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ORIGINAL RESEARCH

Derivation of baseline lung impedance in chronic heart failure patients: use for monitoring pulmonary congestion and predicting admissions for decompensation

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Abstract The instantaneous lung impedance (ILI) is one of the methods to assess pulmonary congestion or edema (PCE) in chronic heart failure (CHF) patients. Due to usually existing PCE in CHF patients when evaluated, baseline lung impedance (BLI) is unknown. Therefore, the relation of ILI to BLI is unknown. Our aim was to evaluate methods to calculate and appraise BLI or its derivative as reflecting the clinical status of CHF patients. ILI and New York Heart Association (NYHA) class were assessed in 222 patients (67 ± 11 years, LVEF <35 %) during 32 months of frequent outpatient clinic visits. ILI, measured in 120 asymptomatic patients at NYHA class I, with no congestion on the chest X-ray and a low-normal 6-min walk, was defined as BLI. Using measured BLI and ILI values in these patients, formulas for BLI calculation were derived based on logistic regression analysis or on the disparity between BLI and ILI values at different NYHA stages. Both models were equally reliable with <3 % difference between measured and calculated BLI (p = NS). $\Delta LIR = (ILI/BLI - 1) \times 100$ % reflected the degree of PCE, or deviation from baseline, correlated with NYHA class ($r = -0.9$, $p < 0.001$) and could serve for monitoring. Of study patients, 123 were re-hospitalized for PCE during follow up. Their ΔLIR decreased gradually from -21.7 ± 8.2 % 4 weeks pre-admission to -37.8 ± 9.3 % on admission ($p < 0.001$). Patients improved during hospital stay (NYHA 3.7 ± 0.5 to 2.9 ± 0.8, $p < 0.0001$) with ΔLIR increasing to -29.1 ± 12.0 % ($p < 0.001$). ΔLIR based on calculated BLI correlated with the clinical status of CHF patients and allowed the prediction of hospitalizations for PCE.

Keywords Lung impedance · Pulmonary congestion · Pulmonary edema · Congestive heart failure

1 Introduction

Decreasing readmissions due to pulmonary congestion or edema (PCE) secondary to decompensated chronic heart failure (CHF) is an unmet challenge. Monitoring of PCE by the instantaneous lung impedance (ILI) technique is a promising approach to address this need. The impedance method is based on the pathophysiological principle that the high-impedance of the normal air-filled lung tissue decreases as PCE develops [1, 2]. This method may potentially enable assessment of changes in the degree of PCE which may permit prediction of admissions for PCE. The conventional method of lung impedance is limited by two main drawbacks that precluded widespread use of the impedance technique. First, the ILI measured in absolute values (Ω) depends on the individual anthropometric characteristics, as well as on the location and type of electrodes and device used [3–5]. Second, there is no method to calculate normal or "dry" baseline lung

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impedance (BLI) in CHF patients who usually have already some degree of PCE when presenting with symptoms. The changes in the absolute value of ILI measured at any clinic visit reflect PCE dynamics but do not indicate the extent of deviation from baseline. The solution to both drawbacks is to devise a method to compute BLI in CHF patients. We propose, herein, a model to calculate BLI and PCE degree based on derived BLI in CHF patients and validate the suitability of the method to assess PCE degree for monitoring.

2 Methods

The design of the present study was a prospective open-label single center registry. The study population included patients with left ventricle ejection fraction (LVEF) <35 % admitted for PCE within 12 months of inclusion. Patients visited the outpatient clinic on a monthly basis, at which time clinical and laboratory parameters, New York Heart Association (NYHA) class and measured ILI were documented. Study design was based on 2 considerations. The first was our intention to follow study patients closely and yet practically in order to identify changes in ILI as correlated with clinical events. The second involved previous findings that transthoracic ILI begins to decrease 2–3 weeks before hospitalizations for PCE [2, 6, 7]. In other words, the kinetics of lung fluid accumulation is characterized by a time constant of 2–3 weeks. Additionally, the NYHA class and the ILI were recorded at least twice during every hospitalization and at discharge. Patient NYHA class was recorded as per the American Heart Association recommendations [8]. The 6-min walk test (6 MWT) and a chest X-ray (CXR) were performed routinely once every 6 months. Results of the 6 MWT were used to modify or update the NYHA class as described by Rostagno et al. [9]. Patients with severe pulmonary disease were excluded from the study.

