Preventive treatment of alveolar pulmonary edema of cardiogenic origin

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Abstract

Objective To evaluate the efficacy of preventive treatment (PT) on alveolar pulmonary edema (APE) of cardiogenic origin using a monitor based on principles of internal thoracic impedance (ITI) measurements. Methods We conducted blinded clinical trials on patients with ST-elevation myocardial infarction (STEMI) and monitored whether the condition would progress to APE. ITI was measured non-invasively by the Edema Guard Monitor (EGM, model RS-207) every 30 min. The measurement threshold for the diagnosis of APE was fixed at > 12% decrease in ITI from baseline as described in our methodology. The patients were divided into one group that received standard treatment after the appearance of clinical signs of APE without considering the prediction of APE by EGM devise (Group 1), and another group of asymptomatic patients in whom development of APE was predicted by using only EGM measurements (Group 2). The latter participants’ PT consisted of furosemide, intravenous nitroglycerine and supplemental oxygen. Results One-hundred and fifty patients with acute STEMI were enrolled into this study. Group 1 included 100 patients (53% males, age 64.1 ± 12.6 years). Treatment was started after the clinical appearance of overt signs of APE. Group 2 included 50 patients (54% males, age 65.2 ± 11.9 years) who received PT based on EGM measurements. Group 2 had significantly fewer cases of APE (n = 4, 8%) than Group 1 (n = 100, 100%) (P < 0.001). While APE was lethal in six (6%) Group 1 patients, PT resulted in prompt resolution of APE in all four (8%) Group 2 patients. Conclusion ITI is a useful modality for early diagnosis and PT of pulmonary edema of cardiogenic origin.


Keywords: Cardiogenic pulmonary edema; Early prediction; Preventive treatment; Monitoring cardiac patients; Internal thoracic impedance

1 Introduction

Currently, therapeutic intervention for acute heart failure (HF) is initiated only after the appearance of clinical signs that characterize the alveolar stage of pulmonary edema (APE). Advanced stages of APE cause considerable distress to patients and are difficult to treat because of a vicious cycle in which deteriorating arterial oxygen saturation due to pulmonary congestion leads to failing myocardial function which, in turn, leads to further decrease in oxygen saturation. Preventive treatment (PT) of APE might interrupt its development by aborting the vicious cycle that progressively leads to HF. The only possible solution for early diagnosis (i.e., before the appearance of clinical symptoms) and PT of APE would be continuous monitoring of every patient at risk of developing acute HF. The existing methods of detecting APE during the preclinical stage are invasive, not reliable enough and cannot be used for predicting APE. Accumulation of water in the lung leads to a decrease in its impedance. The non-invasive impedance plethysmographs are unsuitable for early prediction of ACE, mainly because of their low sensitivity. They cannot isolate or differentiate the measurement of electrical resistance of the lungs from the electrical resistance of all
the other organs of the thorax because they measure electrical resistance along the thorax. Most of the electric current passes through the carotid arteries and aorta because blood is a better conductor than other living tissues. Devices, such as plethysmographs, are unable to distinguish between the small changes of the electric current passing through the lungs at the onset of pulmonary edema from the background noises of the thoracic electrical circuit. Yu et al. recently reported successful prediction of APE by surgically implanting an impedance plethysmograph integrated into a pacemaker (Opti-Vol System) with electrodes located in the thorax. These authors demonstrated that deducing the value of the skin-to-electrode contact electrical resistance from the value of the transthoracic electrical resistance makes the impedance of the plethysmograph sufficiently sensitive for predicting APE.

We used the Edema Guard Monitor (EGM) model RS-207 (RS Medical Monitoring Ltd., Jerusalem, Israel) for predicting APE. We had previously reported preliminary results on the effective use of EGM for early prediction of APE. The purpose of the current study was not only to further examine early diagnosis of APE, but also to evaluate the results of PT for APE. The treatment was administered to one group of patients on the basis of early prediction of APE by EGM measurements. The clinical outcomes of those patients were compared to the other group of well-matched patients that received standard treatment consistent with the appearance of clinical symptoms.

2 Methods

2.1 Study design

The protocol of the investigation was approved by the local Ethical Commission of the participating Medical Center and the Israeli Ministry of Health. The participants of the study were recruited from all patients treated in our institution between 2008–2010 for ST-elevation acute myocardial infarction (STEMI) without clinical and radiographic signs of APE and without a history of HF. Monitoring via the EGM was used to predict the development of APE in those patients, and it was initiated at the time of their admission to the hospital. All subsequent measurements were performed at 30 min intervals. APE was predicted if the internal thoracic impedance (ITI) value decreased by > 12% from baseline, which is the level established as the APE prediction criterion in our previous studies. Patients who were randomly assigned to Group 1 were treated only after the appearance of the clinical and X-ray signs of APE, without considering the prediction of APE by EGM. The patients who were randomly assigned to Group 2 received PT after EGM monitoring predicted APE.

