

## Internal thoracic impedance monitoring: a novel method for the preclinical detection of acute heart failure

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### Abstract

**Background:** Acute heart failure (AHF) evolves through two phases. In the first phase, there is interstitial congestion with no clinical sign of edema (preclinical phase); the second, during which lung alveoli begin to fill with fluid, manifests as clinically overt alveolar edema. Treatment of AHF at its preclinical phase can alleviate its clinical impact. Presently, there is no technique that detects the interstitial phase of AHF. We used a device based on a new method of lung bioimpedance measurement. The device measures internal thoracic impedance (ITI), which nearly equals inherent lung bioimpedance. This method can detect small changes in lung fluid that occur during the interstitial stage of AHF.

**Aim:** The objective of this study was to assess the feasibility and efficacy of the said new method in detecting preclinical AHF.

**Methods:** Internal thoracic impedance and pertinent clinical parameters were monitored for 72 h in 403 patients hospitalized for an acute coronary syndrome without evidence of AHF at study entry.

**Results:** Seventy patients developed AHF during monitoring. Internal thoracic impedance decreased in these patients by 16.4% (95% CI=−12.2% to −20.6%;  $P<.0001$ ) from the baseline level at  $44\pm 15.1$  min prior to the onset of lung rales. The other 333 patients had no clinical sign of AHF, and their ITI declined only by 4.5% (95% CI=2.5% to −11.5%;  $P=.3$ ) compared with the baseline level.

**Conclusion:** The new method for ITI measurement is sufficiently sensitive in detecting AHF at its preclinical stage. An ITI decrease of more than 12% heralds the appearance of clinically overt AHF and, thus, allows earlier therapy.

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**Keywords:** Acute heart failure; Internal thoracic impedance; Preclinical detection; Pulmonary congestion; Monitoring

### 1. Introduction

Acute heart failure (AHF) evolves through two phases. The first phase, considered as the preclinical phase, involves fluid accumulation in the interstitial spaces of the lung with

virtually no clinical sign of edema; the second, during which lung alveoli begin to fill with fluid, manifests as clinically overt alveolar edema. Treatment of AHF at its preclinical stage can prevent its occurrence or alleviate its clinical impact [1,2]. Diagnosing the interstitial stage of AHF by auscultation may be difficult because the lungs may still be clear as rales are not present at this stage [3]. Clinical signs of alveolar congestion develop only after the interstitial fluid volume increases approximately sixfold or more. At this stage, the interstitial phase transforms into the alveolar phase [4]. The

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diagnosis of the interstitial stage of AHF may be established by a chest X-ray. Signs of interstitial edema detected by X-ray may precede the appearance of alveolar edema [5]. However, alveolar edema may develop gradually within hours and it is impractical to monitor its evolution by performing an X-ray every 30–60 min. Chest bioimpedance is a simple and noninvasive method that may be used to detect the interstitial stage of pulmonary congestion. Currently, however, the diagnosis of this interstitial phase by chest bioimpedance is not feasible [2,6] because the methods used for impedance measurement are not sensitive enough. Therefore, this method has not yet been applied in clinical practice [6–9].

A new impedance monitor has been developed to overcome this limitation [10]. Unlike currently available impedance monitors, this device is based on a new method of internal thoracic impedance (ITI) measurement. The purposes of the current study were to examine the feasibility of continuous ITI measurement by the new device in detecting preclinical (interstitial stage) AHF and to evaluate the clinical relevance of this method.

## 2. Patients and methods

### 2.1. Patients

The study included 403 consecutive patients admitted from January 1, 2000, to December 31, 2004, to two intensive cardiac care units and one medical ward in three medical centers.

#### 2.1.1. Inclusion criterion

The participant criterion for study entry was being admitted with an acute coronary syndrome (ACS) without a history of chronic heart failure.

#### 2.1.2. Exclusion criteria

Evidence of clinical or radiographic (interstitial or alveolar edema) signs AHF on admission and respiratory failure caused by lung disease were the exclusion criteria.

### 2.2. Methods

All patients underwent physical examination and had a chest X-ray on admission. A pilot study with 6-min interval measurements of heart rate (HR), respiratory rate (RR), pulse oximetry (PO), and ITI recording, as well as lung auscultation, demonstrated that a 30-min sampling time interval is sufficient to detect changes in ITI and in the other parameters during the evolution of AHF and resolution [11]. Therefore, a sampling rate of 2/h (every 30 min) for these parameters and duration of monitoring of at least 72 h were chosen for the present study.