2.1 Measurement of ILI

These measurements were accomplished by the noninvasive impedance monitor (RSMM Company, Tel Aviv, Israel) which is 25-fold more sensitive for detection of changes in pulmonary congestion than existing devices [10, 11]. Inter-measurement variability of $\leq 1\ \Omega$ for ILI values was acceptable. Six standard ECG monitor patches were used. Electrodes were placed at the same location at each clinic visit. Three electrodes were placed vertically on the right side of the chest, 4.5 cm from the midline of the sternum with the upper electrode attached precisely under clavicle. An additional set of 3 electrodes was placed along the horizontal line crossing the low edge of the right scapula, with the most leftward electrode placed at the crossing point of the horizontal line with spine. ILI was assessed in the sitting position.

2.2 Definition of BLI

Among CHF patients evaluated periodically at the outpatient clinic, those who achieved NYHA I class were asked also to perform the 6 MWT. When the distance achieved was more than 430 m, considered an acceptable low threshold effort in normal 55–75 year-old healthy adults [12], and if the CXR showed no sign of interstitial lung edema, the patient was considered to be in a "dry" state or with baseline lung fluid content. Corresponding ILI was defined as the BLI. CXRs were interpreted by an independent radiologist according to the radiological score described previously [13]. We have applied the above described criteria with the exception of the cardiothoracic ratio criterion since this ratio is increased in 95 % of patients with CHF (unpublished data).

Model derivation was based on the analysis of the results obtained in 120 CHF patients who achieved BLI at one visit or more. Of these, 60 patients were chosen arbitrarily to form the basis for formulation of the BLI equations (group 1), while the remaining 60 patients (group 2) served as the validation group for the derived models. A second arbitrary grouping into two others groups (60 patients each) was carried out in order to prove that a different partition of patients into 2 other groups, similarly used to derive the formulas and validate the models, yielded the same results.

2.3 Models

We have evaluated 3 models to calculate BLI whose details are presented in Fig. 1. Calculation of BLI of any new patient according to the first model was based on logistic regression analysis of 60 CHF patients who achieved normal lung status (group 1). Calculation of BLI for any new patient according to the second model was based on results of calculated ratio between measured BLI and mean of measured ILI_i at NYHA stage i in group 1 patients ($n = 60$). The third model applied logistic regression analysis to age, weigh, height and gender of 650 healthy volunteers as correlating with measured BLI in these subjects. Obtained coefficients were used to calculate BLI for any new patient.

2.4 Model validation

Models 1 and 2 were validated by using the equations (Fig. 1), whose derivation was based on ILI values obtained in group 1, to calculate BLI values for patients in

Model 1

$BLI_c = [A_i + B_i \times (\overline{ILI_i})]$

Where BLI_c stands for calculated baseline lung impedance of a new patient

$\overline{ILI_i}$ - mean of several measurements of the instantaneous lung impedance for a specific patient at NYHA stage i (i=I-IV)

A_i, B_i -the regression analysis coefficients for NYHA class i (obtained by model).

Model 2

$BLI_c = \overline{LIR_i} \times \overline{ILI_i}$ for new patient

$\overline{ILI_i}$ - mean of several measurements of the instantaneous lung impedance for a specific patient at NYHA stage i (i=I-IV)

LIR_i = measured BLI (BLI_m)/ ILI_i , where i represents the NYHA class of the new patient.

$\overline{LIR_i} = (\Sigma\ LIR_i)/n$

Model 3

$BLI_{c,\ male} = A_{male} + B_{male} \times Age + C_{male} \times$ body mass index (BMI)

$BLI_{c,\ female} = A_{female} + B_{female} \times Age + C_{female} \times BMI.$

Fig. 1 Equations for calculation BLI_c according to models 1–3

group 2. As the next step we compared the calculated and the actually measured BLI values. For this evaluation the measured BLI of group 2 was considered the gold standard. For validation of model 3 obtained equations were used to calculate BLI in all 120 CHF patients. In order to overcome the drawbacks of ILI measurement in Ω we defined a new variable—the ILI ratio difference (ΔLIR) = (ILI/BLI − 1) × 100 %, which reflects deviation from baseline. If some degree of PCE was present at the visit then ILI < BLI and ΔLIR was negative with a decreasing value of ΔLIR (or increasing absolute value of ΔLIR) reflecting worsening PCE. For assessment of the risk of re-hospitalization due to PCE we introduced an additional parameter, the mean annual ΔLI Ratio (ΔLIR_{year}). ΔLIR_{year} was calculated as the arithmetic average of all available monthly measurements within the same year. If spacing's between visits were not equal (i.e. intervals between monthly visits were more than 30 ± 10 days) interpolation of ΔLIR values was used. Adjudication of the primary diagnosis of any hospitalizations was determined by 3 independent physicians blinded to ΔLIR.

