

Peak-to-Peak Work of Breathing Detection Algorithm as a Means of Guiding Weaning from Ventilation in Preterm Infants.

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The problem of premature births is widespread throughout the world affecting 41000 newborns daily; the issues that follow, often related to breathing, require the use of mechanical ventilation to compensate for the poor compliance of the respiratory muscles of newborns. However, side effects associated with artificial ventilation, including atrophy, require a cyclic interruption of automatic ventilation so that infants can develop and train their respiratory muscles (the so-called weaning from ventilation). However, the criteria for judging the readiness and progression of the detachment from ventilation are poor since they rely on the subjective judgments of the clinicians. As a consequence, a research project in collaboration between TU Delft and the Erasmus Medical Center of Rotterdam was carried out to look for an objective measure, provided with visual feedback, to give indications of the respiratory fatigue of newborns to the clinicians, also referred as work of breathing (WOB). This research revealed that the analysis of the diaphragmatic electromyography (dEMG) is a non-invasive tool that can be used to measure the WOB. As a result, a WOB detection algorithm named peak-to-peak, also abbreviated as P2P, was developed. The relevance of this algorithm consists in extracting the WOB information from the dEMG and giving a direct visual feedback to the clinicians.

1. INTRODUCTION

A. Premature Birth

Premature birth is the one that takes place before the 37th gestational week: the number of premature births amounts to 41000 per day [1]. Premature birth is a significant cause of morbidity, and infant mortality [2] and is the second leading cause of mortality in children under five years [3]. The more significant problems that occur concurrently with premature births are the respiratory ones [4]; premature infants are at risk of developing both infectious and non-infectious respiratory diseases, and 40% of survivors are affected by bronchopulmonary dysplasia (BPD) [5].

Strategies to cope with BPD are both medical (such as the usage of antenatal steroids and surfactant) and mechanical (mechanical ventilation) [6]. Unfortunately, mechanical ventilation, if done invasively, leads to ventilator lung injury (VLI); consequently, over the years there has been a shift towards non-invasive ventilation. [7]. However, non-invasive mechanical ventilation unloads the diaphragm and alters its structure and function, thus does not allow it to develop correctly, leading to muscular atrophy [8]. As a result, the neonatologists tend to gradually reduce the

amount of mechanical ventilation, up to the point where the neonates can be taken off respiratory support completely (the so-called weaning from ventilation) [9].

Nowadays, weaning procedures are scarce and lack objectivity; in fact, they rely on the personal judgment of the clinicians [9]. The majority of the clinicians use the trial and error strategy to assess the weaning outcomes [10, 11]: basically, they wean the infants if their clinical conditions are stable and they reintubate them in case their status deteriorate. However, the trial and error method leads either to overtreatment or undertreatment and the need for a more objective parameter arises; the dEMG could be a feasible solution [12].

B. dEMG

The dEMG measures the electrical activity of the phrenic nerve, which is essential for breathing, as it sends motor information to the diaphragm and receives sensory information from it [13]. Therefore, the dEMG measures the diaphragm electrical activity [14] and monitors the respiration of the newborns [15], and its change in magnitude is related to the respiratory fatigue [16, 17].

B.1. Measurements Procedure

The amplitude of the dEMG in the preterm infants is very low; therefore the electrodes should be placed at the minimal muscle-skin distance [18]. As a consequence, the clinicians place the electrodes in the zone of apposition [18]. Accordingly, the clinicians place the electrodes in the right six and the seventh interspace between the midclavicular and midaxillary lines [19] (see figure 1). Since the infants are moving a lot during the wake phase and create several movement artifacts, the measurements need to be performed during the sleeping phase [15].



Fig. 1. Electrodes placements in neonates example, source: [12]

B.2. dEMG Relation with the Work of Breathing

Previous researches state that the usefulness of the dEMG is strictly related to the fact that it gives information on the WOB. Research by Maaesingh et al. [20] showed a correlation between the logarithm of the dEMG and the severity of asthma, showing that dEMG decreases when the asthma level decreases, thus demonstrating that asthma causes the diaphragm to work more than during the usual conditions. Research by Sprikkelman et al. [21] corroborates the idea that increases in dEMG indicate difficulty in respiration, by demonstrating that the dEMG in children increases upon histamine-induced bronchoconstriction. Research by Stein et al. [22] also link the dEMG with the increase in the respiratory effort. Research by Kraaijenga et al. [12] demonstrated that the dEMG level in infants who fail weaning from ventilation is higher than those who succeeded. Based on the previous considerations, the dEMG reveals as a suitable tool to investigate the WOB during the weaning from mechanical ventilation.

