Reimagining apnea monitoring in the neonatal ICU

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Purpose of review
This review outlines the prevalence and complications of apneas and intermittent hypoxemic events in preterm infants, examines current monitoring limitations in neonatal ICUs (NICUs), and explores emerging technologies addressing these challenges.

Recent findings
New evidence from the Prematurity-Related Ventilatory Control (Pre-Vent) study, which analyzed cardiorespiratory data from 717 extremely preterm infants, exposes the varying frequency, duration, and severity of apneas, intermittent hypoxemia, bradycardias, and periodic breathing during hospitalization, and highlights the negative impact of intermittent hypoxemia on pulmonary outcomes at discharge. Although traditional monitoring methods cannot differentiate between apnea types and quantify their burden, recent advancements in sensor technologies and data integration hold promise for improving real-time detection and evaluation of apneas in the NICU. Notably, small wearable mechano-acoustic sensors could improve apnea monitoring through continuous detection of airflow and respiratory efforts. Additionally, integrating bedside physiological data with modalities such as near-infrared spectroscopy, diaphragmatic activity, and electrical impedance tomography could help predict adverse outcomes by monitoring regional oxygen saturation and lung function in relation to apneas.

Summary
Enhancing our understanding of neonatal apneas and overcoming the current limitations in apnea monitoring through advanced sensor technologies and data integration could lead to more personalized management and improved outcomes for preterm infants.

Keywords
apneas, cardiorespiratory events, monitoring, neonatal ICU, preterm infants

INTRODUCTION

Apneas, bradycardias, and oxygen desaturations, commonly referred to as cardiorespiratory events, are common in term and especially preterm infants admitted to the neonatal ICU (NICU) [1]. Apneas are believed to be a major catalyst for intermittent hypoxemia, which have been associated with a range of short and long-term morbidities affecting respiratory and neurodevelopmental outcomes [2]. Despite that, major limitations persist in the practices surrounding apnea monitoring in the NICU, thereby limiting apnea detection and differentiation in neonates. In this review, we will first highlight the latest evidence surrounding the prevalence and complications associated with apneas and intermittent hypoxemia in neonates, with a focus on the preterm population. Secondly, we will review the ongoing limitations and clinical implications of suboptimal apnea monitoring in the NICU. Lastly, we will review the literature for innovative solutions that may improve neonatal apnea monitoring in the not-so-distant future.

THE CURRENT LANDSCAPE OF NEONATAL APNEAS

Extremely preterm infants develop apneas for many complex and coexisting reasons (Table 1) [3,4]. Traditionally, apneas have been classified as central, obstructive, or mixed, depending on the presence of respiratory efforts and signs of upper airway obstruction. These distinctions have become less clear with emerging evidence that central apneas can occur with airway obstruction (silent obstruction). Central

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KEY POINTS

- Apneas and intermittent hypoxias are extremely common in preterm infants admitted to the neonatal ICU (NICU) and associated with significant long-term morbidities.
- Current apnea monitoring practices lack reliability and do not provide sufficient information on respiratory events and their burden.
- Through innovative sensor technologies and advancing data integration platforms, methods may be implemented to improve the detection and differentiation of apneas and monitor their effect on end-organ function.

apneas are characterized by a lack of respiratory efforts as measured by the diaphragmatic activity or by chest or abdominal movements. Obstructive apneas are characterized by absent respiratory flow, captured usually at the nasal level, with persisting respiratory efforts. Purely obstructive apneas are rare, usually short (less than 10 s) and occur generally before or after generalized body movements. Longer obstructive apneas are usually observed in newborn infants with Pierre-Robin syndrome (mandibular hypoplasia), bronchopulmonary dysplasia or severe neurological findings such as an intracranial bleed, hydrocephalus, or severe perinatal depression leading to significant hypotonia and collapse of supporting muscles in the pharynx [5]. Mixed apneas are the most common types and are composed of a central and obstructive component [6]. These apneas may go undetected with thoracic impedance monitors and be assumed only by the presence of bradycardia or hypoxemia [7,8]. Because most mixed apneas begin with a central component and are followed by airway obstruction, they are typically associated with longer durations [9,10]. Although the pathophysiology and management of immature control of breathing in neonates have been studied for decades, ever-changing practices have influenced the types of apneas encountered in the NICU. With a growing trend towards early adoption of noninvasive respiratory support in an increasingly smaller and more immature population of preterm infants, the definitions, prevalence, natural course, and short and long-term clinical implications of apneas have also evolved [11,12].