The clinical severity of AHF was graded as follows: Grade 0, no rales (no or interstitial edema); Grade 1, detection of rales only at lung bases (mild or beginning of alveolar

edema); Grade 2, rales over the lower half of lung fields (moderate alveolar edema); and Grade 3, rales over full lung fields (severe alveolar edema or full pulmonary edema).

Pulmonary artery blood pressure and capillary wedge pressure measurements were not part of the study protocol. Many of the patients were treated by thrombolytics; a central venous puncture carries an increased risk under such circumstances and invasive methods are currently not indicated in patients without evidence of AHF [1,2].

We have previously found that the earliest clinical sign of AHF is auscultatory (i.e., appearance of rales at lung bases) [12]. Dyspnea usually developed later, followed by an increase in HR and a decrease in blood oxygen saturation. We therefore defined the time of the first detection of rales as the onset of the clinically overt (alveolar) stage of AHF. Chest X-ray was repeated at this stage and at the end of monitoring. All X-rays were performed after 5 min in the sitting position. This time interval was used for achieving steady state after the change in position. Demographic data, including age, sex, height, and body weight, were recorded. The study was designed to compare ITI in patients who did not develop clinically overt AHF (Group 1) with ITI in those who did develop AHF during 72 h of monitoring (Group 2).

Chest bioimpedance correlates inversely with changes in lung fluid content [13]. Fig. 1A shows the components of the electrical impedance of the chest. Transthoracic impedance (TTI) [2] in Fig. 1 consists of two components: ITI [1] that nearly equals inherent lung impedance plus twice the high skin-electrode impedance [3]. Internal thoracic impedance is low-magnitude impedance (30–100  $\Omega$ ) that decreases by 15–50% with the development of pulmonary congestion or edema. The high skin-electrode impedance (800–1000  $\Omega$ ) does not change as a result of changes in lung fluid content but rather as a result of slow changes in skin ionic balance throughout monitoring of several hours' duration [14]. The absolute values of TTI are higher than 1000  $\Omega$ . The magnitude of change of ITI during AHF is approximately 15–50% (5–50  $\Omega$ ) from the baseline level. Obviously, this change in ITI represents only a small percentage (0.5–5%) of the high TTI and is, therefore, barely measurable. Thus, this method used today to measure lung bioimpedance has a very low sensitivity.

A new impedance monitor unlike devices currently available was developed based on the novel method of ITI measurement (Fig. 1A). This was attained by calculating skin-electrode impedance and subtracting it on each measurement from measured TTI [10,11] to yield ITI. Thus, a change in lung impedance that occurs during the development of pulmonary edema (15–50  $\Omega$ ) represents approximately 15–50% of baseline ITI (30–100  $\Omega$ ) and confers approximately a 20- to 30-fold higher sensitivity. The algorithm developed also provides the option of neutralizing the drift in skin-electrode impedance that takes place during monitoring. We have demonstrated in a preliminary evaluation in a small patient group ( $n=30$ ) that

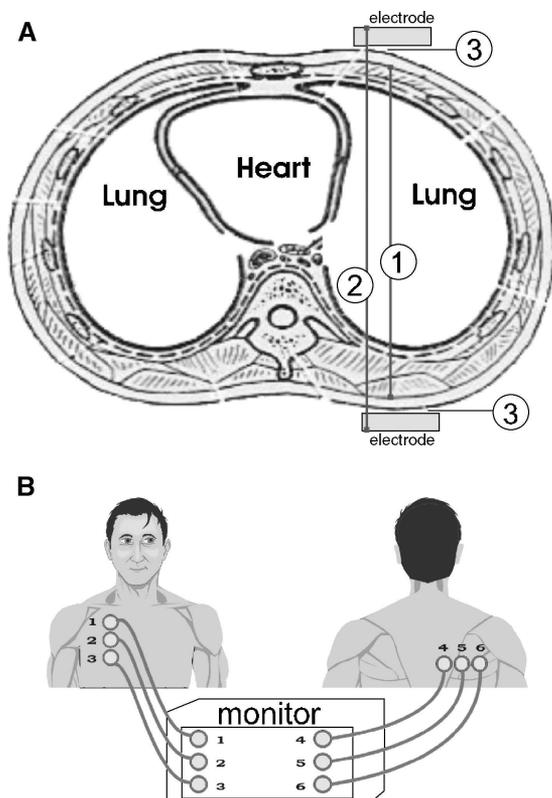


Fig. 1. (A) The components of TTI with depiction of the thoracic cross-section. 1: ITI, 30–100  $\Omega$ ; 2: TTI, 1030–1200  $\Omega$ ; 3: skin-electrode impedance, 500–600  $\Omega$ . (B) Connections of impedance monitor electrodes.

this algorithm has sufficient sensitivity to differentiate between normal patients and patients with overt (alveolar) AHF [11].

