	114	1.69	1.53-1.86	<0.01
Mean year blood creatinine	0.11	16.9	1.1	1.06-1.17	<0.01
Mean year blood sodium	-0.01	0.05	0.99	0.94-1.05	=0.83
Mean year blood potassium	-0.01	0.15	0.99	0.92-1.05	=069
Mean year blood hemoglobin	-0.04	3.01	0.96	0.92-1.01	=0.08
Mean year blood troponin	0.07	3.20	1.08	0.99-1.16	=0.07
Supplement Table 1B. Stepwise analysis of standardized variables. HF hospitalizations					
Male/Female	-0.41	28.1	0.66	0.57-0.77	<0.01
Age	-0.20	9.20	0.82	0.72-0.93	<0.01
Hypertension	-0.18	7.31	0.83	0.73-0.95	<0.01
Mean year degree of PC according ΔLIR	-1.08	783	0.34	0.31-0.37	<0.01
Mean year degree of PC according NT-proBNP	0.52	121	1.68	1.53-1.84	<0.01
Mean year blood creatinine	0.11	19.1	1.12	1.06-1.17	<0.01
Supplement Table 1C. Univariate analysis of standardized variables. All-cause death					
LI-guided group/Control group	-0.1	1.3	0.93	0.82-1.05	=0.25
Male/Female	-0.5	6.3	0.60	0.41-0.90	=0.01
Age	0.6	10.7	1.88	1.28-2.75	<0.01
Mean year Body Mass Index	-0.1	0.2	0.94	0.71-1.26	=0.70
BMI at entry to the study	0.1	0.1	1.04	0.58-1.84	=0.90
Left Ventricular Ejection Fraction at study entry	-0.5	6.4	0.62	0.43-0.90	<0.02
Diabetes Mellitus	-0.1	0.5	0.88	0.61-1.25	=0.47

Hypertension	-0.1	0.7	0.87	0.62-1.22	=0.42
Mean year degree of PC according ΔLIR	-0.8	50.3	0.46	0.37-0.57	<0.01
Mean year degree of PC according NT-proBNP	0.2	1.8	1.22	0.91-1.64	=0.18
Mean year blood creatinine	0.2	21.3	1.21	1.12-1.32	<0.01
Mean year blood sodium	-0.1	2.9	0.90	0.80-1.02	=0.09
Mean year blood potassium	-0.1	2.6	1.16	0.97-1.38	=0.10
Mean year blood hemoglobin	-0.1	5.8	0.89	0.82-0.98	<0.02
Mean year blood troponin	0.1	3.2	1.12	0.99-1.28	=0.08
Supplement Table 1D. Stepwise analysis of standardized variables. All-cause death					
Male/Female	-0.4	5.4	0.66	0.46-0.94	=0.02
Age	0.6	10.7	1.79	1.26-2.54	<0.01
Left Ventricular Ejection Fraction at study entry	-0.4	5.3	0.66	0.47-0.94	=0.02
Mean year degree of PC according ΔLIR	-0.8	109	0.44	0.38-0.51	<0.01
Mean year blood creatinine	0.2	37.2	1.24	1.16-1.34	<0.01
Mean year blood hemoglobin	-0.1	8.9	0.88	0.80-0.96	<0.01

Supplement Table 1A-D: Univariate and stepwise analyses of the impact of standardized mean year variables on HF hospitalization and All-cause death within the same year.
HF, heart failure; PC, pulmonary congestion; ΔLIR, lung impedance ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide.