Neola Medical

White Paper

MD Ph.D. Tetiana Kovtiukh
Ph.D. Martin Hansson

April 2023

Neonatal lung analyzer

Breakthrough in monitoring of the lungs of preterm born infants

Introduction

Preterm birth rates continue to rise globally, prompting healthcare providers to seek ways to improve care for this vulnerable patient group. From the United States with a rate of 10.5%[1], to Europe and other developed countries with 5-11%[2], the medical care of preterm born infants presents unique challenges and requires specialized methods of diagnosis and treatment. As their lungs are not fully developed, pulmonary disorders, such as respiratory distress syndrome, pneumothorax, and atelectasis, are common in these neonates and require prompt detection, diagnosis, and treatment to improve patient outcomes. This is where Neola® comes in as a potential game-changer in the Neonatal Intensive Care Unit (NICU), offering a non-invasive, and continuous monitoring of the lungs of neonates. Based on cutting-edge optical technology, *Gas-in-scattering-media absorption spectroscopy* (GASMAS), variations in the lung volume and free oxygen gas concentration in the patient's lungs are detected instantaneously. This provides effective lung monitoring for early detection of, possibly life-threatening or irreversible, pulmonary disorders, allowing treatment to start promptly. By bringing this medical device to the market, Neola Medical aims to save more lives, reduce the need for extensive hospitalization, and improve the quality of life for millions of preterm born babies.

Background

Every year, medical practitioners and researchers search for new ways to save the life of preterm born infants and to decrease the number of individuals with major disabilities in adult life resulting from preterm birth. The most common ailments that affect preterm born infants are pulmonary disorders including bronchopulmonary dysplasia (BPD) and respiratory distress syndrome (RDS). The incidence of BPD remains high and has been mostly unchanged during the last decade, ranging from 20% in California to 28% across the U.S., and 42% among infants less than 28 weeks' gestation[3]. RDS is one of the most common reasons an infant is admitted to the neonatal intensive care unit. Fifteen percent of term infants and 29% of late preterm born infants admitted to the neonatal intensive care unit develop significant respiratory morbidity. Respiratory problems are typically accompanied by hypoxia affecting all organs and systems. Respiratory distress can escalate to respiratory failure and cardiopulmonary arrest[4]. RDS can cause hypoxemia through alveolar hyperventilation, diffusion abnormality, ventilation-perfusion mismatch, intrapulmonary shunting, or a combination of these mechanisms. This hypoxemia and tissue hypoperfusion ultimately lead to increased anaerobic metabolism at a cellular level with resultant lactic acidemia[5].

Due to environmental stress factors, preterm born infants can experience inadequate oxygenation, intraventricular hemorrhage, and periventricular leukomalacia which occur much more frequently

compared to their term counterparts[6]. Once these children reach school age, other cognitive impairments including learning disabilities and behavioral problems are more frequently observed.

The patient group described above is large. In 2021, preterm birth affected 1 of every 10 infants born in the United States, or approximately 385,000 infants. The U.S. preterm birth rate rose 4% in 2021 to 10.49%, the highest level reported since at least 2007[1]. Preterm birth is defined as a birth that occurs before the start of the 37th week of pregnancy. These infants deserve a complete life without limitations, whether physical or mental. Therefore, innovative solutions are needed to address the challenges of preterm birth and help improve the long-term outcomes of affected infants.

Today's standard of care

The most frequently used method for the diagnosis of lung conditions is x-ray radiography. For instance, as assessed by x-ray studies, lung compliance and volume, help determine the patient's response to various ventilator rates and pressures; therefore, the x-ray findings can be very useful in selecting the most appropriate ventilator settings[7]. It is common to perform repeated pulmonary radiography to assess disease severity and the effects of ventilation in this patient group. Clinical use of x-rays flourished since its invention, from the beginning with little regard for potential side effects from radiation exposure. X-ray radiography is typically used as a simple and reliable way to define tube and line position. From peripherally inserted central catheters to endotracheal, thoracostomy, and feeding tubes, a simple radiograph can help eliminate suboptimal line or tube placement complications. However, preterm born infants are highly vulnerable to ionization x-ray radiation and its influence on their body leads to more harmful effects than on adults[8].