Internal thoracic impedance was measured by an RS-205 impedance monitor (RS Medical Monitoring, Jerusalem, Israel). The noise-to-signal ratio of the device for ITI measurements was 0.5%. Six standard 1-cm electrocardiographic electrodes (Nice Medical Products, Type 4500 foam, TUV, Rhineland) were attached to the surface of the right chest and connected to the RS-205 monitor, as shown in Fig. 1B. The effect on ITI values of body position change from the horizontal to the sitting and return to the horizontal was studied in all patients at admission, at a stage when they had no sign of pulmonary congestion. Study protocol was approved by the local institutional review board and Helsinki Committee of the Ministry of Health. All participants gave written informed consent before their enrollment into the study.

### 2.3. Statistics

Internal thoracic impedance, HR, RR, and PO were expressed as absolute values. Changes of measured parameters during monitoring were expressed as percentages of deviation from the initial value. This presentation is more physiological because each patient has an individual initial

value for each parameter. Internal thoracic impedance is usually influenced by age, sex, body mass index (BMI), and individual lung physiology. All measured parameters had a normal distribution. The influence of age, height, weight, and BMI on absolute ITI values was studied by the Pearson index of correlation coefficient ( $r$ ). Internal thoracic impedance changes and other quantitative variables were evaluated by two-tailed Student's  $t$  test. The significance of difference between ITI values during monitoring was assessed by analysis of variance with repeated measures. The predictive power of ITI and other used indices (RR, pulse rate, and blood oxygen saturation) on the appearance of lung rales was assessed by logistic regression analysis and confirmed by the estimation of the area under the curve criteria. Chest X-ray interpretation was evaluated for intra-observer and interobserver variability using the  $\kappa$  index. Values were expressed as mean  $\pm$  S.D. and in ranges; 95% CIs, as mean  $\pm$  2 S.D. Results were considered statistically significant when the appropriate  $P$  value was  $<.05$ . Calculations were performed using SAS Version 8 (SAS Institute, Cary, NC, USA).

## 3. Results

### 3.1. Patients

All enrolled patients were admitted for an ACS and had no clinical and radiographic sign of AHF on admission. Of the 403 enrolled patients, 333 (82.6%) did not develop clinical and radiographic signs of AHF (Group 1) whereas the other 70 patients did during monitoring (de novo AHF; Group 2). The ages of the patients in Group 1 ( $60.6 \pm 12.9$  years; range=30–81 years) were lower than those of the patients in Group 2 ( $66.7 \pm 12.1$  years; range=41–83 years;  $P < .0001$ ). The proportion of male/female patients did not differ between groups (male/female ratio: 72/28 and 74/26 in Groups 1 and 2, respectively).

Baseline ITI values correlated with age ( $r = .26$ ;  $P < .0001$ ) and BMI ( $r = .46$ ;  $P < .00005$ ). On average, ITI increased each 10 years by 2.1  $\Omega$ . Baseline ITI and height correlated negatively but only weakly ( $r = -.15$ ;  $P < .02$ ). Mean initial ITI was 1.3 times greater in females than in males ( $P < .001$ ).

### 3.2. Body position

The effect of changes in body position on the baseline ITI value was studied in all 403 patients at admission. Internal thoracic impedance increased by 3.2% (95% CI=–1.0% to 7.4%;  $P = .7$ ) during first 3 min of sitting and did not change further during the following 2 min.

Fig. 2 shows the kinetics of measured parameters in Groups 1 and 2 during 72 h of monitoring. In Group 1, the initial ITI (ITI on admission) was 60.7  $\Omega$  (95% CI=31.9–89.5  $\Omega$ ). The maximal ITI decline during the 72-h study period was 4.5% (95% CI=2.5% to

