Highly sensitive monitoring of chest wall dynamics and acoustics provides diverse valuable information for evaluating ventilation and diagnosing pneumothorax

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Preterm infants often suffer from significant lung dysfunction due to surfactant deficiency and immaturity of the respiratory system (13, 27, 29). These critically ill children require continuous monitoring over extended periods to identify and prevent the development of severe complications, such as pneumothorax (PTX), and to secure appropriate oxygen saturation of the blood (29). According to the US National Library of Medicine (34a), PTX is an accumulation of air inside the chest and around the lungs (pleural space), which may eventually lead to a lung collapse and to hemodynamic deterioration. However, despite the tight monitoring, using current monitoring methods in neonatal intensive care units (ICUs), studies have revealed that the delay from PTX onset to diagnosis and treatment ranges from 45 to 660 min (median 127 min) (22, 23). An early diagnosis would allow treatment, lessening the potential for irreversible damage to occur (22, 38). Moreover, almost one-half of the life-threatening events in neonate and pediatric ICUs fail to be detected by the available monitoring devices and are discerned by the attending staff (10, 38).

Pulse oximetry has been used for several decades as an easy means of noninvasively measuring oxygen saturation and to assess the adequacy of lung ventilation (34, 40). However, when lung ventilation deteriorates, the body recruits physiological compensatory mechanisms to maintain the normal oxygen saturation level, and consequently, the oxygen saturation can decrease suddenly and at a relatively late stage (19, 26, 39). Moreover, pulse oximetry relies on pulsatile blood flow; thus body motion, poor peripheral circulation, vasoconstriction, and hypotension can create artifacts (26, 40). In addition, the sensor’s effectiveness is subject to ambient light and skin pigmentation of the patient (4).

Other methods employed for respiratory monitoring are respiratory inductance plethysmography (RIP), and electrical impedance tomography (EIT). RIP bands are fitted and secured around the rib cage and abdomen to indirectly assess volume change in their displacement (13). Physical effort is required to stretch these bands, which places additional load onto the premature infant, and the associated friction peels the tender and sensitive skin of premature neonates. EIT is a technique that measures potential differences on the surface of the body using an array of multiple electrodes. Electrodes are equidistantly positioned around the body, and adjacent electrodes inject small alternating currents (5 mA between 50 and 80 kHz) (5, 9). The recorded impedance changes correspond to lung volume changes. The EIT technique is limited due to a low signal-to-noise ratio and low spatial resolution (5, 9, 29). A bioimpedance hybrid technique of EIT and transthoracic impedance measurement have been developed (43, 44) as a way to improve the practicality of EIT. These two methods are cumbersome for continuous monitoring in the setting of neonatal ICUs.

Measurement of acceleration, such as gait analysis (11) and acquisition of heart rate, heart rate variability, respiration rate, and snoring sounds during sleep apnea screening (24, 25), provides valuable information that is used to distinguish between different types of biomechanical pathologies. An accelerometer positioned on the thorax, near the heart, has been shown to identify changes in the respiration rhythm (14–16).
In an attempt to quantify respiratory effort, the entropy from an accelerometer placed on the costal wall was used for assessing the inspiratory pressure (32, 33).

Our group recently described the feasibility and potential utility of miniature accelerometers, attached to both chest wall sides, in monitoring the amplitude and symmetry of lung ventilation in infants ventilated with high-frequency (HF) oscillatory ventilation (37). The high sensitivity to changes in lung ventilation was further validated in rabbits (36). However, in both studies, we only described the changes in the amplitude of the tidal displacement of the chest wall.

The hypothesis underlying the present study is that bilateral measurement of the ventilation dynamics and the acoustic sounds, by miniature and sensitive accelerometers, innately provides an assortment of diverse characteristics that are related to changes in respiratory function. These quantifiable characteristics can be exploited toward understanding the development of respiratory distress and can even be used for early detection of deteriorating ventilation, as in cases of slowly progressing PTX.

The study strongly supports this hypothesis, and miniature accelerometers placed on each side of the chest can effectively, conveniently, and nonconstrictively provide large quantities of data and diverse indexes that relate to the low frequency (LF) of chest dynamics and the HF acoustics of breath sounds. Interestingly, the chest dynamic provides more instrumental indexes for both early detection and side localization.