Newborn infants in need of respiratory support are continuously monitored using pulse oximetry and intermittent arterial blood gases. Blood gas analysis is a potentially harmful procedure. Blood loss due to sampling is considered a major cause of anemia in preterm born infants. Capillary blood sampling is the most commonly performed invasive procedure during the neonatal period[9]. However, this promotes significant iatrogenic blood loss and arterial puncture may be painful, placing a peripheral arterial catheter may be both painful and risk compromising circulation, and placing a central line may increase the risk of infection and bleeding. This procedure bypasses natural physical barriers, which may allow colonization to occur and a nosocomial (late-onset) infection to develop. Central line-associated bloodstream infections, also called catheter-related bloodstream infections, are the most frequent hospital-acquired infections. The requirements for different blood sampling procedures in preterm infants can equal or exceed half of their total blood volume, particularly in infants weighing less than 1 kg[7].

The most accurate ventilation analysis for very preterm infants is through measuring the partial pressure of carbon dioxide, pCO_2, in arterial, venous, or capillary blood. However, this promotes significant iatrogenic blood loss and arterial puncture may be painful, placing a peripheral arterial catheter may be both painful and risk compromising circulation, and placing a central line may increase the risk of infection and bleeding. Non-invasive methods for monitoring ventilation, namely end-tidal CO_2 ($EtCO_2$) and transcutaneous CO_2 ($TrcCO_2$), enable continuous monitoring and decrease sampling blood loss[7].

Introduced about 30 years ago, pulse oximetry has been shown to be a useful noninvasive tool for evaluating the respiratory and cardiovascular systems. Oxygen saturation monitoring is the most common and widely used method for assessing oxygenation status. This method uses the core body to obtain oxygen saturation and is useful when the patient's peripheral blood flow is diminished[7]. Changing these parameters on the pulse oximeter screen could delay the onset of pulmonary complications. Pulse oximetry cannot estimate the oxygen concentration in the lungs.

Lung ultrasound is a new innovative tool that has gained attention as a non-invasive and radiation-free alternative to traditional X-ray imaging techniques in the NICU[10]. However, its interpretation is highly user-dependent and requires specific training and expertise. This underscores the need for more objective and standardized methods of assessing pulmonary complications in preterm infants.

Many researchers and engineers direct their efforts on finding new methods of detection, diagnosis, and treatment of pulmonary disorders which can answer the shortcomings of the methods described above. A breakthrough technology emerged in the early 2000 that showed many potential user opportunities in the clinical field for measuring and detecting gases, such as oxygen and water vapor, inside the human body. The technology is called *Gas-in-scattering-media absorption spectroscopy* (GASMAS) and employs non-ionizing near-infrared light for quantifying gas concentrations in cavities embedded in the tissue.

As the number of preterm births continues to be high globally, it is essential to explore alternative diagnostic methods that can improve patient outcomes and reduce the need for invasive procedures. Inspired by the opportunity to help the smallest and most vulnerable patients, Neola Medical has integrated the GASMAS technology into a medical device for non-invasive, continuous monitoring of preterm born infant's lungs.