2.5 Statistical analysis

Continuous variables were presented as mean ± SD or median and interquartile range (IQR; 25th to 75th percentiles) depending on the distribution of the data. Comparisons between values within same or different groups were carried out by using one-way analysis of variance (ANOVA) or Chi Square and Fisher tests. Pearson and Spearman's rho correlations were calculated for relation between quantitative and qualitative parameters. Linear regression analysis was used for model 1 construction, or to predict number of hospitalizations for PCE. R square was used to assess model linearity. Multivariate regression analysis was employed for derivation of model 3 and univariate logistic regression analysis was employed to calculation Odds Ratio (OR) to study parameters

Table 1 Patient demographics, clinical and laboratory data at study recruitment

Chronic heart failure patients (N = 222)	
Age (years) mean ± SD	67.2 ± 10.4
Male	189 (85 %)
Body mass index	29 ± 4.9
New York Heart Association stage I (NYHA I)	20 (9.0 %)
NYHA II	118 (53 %)
NYHA III	54 (24 %)
NYHA IV	30 (14 %)
Left ventricular ejection fraction (mean ± SD)	28 ± 3.4 %
Cardiomyopathy ischemic (%)	179 (81 %)
Cardiomyopathy non-ischemic (%)	43 (19 %)
Diabetes mellitus	112 (50 %)
Arterial hypertension	156 (70 %)
Hyperlipidemia	149 (67 %)
Smoking	85 (38 %)
Peripheral vascular disease	18 (8 %)
Chronic atrial fibrillation	50 (23 %)
Chronic renal failure	125 (56 %)
Status post myocardial infraction	175 (79 %)
Status post coronary arterial bypass graft	49 (22 %)
Cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillator (ICD)	132 (59 %)
CRT or ICD implanted before study entry	80 (36 %)
CRT or ICD implanted during study	52 (23 %)
Aspirin	76 %
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker	95 %
Beta blockers	90 %
Statins	83 %
Mineralocorticoid receptor antagonist	52 %
Digoxin	33 %
Diuretics	95 %
NT-proBNP (pg/mL), (median and interquartile range Q1–Q3) at study entry	1,566 (926–4,406)
Blood Creatinine (mg/dL), (mean ± SD) at study entry	1.35 ± 0.6
Blood Hemoglobin (g/dL), (mean ± SD) at study entry	13 ± 1.6
Potassium (mmol/L, (mean ± SD) at study entry	4.5 ± 0.5
Sodium (mmol/L), (mean ± SD) at study entry	139 ± 3.8
HbA1C (%),(mean ± SD) at study entry	7.4 ± 1.6
Glucose (mg/dl), (mean ± SD) at study entry	135 ± 56

associated with death and hospitalization. We used White and Breusch–Pagan test for the assessment of heteroscedasticity of ILI values corresponding to different NYHA stages. A value of $p < 0.05$ was considered significant. The SPSS 21.0 statistical package (SPSS Inc., Chicago, IL, USA) was used.

3 Results

We screened 307 CHF patients with LVEF <35 %. Thirty-two patients with severe renal disease (estimated glomerular filtration rate <15 mL/min at screening) were excluded. Twenty-five patients who did not agree to participate in the study, 24 patients who withdrew their consent, and 4 patients who died at less than 3 months after recruitment were excluded. The demographic, clinical and laboratory data of 222 study patients are presented in Table 1. During a mean follow up period of 32 months (median 29), patients were evaluated on 6090 clinic visits. The clinical status of patients during these visits was defined as NYHA FC I-IV in 30.4, 38.5, 16.7 and 14.4 % respectively. Thirty-nine percent of NYHA FC I visits fulfilled the criteria for BLI.

