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Prediction of cardiogenic pulmonary edema onset by monitoring right lung impedance

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Abstract *Objective:* To evaluate the ability of internal thoracic impedance (ITI) monitors to predict cardiogenic pulmonary edema in patients at risk. *Design and Setting:* Prospective, controlled multicenter study. *Patients:* We examined 328 consecutive patients admitted for cardiac conditions. Of these 265 patients aged 27–83 years with no clinical signs of pulmonary edema, extracardiac respiratory failure or pacemakers comprised the study cohort. *Intervention:* Monitoring of the lung's electrical impedance was used for predicting cardiogenic pulmonary edema since accumulation of blood and fluid decreases impedance values. *Measurements and results:* Impedance of the lung is the main feature of ITI measured by the RS-207 monitor: decreased ITI prior to the clinical signs of cardiogenic pulmonary edema was used as the prediction criterion. The clinical signs used for confirmation of its prediction were dyspnea, cyanosis, pulmonary rales, crepitations, arterial hypoxemia, and radiographic evidence of pulmonary congestion in chest radiographs. Clinicians were blinded to the results of ITI measurements and radiologists were blinded to both ITI and clinical data. Thirty-seven patients developed cardiogenic pulmonary edema while being monitored. ITI decreased by more than 12% of baseline in all of them; this occurred at 30 min or longer (26 patients) and at 60 min or longer (11 patients) before the appearance of clinical signs. ITI fell by less then 10.1% of baseline in all 228 patients who did not develop the edema. *Conclusion:* Monitoring ITI is suitable for early prediction of cardiogenic pulmonary edema, before the appearance of the clinical signs.

Keywords Cardiogenic pulmonary edema · Monitoring cardiac patients · Early prediction · Thoracic impedance · Noninvasive measurement

Introduction

Early recognition and treatment of cardiogenic pulmonary edema might prevent its development. Existing clinical methods can detect cardiogenic pulmonary edema only when its clinical signs have already appeared. Pulmonary capillary wedge pressure measurement could be used for early detection of cardiogenic pulmonary edema, but this is an invasive and expensive method marked by serious complications. Radiography cannot be applied for monitoring patients at risk of cardiogenic pulmonary edema because frequent X-rays are impractical due to their expense, inconvenience, and repeated exposure to radiation. This means that the available methods for detecting an existing cardiogenic pulmonary edema cannot be used for its prediction.

The increased content of blood and extravascular fluid in lungs can be monitored by impedance plethysmogra-

phy [1, 2, 3, 4, 5, 6]. Accumulation of the water in a lung leads to a decrease in its impedance [7]. Existing noninvasive impedance plethysmographs are, however, unsuitable for early diagnosis of cardiogenic pulmonary edema [8, 9], mainly because of their low sensitivity due to high skin-to-electrode contact resistance and its drift during monitoring [10, 11, 12]. These values are much higher than those of lung impedance, making it impossible to detect small changes in the lung's impedance during the initiation of the cardiogenic pulmonary edema. Moreover, the electrodes' placement on the neck and along the thorax in the modern plethysmographs forces most of the electrical current to pass through the carotid arteries and aorta because blood is a better conductor than other tissues. A report of successful prediction of the cardiogenic pulmonary edema by implanted impedance plethysmograph was recently published [13]. This plethysmograph is integrated into a pacemaker which has a defibrillator implanted into the right ventricular apex and sensors that are placed in the left pectoral region. The system was shown to be sufficiently sensitive for detecting changes in contents of blood and fluid in the lungs preceding the appearance of the cardiogenic pulmonary edema clinical onset. This device, however, is a part of a pacemaker and as such can be used only by patients who need one.

The Edema Guard Monitor (EGM) model RS-207 (RS Medical Monitoring, Jerusalem, Israel) was developed to address the above monitoring problems [14, 15, 16, 17, 18, 19, 20]. It is designed to noninvasively monitor with better signal-to-noise characteristics than other noninvasive devices. Unlike the other available noninvasive plethysmographs, the EGM's electrical field is moved away from the large arteries to the lungs' area (Figs. 1, 2). This model has also solved the problems of high skin-to-electrode impedances and their drifts during prolonged monitoring by separating internal thoracic impedance (ITI) from skin-to-electrode impedances (Fig. 1). The calculated ITI values based on noninvasive measurements thereby correspond to ITI's measurements as if they were performed invasively via electrodes placed within the thorax.