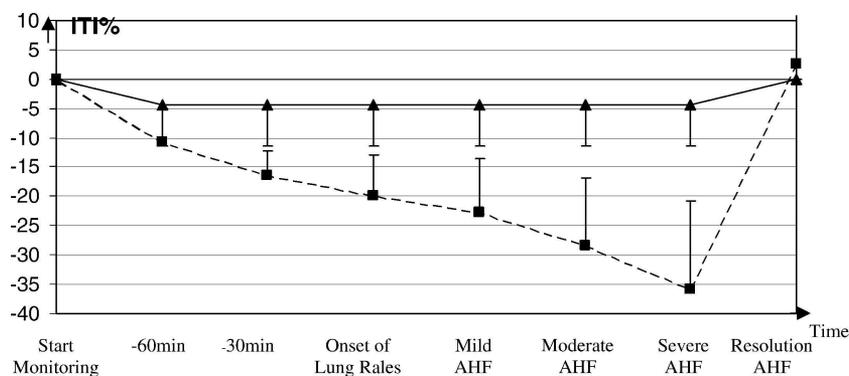


Fig. 2. Internal thoracic impedance kinetics during 72 h of monitoring in study groups: Group 1 patients (—) and Group 2 patients (---). The negative error bar in Group 1 patients and the positive error bar in Group 2 patients represent  $-2$  S.D. and  $+2$  S.D., respectively.

$-11.5\%$ ;  $P=.3$ ); RR, HR, and PO also did not change significantly. None of the patients died during monitoring or hospitalization.

By definition, all Group 2 patients had a normal chest X-ray and no clinical sign of AHF at entry and developed clinical and radiographic signs of AHF during monitoring. The initial ITI value in this group was  $58.6 \Omega$  (95% CI= $34.4-82.8 \Omega$ ), similar to that in Group 1 ( $P=.15$ ). During monitoring, ITI decreased gradually. Sixty minutes prior to first auscultatory evidence of rales (during the interstitial phase of AHF), ITI decreased by  $10.7\%$  (95% CI= $-5.1\%$  to  $-16.3\%$ ;  $P=.002$ ) from the initial value. Thirty minutes prior to the appearance of rales, ITI decreased by  $16.4\%$  (95% CI= $-12.2\%$  to  $-20.6\%$ ;  $P<.00001$ ) from the initial level. At the onset of lung rales, ITI decreased by  $19.9\%$  (95% CI= $-12.9\%$  to  $-26.9\%$ ;  $P<.00001$ ) from the initial value. Progression of AHF was accompanied by a further decrease in ITI. At mild AHF, ITI decreased by  $22.7\%$  (95% CI= $-13.5\%$  to  $-31.9\%$ ;  $P<.00001$ ); at moderate AHF, the ITI decreased by  $28.5\%$  (95% CI= $-16.9\%$  to  $-40.1\%$ ;  $P<.0001$ ); and at severe AHF, ITI decreased by  $35.8\%$  (95% CI= $-20.3\%$  to  $-50.8\%$ ;  $P<.00001$ ) from the initial value. During resolution of pulmonary edema, ITI had progressively increased and returned to its initial and even higher level by  $+2.5\%$  (95% CI= $-7.9\%$  to  $12.9\%$ ;  $P=NS$ ). The RR of patients in this group increased from the initial value by  $1.0\%$  (95% CI= $-10.0\%$  to  $12.0\%$ ;  $P=.7$ ) at 60 min and by  $3.2\%$  (95% CI= $-7.4\%$  to  $13.8\%$ ;  $P=.4$ ) at 30 min prior to the appearance of rales. At the time of detection of rales at lung bases (beginning of the alveolar stage of AHF), RR increased by  $7.0\%$  (95% CI= $-15\%$  to  $29\%$ ;  $P=.053$ ); at the stage of mild AHF, RR increased by  $12.8\%$  (95% CI= $-16.8\%$  to  $42.4\%$ ;  $P=.0015$ ). Heart rate and PO demonstrated the same kinetics. Heart rate increased significantly and PO decreased significantly only at the stage of mild AHF ( $P=.015$ ) (Fig. 2).

Treatment was successful in 94% of the Group 2 patients. Four patients (6%) died during monitoring; all were in the stage of fulminant pulmonary edema and none showed clinical signs of improvement or ITI increase during treatment.

Using the ROC model, we studied in Group 2 the power of each measured parameter to predict the appearance of rales (beginning of the alveolar stage of AHF) 30 min prior to their onset. The ROC values for oxygen saturation, pulse rate, and RR were 0.651, 0.599, and 0.700, respectively; for ITI ratio, it was 0.997.

Interobserver agreement ( $\kappa=.80-.84$ ; mean value= $.82$ ) and intraobserver agreement ( $\kappa=.80-.86$ ; mean value= $.83$ ) between four readers of the chest X-rays were statistically significant ( $P<.0001$ ).