**METHODS**

**Experimental setup.** Rabbits were chosen for the experimental model due to their size, weight, and respiratory and cardiac functions resembling those of preterm infants (17). Experiments were performed on nine healthy New Zealand White rabbits with the approval of the Institutional Ethics Committee for the Care and Use of Animals. The rabbits were anesthetized via an intramuscular injection of xylazine (5 mg/kg), ketamine (35 mg/kg), and acetylcholine (1 mg/kg), followed by one-third of a dose every 20 min. The rabbit was placed in the supine position, intubated through tracheotomy, and ventilated with a pressure-controlled ventilator (SLE 2000, SLE, Surrey, UK), under continuous mandatory ventilation. Initial ventilator settings were a respiratory rate of 20 breaths/min, a peak inspiratory pressure of 18 cmH₂O, and positive end-expiratory pressure of 3 cmH₂O (36). These values were adjusted for each animal to maintain normal arterial blood gases.

Three miniature accelerometers (weighing <1 g each) were attached to the rabbit, as previously described (36). The acceleration signals were acquired using the Pneumonitor (Pneumedicare, Yokneam, Israel). Only signals detected by the two chest sensors were employed in the analysis, while data collected by the abdominal sensor were disregarded during implementation of the algorithms presented here.

PTX was induced in nine rabbits by inserting a chest tube into the left (5 rabbits) or right (4 rabbits) pleural space, in the 10th intercostal space at the midaxillary line (36). The tube was connected to an automatic syringe pump (Graseby 3100, SIMS Graseby). Once arterial blood gases were stabilized and the ventilation parameters were set, baseline (BL) measurements were recorded for at least 5 min. PTX was gradually induced by injection of air into the pleural space, via the inserted chest tube, at a constant rate of 1 ml/min. Time zero was defined as the time when air injection was initiated. Signs of desaturation and overt respiratory distress are expected to lead to the detection of progressing PTX in the clinics. Therefore, injection continued until arterial O₂ saturation from pulse oximetry (SpO₂) dropped <90% or until cardiovascular decompensation with vigorous spontaneous breathing due to respiratory distress was evident, whichever occurred first (36). This time location, at which PTX is usually detected in the clinics, was designated as the end of the experiment (t PTX). Thereafter air injection was stopped. Throughout the experiments, PTX was confirmed by transillumination of the chest. On completion of the experiment, animals were euthanized by pentobarbital overdose.

**Signal processing.** The data acquisition system sampled all the channels at 5 kHz. All of the data were initially down-sampled to 500 Hz. The signals acquired from the accelerometers included low subsonic frequency (LF) of lung ventilation dynamics and HF acoustics. The acceleration channels were analyzed separately at LF and HF bands. For LF analysis, the signals were filtered with a zero-phase 10-Hz LP finite impulse response filter. Following filtering, the LF data were analyzed by averaging 10 consecutive breaths, where the pressure signal was used as a trigger to align single breaths and to improve the signal-to-noise ratio. Parameters of interest were then extracted from this averaged breath. For HF analysis, signals were band-pass filtered from 10 to 200 Hz. As the HF band did not include any dynamics, no averaged breath was used; instead, a moving 10-s window with 50% overlap was implemented.

The following indexes were calculated and monitored to identify temporal patterns with progressing PTX: tilt, amplitude of tidal breath displacement, LF energy, HF energy, autoregressive (AR) poles, and HF entropy. These indexes were calculated at the PTX side and at the contralateral side.

The tilt of the sensor at end expiration demonstrated how the chest volume changed throughout the experiment. The tilt was calculated from the trajectories of the earth gravity on the tangential accelerometers, within each sensor.

The acceleration axis perpendicular to the body surface (aRAD) was thought to be the second derivative of the displacement of the chest. Therefore, aRAD was integrated twice, and the range of the displacement provided the amplitude of tidal breath displacement.

The energy, unlike the amplitude, was calculated directly from the averaged breath, as the integral of the square of the acquired signal over the entire breath period. The LF and HF energy were obtained from the same equation, but the LF energy and the HF energy utilized the above LF and HF data, respectively.

An AR model was used to model each side of the chest separately. Based on the Akaike information criterion, a three-pole AR model was chosen to represent each sensor signal. These poles are a description of the system (chest) transfer function, and temporal changes of these poles indicated that the system was changing with time (28). As PTX progresses, the system (chest) transfer function was expected to change, and the pole movement would reflect these changes.

Only two parameters were calculated from the HF band: HF energy and Shannon entropy. The entropy was calculated by estimating the histogram of the windowed HF signal. The entropy (H) was then defined as:

\[ H = -\sum E[a_{RAD}] \log_2[\sum E[a_{RAD}]], \]

where P is the probability obtained from the histogram and aRAD is HF aRAD.