Neonatal lung analyzer – Neola®

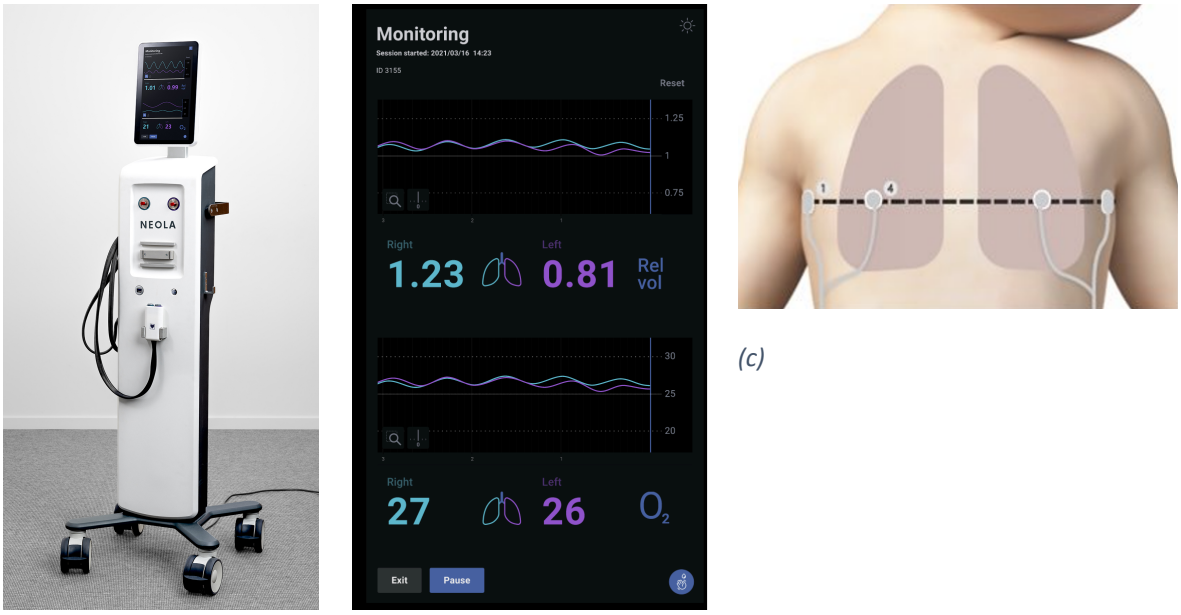
Neola® is a non-invasive and stand-alone medical device in class II intended to be used in neonatal intensive care units for continuous monitoring of the relative lung volume and oxygen gas concentration of the lungs of neonates. Neola® consists of a stand-alone main unit including a touch screen providing a graphical user interface on which the data is displayed. Two clinical parameters for the right and the left lung are presented on the graphical user interface, both as instantaneous values and as a graph for identifying trends. The presented data provide the user with objective decision support for pulmonary disorders such as respiratory distress syndrome, pneumothorax, and atelectasis; changes in lung aeration and respiration due to issues such as tracheal tube misplacement; and slow trends that may not be detectable by the current standard of care.

Two sets of probes are dermally attached to the thorax of the infant to monitor each side of the patient's lungs separately. The probe sets are disposable and designed for single-patient multiple uses. Each set consists of one emitter probe, fiber optically connected to the main unit, and one detector probe connected to the main unit. The emitter probes administer the near-infrared light to the patient's skin and distribute it evenly over an area. The detector probes collect the weak light that has passed through the body and convert the light into electrical signals that are amplified and processed by the main unit. The small (1-2 cm^2), lightweight, and skin-friendly probes are attached to the body using a gentle silicone adhesive, transparent in the wavelength region used by the device. The silicone

adhesive is designed to be attached and re-attached several times, still being gentle enough not to damage the skin when removed. The probes can remain in place for up to 24 hours, after which replacement with a new set of probes is recommended.

Positioning of the probes on the thorax must be done with care to achieve sufficient signal quality. For best performance, the emitter and detector probes should be placed 3-4 cm apart to allow the detected light to penetrate into the lung tissue before reaching the detector. The graphical user interface provides guidance and direct feedback during positioning.

All parts of the device, including probes and graphical user interface, are developed for comfortable and easy handling using feedback from healthcare professionals working in neonatal intensive care units.



(a) *(b)* *(c)*

Figure 1 Photo of the Neola® device (a) and the monitoring view in the graphical user interface (b). Figure (c) illustrates the optimal placement of the probes for best performance.

Relative lung volume

Pulmonary disorders, such as respiratory distress syndrome and pneumothorax, have an impact on the distribution of air within the lungs. Respiratory distress syndrome is a condition in which a significant portion of the alveoli close during the exhalation phase, resulting in increased effort during inhalation to generate sufficient pressure to open the closed alveoli. This process alters the distribution of gas within the lungs, and because the measurement method relies on the average distance that photons travel through gas-filled cavities in the lungs, a greater number of closed alveoli will directly affect this measurement.

Pneumothorax can occur when some of the alveoli become over-inflated and burst, releasing air into the pleural space between the lung and chest wall. This causes the lung tissue to contract, altering the anatomy of the lung and consequently affecting the measurement of the average path length of photons through gas-filled cavities. Pre-clinical testing has demonstrated a rapid change in the measured parameters after inducing pneumothorax and atelectasis[9]. This indicates that the

technology can detect changes in respiration, enabling instant awareness and treatment, potentially resulting in an overall improved clinical outcome.

Oxygen gas concentration

If a portion of the lungs becomes partially or fully obstructed, such as in the case of tracheal tube misplacement or blockage from mucus, it can result in inadequate ventilation. This can be observed by a reduction in the measured concentration of oxygen gas in the affected portion of the lung (either right or left side). While the gas exchange between the capillaries in the alveoli and the gas within the lung continues, carbon dioxide may not be adequately eliminated.