The aim of the present study was to evaluate the ability of an ITI monitoring protocol to accurately predict impending cardiogenic pulmonary edema in cardiac patients at risk.

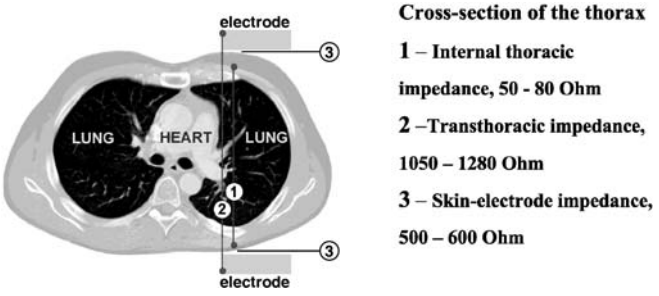

Fig. 1 The structure of transthoracic impedance

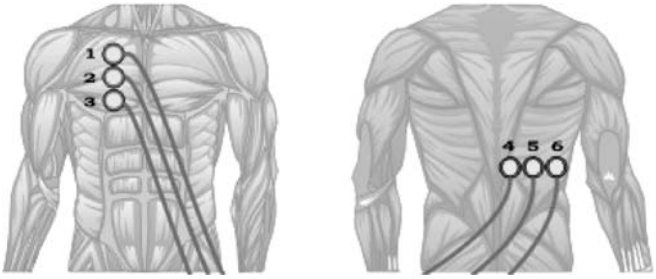

Fig. 2 The placement of Edema Guard Monitor electrodes

Materials and methods

The study protocol was approved by the local institutional review board of each participating hospital and by the Helsinki committee of the Israel Ministry of Health. The Israel Ministry of Health, however, stipulated that clinicians must not be informed about the results of the ITI measurements and use them for guiding patient management. All participants had signed informed consent forms before being enrolled. A total of 328 consecutive patients who were admitted to the participating hospitals for cardiac conditions that involve a risk of cardiogenic pulmonary edema were examined for suitability to participate in the study, and 265 of them were recruited. They all fulfilled at least one of the following criteria: acute coronary syndrome, acute myocardial infarction (ST or non-ST), unstable angina pectoris, valvular heart disease, and congestive heart failure (CCS I or II; Table 1). Exclusion criteria included preexistent clinical or radiographic signs of cardiogenic pulmonary edema, respiratory failure due to extracardiac diseases, permanent pacemaker, coma, uremia, and thoracic deformation. Sixty-three patients were excluded: 39 had clinical and/or radiological signs of the cardiogenic pulmonary edema, 21 had respiratory failure due to extracardiac diseases, and three had permanent

Table 1 Characteristics of the study groups (*ACS* acute coronary syndrome, *AMI* acute myocardial infarction, *UAP* unstable angina pectoris, *CHF* congestive heart failure, *VHD* valvular heart disease)

	Group DNDE	Group DE	Total
Sex: M/F	159/69	29/8	188/77
Age, mean ± SD (years)	6411	6911	6411
Age, range (years)	27–73	46–83	27–83
Diagnoses			
CHF	12	2	260
ACS AMI	168	27	
ACS UAP	44	7	
VHD	4	1	5
Total	228	37	265

pacemakers. The study participants' demographic data are listed in Table 1.

Coincidence between the decrease in the ITI value and the consequent appearance of cardiogenic pulmonary edema (CPE) was used as the criterion of successful early prediction of cardiogenic pulmonary edema by EGM. The cardiogenic pulmonary edema is usually defined by the presence of all of the following signs: dyspnea at rest, cyanosis, pulmonary rales, crepitation, arterial hypoxemia, and radiographic evidence of pulmonary edema [21, 22, 23]. The presence of any one of these signs was sufficient to identify the clinical onset of the cardiogenic pulmonary edema. Prediction of an impending CPE was considered successful only if a fully developed cardiogenic pulmonary edema with the presence of all or most of all clinical signs as well as radiographic signs subsequently developed. ITI was estimated by EGM by measuring transthoracic impedance (TTI) using electrodes 2 and 5 (Figs. 1, 2) and by measuring the skin-to-electrodes and skin impedances under each of the electrodes. The ITI value may be presented in the following way: ITI = TTI-I2-I5, where I2 and I5 represent the values of the impedances of skin-to-electrode and skin impedances under the electrodes 2 and 5, respectively.