2.2 Clinical and laboratory measurements and treatment

Both study groups were matched for sex, age, body mass index (BMI) and initial ITI value. The patients received primary percutaneous intervention (PCI) or thrombolytic therapy by streptokinase at the time of admission. Patients for whom thrombolytic treatment failed to produce signs of reperfusion were referred to rescue PCI. Additional treatment included oxygen inhalation, aspirin, clopidogrel, β-blockers, angiotensin-converting enzyme inhibitors and statins, and low molecular weight heparin. Respiration and pulse rate, auscultation lung findings and blood oxygen saturation levels were recorded every 30 min along with ITI. The EGM monitoring continued during hospitalization from 72 h to 480 h periods.

The first chest X-ray examination of each study participant was used to exclude the ones who were diagnosed as having APE at presentation. Additional chest X-rays were performed in all patients who subsequently developed APE, and the films were interpreted retrospectively by six senior radiologists who were unaware of the patients’ clinical condition and ITI values. The inter-investigator coefficient of agreement for chest X-ray examinations was high (kappa = 0.95).

2.3 EGM monitor description and assessment of use

The EGM differs from all the existing, non-invasive plethysmographs by measuring the electrical resistance of the right lung across the right half of the thorax. The EGM-measured electrical field is distanced from the thoracic large blood vessels to the area of the right lung (Figures 1 and 2). The low sensitivity of the device for measuring transthoracic electrical resistance was found to be due to high skin-to-electrode contact resistance and its drift during monitoring. The sum of the values of the two skin-to-electrode contact electrical resistance is much higher than lung electrical resistance (i.e., 15 times), making it impossible to reliably detect small changes of the electrical resistance of the lung during the initial anatomical changes at the onset of APE. The EGM design has solved the problem of high skin-to-electrode electrical resistance and its drift by calculating this resistance and subtracting its value from the transthoracic electrical resistance value. The result of the above-described actions was a sharp increase of the monitor’s sensitivity (i.e., 16 times) which measures only ITI, a value that is roughly equal to lung impedance. Thus, the EGM’s high increased sensitivity and the elimination of contact electrode drift allow for the prediction of APE by reliable measurement of internal thoracic electrical resistance (impedance, ITI).
Figure 1. The structure of transthoracic impedance. 1: Internal thoracic impedance, 50–80 Ohm; 2: Transthoracic impedance, 1050–1280 Ohm; 3: Each skin-electrode impedance, 500–600 Ohm.

Monitoring of pulmonary edema is carried out by placing three electrodes on the front and three electrodes on the back of the thorax (Figure 1). The impedance measurement between electrodes 2 and 5, Figure 2) produces the transthoracic impedance (TTI) value identified as Item 2. The reference electrodes 1, 3, 4, and 6 are symmetrically attached in pairs to the thorax on both sides of electrodes 2 and 5 in one line. All six electrodes are connected to the impedance monitor. The TTI value may be presented in the following way:

\[ TTI = ITI + I_2 + I_5 \]  \[ (1) \]

where ITI indicates internal thoracic impedance, I2 represents the impedance values of the second electrode, i.e., the contact between the skin and the second electrode and the skin proper under the second electrode, and I5 represents impedance of the fifth electrode, i.e., the contact between skin and the fifth electrode and skin itself under the fifth electrode. Therefore:

\[ ITI = TTI - I_2 - I_5 \]  \[ (2) \]

Impedance measurements are conducted between electrodes 4 and 5 (IE), 5 and 6 (IF), and 4 and 6 (IG). The difference between the impedance measured between electrodes 1 and 3 directly and the impedance between the same electrodes when measured through electrode 2 equals twice the I2. This may be presented as follows:

\[ IA + IB - IC = 2 \times I_2 \]

ITI values correspond to measurements of the electrical resistance as if they were performed via surgically placed subcutaneous electrodes. The electrical resistance of the lung constitutes the major part of the ITI value. Individual ITI values vary widely (from 40 ohms up to 100 ohms).[16–18] In order to standardize the ITI value for practical applications, the value of the first ITI measurement of each patient is set at 0%, thus eliminating individual differences at baseline. Results of all further measurements are calculated as deviations of ITI values from baseline and they are expressed in percentages.