The prompt detection of changes in the concentration of oxygen gas in the lungs, whether they occur rapidly or more gradually, can provide early awareness and the opportunity for adjustments. This, in turn, can lead to better care and improved clinical outcomes.

The GASMAS technology

Neola® employs a technology called *Gas in Scattering Media Absorption Spectroscopy* (GASMAS), which utilizes near-infrared light to detect free gas molecules within gas-filled cavities embedded in highly scattering tissue. This innovative optical technology, patented for medical use, has the potential to be a valuable tool for medical monitoring and diagnosis, particularly in respiratory care, as it provides unique information about molecular oxygen content inside the lungs and relative lung volume. Compared to other monitoring technologies currently used in clinical practice, GASMAS has several advantages. It is non-invasive, meaning that it does not require any physical intrusion into the patient's body. It is also continuous, providing real-time information without the need for repeated measurements. Additionally, GASMAS is a non-ionizing technology and does not induce any heating, making it safe for patients and healthcare professionals.

Spectroscopy of gas embedded in tissue

Matter in the gas phase displays vastly different optical properties than matter in the liquid and solid phases. The quantum nature of the energy states in the molecules becomes apparent in a gas, as the individual particles are widely separated. Transitions between the quantized states of energy in the molecules by the absorption of a photon can occur only if the energy of the photon precisely matches the difference in energy between the states. This corresponds directly to the absorption at very specific wavelengths. Within the field of gas spectroscopy, the term absorption line refers to a particular photon energy or wavelength for which a gas molecule absorbs light.

The set of absorption lines is unique for each species of gas molecules and can thus be regarded as a fingerprint that identifies the species. Figure 2 shows the absorption spectra for oxygen gas and water

vapor, *i.e.,* water molecules in the gas phase. If absorption is identified at any of the lines shown in blue, it is evidence of the presence of oxygen, the amount of which can furthermore be quantified.

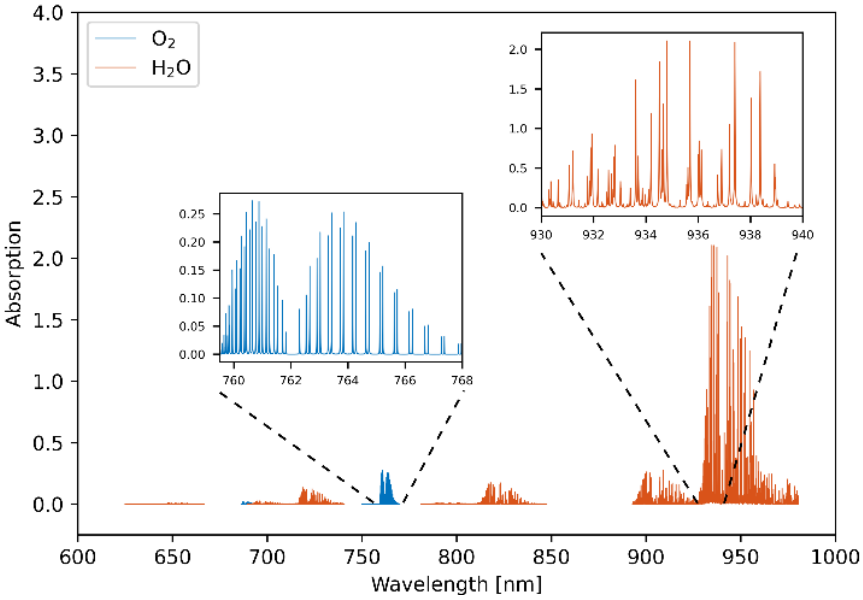


Figure 2 Absorption of light after propagation through 10 cm of gas composed of 21% oxygen and 6% water vapor. The absorption spectrum illustrates the sharp lines typical for gases.

While employing spectroscopy to detect and quantify gas embedded in biological tissue, the light will experience both absorption and scattering in the non-gaseous tissue. The attenuation due to these effects is several orders of magnitude larger than the absorption features due to the gas. The light in tissue is attenuated by a factor $e \approx 2.7$ in a characteristic length of only a few millimeters. The attenuation of light going through 5 mm of an example biological tissue is shown in Figure 3.