There is no practical way to directly measure I2 and I5 values. This is achieved by adding the measurements made by the reference electrodes 1, 3, 4, and 6 (Fig. 2). The difference between the impedance measured directly between the reference electrodes 1 and 3 and the impedance between the same electrodes when measurement was performed through electrode 2 equals twice the sum of contact electrode-skin and skin impedances values of the electrode I2. A similar approach will yield the value for I5. Because all the required values are measurable, it is possible to obtain the ITI value using this algorithm [14, 15, 16, 17, 18, 19, 20]. This approach results in about a threefold increase in the sensitivity of monitoring and eliminates the drift of the skin-to-electrode impedances. The influence of cardiac cycles, respiration, and other incidental factors on the ITI data was eliminated by repeating the ITI measurement ten times during 1 minute and calculating the average values. Only average values of the initial and current ITI measurements were used for predicting the cardiogenic pulmonary edema. The period of EGM's stabilization after switching on the device was estimated by the electronic simulator of the patient's chest and found to be equal to 15 min, thus initial measurements were performed 15 min after switching on the device.

ITI measurements and clinical examinations were performed immediately upon the patient's recruitment into the study when there were no clinical or radiographic signs of the cardiogenic pulmonary edema. The first ITI measurement in each patient was expressed in ohms and used as his/her individual initial value (baseline). The individual ITI values varied widely (from 40 to 100 Ω). Because there is no normative ITI value, it is impossible to directly compare the results of ITI measurements among individuals, and therefore standardization of the ITI value is needed for practical application. For this purpose the value of the first ITI measurement of each patient is accepted as 100%, thus eliminating individual differences at baseline. Results of all further measurements are calculated as deviations of ITI values from baseline and expressed in percentage. This operation eliminates the incompatibility of individual differences in ITI values while preserving the ability to observe the ITI changes during monitoring in each patient. All subsequent measurements that were performed at 30-min intervals and expressed as percentage of deviation could be used for prediction of the cardiogenic pulmonary edema onset. Respiration and pulse rate, auscultation lung findings and blood oxygen saturation levels were recorded every 30 min along with ITI. Thirty-minute intervals between measurements were chosen because that figure was estimated to be the time required for slowing down or stopping the further development of the cardiogenic pulmonary edema by medications, such as furosemide, nitrates and oxygen [24, 25, 26, 27, 28]. The collection of ITI data was discontinued when either a clinical onset of the cardiogenic pulmonary edema was detected or when 24 h had elapsed without evidence of cardiogenic pulmonary edema development. The clinical observation of the patients, however, was not interrupted.

The first chest radiographic examination for each study participant was used to exclude the cases in which the cardiogenic pulmonary edema was already present at the beginning of the monitoring procedure. Subsequent chest radiographs were performed in all patients with fully developed the cardiogenic pulmonary edema and the films were interpreted retrospectively by six senior radiologists who were blinded to the patients' clinical condition and ITI results. The interinvestigator coefficient of agreement for chest radiographic examinations was high ($\kappa = 0.95$). The clinicians were blinded to the results of the ITI measurements. All the results were expressed by their mean ± SD and range. The normality of each ITI variable's distribution in each array was verified by a descriptive statistics program. Current ITI values were presented as deviation from the initial value (baseline) expressed in percentage.