Regression logistic analysis used to derive model 1 demonstrated a high degree of collinearity between ILI values of patients at different NYHA stages signifying an inherent inter-relationship. This precluded the derivation of a uniform overall equation associating ILI at all NYHA stages and measured BLI. Consequently, four different equations needed to be derived to calculate BLI based on measured ILI values of any particular patient according to his specific NYHA stage. Results of BLI calculation according to the 3 models and their validation are presented in Table 2. It can be seen that the differences between measured and calculated values of BLI for group 2 in the first and second grouping based on models 1 and 2 were virtually identical (deviation ≤1.9 %, $p = 0.92$). In contrast, the differences between measured and calculated values of BLI by model 3 were considerable (18.4 %, $p < 0.001$). We calculated BLI using model 1 equations in the remaining 102 study patients who did not achieve a BLI status during the monitoring period.

Table 2 Results calculation of models 1–3

Grouping 1	
Measured BLI (BLI_m) in Ω (Group 2)	74.2*
Model 1	
$BLI_c = -1.65 + 1.14 \times \overline{ILI}_1$ (at NYHA I)	73.9*
$BLI_c = -3.25 + 1.25 \times \overline{ILI}_2$ (at NYHA II)	73.9*
$BLI_c = -6.84 + 1.51 \times \overline{ILI}_3$ (at NYHA III)	73.7*
$BLI_c = 20.6 + 1.23 \times \overline{ILI}_4$ (at NYHA IV)	73.6*
Model 2	
$BLI_c = 1.09 \times \overline{ILI}_1$ (at NYHA I)	74.0*
$BLI_c = 1.20 \times \overline{ILI}_2$ (at NYHA II)	73.9*
$BLI_c = 1.39 \times \overline{ILI}_3$ (at NYHA III)	73.7*
$BLI_c = 1.72 \times \overline{ILI}_4$ (at NYHA IV)	72.8*
Grouping 2	
Measured BLI (BLI_m) in Ω (Group 2)	75.9*
Model 1	
$BLI_c = -3.52 + 1.14 \times \overline{ILI}_1$ (at NYHA I)	76.7*
$BLI_c = -2.53 + 1.24 \times \overline{ILI}_2$ (at NYHA II)	76.3*
$BLI_c = -2.45 + 1.43 \times \overline{ILI}_3$ (at NYHA III)	76.8*
$BLI_c = 20.9 + 1.24 \times \overline{ILI}_4$ (at NYHA IV)	76.1*
Model 2	
$BLI_c = 1.09 \times \overline{ILI}_1$ (at NYHA I)	76.1*
$BLI_c = 1.21 \times \overline{ILI}_2$ (at NYHA II)	77.4*
$BLI_c = 1.38 \times \overline{ILI}_3$ (at NYHA III)	75.9*
$BLI_c = 1.73 \times \overline{ILI}_4$ (at NYHA IV)	77.9*
Model 3	
$BLI_{cfemale} = 6.62 + 0.10 \times Age + 2.04 \times BMI$ (n = 202) $BLI_{cmale} = 5.95 + 0.26 \times Age + 1.33 \times BMI$ (n = 448)	61.4†
BLI_m for 120 patients (grouping 1 and 2 together).	75.2†

* p = NS, and † $p < 0.001$ for the difference between measured and calculated values. $\overline{ILI}_i$—mean of measurements of the instantaneous lung impedance for a specific patient at NYHA stage i (i = I − IV). *BLI* Basal lung impedance, BLI_c calculated BLI

3.1 Validation of ΔLIR for PCE monitoring

We evaluated the correlation between ILI and corresponding ΔLIR at different NYHA stages (Fig. 2). There was a moderate correlation between NYHA values and the absolute ILI values ($r = -0.5$, $p < 0.001$) and an excellent correlation with corresponding ΔLIR ($r = -0.9$, $p < 0.001$) measured during 6090 clinical visits. On the other hand, the correlations between weight and ILI or ΔLIR ($r = -0.1$, $p < 0.01$; $r = -0.2$, $p < 0.01$, respectively), or between weight with NYHA values on the same visits were weak ($r = 0.1$, $p < 0.01$). Coefficient of determination (R^2) reflecting the degree of curve linearity was higher for ΔLIR than for ILI (0.9 and 0.3, respectively).