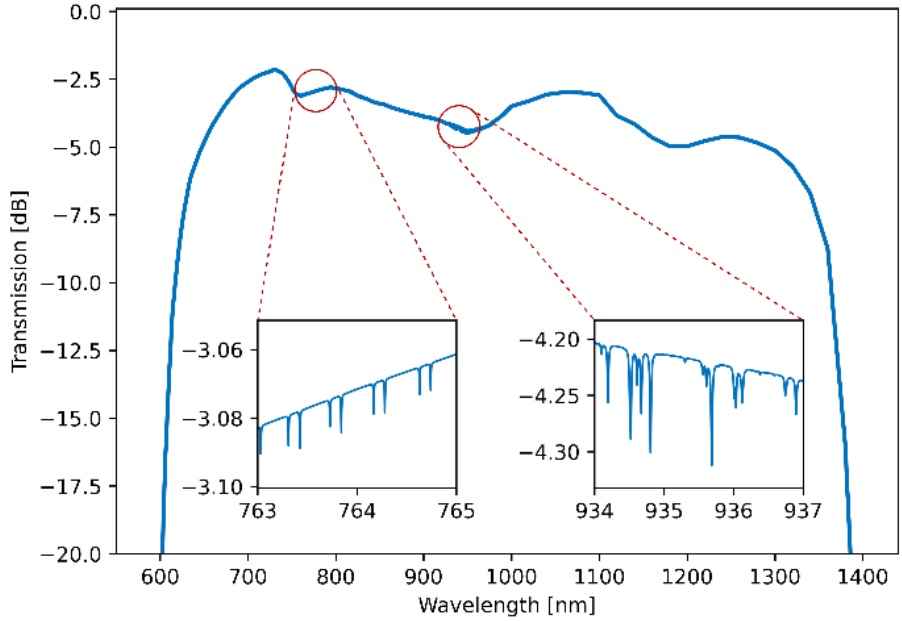


Figure 3 Light propagating through tissue experiences both scattering and absorption. Both effects result in a decreased amount of light reaching through the tissue. The spectrum here illustrates the transmission through a thin (5 mm) tissue sample. In the region from 700 nm to 1300 nm, the transmission is both high and reasonably flat.

In contrast to matter in the gas phase, the attenuation in tissue demonstrates only spectrally wide features and any peaks or valleys are significantly wider than the absorption lines of the gas molecules. This difference in spectral width enables the gas absorption lines to be isolated and quantified, despite being much weaker than the attenuation due to tissue. Zooming in on the attenuation curve in the Figure 3 centered around 764 nm and 935 nm, clearly shows the absorption lines of oxygen and water vapor, respectively, on top of an approximately flat background.

Gas absorption spectroscopy is employed in Neola® using a pair of an emitter probe and a detector probe to monitor each side of the patient's lungs. The emitter probe and the detector probe are placed on the patient's torso a few centimeters apart as illustrated in Figure 4. The light propagating from the emitter to the detector experiences both attenuations, due to absorption and scattering in the tissue, as well as absorption of the gas molecules. As described above, the gas absorption lines are used to quantify the amount of gas which then is further evaluated to extract the concentration of oxygen inside the lungs and to monitor variations in the size of the lungs.