Additional indexes were used to quantify the development of asymmetric ventilation and to define the affected side. The covariance measure was used to demonstrate the statistical synchrony between the two sides of the chest. The covariance between the left (L) and right (R) side averaged breath accelerations (a) was defined by σ(aL, aR) = E[(aL - μL)(aR - μR)], where E[] is the expectation operator, and μ is the mean of the signal.

The amplitude ratio, LF energy ratio, HF energy ratio, and HF entropy ratio are ratios expressing the relation between the parameters of the PTX and the contralateral sides. The product of these four ratios was also used to identify the side with PTX.

As each animal exhibited different temporal response to the experimental conditions, the time axis of each experiment was linearly aligned between the start of air injection (t = 0% tPTX) and 100% tPTX. Values for all 15 parameters were calculated at BL and at 5%
\(t_{PTX}\) increments up to, and including, 100\% \(t_{PTX}\). For each 5\% \(t_{PTX}\) increment, 1 min of data was averaged, resulting in nine data points for each increment (1 point for each animal) for the BL measurement and, similarly, nine data points for the PTX state.

K-means clustering, using a cosine distance measure, was implemented to separate the 18 observations into BL and PTX clusters. Each variable was statistically normalized by its mean and standard deviation to remove any weights that occurred from measuring different quantities. To reduce the dimensionality of the space, principal component analysis was performed, and the first three principal components were chosen, representing at least 80\% of the variance in the data. Clustering was performed at each 5\% \(t_{PTX}\) increment to determine how classification improved over time. Positive identification of the affected side was determined when a 20\% change from the BL value of this metric was observed.

RESULTS

The rabbits (\(n = 9\)) weighed 2.26 ± 0.44 kg and were ventilated at the following settings: respiratory rate of 19.22 ± 2.54 min\(^{-1}\), peak inspiratory pressure of 17.33 ± 1.32 cmH\(_2\)O, and positive end-expiratory pressure of 3.22 ± 0.44 cmH\(_2\)O.

The blood pressure, oxygen saturation, determined by the pulse oximetry, and the end-tidal CO\(_2\) (EtCO\(_2\)), from one experiment where PTX was induced on the right side of the chest, are presented in Fig. 1. Time zero denotes the start of air injection into the pleural space, and the time before zero is the BL measurement period. The second vertical line on each subplot indicates the time at which the SpO\(_2\) dropped to 90\%, in this case, at minute 92. Note the slow decline in blood pressure and the biphasic changes in the EtCO\(_2\). The EtCO\(_2\) initially declined, reaching the minimal value after \(\approx 45\) min. It increased to above the BL value, only after \(\approx 90\) min. Interestingly, changes in the SpO\(_2\) appeared relatively late. The SpO\(_2\) was stable for \(\approx 70\) min and only began to decline thereafter.

In only one of the nine animals did overt spontaneous breathing begin before the SpO\(_2\) dropped to below 90\%; \(t_{PTX}\) was designated at that time point. Similar changes in vital signs were observed in all the animals. The SpO\(_2\) remained stable until falling below 90\% at 52.3 ± 22.1 min. After the initial injection, a gradual decrease in EtCO\(_2\) continued until \(-26.7 ± 11.1\) min and then began to increase, approaching the BL EtCO\(_2\) value at 57.1 ± 23.9 min after initial injection.

The following figures (Figs. 2–5) present the various indexes derived from the miniature accelerometers, positioned on both sides of the chest, as collected in one animal with right-side PTX. Figure 2 demonstrates the changes in tilt of the sensors that were placed on the chest. The tilt increased with increasing PTX on both sides of the chest. The changes in amplitude and LF energy of the breaths normalized to their own BL values were greater and appeared earlier on the PTX side, as shown in Fig. 3.

For all of the experiments, three real AR poles were found. The first pole did not change with time and was ignored. In contrast, the changes in the second and third poles reflected the response to changes that occurred throughout the experiment, as shown in Fig. 4. Pole 2 exhibited greater changes than pole 3. Much like the amplitude, the response on the PTX side was stronger and earlier than that of the contralateral side.

Representative indexes quantifying the development of asymmetric changes between the left and right side of the chest are presented in Fig. 5. All plots were normalized to their own BL values. The upper subplot presents the covariance between the right and left sensor output. The covariance began to decrease after the initiation of air injection, and the deviation from unity indicated the development of progressing asymmetry. The following subplots, in conjunction, help identify the side on which PTX was induced (right side in this experiment), by observing the ratio between the data collected from both sides of the chest. The amplitude ratio, LF energy ratio, HF energy ratio, and HF entropy ratio all progressively decreased after PTX began.