For practical purposes ranges rather than averages of monitored values were used because the reliable prediction of the cardiogenic pulmonary edema is possible only if there is a gap between limits of ITI ranges in the patients with and without the cardiogenic pulmonary edema. A one-sided confidence interval approach based on the uniform distribution model [29] was used to determine the upper and lower limits of ITI results in the compared groups of the patients. The significance of the differences between averaged values was evaluated by the *t* test. The influence of patients' demographic data on absolute and relative ITI values was studied by the calculation of Pearson's correlation coefficient *r* [29] between age, height, weight, and ITI values. The effect of gender on ITI was evaluated by com-

paring the values of ITI by the Mann-Whitney test [29]. The ITI cutoff point for early prediction of cardiogenic pulmonary edema was calculated by the receiver operating characteristic (ROC) model [29] that is generated by plotting the method's sensitivity against its specificity.

The patients were divided into two groups: those who did not develop the cardiogenic pulmonary edema during monitoring (group DNDE) and those who did (group DE). The mean age (64 ± 11 years, range 27–73) and the male/female ratio (2.3/1) were slightly lower in group DNDE than group DE (69 ± 11 years, range 46–83; and 3/1; Table 1). The normality of the ITI variables' distributions in each group was confirmed. Group DNDE included 228 patients with heart diseases at risk of the cardiogenic pulmonary edema: 212 were admitted for acute coronary syndrome, 12 for chronic congestive heart failure and 4 for valvular heart disease (Table 1). Their mean initial ITI value was $62.5 \pm 14.46\,\Omega$. Group DE consisted of 37 patients, 34 of whom suffered from acute coronary syndrome, two from congestive heart failure, and one from valvular heart disease (Table 1). No patient in this group had any clinical or radiographic signs of cardiogenic pulmonary edema at the time of baseline ITI measurement. There was no statistically significant difference between the average initial ITI values of the two study groups: $62.5 \pm 14.5\,\Omega$ in group DNDE and $60.0 \pm 9.3\,\Omega$ in group DE.

The differences between these groups were considered significant when the appropriate p value was less than 0.05. Calculations were performed using SAS 8 software (SAS Institute, Cary, N.C., USA).

Results

During monitoring, fluctuation in ITI values in group DNDE patients ranged from +11% to –10.1% compared to baseline (Table 2). The maximum decrease in the individual ITI value (–10.1%) was recorded in only seven patients (3.3% of the group). The results can be illustrated by the following example. A 69-year-old patient was admitted with acute myocardial infarction. He was monitored by EGM for 24 h during which the clinical parameters: respiratory rate, pulse rate and oxygen saturation were simultaneously recorded. Figure 3 shows the results of a 7.5-h fragment of this recording: the decrease in ITI ranged from 0% to 6% compared to his baseline, and the fluctuations of the other indexes were small as well.

In all group DE patients the ITI value decreased by more than 12% ($p < 0.02$). This was observed 30 min

Table 2 Relative changes (%) in clinical and internal thoracic impedance (*ITI*) data for patients who did not develop cardiogenic pulmonary edema (study group DNDE)

	Initial values	Relative change	
		Range	Mean SD
Respiration rate (min)	17 ± 3.3	–16 to +18	0 ± 9.8
Pulse rate (min)	74 ± 12.6	–29 to +34	0 ± 11.7
Oxygen saturation (%)	96.7 ± 1.73	–3 to +3	0 ± 0.8
Crepitation, rhonchi	Absent	–	–
ITI values (Ω)	62.5 ± 14.55	–10.1 to +11.0	2.5 ± 4.62