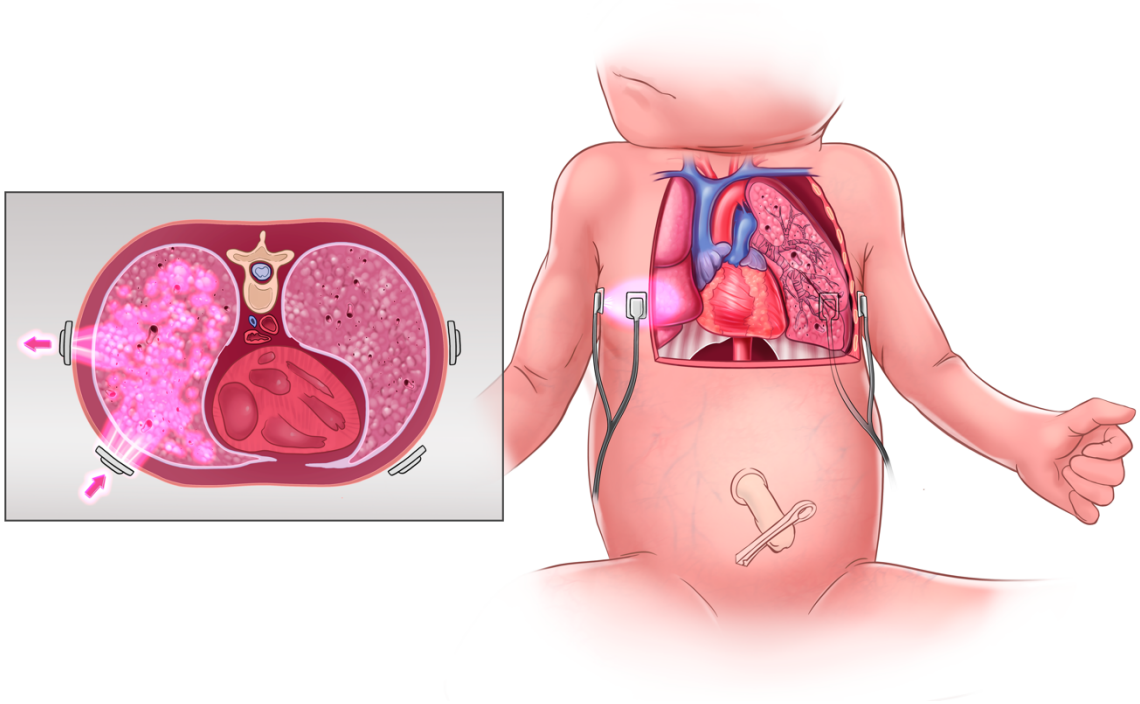


Figure 4 Illustration of how the light used for gas spectroscopy is administered using emitter probes. After entering the body, the light is distributed by scattering therein. A small fraction of the light reaches a detector probe, for processing to quantify the gas content.

The scattering of the light in tissue, together with absorption, implicates severe technical challenges for the detection and measurement technique. Only a small fraction of the photons emitted from the source finally reaches the detector after propagating through both tissue and gas. As the number of photons decreases, the signal level becomes comparable to intrinsic and unavoidable noise. However, the scattering light provides one of the key elements which makes this technique successful. The photons leaving the source will all take different paths through the tissue and the gas. This means that any directionality of the source light is lost as the light enters the tissue, and there is no need to aim the source light toward the detector. Secondly, a single pair of sources and detector is sufficient to

quantify the gas in the full gas volume. The measurement of absorption lines represents an average over the volume.

This technique is implemented in Neola® to detect and quantity both oxygen gas and water vapor, *i.e.,* water in the gas phase, simultaneously. Due to the fact that water in the liquid phase is present within all tissue, the concentration of water vapor is known and constant. This implies that any change in the water vapor absorption line corresponds to a change in the size of the probed volume. Furthermore, using the known concentration of water vapor, the measurement of the oxygen gas absorption line, together with the measured water vapor absorption line is used to calculate the concentration of oxygen gas in the probed volume.

Further benefits of the technique include the use of non-ionizing radiation. The absorption lines used in Neola® are in the near-infrared region with photon energies that are harmless for biological tissue. While the photon energy is converted into heat in the processes of photon absorption in the tissue, the net amount of energy supplied by the emitter probes is so low that the temperature increase is insignificant.

Discussion

While many healthcare professionals may argue that the traditional diagnostic methods that have been used for years are sufficient, the new technology brought to the clinic by Neola® has the potential to enhance the care and treatment of preterm born infants. What makes this technology particularly noteworthy is that it is non-invasive and provides continuous round-the-clock monitoring of the lungs. With this technology, healthcare professionals can more easily assess the condition of a patient's lungs, and by providing objective information, the practitioners can make informed decisions early about, *e.g.*, respiratory support and surfactant therapy.

Visual observation by nurses in the NICU is crucial for the early detection of any changes in the condition of infants, especially those with pulmonary complications[11]. However, it is a subjective and qualitative method that can lead to differences in interpretation and delays in response.

The technology on which Neola® is based has already been proven both in preclinical studies and in clinical research studies. For example, a prototype of Neola® was used in a study on a model of preterm infants based on neonatal piglets. Figure 5a shows signals acquired by the device while inducing pneumothorax on four different subjects. The decreased gas volume due to atelectasis is clearly visible in the acquired signals. After subsequent recruitment of the lungs, the acquired signals return to their initial values. Figure 5b shows signals acquired during the same type of intervention but with a higher acquisition rate. In the right panel, which is a zoomed-in version of the left panel, the variations in lung volume due to breathing are well resolved[12].