The plots in Fig. 6 compile the data from all of the nine experiments and illustrate the mean and a 95\% confidence interval of temporal changes for the same parameters depicted in Fig. 5. All showed a decreasing trend after injection of air began. The last plot is a product of amplitude, LF energy, HF energy, and HF entropy ratios. This product of ratios accentuates the asymmetrical changes as a percentage of the BL value.
All described calculated parameters and ratios were significantly different at 100% $t_{PTX}$ (Table 1). Fifteen parameters were calculated for both sides of the chest; five parameters present the ratio between both sides of the chest. The tilt of the sensor increased on both sides of the chest, while values of all the other parameters decreased with progressing PTX.

Assessment of the temporal profiles of the various parameters was performed to test the feasibility of early detection of deteriorating ventilation. Table 2 compiles the mean ± SD at four time points: 30, 50, 70, and 100% $t_{PTX}$. The parameters are shown in the order in which they first became statistically significant and thus order of importance in earlier detection. For each parameter, an asterisk indicates whether the parameter was statistically significant at this time point. The temporal changes in the amplitude, covariance, and AR third pole were statistically significant already at 30% $t_{PTX}$. With increasing PTX, more parameters became statistically significant. For clarity and simplicity, the clustering at 30, 50, 70, and 100% $t_{PTX}$ of only the first two principal components is presented in Fig. 7. The clustering demonstrates that PTX could be correctly

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**Fig. 3.** Amplitude (Amp) and low-frequency (LF) energy of breaths decreased with progressing PTX. Stronger and faster responses developed at the PTX side (right).

**Fig. 4.** The second (black) and third (gray) poles of the autoregressive (AR) modeling of each sensor presented monotonic changes that were capable of tracking system changes with progressing PTX. The changes were greater on the side of PTX (right). Mag, magnitude.

**Fig. 5.** The covariance (top subplot) identified progressing asymmetric ventilation between the L and R sides. The ratios of the PTX side to contralateral side (PTX/Contra) of the amplitude, LF energy, high-frequency (HF) energy, and entropy (the successive subplots) detected the PTX side. All parameters are normalized to their own baseline value.
classified and differentiated from BL in six out of nine experiments (66.7%), as early as 30% \( t_{PTX} \), due to a significant cumulative deviation in parameters from the BL. The three animals that did not demonstrate large enough changes were clustered as BL; however, with increasing \( t_{PTX} \), these animals moved into the PTX cluster. At 50% \( t_{PTX} \), classification was correct in 88.9% of the cases. All of the experiments were correctly classified at 70% \( t_{PTX} \) and thereafter.

After successful detection of deteriorating ventilation, the side of the chest with the PTX was identified. Identification of the PTX side is based on detecting significant decreases in the amplitude, LF energy, HF energy, entropy, and the product of these parameters, as shown in Fig. 6. The ability to identify the PTX side is based on 20% change in ratio between the PTX and the contralateral side in each of these five parameters. The results for identification of the side afflicted with PTX are shown in Table 3. The product of the amplitude, LF energy, HF energy, and HF entropy ratios facilitated the identification of the side with PTX. After 50% \( t_{PTX} \), the side of PTX can be identified within a 95% confidence interval, based on this product, as shown in Fig. 6. The time lag between the initial classification time and 100% \( t_{PTX} \), in min, is shown in Table 4. All of the animals were correctly diagnosed with PTX, along with correct identification of the afflicted side within an average 34.1 ± 18.8 min before \( t_{PTX} \). On average, PTX was detected within −18.2 ± 6.1 min of initiation of injection, or after injection of 18.2 ± 6.1 ml of air.

DISCUSSION

Utilization of two accelerometers, positioned on both sides of the chest, has shown here to provide a plethora of information that is not detected by other simple respiratory monitoring techniques. The data were analyzed separately at LF and HF bands. The LF captures the chest wall dynamics (i.e., tilt, amplitude, LF energy, covariance, and AR poles), while the HF band provide parameters detectable by a physician via a stethoscope. The HF band data relates to breath sounds, from which HF energy and entropy can be monitored. Both bands detect parameters that significantly contributed to PTX detection and side localization. However, LF dynamics are more instrumental and more sensitive to early detection and asymmetry discrimination. This methodology combines a gamut of parameters in a manner that provides a measurement with 100% sensitivity at 70% \( t_{PTX} \), 34.1 ± 18.8 min before the development of desaturation and respiratory distress that are detectable by the current available technology in the clinical practice. Technically, this method is more convenient, since it requires significantly fewer sensors than EIT, and is less constrictive than RIP.