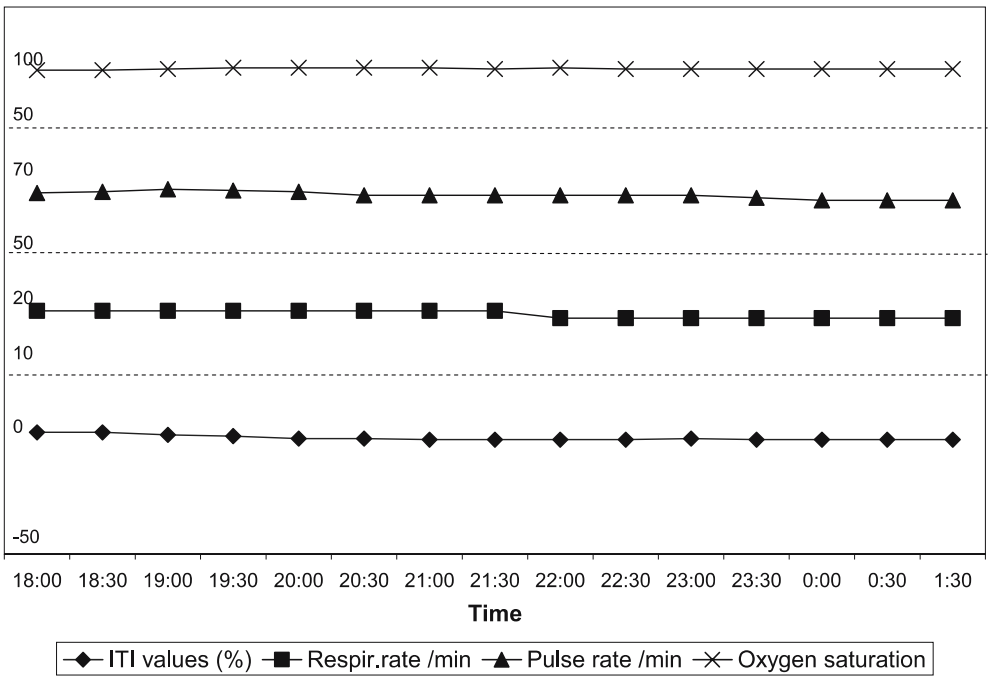

Fig. 3 Dynamics of clinical and internal thoracic impedance (*ITI*) data for a patient who did not develop cardiogenic pulmonary edema: study group DNDE

Table 3 Internal thoracic impedance (*ITI*) data for patients approaching cardiogenic pulmonary edema (*CPE*) onset (study group DE) (*UAP* unstable angina pectoris, *AMI* acute myocardial infarction)

Patient no.	Age (years)	Sex	Diagnosis	ITI values (Ω)				
				Initial[a]	90 min[b]	60 min[b]	30 min[b]	CPE onset
1	80	M	UAP	60	57	56	50	47
2	80	M	AMI	70	70	67	58	55
3	62	M	AMI	56	56	53	45	43
4	71	F	AMI	53	53	49	43	42
5	57	M	AMI	63	63	60	51	46
6	75	F	AMI	77	77	70	65	60
7	75	F	AMI	54	51	48	45	43
8	47	F	AMI	75	71	65	60	55
9	79	M	AMI	53	48	46	43	40
10	73	M	CHF	70	64	60	59	57
11	80	M	CHF	41	40	39	36	34
12	46	M	AMI	48	46	43	40	37
13	60	M	AMI	60	58	54	50	48
14	73	M	UAP	64	61	58	54	49
15	59	M	UAP	52	49	47	44	42
16	72	M	AMI	46	42	38	37	36
17	70	F	AMI	55	51	48	47	45
18	72	M	UAP	49	45	42	39	37
19	82	F	AMI	82	79	76	72	70
20	58	M	AMI	63	60	58	55	54
21	83	F	AMI	65	60	56	54	53
22	78	M	AMI	70	67	65	60	59
23	76	M	AMI	62	60	58	54	49
24	80	M	AMI	56	53	47	46	45
25	48	M	AMI	64	62	58	54	50
26	78	F	UAP	60	56	52	50	47
27	66	M	UAP	58	55	50	48	45
28	53	M	UAP	45	43	40	37	34
29	78	M	AMI	60	57	54	52	49
30	78	M	AMI	72	70	65	62	61
31	51	M	AMI	61	58	53	49	46
32	72	M	AMI	57	55	53	50	48
33	78	F	AMI	65	63	58	55	54
34	53	M	AMI	53	50	48	46	44
35	83	M	AMI	58	56	53	50	45
36	79	M	AMI	62	60	57	54	53
37	59	M	AMI	45	44	42	40	37
Mean $\pm$ SD	–	–	–	60 ± 9.3	57 ± 9.4	53 ± 8.4	50 ± 8.1	47 ± 8.0
p (t test)[c]	–	–	–	–	< 0.2	< 0.01	$< 10^{-4}$	$< 10^{-5}$