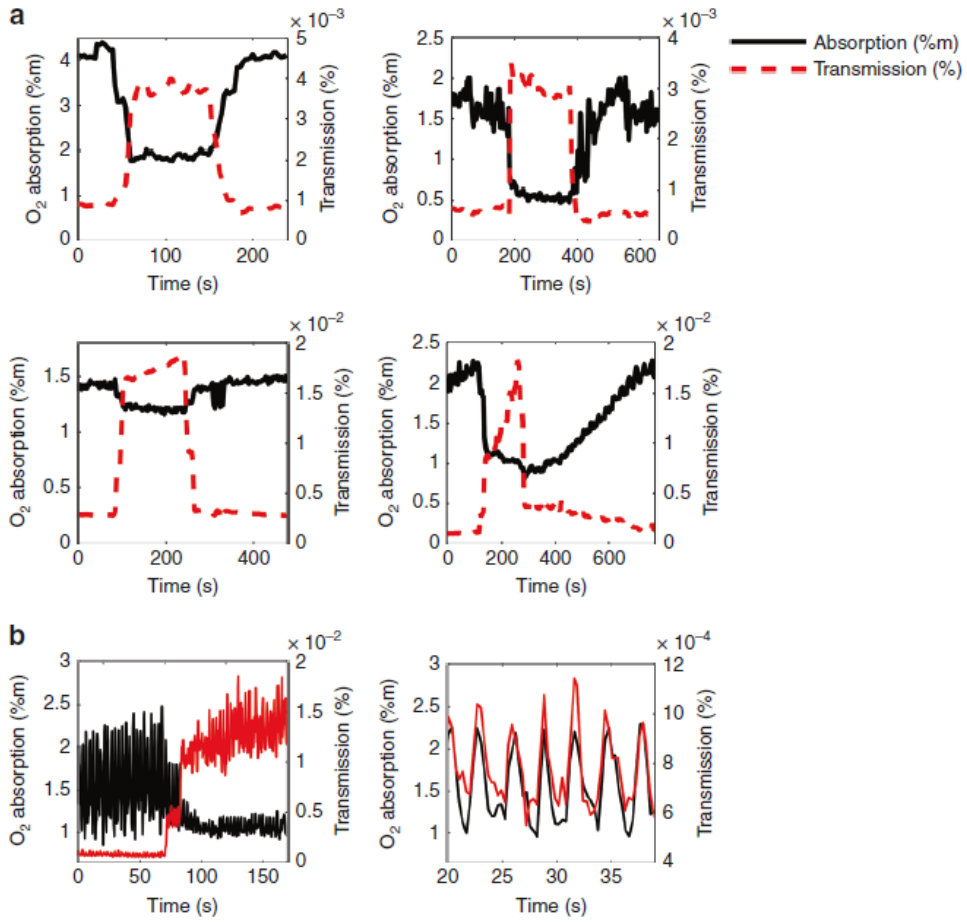


Figure 5 Excerpt from Svanberg, et al. (2020) showing signals acquired using a prototype of the Neola device.

In a clinical research trial, the technology was used to detect oxygen and water vapor non-invasively. The study was performed on 29 healthy newborn infants, with weights in the range from 3,000 g to 4,000 g. Oxygen signals were observed at least on one measurement location on every subject. The study investigated the signal quality dependence on weight, as it was expected that better signals would be acquired for smaller infants. The reason is that the thickness of the tissue surrounding the lungs is smaller, leading to smaller attenuation of the light as it reaches the detector. However, no significant difference could be observed. One plausible reason is that the smaller infants also have smaller lung volumes, thus the signal-to-noise ratio remains rather constant with respect to weight[13].

By leveraging the latest technology, Neola® has the potential to revolutionize the way healthcare professionals monitor and diagnose lung health, ultimately leading to better outcomes for patients. Neola® may represent a new level of precision care, upgrading the current standard of care, possibly giving:

- Faster detection of pulmonary complications leading to faster clinical decision making, thus reducing the risk of major morbidities.
- Continuous monitoring, reducing the time required for visual observation by nurses.
- Improved care for this vulnerable patient population, leading to decreased time spent in the NICU.