Early detection. Noninvasive monitoring of blood oxygen saturation and arterial blood sampling for blood-gas analyses

Table 1. \( P \) values of the changes in all the parameters at 100% \( t_{PTX} \) were statistically significant (\( P < 0.05 \))

<table>
<thead>
<tr>
<th>Parameter</th>
<th>100% ( t_{PTX} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔTilt (PTX)</td>
<td>0.0039</td>
</tr>
<tr>
<td>ΔTilt (contralateral)</td>
<td>0.0039</td>
</tr>
<tr>
<td>Amplitude (PTX)</td>
<td>0.0039</td>
</tr>
<tr>
<td>Amplitude (contralateral)</td>
<td>0.0195</td>
</tr>
<tr>
<td>Amplitude ratio</td>
<td>0.0039</td>
</tr>
<tr>
<td>Covariance left-right</td>
<td>0.0039</td>
</tr>
<tr>
<td>AR pole 2 (PTX)</td>
<td>0.0039</td>
</tr>
<tr>
<td>AR pole 2 (contralateral)</td>
<td>0.0039</td>
</tr>
<tr>
<td>AR pole 3 (PTX)</td>
<td>0.0039</td>
</tr>
<tr>
<td>AR pole 3 (contralateral)</td>
<td>0.0039</td>
</tr>
<tr>
<td>LF energy (PTX)</td>
<td>0.0039</td>
</tr>
<tr>
<td>LF energy (contralateral)</td>
<td>0.0039</td>
</tr>
<tr>
<td>LF energy ratio</td>
<td>0.0078</td>
</tr>
<tr>
<td>HF energy ratio</td>
<td>0.0039</td>
</tr>
<tr>
<td>HF entropy ratio</td>
<td>0.0039</td>
</tr>
</tbody>
</table>

\( t_{PTX} \), time of the end of experiments; Δ, change; AR, autoregressive; LF, low frequency; HF, high frequency.
are employed in ICUs to monitor lung function and the delivery of oxygen to the body. Regular, repetitive measurement of blood gases on premature infants is invasive, sporadic, and may cause too much blood loss in premature infants. Pulse oximetry is the simplest and most common mode for monitoring lung function in ICUs. Therefore, the time of detectable PTX (100% \( t_{PTX} \)) was designated based on the pulse oximetry measurement. However, the delay from PTX onset to diagnosis and treatment using current monitoring methods in neonatal ICUs ranges from 45 to 660 min (median 127 min) (22, 23).

PTX experiments in piglets showed that SpO\(_2\) remained stable at 95\%/11006 3%, up to 80 ml of injected air, and dropped to 89\%/11006 6% only after injection of 100 ml air (3). In another study in neonatal piglets, an injection of at least 20 ml/kg was required to cause a substantial change in SpO\(_2\) (19). A decrease to SpO\(_2\) below 90% in dogs was reached only after the bolus of

Table 2. Temporal changes of monitored parameters sorted by the time at which the parameter became statistically significant