3.2 Hospitalizations and death

Of 222 study patients, 123 were re-admitted for PCE with or without admissions for other diagnoses, 47 for non-PCE causes and only 52 were not hospitalized at all during the follow up period. Overall, there were 388 admissions for PCE and 345 for non-PCE cause. Sixty-one patients died, of which 42 due to PCE-associated and 19 for non-PCE associated causes. Changes in ΔLIR value at admission and

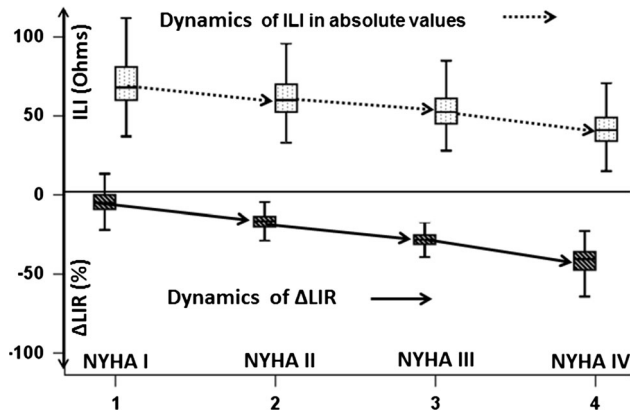

Fig. 2 *Box plot* showing distribution of instantaneous lung impedance (ILI) absolute values—*upper line* and relative values of ILI [ΔLIR = (ILI/BLI − 1) × 100 %]—*lower line* at different NYHA classes. *BLI* basal lung impedance

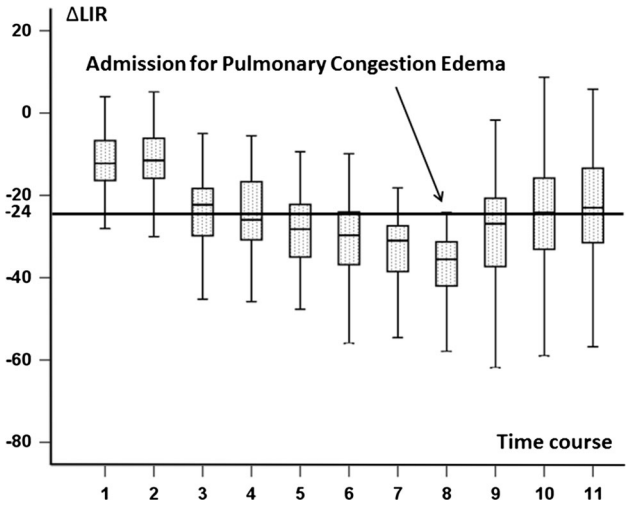

Fig. 3 *Box plot* showing dynamics of ΔLIR [ΔLIR = (ILI/BLI − 1) × 100 %] before, in time and after PCE (pulmonary congestion-edema) and non-PCE hospitalizations. *1*—ΔLIR at admission for non-PCE causes (n = 345). *2*—ΔLIR at discharge for non-PCE cases (n = 312). *3*—ΔLIR within 28 ± 3 days pre-hospitalization (n = 75). *4*—ΔLIR within 21 ± 3 days pre-hospitalization (n = 46). *5*—ΔLIR within 14 ± 3 pre-hospitalization (n = 62). *6*—ΔLIR within 7 ± 3 pre-hospitalization (n = 75). *7*—ΔLIR within 3 ± 2 pre-hospitalization (n = 25). *8*—ΔLIR at admission for PCE (n = 388). *9*—ΔLIR at discharge for PCE (n = 362). *10*—ΔLIR within 14 ± 3 post discharge (n = 150). *11*—ΔLIR within 28 ± 3 days after discharge for PCE (n = 149)

discharge for non-PCE causes, as well as prior to, during and following hospitalization due to PCE are presented at Fig. 3. Non-PCE hospitalizations were not accompanied by ΔLIR changes (Fig. 3, p = NS). In patients hospitalized for PCE, significant ΔLIR decrease were recorded 2 weeks before hospitalization in comparison with its level 4 weeks before hospitalization (Fig. 3, $p < 0.001$). Dispersion of ΔLIR values at admission showed that there were no hospitalizations due to PCE when ΔLIR decreased by less than 24 % (Fig. 4). Most of CHF patients demonstrated a ΔLIR decrease of 24–40 % at admission. During hospitalization a significant improvement in the clinical status (NYHA decreased from 3.7 ± 0.5 to 2.9 ± 0.8, $p < 0.001$) coincided with an increase in ΔLIR ($p < 0.0001$), which reflected an amelioration in lung congestion (Fig. 3). However, ΔLIR at discharge was at the same level as it was 1 week before hospitalization (ΔLIR = −29.1 and −30.8 %, respectfully, $p = 0.2$). There was a significant difference between the extent of ΔLIR decrease during PCE in comparison with non PCE admissions (−37.8 ± 9.3 and −12.3 ± 8.1 %, respectively, $p < 0.001$). Important to note that in 312 of 345 non-PCE admissions ΔLIR decrease was less than 24 % while ΔLIR decrease exceeded 24 % in all PCE hospitalizations. The sensitivity and specificity of ΔLIR ≤24 % to differentiate between PCE and non-PCE hospitalizations was 100 and 90 %, respectively. If ΔLIR = −30 % is chosen as the threshold to discriminate between PCE and non-PCE hospitalization then the calculated sensitivity and specificity is 79 and 95 %, respectively. Length of hospital stay for PCE hospitalizations was 4.6 ± 5.3 (median 3.8 days). Twenty patients died due to PCE during hospitalization. Importantly, ΔLIR was −37.3 ± 9.1 % at admission in patients that survived hospitalizations for PCE while in patients