B.3. Diaphragm-Abdomen Electrical Activity Relation

The electrical activity of the diaphragm is conducted through the body. That's why it can be measured at the abdominal surface. Moreover, since the abdomen motion reflects diaphragm contributions to breathing [23], we can state that the abdomen electrical activity correlates the diaphragm one. In fact, when the sleeping patient contracts and relaxes the diaphragm, the abdomen contracts and relaxes in turn. However, abdominal muscles contribute significantly to postural control [24], have an essential role in the control and movement of the lumbar spine

and pelvis [25], participate in a wide range of postural adjustments in response to external bio-mechanical perturbations [25] and can also be activated to compensate predictable movement-related postural disturbances [26]. As a result, when the patient is not at rest, the abdominal electrical activity deviates from the diaphragmatic activity. Consequently, in the analysis of the dEMG, it is essential to distinguish when the signal refers to respiration (undisturbed dEMG) and when it refers to movements (disturbed dEMG).

2. MATERIALS AND MEASUREMENTS

A. Instrumentation

The dEMGs have been extracted according to the procedures shown in section B.1. However, apart from it, only the abdominal and the reference electrodes were used, which in figure 1 are the electrodes number 1 and 2 and the black one respectively. The collection and transmission of the electromyographic signals during the research have been enabled by the Dipha@16 device (specifications are available at the following link: <http://www.macawi.com/wp-content/uploads/2015/10/Dipha.pdf>). The Dipha@16 allows the data acquisition and pre-processing to take place in a lightweight, smartphone-sized, battery-powered measurement box.



Fig. 2. Dipha@16

The dEMG data were transmitted with low power from the Dipha @device to a transceiver USB stick connected to a personal computer.

B. Measurements Data

The measurements data are the dEMG signals recorded by the electrodes and transmitted to Dipha@16. The dEMG is contaminated by a various source of noises, such as the movement artefacts [27], the adjacent muscles interference (also known as cross-talk) [28], the inherent noise [29], and the electrocardiography (ECG) interference[30, 31]. If Dipha@16 extracted the dEMG in the raw state, it would look similar to the one in the figure 3.



Fig. 3. Raw dEMG signal example, time [s] vs μv

Dipha@16 device, however, is equipped with an embedded system that takes care of eliminating the various sources of

pollution, returning to the user a signal similar to the one in the figure 4.

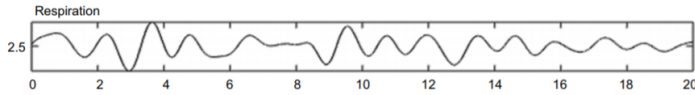


Fig. 4. Clean dEMG signal example, time [s] vs μV . Source: [32]

3. METHODOLOGY

A. Data Acquisition and Analysis

The electromyographic data acquired by DIPA@16 were transmitted on a personal computer and imported into MATLAB, and subsequently in Simulink for offline analysis. Finally, an algorithm was written in Simulink that analyzes the electromyographic data in real-time and extracts the WOB. This algorithm takes in the name of peak-to-peak (P2P).

B. Research Procedure

After obtaining parental consent, the dEMG was extracted on three premature infants and saved on a USB key to be subsequently analyzed. The envelope of the dEMG was displayed in real time on a portable screen so that it was possible to understand how the qualitative behaviour of this envelope changed according to the infant's response. It has been shown that it varies according to whether the newborn is quiet, restless or apneic. Subsequently, the criteria for judging whether the electromyographic signal refers to when the child is at rest or not have been established. Finally, based on these criteria, the P2P algorithm was written. In fact, P2P is proposed to extract the WOB only from the electromyographic segments when the newborn is at rest (undisturbed dEMG), discarding instead the sections that refer to when the newborn is restless (disturbed dEMG).

C. P2P Algorithm Development

One can simplify the shape of the dEMG envelope as a kind of sinusoid which continuously oscillates from points of minima to points of maxima. When the signal shifts from a minimum to a maximum point, the patient inhales. When the signal shifts from a maximum to a minimum point, the patient exhales.

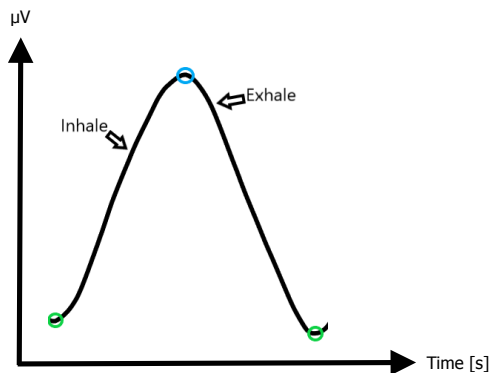


Fig. 5. Real dEMG fragment, time [s] vs μV . Two minima and one maximum point are highlighted by green and blue points respectively.