[a] Initial ITI value: baseline measured 2–20 h before the appearance of CPE symptoms [b] Time before the appearance of CPE symptoms [c] t test: two-samples assuming equal variances showing the differences from initial ITI values

before the appearance of the first clinical signs of cardiogenic pulmonary edema in 26 patients and at 1 hour before the appearance of the first clinical signs of cardiogenic pulmonary edema in 11 (Table 3). These ITI values differed significantly from those recorded in group DNDE ($p < 0.001$). The values of respiration and pulse rate as well of O_2 blood saturation had small symmetrical fluctuations during this period. Crepitation and pulmonary rales were absent throughout the entire period of monitoring until the onset of clinically detectable cardiogenic pulmonary edema (Table 4). The results in group DE can be illustrated by the following example. A 75-year-old patient was admitted with acute myocardial infarction. The decrease in ITI was 15% at 30 min before the appearance of the first clinical sign (crepitation) of the cardiogenic pulmonary edema (Fig. 4). The bold vertical line in Fig. 4 indicates the moment crepitation appeared in the lungs. The interval between the ITI falling 15% from initial value and the appearance of crepitation was 30 min. The evidence of successful prediction was confirmed only by the appearance of the typical clinical and radiographic signs of developed the cardiogenic pulmonary edema.

There was no correlation between the initial ITI values and patient's age ($r = +0.089$) or height ($r = -0.075$) in either groups. ITI was weakly correlated with patients' weight ($r = +0.26$, $p < 0.05$, group DNDE; $r = +0.22$, NS in group DE). The initial ITI values in all patients and the

Table 4 Relative changes (%) of clinical and internal thoracic impedance (ITI) data for patients approaching cardiogenic pulmonary edema (*CPE*) onset (study group DE)

	Initial values	Relative change at 90 min[a]		Relative change at 60 min[a]		Relative change at 30 min[a]	
		Range	Mean SD	Range	Mean SD	Range	Mean SD
Respiration rate (min)	18 ± 2.2	–5 to +5	0 ± 3.9	–5 to +6	1 ± 6.7	–4 to +12	3 ± 6.1
Pulse rate (min)	79 ± 10.6	–9.2 to +13.9	0 ± 5.2	–11.4 to +21.6	0 ± 6.8	–18.2 to +33.1	2 ± 9.2
Oxygen saturation 96.8 ± 1.40 (%)		–1 to +1	0 ± 0.6	–1 to +1	0 ± 0.6	–2 to +1	0 ± 0.7
Crepitation, rhonchi	Absent	–	–	–	–	–	–
ITI values (Ω)	60.0 ± 9.34	0 to –9	–4 ± 2.5	–4 to –17	–6 ± 2.0	–12 to –20	–16 ± 2.5