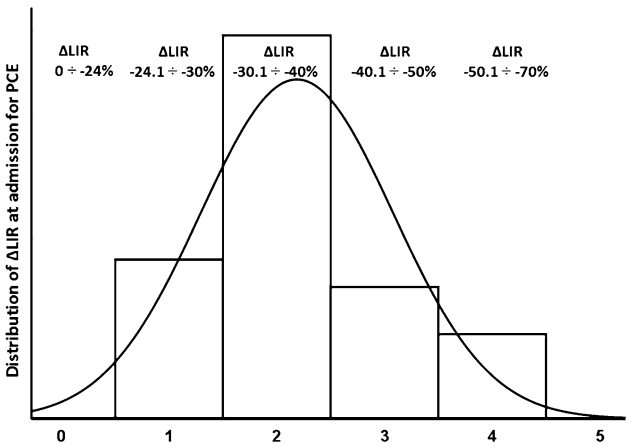

Fig. 4 Dispersion of ΔLIR at admission for pulmonary congestion edema, where ΔLIR = (ILI/BLI − 1) × 100 %

who died ΔLIR = −50 ± 8.7 % ($p < 0.001$). Of 108 CHF patients who were followed for period of more than 4 years, 57 patients with at least one admission for PCE during 3 different years after study initiation were chosen (overall 253 re-hospitalizations). Mean admission ΔLIR values during the first to fourth year of follow up were −33.2 ± 5.8, −37.8 ± 6.1, −43.3 ± 5.7 and −45.2 ± 6.1 %, respectively ($p < 0.001$).

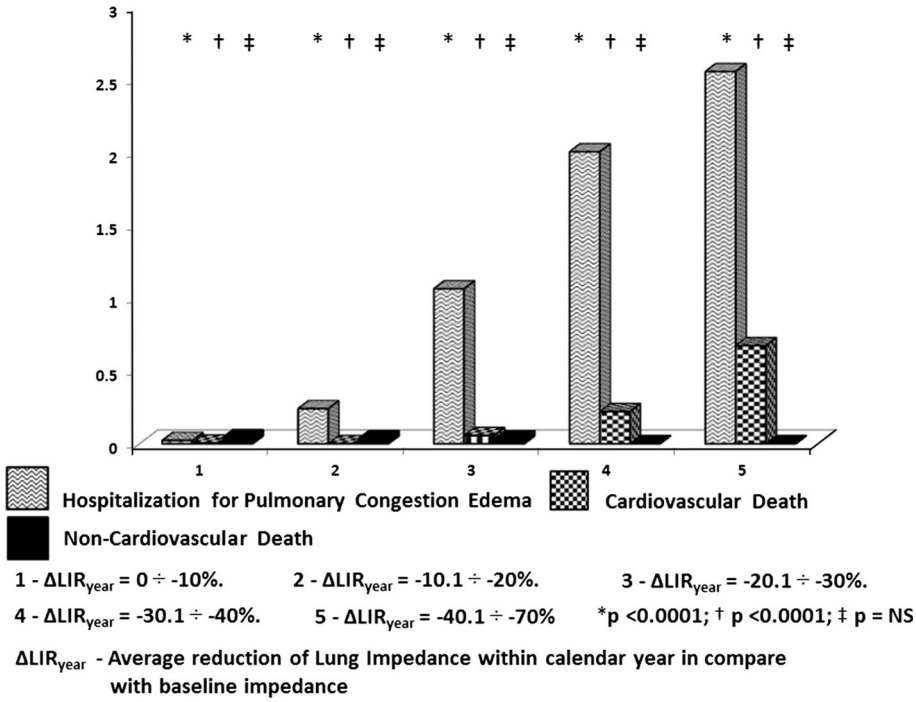

Fig. 5 Distribution of hospitalizations, cardiovascular and non-cardiovascular death according ΔLIR_{year}