Summary

Neola® is a monitoring device for the lungs of preterm born infants. The device uses a breakthrough technology of spectroscopy of gas in cavities embedded in tissue. Monitoring using the device is performed non-invasively using gentle and lightweight probes attached to the thorax of the patient. This allows for continuous monitoring over extended periods, such that the development of the conditions of the lungs can be followed during treatment in neonatal intensive care units. The device offers multiple benefits, including detailed visualization of lung status changes over time, round-the-clock continuous monitoring, the possibility of immediate detection of complications like pneumothorax and atelectasis, and additional data that might aid decisions regarding surfactant therapy. The device is designed to instantly detect changes in lung volume and free oxygen gas concentration indicating pulmonary disorders such as atelectasis, pneumothorax, and intubation tube mispositioning or respiratory complications caused by mucus in the bronchi. Additionally, Neola® stores all measured parameters for clinicians to review data from the previous 24 hours and observe gradual trends. Whilst still more clinical research is needed to determine the future role of Neola® in the NICU, the aim is to support healthcare professionals to effectively diagnose and monitor pulmonary complications, leading to faster discharge from the NICU, reducing handling of preterm-born babies during their management, and improving outcomes for patients. Neola® aims to save more lives, reduce the need for prolonged hospitalization, and improve the quality of life for millions of preterm infants by providing early detection of life-threatening or irreversibly debilitating pulmonary disorders.

References

[1] Osterman M. J. K., Hamilton B. E.; Martin, J. A. et al. (2023) Births: Final Data for 2020. National Vital Statistics Reports 70, 1-49. https://stacks.cdc.gov/view/cdc/122047

[2] Zeitlin J., Szamotulska K., Drewniak N. (2014) Preterm birth time trends in Europe: a study of 19 countries. BJOG: An International Journal of Obstetrics & Gynaecology. V. 120:1356–1365. https://onlinelibrary.wiley.com/doi/abs/10.1111/1471-0528.12281

[3] Villosis M. Fe B., Barseghyan K., Ambat M.T. (2021). Rates of Bronchopulmonary Dysplasia Following Implementation of a Novel Prevention Bundle. JAMA Netw Open. 2021;4(6):e2114140. https://doi.org/10.1001/jamanetworkopen.2021.14140

[4] Reuter S., Moser C., Baack M. (2014). Respiratory Distress in the Newborn. Pediatrics in Review. Vol. 35 No. 10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4533247/

[5] Yadav S., Lee B., Kamity R. (2022). Neonatal Respiratory Distress Syndrome. StatPearls Publishing LLC. Bookshelf ID: NBK560779.

[6] Soleimani, F., Zaheri, F., Abdi, F. (2014). Long-Term Neurodevelopmental Outcomes After Preterm Birth. Iran Red Crescent Med J. 2014; 16(6), from Long-Term Neurodevelopmental Outcomes After Preterm Birth - PMC (nih.gov)

[7] Gardner, S.L., Carter, B.S., Hines, M.E., et al. Merenstein & Gardner's Handbook of neonatal intensive care, eighth edition. 2016 by Elsevier, Inc. ISBN: 978-0-323-32083-2.

[8] Olgar T., Onal E., Bor D., et al. (2008). Radiation Exposure to Premature Infants in a Neonatal Intensive Care Unit in Turkey. Korean J Radiol. 9(5): 416–419. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2627210/

[9] Krleza, J.L., Dorotic, A., Grzunov, A., Maradin, M. (2015). Capillary blood sampling: national recommendations on behalf of the Croatian Society of Medical Biochemistry and Laboratory Medicine. Biochem Med (Zagreb). 2015 Oct 15; 25(3): 335–358, from Capillary blood sampling: national recommendations on behalf of the Croatian Society of Medical Biochemistry and Laboratory Medicine - PMC (nih.gov)

[10] Marini T.J., Rubens D.J., Zhao Y.T. (2021). Lung Ultrasound: The Essentials. Radiology: Cardiothoracic Imaging, 3(2):e200564. https://doi.org/10.1148/ryct.2021200564

[11] Lee H., Kim D-J., Han J-W. (2020). Developing Nursing Standard Guidelines for Nurses in a Neonatal Intensive Care Unit: A Delphi Study. Healthcare, 8(3), 320; https://doi.org/10.3390/healthcare8030320

[12] Svanberg E.K., Larsson J, Rasmussen M. Changes in pulmonary oxygen content are detectable with laser absorption spectroscopy: proof of concept in newborn piglets. Pediatric Research. 2020. https://doi.org/10.1038/s41390-020-0971-x

[13] Svanberg E.K., Lundin P., Larsson M. et al. (2016). Diode laser spectroscopy for noninvasive monitoring of oxygen in the lungs of newborn infants. Pediatric Research volume 79, 621–628. https://www.nature.com/articles/pr2015267