[a] Time before the appearance of CPE symptoms

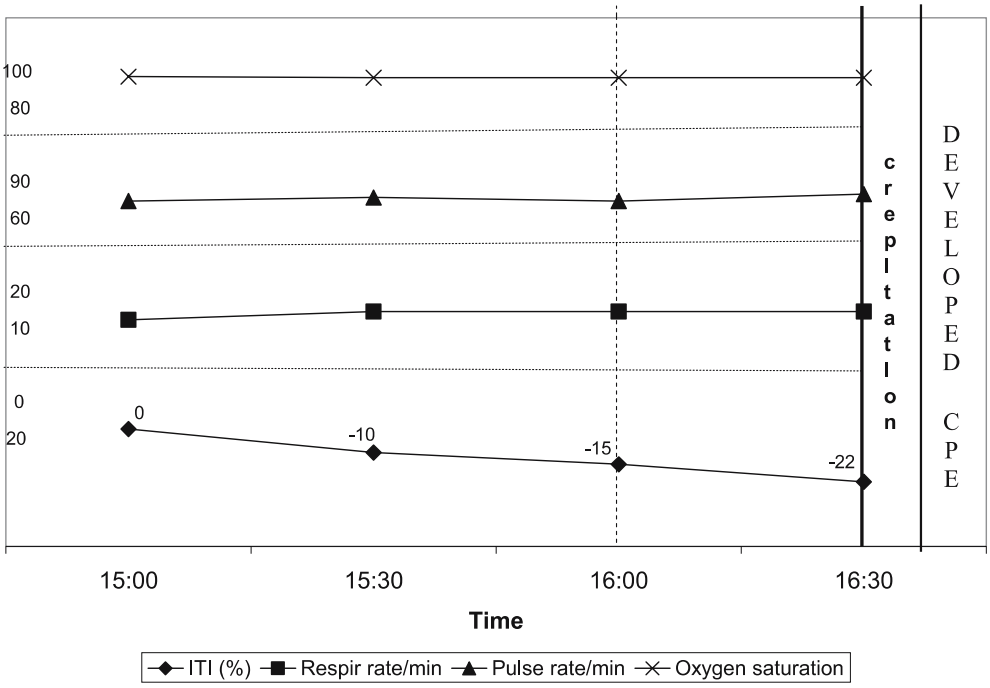

Fig. 4 Dynamics of clinical and internal thoracic impedance (*ITI*) data for a patient who developed cardiogenic pulmonary edema (*CPE*): study group DE

ITI at 30 min before the clinical onset of the cardiogenic pulmonary edema was on the average 1.2 times greater in women than in men ($p < 0.01$).

Discussion

This study shows that continuous ITI monitoring by EGM RS-207 of patients at risk of the cardiogenic pulmonary edema can predict its impending development before the appearance of clinical signs. All 37 patients who developed CPE had a decrease in their ITI value of more than 12% compared to their baseline values at 30–60 min before the actual onset of cardiogenic pulmonary edema. Clinical signs, such as crepitation and rales, were still absent at the time when ITI reached the limit of –12% from baseline, while respiratory rate and oxygen blood saturation remained relative stable in these patients (group DE). In contrast, no patient without clinical CPE had an ITI decrease in more than 10.1% (group DNDE). The fact that the ranges of relative changes in ITI in the patients of the two groups did not overlap suggests that ITI may be used as a predictive index for cardiogenic pulmonary edema.

Using EGM for predicting impending the cardiogenic pulmonary edema involved assigning definitions for the ITI "baseline" and the "optimal limit of ITI predictive value" as well as deciding appropriate cutoff points. The term "baseline" indicates the first ITI value recorded for a given patient at potential risk of developing the cardiogenic pulmonary edema. These values were determined when there was no difference either in clinical examination or in radiographic tests between the 265 patients. Moreover, there was no statistical difference between the average initial ITI values of the two study groups: 62.5 ± 14.55 Ω in group DNDE and 60.0 ± 9.34 Ω in group DE ($p > 0.05$). Given these values in the absence of clinical evidence of cardiogenic pulmonary edema, the results of the first measurement could be considered as being "baseline."

Analysis of the data of the 37 patients who developed cardiogenic pulmonary edema after ITI prediction

Table 5 Determination of internal thoracic impedance (*ITI*) predictive value

ITI predictive value (%)	Probability of false-positive errors (%)	Probability of false-negative errors (%)
–10	5×10^{-3}	6×10^{-6}
–10.5	2×10^{-4}	2×10^{-4}
–11	6×10^{-6}	5×10^{-3}
–11.5	2×10^{-7}	0.1
–12	1×10^{-8}	2.0

(group DE), based on the one-sided confidence interval approach [29], showed that the probability of having a decrease of ITI of less than 12% before the cardiogenic pulmonary edema onset is 2%. Specificity and sensitivity for various ITI predictive values were compared according to the procedure described [30]. As can be seen from the results listed in Table 5, –10% is the ITI predictive value that practically eliminates the chance of false-negative predictions.

The present results on larger numbers of patients confirm our preliminary findings that had been based on six patients [15]. The present data may be used for the development of a practical approach for prediction of the cardiogenic pulmonary edema in the hospital setting and of preventive treatment of the condition.

We conclude that continuous monitoring of ITI by EGM is an accurate and reliable method for early prediction of the cardiogenic pulmonary edema before the appearance of clinical signs in patients at risk for cardiogenic pulmonary edema. A decrease in ITI of more than 12% from baseline indicates that the onset of the cardiogenic pulmonary edema is likely to occur 30–60 min later.

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