3.3 Validation of ΔLIR_{year}

The calculation of the ΔLIR_{year} parameter was possible in 222 CHF patients and included, overall, 621 years of follow up. Frequency distribution of PCE hospitalizations and deaths according to the different degrees of ΔLIR_{year} reduction is presented in Fig. 5. The incidence of hospitalizations for PCE and death was low in patients with ΔLIR_{year} decrease between 0 and -30 % but increased dramatically in those with a ΔLIR_{year} decrease of more than -30 %. The odds ratio for risk of hospitalization due to PCE for a ΔLIR_{year} decrease of -30 to -40 % and more than -40 % in comparison with ΔLIR_{year} decrease 0 to -20 % was 42 [95 % confidence interval (CI), 24–76] and 133 (95 %CI 48–376, $p < 0.0001$), respectively. Also, we found a high level of correlation according to Spearman test between the degree of ΔLIR_{year} decrease and frequency of re-hospitalizations for PCE ($R = -0.73$, $p < 0.0001$). A similar correlation between the extent of ΔLIR_{year} decrease and death due to PCE was found. The odds ratio for death due to PCE at ΔLIR_{year} decrease more than -40 % in comparison with that at ΔLIR_{year} decrease less than -30 % was 145 (95 %CI 32–659, $p < 0.0001$). Furthermore, in the subgroup of patients (n = 42) who died because of PCE, the ΔLIR_{year} in the year before death was -41.0 ± 9.5 % in comparison with -13.3 ± 9.5 % in the subgroup of patients (n = 19) who died due to a non-PCE cause ($p < 0.001$).

4 Discussion

In an era when hemodynamic monitoring of pulmonary artery pressure in CHF patients did not clearly prove to be helpful [14, 15], monitoring of pulmonary congestion by the non-invasive impedance technique seems to be a promising alternative. The main limitation of using the impedance technique is that the "dry" or normal BLI is unknown. This is so because some degree of PCE usually exists in CHF patients at the time of the actual visit or when presenting with symptoms. During prolonged monitoring we have noticed that some CHF patients achieved good functional state with no lung fluid overload according to their CXR. ILI, under these conditions, was defined as BLI used to calculate $\Delta LIR = (ILI/BLI - 1) \times 100$ % as the parameter that characterizes the degree of pulmonary congestion in relation to the normal condition and to be applied to monitor PCE in CHF patients.

Noninvasive impedance devices have been previously investigated as a method to monitor CHF. These devices measured hemodynamic parameters as cardiac output (CO) and thoracic fluid content based on the traditional Kubichek scheme of intrathoracic impedance measurement with longitudinal distribution of the electrical current across patient chest [16]. This method demonstrated a modest correlation when compared with invasively measured parameters with a limited power to predict hospitalizations for PCE and fatal outcome [9, 17, 18]. These findings can

be explained by the technique of thoracic impedance measurement. When there is longitudinal distribution of the current within the chest it passes preferably through the 10-fold lower resistant blood in the aorta in parallel to current via the high-resistance lung. This current distribution precludes precise measurement of changes in lung resistance and reduces method sensitivity.

The impedance method was also applied in pacemakers to measure intrathoracic impedance in an attempt to detect early accumulation of intrathoracic fluid as a harbinger of symptomatic congestion. According to the original hypothesis the current was thought to pass from electrode tips to the pacemaker body in different configurations. Clinical investigations have shown that clinical utility is limited [19, 20]. It was realized later that the resistance between electrodes and myocardium is so high [21, 22] as to preclude precise measurement of ILI, with current flowing mainly through the large veins.

In the present study was used a device when current passing chest cavity between electrodes in the sagittal direction [4, 6, 10, 11]. Such a scheme precludes passage of current through the large vessels and significantly limits redundant redistribution of electrical flow current through the large vessels. Noninvasive measurement of the total transthoracic impedance including the high electrode–skin (of cutaneous and subcutaneous tissue) impedance (500–1,200 Ω) and the targeted low ILI (30–100 Ω) precludes precise measurement of ILI whose value falls within the range of the electrode–skin tissue detection error [10, 11, 23]. The device used in the current study includes an algorithm that subtracts electrode–skin and under skin tissue impedance from the total transthoracic impedance resulting in net ILI. Measurement of net ILI renders the device more sensitive to small changes in pulmonary fluid content, or congestion and less depended from individual changes in electrode–skin and under skin impedance changes [8, 9].