2.4 PT

PT consisted of additional administration of furosemide 40–160 mg/day and supplemental oxygen.[23,25,26] Infusion of nitrates was started or increased in all patients with a systolic blood pressure > 100 mmHg.[27] EGM monitoring helped to determine the optimal dosage of the PT medications: this dosage was considered sufficient for effective treatment when the ITI value began to rise. Notably, the ITI measurement is the only useful method for monitoring the dosage of medications administrated to prevent APE since clinical criteria are absent during the entire period of PT and EGM monitoring.

2.5 Outcome ascertainment

The criterion of success in PT was defined as the absence, or alleviation, of APE in Group 2 patients who received PT after APE prediction by EGM compared to the Group 1 patients who did not receive PT whether or not there had been APE prediction by EGM. APE was diagnosed in Group 1 by the presence of the following clinical signs: dyspnea at rest, cyanosis, pulmonary rales, crepitation, arterial hypoxemia and X-ray evidence of pulmonary edema.[23–25]

2.6 Statistical analysis

The evaluation of the significance of the difference between the results received from the two study groups, expressed as means ± SD, was performed by Student’s t-test. The normality of each ITI variable’s distribution in each array was verified by Excel’s descriptive statistics. The effectiveness of PT for APE was assessed by the Pearson’s \( \chi^2 \) index in the form of “table of the four fields”. The results of the
comparisons were considered significant when $P < 0.05$. Calculations were performed using SAS 8 software (SAS Institute, Cary, NC).

3 Results

The study cohort included 150 patients with no previous history of HF who were admitted with STEMI and monitored by EGM. All of the patients underwent primary PCI and received standard treatment consisting of oxygen mask, intravenous or oral nitroglycerine, subcutaneous low molecular weight heparin, beta-blockers, ACE or ARB inhibitors and statins.[23–26] One-hundred patients were randomly assigned to Group 1 and received standard treatment for pulmonary edema only after the appearance of clinical and roentgenological signs of APE with no relation to monitor ITI changes. The treatment for APE included oxygen mask, large doses of furosemide (80–160 mg), intravenous nitroglycerine, and morphine. The prediction APE was not considered in this group. The remaining 50 patients were randomly assigned to Group 2 and they were given PT when EGM monitoring predicted APE (a decrease in ITI $\geq 12\%$). The treatment, if needed, included mainly furosemide, oxygen and intravenous nitroglycerine. Those patients did not receive other additional medicine, such as morphine, because they were asymptomatic. The demographic data of both groups are listed in Table 1. Groups 1 and 2 were matched for age ($64.1 \pm 12.6$ years and $65.2 \pm 11.9$ years, respectively, $P = \text{NS}$) and gender (53% and 54% makes, respectively, $P = \text{NS}$) (Table 1). Their average BMI was 26.6 $\pm$ 13.9 kg/m$^2$ and 27.5 $\pm$ 3.5 kg/m$^2$ ($P = \text{NS}$). There were no differences in laboratory data relevant to HF development, such as left ventricular ejection fraction (LVEF), creatinine kinase level, or number of patients with STEMI ($P = \text{NS}$) (Table 1). Some differences were noted in serum glutamate pyruvate transaminase, however, all the values were within normal limits. Finally, there was no significant difference in their average baseline ITI values.

None of the patients in either group had any clinical or roentgenological signs of APE at the time of baseline ITI measurements. APE developed in all (100%) of Group 1 patients in comparison to 4 (8%) Group 2 patients ($P < 0.001$): one of the latter patients (2%) developed moderate APE and the other 3 (6%) developed mild APE. The APE in Group 1 was mild in 51 (51%) patients, moderate in 24 (24%) and severe in 25 (25%) (Table 2). There were no significant differences of ITI values between the mild, moderate and severe pulmonary edema cases at the time of APE prediction ($P = \text{NS}$, Table 2).

The initial ITI in both groups was similar ($57.5 \pm 15.4$ ohms in Group 1 and $56.4 \pm 13.4$ ohms in Group 2; $P = \text{NS}$). Six Group 1 patients died of APE (6%; Table 2). Their decrease of ITI at the time of EGM prediction was different from that of the severe APE in the Group 1 patients ($15.0\% \pm 2.47\% \text{ vs. } 13.3\% \pm 1.34\%$, $P < 0.01$) (Table 2). In contrast, there were no fatalities in Group 2 (0 vs. 6 patients, $P < 0.001$ compared to Group 1) (Table 2).