Values of maximal ITI decrease during monitoring in Group 1 (95% CI= $-2.5\%$  to  $-11.5\%$ ) and ITI decrease in Group 2 60 min prior to the appearance of lung rales (95% CI= $-5.1\%$  to  $-16.3\%$ ) have a large overlap and cannot be used as criteria for the prediction of the approaching alveolar stage of AHF. In contrast, 30 min prior to the beginning of alveolar edema, ITI decreased more in Group 2 patients and their ITI values (95% CI= $-12.2\%$  to  $-20.6\%$ ) did not overlap with those of Group 1 patients. This means that fewer than 2.5% of Group 2 patients failed to be correctly identified 30 min prior to the appearance of lung rales. Thus, an ITI decrease of 12% yielded a specificity of 98% and a sensitivity of 97.5% to predict transformation of the interstitial phase of AHF to an alveolar stage 30 min prior to its onset.

#### 4. Discussion

Pulmonary interstitial and alveolar edema is the result of progressive accumulation of fluid in the lungs, leading to a decrease of pulmonary bioimpedance. Preclinical diagnosis of evolving pulmonary edema (i.e., diagnosis at its interstitial stage prior to the appearance of overt symptoms) may allow early initiation of therapy. We studied the kinetics of ITI as well as changes in HR, RR, and PO in patients admitted for an ACS who did or did not develop AHF during 72 h of monitoring. This study shows that respiration, HR, and PO were not sensitive enough to predict at the stage of interstitial edema the development of the alveolar (overt) stage of AHF. Only ITI changes can detect AHF at its preclinical interstitial stage. All patients who developed clinically overt AHF

( $n=70$ ) demonstrated an ITI decrease of more than 12% from the baseline value at  $44\pm 15.1$  min prior to the beginning of the alveolar phase of AHF. In contrast, in no patient who remained free of AHF did ITI decrease by more than 12%. The threshold of ITI decrease of 12% yielded a high sensitivity (97.5%) and specificity (98%). These results prove that this method is reliable and can be widely applied in the clinical arena.

In patients who did not develop AHF (Group 1), we found that maximal ITI decrease during monitoring was less than  $-11.5\%$ . At the moment of appearance of alveolar edema (Group 2), ITI decrease was between  $-12.9\%$  and  $-26.9\%$ . Apparently, an ITI decrease of approximately 12% reflects the maximal capacity of lung interstitium to accumulate fluid. Whenever this capacity is exceeded (at ITI decrease of  $>12\%$ ), fluid begins to permeate into the alveolar spaces. When ITI decrease reached 12% in our monitored patients (Group 2), they did not yet manifest any detectable clinical sign of pulmonary congestion. The time delay between ITI decline by 12% and the appearance of rales was  $44\pm 15.1$  min. The relatively wide range of ITI decrease prior to the detection of rales may be a result of the individual susceptibility of patients to fluid accumulation in their lungs. In addition, some of the patients may have had a certain degree of lung fluid accumulation at the beginning of monitoring that could not be detected clinically or radiologically. After comparing the specificity and sensitivity of various thresholds values, we have chosen an ITI decline of 12% as the cutoff point. This value corresponds to a sensitivity of 97.5% in the normal population and would limit the incidence of false-positive results to 2% and that of false-negative results to approximately 2.5%, as accepted in clinical investigations [15].

It is important to note that lung rales were not an indication for treatment in the present study. Treatment was initiated, as often practiced presently, only when patients became symptomatic with overt dyspnea and other complaints developed. Our records indicate that therapy was initiated at 30–390 min after the detection of lung rales in the present study. The application of ITI monitoring with the intent to treat upon ITI decrease of 12% may enable the initiation of effective therapy 60–420 min earlier than currently administered. This option could have profound salutary clinical benefits.

Our findings correlate with those of previous studies [8,16–19]. Campbell et al. [8] rapidly infused 1 L of 0.9% NaCl to volunteers and induced a 21% reduction in lung impedance. Noble et al. [17] actively induced diuresis, resulting in a urine output of 1220 ml and a thoracic impedance increase of 13.6%. In our study, the fluid balance of treated patients was  $-4278\pm 890$  ml during the period of treatment and ITI increased by  $35.8\pm 7.5\%$ . Regarding the effect of age on ITI, Gotshall and Davrath [18] and Metry et al. [19] found that the impedance increased by 1.5  $\Omega$  for each decade of age, similar to our study (2.1  $\Omega$  increase), and that the impedance of women is 1.1- to 1.3-fold higher than that in men (1.3 in our study).

In conclusion, continuous monitoring of ITI is a non-invasive, accurate, and reliable method for detecting pulmonary congestion in the preclinical stage. An ITI decline of more than 12% from the baseline level heralds the development of overt AHF in 97.5% of patients.

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