An additional limitation of current devices is that yielded absolute ILI values are dependent on individual patient characteristics and equipment specifications. Calculation of changes in lung fluid status according $\Delta LIR = (ILI/BLI - 1) \times 100\ \%$ equation presents pulmonary congestion in relative values and makes this parameter less dependent on individual patient and device characteristics. ΔLIR may help to monitor CHF patients both in out-of-hospital and hospital settings and predict and possibly prevent hospitalizations.

We found that ΔLIR highly correlated with clinical variables, reliably predicted hospitalizations for PCE and the risk of death. ΔLIR was found to be more sensitive, and hence more discriminative than NYHA functional class, and tended to precede later changes in NYHA class. Patients in the same NYHA class corresponded to a wide range of ΔLIR changes. In other words, patients were at the same NYHA class during several consecutive visits while ΔLIR changed for the better or worse. The expected NYHA class change was clinically evident only later after additional visits.

During the 4-year follow-up we have realized that ΔLIR progressively decreased in patients with multiple re-hospitalizations for PCE as hospital admissions recurred. This phenomenon is in the line with previous findings [7]. These results question the existence of an absolute impedance threshold to be used for prediction of PCE hospitalization as attempted by Yu et al. [7]. Apparently, as the years pass the impedance threshold (or ΔLIR) decreases beyond the pre-specified value, which means that a certain degree of tolerance develops and more severe pulmonary congestion is required to induce clinical symptoms. This confirms patient adaptation to a higher degree of pulmonary congestion which is in keeping with the recognized long-term clinical course of CHF patients whose medical status deteriorates progressively as they experience multiple re-hospitalizations due to PCE [24]. This observation makes the calculation of the positive predictive value of a pre-specified ΔLIR decrease as a predictor for PCE hospitalization less relevant. On the other hand, ΔLIR_{year} may serve as a powerful predictor for PCE-related hospitalizations and death. We have found that patients who experienced higher degrees of long-standing pulmonary congestion (ΔLIR_{year} in the range -30 to -70 % vs. 0 to -30 %) had a higher probability for PCE-associated hospitalization and death. A possible implication based on these findings is the need to intervene more aggressively once the threshold of $\Delta LIR_{year} < -30$ % is recorded. Although no evidence is available that a therapeutic intervention may alter prognosis, the treating physician must make maximal effort to reduce measured ΔLIR level to the range of 0 to -20 %, hoping to improve patient outcome. Conversely, in case achieved ΔLIR_{year} is between 0 and -20 % then only slight changes in therapy may be indicated as to avoid the deleterious effects of excessive treatment.

Indeed, basing the derivation of a model for BLI calculation on the clinical assessment of NYHA may involve some inaccuracy due to the known subjective nature of determining the NYHA class in individual cases [9]. However, to minimize this effect, we have also incorporated in the clinical assessment of the NYHA class, the results of the 6MWT and CXR interpretation. More importantly, the calculation of BLI in this study was based on more than 6,000 repeated clinical visits so that it is reasonable that misclassifications probably cancel out in light of this large patient visit database.

4.1 Limitations

First, in patients achieved BLI was deviation between BLI values at different visits ≤ 2 %. In several cases of

hospitalizations for non PCE causes such as deterioration of renal function due to dehydration, measured ILI was higher than BLI by 8−12 %. We did not regard these cases with high ILI values as disproving the model accuracy but may actually help to differentiate congestion from dehydration as a reason for hospitalization. Second, 30 patients stopped participation into the study after 1.9 ± 1.2 years follow up according owns require. Third, patients with severe pulmonary disease were excluded.

In conclusion, ΔLIR and ΔLIR_{year}, based on the current model for BLI calculation, enable to monitor PCE in relative values independently of the patient's individual anthropomorphic parameters and reflect not only the dynamics of pulmonary congestion but also the degree of lung congestion in compare with normal "dry" lung. These parameters were found to correlate well with the clinical status of CHF patients and predicted future events. ΔLIR and ΔLIR_{year} demonstrated a strong predictive power for hospitalizations for PCE and death, and therefore, seem suitable for monitoring pulmonary congestion.

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Conflicts of interest All other authors have no potential conflicts of interest.

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