Importantly, none of the first clinical signs appeared in any of the patients earlier than 30 min after EGM prediction: they appeared between 30–60 min in 14 patients and after

<table>
<thead>
<tr>
<th>Table 1. Patients general data.</th>
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</thead>
<tbody>
<tr>
<td><strong>Group 1 (no PT) (n = 100)</strong></td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>HTN (%)</td>
</tr>
<tr>
<td>DM (%)</td>
</tr>
<tr>
<td>Smokers (%)</td>
</tr>
<tr>
<td>LVEF (%)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
</tr>
<tr>
<td>Anterior STEMI (%)</td>
</tr>
<tr>
<td>CK peak, u/L</td>
</tr>
<tr>
<td>Baseline ITI, ohms</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
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<tr>
<td>Hemoglobin, g/dL</td>
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</tbody>
</table>

Data are presented as mean ± SD. BMI: body mass index; CK: creatinine kinase; DM: diabetes mellitus; HTN: hypertension; ITI: internal thoracic impedance; LVEF: left ventricular ejection fraction; NS: not significant; PT: preventive treatment; STEMI: ST-segment elevation myocardial infarction.
Table 2. Results of treatment in patients with predicted alveolar pulmonary edema (APE).

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Developed overt APE</th>
<th>APE predicted but not developed</th>
<th>Between mean ITI in both groups</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n = 100)</td>
<td>Severe (III) 25%</td>
<td>Moderate (II) 24%</td>
<td>Mild (I) 51%</td>
<td>0</td>
</tr>
<tr>
<td>Mean ITI decline at prediction</td>
<td>13.3 ± 1.34</td>
<td>13.6 ± 1.30</td>
<td>13.4 ± 1.28</td>
<td>92% (n = 46)</td>
</tr>
<tr>
<td>Group 2 (n = 50)</td>
<td>0</td>
<td>2% (n = 1)</td>
<td>6% (n = 3)</td>
<td>92% (n = 46)</td>
</tr>
<tr>
<td>Mean ITI decline at prediction</td>
<td>0</td>
<td>12.9 ± 1.0</td>
<td>13.3 ± 0.62</td>
<td>13.2 ± 0.8</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.

more than 60 min in 86 patients (86%) (Table 3). The average duration of hospitalization was 8.6 days for the Group 1 patients and 6.2 days (1.4 fold shorter, \( P < 0.001 \)) for the Group 2 patients.

According ITI measurements by EGM, PT resulted in significantly fewer life-threatening MI complications as APE events. Figure 3 is representative of ITI over time in Group 1: the vertical line in bold indicates the appearance of the first clinical sign (crepitation) of APE. Typical clinical and X-ray signs of APE appeared soon afterwards in the depicted patient. Figure 4 is an example of a typical Group 2 patient’s EGM reading. In that patient, PT by furosemide was started when the decrease of EGM value reached 14.5% (vertical line, Figure 3). The development of APE was arrested and the EGM value subsequently returned to a level higher than the initial one (Figure 4). Notably, parameters other than the EGM value failed to contribute to early APE prediction in any of the study patients.

4 Discussion

The significance of the current study, unlike previous ones that dealt with early diagnosis, is that it affirms the efficacy of early treatment for APE. The results of this study demonstrate that continuous ITI monitoring of patients at risk of developing overt APE is a highly accurate method for predicting it with the intent of implementing appropriate preventive therapeutic management. The patients were given PT based on ITI measurements, before the presentation of clinical symptoms or roentgenological signs. Typical APE developed in all 100 patients of Group 1, whose APE onset was predicted, but no PT was given, and six died. In contrast,
APE development was completely arrested in the majority (92%) of Group 2 patients who underwent early intervention, its progression was significantly alleviated in 8%, and there were no fatalities. The benefits of PT for APE were also reflected by the shorter periods of hospitalization for the treated patients. Importantly, our data provide evidence that the 30 min interval between prediction of APE and the appearance of its first clinical signs is sufficient for the successful prevention of APE’s clinical onset.

It is worth pointing out that the similarity of average values of basic anthropologic characteristics (age, gender, BMI) and LVEF, STEMI, as well as of the initial ITI values and the ITI values at the moment of APE prediction, support the contention that the studied groups were comparable. The similarity of average values of the initial ITI in both groups is evidence that the initial condition of the right lung was similar among all the patients. Thus, the anthropologic indexes and initial values of ITI made no significant contribution to the efficacy of early preventive treatment and its outcome.

We contend that the EGM device will be used in the future not only for hospitalized patients, but for outpatients with moderate or severe HF as well, and make it possible for them to receive PT with no need for hospitalization.

In conclusion, the monitoring of ITI by EGM using the described technique allows early diagnosis and prompt administration of treatment of life-threatening HF complications before the appearance of its clinical symptoms and signs, thus turning the treatment of APE from an acute corrective procedure to a predictive, and therefore, preventive one.

References