The higher is the difference between each minimum-maximum point; the higher is the diaphragmatic electrical activity, the

higher is the muscular effort required to breathing.

A specialized nurse practitioner in the neonatology intensive care unit (NICU) at Erasmus Medical Center in Rotterdam who took part in the measurements, expressed the need to have a measure of such maximum-minimum oscillations as a measure of WOB. As a consequence, the idea of developing the P2P algorithm arose. Such an algorithm was born to calculate the subsequent difference between each maximum-minimum (or positive-negative peak, hence its name) and return its trend over time to the clinicians. The P2P was also designed to recognise and discard the disturbed dEMG segments in order to analyse only the undisturbed ones.

D. Undisturbed dEMG Recognition

During the research, it was essential to observe both the infants and the dEMG monitor simultaneously. In this way, the qualitative characteristics of an undisturbed and a disturbed dEMG could be noticed. Subsequently, thanks to these qualitative evaluations it was then possible to give a quantitative definition of what a respiratory wave is. This very definition is of crucial importance because it is then implemented in the P2P.

D.1. Undisturbed dEMG Characteristics

The dEMG envelope in figure 6 is an example that shows a real measurement fragment in which the infant is at rest.

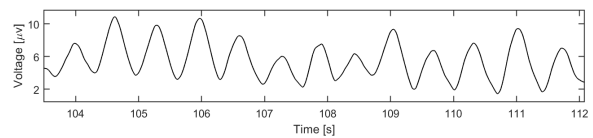


Fig. 6. Real undisturbed dEMG fragment, time [s] vs μV .

By observing the signal, it comes up that:

- The signal oscillates around a mean value ($6 \mu\text{V}$ in the example).
- The signal amplitude remains inside a lower and upper boundary.
- The tonic level (i.e. the minima points) oscillations do not exceed the $1.5 \mu\text{V}$ range.
- The signal period T (where $T = \frac{1}{freq}$) seems to be around 1 second according to the infants respiration frequency $freq = 1\text{Hz}$.
- The signal has a "smooth" shape: it recalls a sine wave, there are no angular points, and there are no abrupt changes in the slope. That means that the function is monotonically increasing when moving from a minimum to a maximum and monotonically decreasing as it moves from a maximum to a minimum.

D.2. Disturbed dEMG Characteristics

The figure 7 reports an example of a real dEMG measurement of a restless infant.

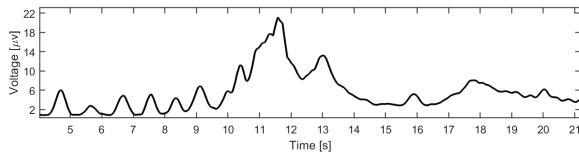


Fig. 7. Real disturbed dEMG fragment, time [s] vs μV .

By performing a qualitative analysis of the signal, it comes up that:

- The signal does not oscillate around a fixed value.
- The signal does not always have a "smooth" shape; the wave shape in fact, after 10 seconds does not recall a sinusoid any more, local maxima and minima are often very close to each other and do not necessarily refer to the maxima and minima we are interested.
- Some waves have a period much longer than 1 second, so they are not consistent with the respiratory frequency of the newborn.
- After 14 seconds, waves are almost absent.

D.3. Undisturbed dEMG Wave Definition

The dEMG wave is a portion of dEMG which begins at a minimum point, reaches a maximum point, and finally ends in a second minimum point.

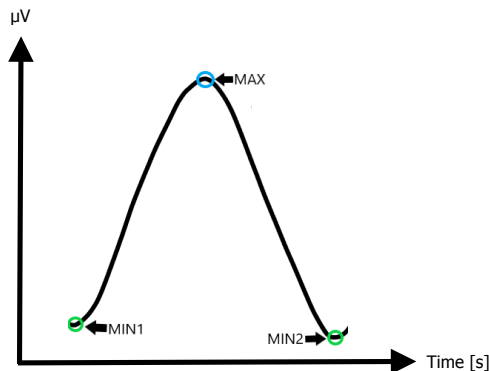


Fig. 8. Real undisturbed dEMG wave example, time [s] vs μV .