<table>
<thead>
<tr>
<th>Parameter</th>
<th>30% ( t_{PTX} )</th>
<th>50% ( t_{PTX} )</th>
<th>70% ( t_{PTX} )</th>
<th>100% ( t_{PTX} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude (PTX)</td>
<td>0.82 ± 0.13*</td>
<td>0.67 ± 0.22*</td>
<td>0.56 ± 0.14*</td>
<td>0.36 ± 0.21*</td>
</tr>
<tr>
<td>Covariance left-right</td>
<td>0.83 ± 0.13*</td>
<td>0.75 ± 0.23*</td>
<td>0.61 ± 0.25*</td>
<td>0.42 ± 0.26*</td>
</tr>
<tr>
<td>AR pole 2 (PTX)</td>
<td>0.63 ± 0.07*</td>
<td>0.62 ± 0.06*</td>
<td>0.60 ± 0.07*</td>
<td>0.57 ± 0.06*</td>
</tr>
<tr>
<td>AR pole 3 (PTX)</td>
<td>0.38 ± 0.02*</td>
<td>0.38 ± 0.02*</td>
<td>0.37 ± 0.02*</td>
<td>0.36 ± 0.02*</td>
</tr>
<tr>
<td>LF energy (PTX)</td>
<td>0.80 ± 0.14</td>
<td>0.69 ± 0.22*</td>
<td>0.51 ± 0.19*</td>
<td>0.34 ± 0.18*</td>
</tr>
<tr>
<td>LF energy (contralateral)</td>
<td>0.84 ± 0.11</td>
<td>0.79 ± 0.14*</td>
<td>0.70 ± 0.13*</td>
<td>0.62 ± 0.21*</td>
</tr>
<tr>
<td>Amplitude ratio</td>
<td>0.91 ± 0.20</td>
<td>0.79 ± 0.25*</td>
<td>0.69 ± 0.12*</td>
<td>0.48 ± 0.19*</td>
</tr>
<tr>
<td>( \Delta )Tilt (PTX)</td>
<td>0.51 ± 0.77</td>
<td>1.00 ± 0.96*</td>
<td>1.53 ± 0.97*</td>
<td>2.14 ± 0.85*</td>
</tr>
<tr>
<td>( \Delta )Tilt (contralateral)</td>
<td>0.27 ± 0.45</td>
<td>0.72 ± 0.60*</td>
<td>1.21 ± 0.82*</td>
<td>1.82 ± 1.26*</td>
</tr>
<tr>
<td>AR pole 2 (contralateral)</td>
<td>0.69 ± 0.07</td>
<td>0.68 ± 0.07*</td>
<td>0.67 ± 0.07*</td>
<td>0.64 ± 0.06*</td>
</tr>
<tr>
<td>AR pole 3 (contralateral)</td>
<td>0.40 ± 0.02</td>
<td>0.40 ± 0.02*</td>
<td>0.39 ± 0.02*</td>
<td>0.38 ± 0.02*</td>
</tr>
<tr>
<td>LF energy ratio</td>
<td>0.96 ± 0.12</td>
<td>0.86 ± 0.16</td>
<td>0.71 ± 0.21*</td>
<td>0.54 ± 0.31*</td>
</tr>
<tr>
<td>HF energy ratio</td>
<td>0.79 ± 0.32</td>
<td>0.79 ± 0.46</td>
<td>0.67 ± 0.27*</td>
<td>0.64 ± 0.24*</td>
</tr>
<tr>
<td>Amplitude (contralateral)</td>
<td>0.94 ± 0.20</td>
<td>0.87 ± 0.17</td>
<td>0.81 ± 0.14</td>
<td>0.75 ± 0.26*</td>
</tr>
</tbody>
</table>

Values are means ± SD. *Time point at which the change in the particular parameter first became statically significant.

Fig. 7. The classification improved with progressing PTX and continuation of air injection into the pleural space. Data points classified as baseline are represented as solid circles (○), PTX are represented by open squares (□), and the center of each cluster by X. A: by 30% \( t_{PTX} \), correct classification was 66.7%. B: by 50% \( t_{PTX} \), correct classification was 88.9%. C: at 70% \( t_{PTX} \) and thereafter, 100% correct classification was attained, as at 100% \( t_{PTX} \) (D). PC1 and PC2, the first and the second principle components, respectively.
Table 3. Ability to detect asymmetric changes and identification of the side with PTX, with a 20% change in ratio threshold

<table>
<thead>
<tr>
<th>tPTX, %</th>
<th>Asymmetry Using Covariance</th>
<th>Asymmetry Using Product Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>0/6</td>
<td>4/6</td>
</tr>
<tr>
<td>50</td>
<td>6/8</td>
<td>9/9</td>
</tr>
<tr>
<td>70</td>
<td>8/9</td>
<td>9/9</td>
</tr>
<tr>
<td>100</td>
<td>8/9</td>
<td>9/9</td>
</tr>
</tbody>
</table>

injected air was 30 ml/kg (39). At 30 ml/kg and using the average weight of 2.26 ± 0.44 kg for the animals used in this study, this would have been >67 ml of air injected into the pleural space. However, the results reported here show that initial diagnosis of PTX in all animals occurred, on average, 18.2 min from initiation of injection or after injection of 18.2 ml air. The difference between continuous injection of air and a bolus injection may appear to be the reason for the discrepancy; however, a second bolus of air was injected in the aforementioned canine study (39) and resulted in only a minimal reduction of SpO2, suggesting that, when measuring.

A bolus injection may appear to be the reason for the discrepancy; however, a second bolus of air was injected in the aforementioned canine study (39) and resulted in only a minimal reduction of SpO2, suggesting that, when measuring SpO2, the amount of air is more significant than the mode of injection. From a clinical study on PTX during anesthesia, it was concluded that pulse oximetry must be regarded as a nonspecific detector due to the large number of false negative results, as desaturation occurred in only 40% of the cases (2).