After examining the behaviour of dEMG waves in both undisturbed and disturbed conditions, the constraints defining an undisturbed wave have been empirically established as follow (take the figure 8 as reference):

- The time distance between MIN1-MIN2 is to be less than 1.3 seconds.
- The MAX-MIN1 and MAX-MIN2 magnitude distances are to be greater than $2 \mu\text{V}$.
- The MIN1-MIN2 distance is to be less than $2 \mu\text{V}$.

It must be pointed out that these constraints are based on a sample of only 3 patients; therefore, it might be possible that future research can show that these values are not fixed, but vary from patient to patient depending on their weight, congenital conditions, etc.

E. P2P as a WOB Detection Algorithm

E.1. P2P Algorithm Implementation

The P2P algorithm is a Simulink block which receives the dEMG as input and outputs the WOB. The P2P algorithm is designed to perform the following instructions real-time:

- Looking for a first minimum point.
- Looking for a maximum point.
- Looking for a second minimum point.
- Determining if such minimum point is a false minimum (this concept would be elucidated in section E.3).
- In case the minimum detected is a false one; the algorithm would ignore it and keep looking for the second minimum.
- If another maximum is found, and its magnitude is greater than the previous maximum, such maximum becomes the new maximum.
- Once the second minimum is detected, the time interval and the magnitude difference between the two minima is calculated.
- The magnitude difference between the maximum and both minima is calculated.
- If the conditions list in section D.3 applies, the peak-to-peak is calculated by subtracting the the average of the two minima to the maximum. In case such conditions are not respected, the segment is discarded.
- The cycle starts again

Figure 9 helps to visualise the P2P instantaneous value as the magnitude difference between the maxima and the average of the two minima.

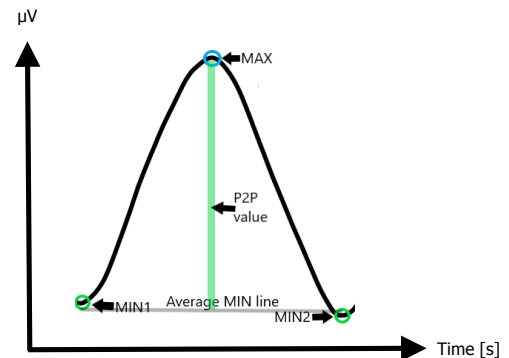


Fig. 9. P2P visualization, time [s] vs μV .

E.2. P2P Trend

The clinicians will not see the P2P instantaneous values as they are. Indeed, we are not interested in the instantaneous WOB, but on how its trend changes over time. As a result, a Simulink block was created to collect the P2P instantaneous values and average them over time. The average default time is set to 30 seconds, but clinicians can change it as they wish, depending on their experience and evaluation.

E.3. False Minimum

The figure 12 elucidates the false minimum problem. In case a minimum point is detected almost right after the maximum point detection and-or the magnitude of the minimum is very close to that of the maximum, it is almost sure that such minimum point is not a "true" one but it is a consequence of the random fluctuations of the function. This is why the algorithm of the P2P is trained to recognize such false minimum and ignore it.

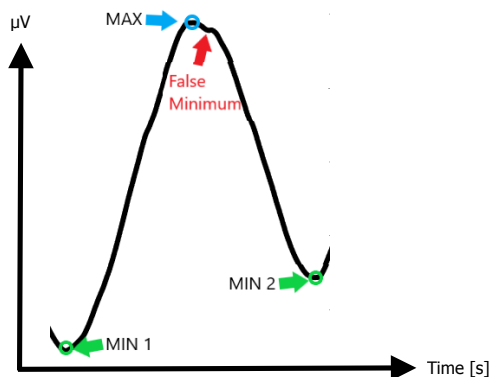


Fig. 10. False Minimum example extracted by a real dEMG measurement, time [s] vs μV .

E.4. Sanity Check

During the measurements in the NICU, the dEMG data were displayed real-time on a portable screen. On such a screen, it was possible to set markers. Therefore, every time the infants were restless, markers were placed to indicate the beginning and the end of the movement artefact. As a result, during the offline analysis, not only it was possible to visualise the acquired dEMG, but it was also possible, thanks to the marker, to know when movements occurred.

A sanity check consisting of offline analysis of the dEMG data was carried out on a personal computer. Both the dEMG data and the instantaneous P2P values were displayed on the same screen. The data were plotted against time. By doing so, knowing in which time frame movements occurred, it was also possible to know which dEMG segments had to be discarded. In case non-null P2P instantaneous values were displayed in conjunction with movements artefacts, the algorithm was considered to fail to reject a movement artefact dEMG segment. In case null P2P instantaneous values were displayed in conjunction with undisturbed dEMG fragments, the algorithm was deemed to fail to recognise a correct dEMG portion.

Such a sanity check revealed that the P2P correctly rejects a movement artefact with a 99% accuracy. On the other hand, it came up that the inherent constraints of the algorithm force it to reject the 20% of the correct measurements. However, we are interested in the trend rather than in the instantaneous values. Therefore, this lack of data might not constitute a great loss unless the magnitude of the discarded segments deviates too much from the previous ones.

4. RESULTS

Figure 11 shows how the results of the P2P trend would be presented to the clinicians. An increase and decrease of the trend would be related to increase and decrease of WOB. The ease

of reading the WOB chart, without the need for extreme interpretations, makes the P2P a practical and easy-to-understand tool for WOB detection of preterm infants. However, since the measurements in the NICU were only 3, the P2P needs future evaluation to confirm its veracity. More precisely, it is necessary through a more significant number of measurements to verify that the constraints that determine a correct respiratory wave are consistent with what is explained in the section D.3. In fact, these constraints might depend on the physical characteristics and the patient instead of having fixed values.

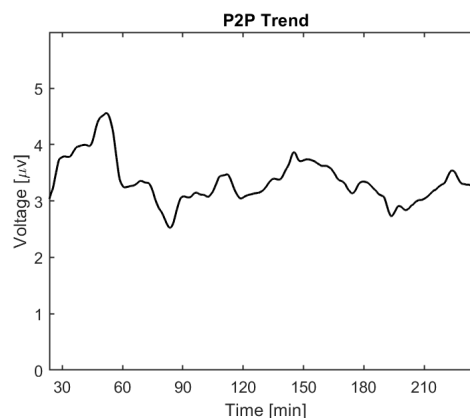


Fig. 11. P2P trend over time.

5. DISCUSSION

Regarding the results, how do can clinicians interpret them during the weaning process from automatic ventilation? The analysis of the P2P trend over time is to be used by clinicians as follows:

- The WOB trend is to be carefully observed in conjunction with the newborn's clinical condition.
- At the time when the newborn seems unstable, and intubation is deemed necessary, a threshold line must be set on the chart.
- This experiment must be repeated several times so that it can be deduced if a threshold line actually exists (i.e. if its value is not changing drastically among different measurements).
- In case a threshold line exists, but varies from patient to patient, it is necessary to identify the reasons for this variation in order to normalize the results. These variations could be related to the weight of the newborns, their tonic dEMG, congenital conditions etc.. The example in the figure 12 graphically elucidates what was previously explained. Once the threshold has been found, a threshold line is set on the WOB chart. As long as the WOB trend remains below the threshold line, the newborn can be considered to be safe. In case the threshold line is overcome, the infant is in an unsafe region and clinicians may consider stopping the weaning.

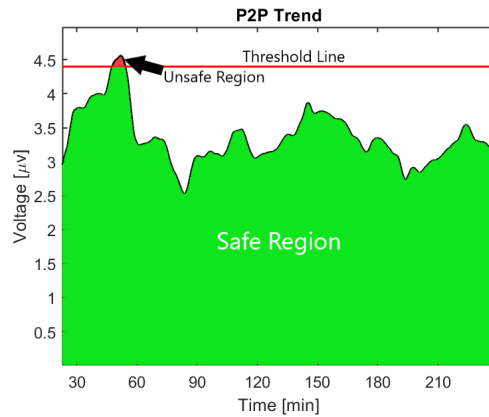


Fig. 12. P2P safety-unsafety region example.

6. CONCLUSIONS

The weaning from the ventilation relies on the individual judgment of the clinicians based on the momentary stability of the infant, since no WOB direct measures are available. Consequently, a research was carried on to give the clinicians visual feedback concerning the WOB of the infants. dEMG is an excellent candidate to receive information on the respiratory sufferings of the subject without the intervention of invasive techniques. However, when the patient is unquiet, it contains misleading information as it no longer refers to breathing but rather to abdominal contractions that contribute to the stabilisation of the body during movement. A WOB detection algorithm named P2P has been developed to extract information about the respiratory distress of the subject directly from the dEMG, taking care to avoid misleading information regarding movements artifacts, but considering only what refers to breathing. This algorithm gives visual feedback to clinicians who could use it in the future to establish a threshold beyond which the WOB of the infants is considered dangerous, and re-intubation can be deemed necessary.

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