The suggested technology enables early detection of deteriorating ventilation since it directly monitors the changes in lung ventilation mechanics from the compartment where the complication developed (the chest), and does not wait for the appearance of significant changes in vital signs. Moreover, other common techniques only monitor one parameter (SpO2, EtCO2, tidal volume, ventilation pressure, heart rate). Here, the accelerometer can provide a variety of indexes, the end-expiratory tilt, tidal amplitude, energy, entropy, AR poles, and breath sounds for each side of the chest. Some of these parameters are extracted separately from a LF or HF band. All parameters demonstrated statistical significance, whereas parameters such as amplitude and covariance were more instrumental in early detection than tilt and HF entropy. The tilt, which is calculated from the trajectories of the earth gravity on the tangential accelerometers, is very sensitive to the noise. This mode of sensor application enables concurrent exploitation of these parameters from each sensor and from the ratio of each parameter between the two sensors (sides of the chest). Consequently, PTX can be detected earlier, and the affected side can be identified.

Using a basic clustering algorithm, the initial boundary of interest was the time at which it was possible to correctly cluster all of the BL measurements. Less than one-third of the way through the experiments, BL and PTX were clearly distinguished, and two-thirds of the PTX observations were adequately separated into their own cluster. As time progressed, the PTX classification improved, and the distance between centroids of each cluster continuously increased. By 70% tPTX, all of the PTX observations were separated from the BL cluster, at a mean 34.1 ± 18.8 min before what would have been observed had only the SpO2 been considered. Prevention of this considerable time lag could be of great benefit to clinicians, allowing them to take corrective action and to prevent further deterioration of the patient in an ICU setting.

The use of multidisciplinary, clinical process improvement programs driven by data obtained from this type of monitoring may significantly reduce PTX-related mortality (38).

Interestingly, the idea of utilizing an accelerometer for monitoring changes in patient conditions and for monitoring the breath sound was suggested about 2 decades ago (USA patent no. 5309922). In the present experimental study, we have established that it is feasible, and we have analyzed the whole spectrum of the accelerometer signals, the LF of the chest wall dynamics, and the HF of the breath sounds. In addition, we have suggested to monitor both side of the chest and presented the ability to detect the development of asymmetric ventilation.

Other technologies for earlier detection of PTX were tested in preclinical studies. RIP was used in an attempt to effectively assess a global change in chest volume of piglets with progressing PTX; however, RIP cannot detect the development of asymmetric ventilation (3). The reported global volumetric changes are analogous to the tilt parameter calculated in the present study. Reliable EIT-based detection of injected air doses as low as 2 ml/kg in piglets (3) and 0.65 ml/kg in adult pigs (6) has been reported. However, the site of PTX was directly underneath the EIT sensors, and the method is quite cumbersome for use in the neonatal ICU. Recently, analysis of breath sounds by using arrays of microphones positioned on the back was attempted to develop a noninvasive diagnostic tool (7, 8, 41), but never seemed to be tested as a tool for early detection of PTX. The use of ultrasound (US) has also been shown to be an effective method in more rapidly identifying PTX, with higher sensitivity and specificity than chest X-ray and CT, without exposing the patient to radiation (1, 12, 18, 30, 31, 35, 42). Although very effective, utilization of US for continuous monitoring of patients is cumbersome and requires highly trained staff attention, rendering the method impractical. However, US can be a useful confirmatory method to corroborate findings detected with the continuous and simple monitoring method presented here.

Asymmetry detection and discrimination. Auscultation is a well-established means of qualitatively assessing a patient’s respiratory state, but is still subjective. Breath sounds for image reconstruction detected both qualitative and quantitative asymmetric differences, but required a technician’s assessment of

Table 4. Time lag between initial classification and 100% tPTX for each experiment

<table>
<thead>
<tr>
<th>Rabbit</th>
<th>Time Lag Between Initial Classification Time and 100% tPTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>30% tPTX 50% tPTX 70% tPTX 100% tPTX Time</td>
</tr>
<tr>
<td>1</td>
<td>49.0  69.0</td>
</tr>
<tr>
<td>2</td>
<td>65.1  92.0</td>
</tr>
<tr>
<td>3</td>
<td>43.4  61.0</td>
</tr>
<tr>
<td>4</td>
<td>24.5  34.0</td>
</tr>
<tr>
<td>5</td>
<td>Not Detected 11.4 37.0</td>
</tr>
<tr>
<td>6</td>
<td>52.5  74.0</td>
</tr>
<tr>
<td>7</td>
<td>Not Detected 19.0 37.0</td>
</tr>
<tr>
<td>8</td>
<td>25.9  36.0</td>
</tr>
<tr>
<td>9</td>
<td>Not Detected 16.0 31.0</td>
</tr>
<tr>
<td>Average</td>
<td>43.4 ± 15.8 36.9 ± 18.0 34.1 ± 18.8 52.3 ± 22.1</td>
</tr>
</tbody>
</table>

Averages include all previous correctly detected animals (means ± SD). Values are in minutes.

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these images (7, 8, 41). Another group (20, 21) validated a decrease in HF sound transmission on the side of PTX, but did not relate to the changes, if any, which occurred on the contralateral side.

Following PTX detection in the present study, the afflicted side was identified using an amalgamation of several ratios. The covariance measure between the left and right sides was used to identify asymmetric changes; however, this index cannot be used to specify which side is affected. From the HF band of the measured acceleration, it was possible to assess the “breath sounds” analogous to auscultation. The PTX/contralateral HF energy and HF entropy ratios decreased, in congruence with earlier studies that used microphones (20, 21). The measurement of HF entropy was statistically significant and contributed to side identification; however, the gravity of its contribution was of least significance, as seen in Fig. 6. Consequently, the product of the amplitude, LF energy, HF energy, and HF entropy ratios successfully identified the side with PTX, after 50% $t_{PTX}$, as supported in Table 3. Significant changes in the HF energy appeared only after 70% $t_{PTX}$, while changes in the LF indexes of chest dynamics (amplitude, covariance right-left, and AR poles) appeared earlier (Table 2).

Easy to comprehend and utilize. EIT application can be difficult, as proper placement, the quantity of electrodes, and the reconstruction algorithms all affect the resulting output (3). Belts of electrodes for EIT would suffer the same constraints as RIP bands, making them ineffective for use with premature infants. Although there have been reports of EIT having high sensitivity (3, 6), the use of EIT by clinical researchers has not reached significant acceptance due the subjectivity of interpretation. The use of microphone arrays for analyzing breath sounds appears to be cumbersome and subjective to the operator interpreting the images. Although US is effective in identifying PTX, it is not clinically practical for continuous monitoring, relies heavily on the efficacy of the operator and requires a trained clinician to recognize the specific signs (1, 12, 18, 30, 31, 35, 42). The proposed placement of two accelerometers on both sides of the chest enables efficient monitoring of progressing PTX without a need for an operator. The modality is simple to use as the various parameters are continuously extracted from the two sensors and are monitored for deviations from the BL measurement.

Limitations. The described analyses were performed during continuous mandatory ventilation, without observed spontaneous breathing before the development of desaturation. Therefore, signal processing was simple. Although the rabbits were anesthetized, no muscle relaxant was used. Monitoring the above indexes in the presence of spontaneous breathing will require a more sophisticated method since spontaneous breathing is associated with significant breath-to-breath variability in amplitude and shape that will increase the standard deviation of the calculated indexes.

Some of the indexes, such as tilt, amplitude/LF energy, and HF energy, have direct physiological significance and relate to the functional residual volume, tidal volume, and breath sounds, respectively. The calculated entropy and AR poles require more comprehensive physiological understanding, but have physical meaning. The product of the four indexes for asymmetry has no physiological support.

Conclusions. Utilization of a miniature (<1 g) accelerometer on each side of the chest effectively, conveniently, noninvasively, and nonconsistently provided large quantities of data. The simplicity of the system allowed for continuous monitoring of progressing PTX and enabled PTX detection earlier than with pulse oximetry. The use of a LF and HF band for analysis demonstrated that each sensor is capable of simultaneously providing dynamics and acoustics of the chest. Interestingly, LF dynamics were more instrumental in both early detection and side localization, as they are more sensitive and have less variability. As a result of the diversity of parameters provided by the accelerometers, few sensors can be utilized to gather more information and accurately help detect the occurrence and location of PTX. The system remains simple to employ, and the result is easy to interpret.

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DISCLOSURES

The technology was developed in the faculty of Biomedical Engineering at the Technion, by A. Landesberg and D. Waismann. The Institute decided to assign the technology to a start-up company, denoted as Pneumedicare, and we are considered founders of this technology. However, we work in the faculty of Biomedical engineering and the faculty of medicine, at the Technion. This is part of the PhD thesis of J. Pesin and A. Faingersh in the faculty of Biomedical Engineering.

AUTHOR CONTRIBUTIONS

Author contributions: J.P., A.F., D.W., and A.L. performed experiments; J.P. and A.L. analyzed data; J.P., D.W., and A.L. interpreted results of experiments; J.P. and A.L. prepared figures; J.P. drafted manuscript; J.P. and A.L. edited and revised manuscript; J.P., A.F., D.W., and A.L. approved final version of manuscript; A.F. and D.W. conception and design of research.

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