Apneas and their clinical significance are hard to define

In a statement on apnea of prematurity from 2016, the American Academy of Pediatrics defined apnea as a pause lasting for 20 s or longer, or a shorter pause if accompanied by bradycardia (heart rate < 100 beats per minute), cyanosis, and/or pallor [13]. Despite this proposed definition, a consensus regarding which apnea durations or thresholds for bradycardia and desaturation are clinically relevant has yet to be reached, resulting in vast heterogeneity in the definitions used to diagnose or treat apneas across clinical settings and across the neonatal literature. While the American Academy of Sleep Medicine Sleep Apnea Definitions Task Force has published guidelines for defining and diagnosing apneas in adult and pediatric patients, no such guidelines exist to standardize the definition of apnea in preterm infants during NICU hospitalization [14]. Moreover, apneas can

Table 1. Causes and management of apneas

Central apnea	Obstructive apnea
Detection Absent breathing efforts and absent respiratory airflow.	Detection Persisting breathing efforts but absent respiratory airflow.
Causes and risk factors •Immature respiratory control at birth •Anemia •Inflammation or infection •Hypoxic-ischemic encephalopathy •Seizures •Therapeutic opioid administration •Anesthesia administration	Causes and risk factors •Airway obstruction at birth •Hypotonia •Structural abnormalities of the airway •Airway secretions •Position of head and neck •Gastroesophageal reflux •Airway inflammation or edema
Interventions •Supplemental oxygen •Mechanical ventilation •Methylxanthines •Corticosteroids •Tactile stimulation •Blood transfusion	Interventions •Supplemental oxygen •Mechanical ventilation •Positive airway pressure therapy •Airway suction •Repositioning •Reflux suppression

have varying clinical severities, from those that resolve spontaneously to severe events that require tactile stimulation, bag-mask ventilation, and/or intubation. Severe events are presumably more significant, as they contribute the greatest burden on patients and the clinical team. However, in the absence of robust evidence to inform the criteria for what constitutes a clinically meaningful apnea, documentation and levels of tolerance for apneas continue to vary widely across NICUs.

Apneas are ubiquitous in the neonatal ICU, especially in the most premature patients

The severity and incidence of apneas increases as a function of the degree of prematurity, with virtually all infants born before 28 weeks' gestation experiencing apneas in the NICU [1]. Fortunately, a wealth of contemporary data on the natural history of apneas, bradycardias, and intermittent hypoxemia, through analysis of waveform data from the bedside monitors, was recently published from the large Prematurity-Related Ventilatory Control (Pre-Vent) study [15,16▪▪]. In a cohort of 717 preterm infants with gestational ages less than 29 weeks, cardiorespiratory events typically peaked around the second to fourth weeks of life, with infants experiencing as many as 2–10 apneas at least 20 s, 2–7 bradycardias (heart rate < 80 beats per minute), and 5–30 cumulative minutes of intermittent hypoxemic events (oxygen saturation < 80%) per day during that period [9]. Nonetheless, physiological trajectories of cardiorespiratory events were highly variable across individuals, fluctuating not only as a function of time but also race, sex, and exposure time to mechanical ventilation. During the convalescing stages between 32 and 40 weeks' postmenstrual age, preterm infants continue to have cardiorespiratory events, which most commonly manifest as periodic breathing, defined as cycles of breathing separated by short regularly spaced respiratory pauses [1,16▪▪,17]. Periodic breathing has increasingly been recognized as an important contributor to intermittent hypoxemia during this period and may persist well beyond term corrected age [18▪].

Apneas carry important clinical implications

Through a combination of inflammation, tissue hypoxia, oxidative stress, and neurotransmitter imbalance, apneas and intermittent hypoxemic events may have deleterious consequences on growth, the developing preterm eyes, lungs, cardiovascular system, and brain [19]. Recurrent apneas and prolonged intermittent hypoxemia are two to four times more frequent amongst infants with severe retinopathy of prematurity and bronchopulmonary dysplasia [20–24], and are associated with a significantly increased probability of death or disability at 18 months' corrected age [25,26▪]. In the most recent data from the Pre-Vent multicenter prospective observational study, the daily number and duration of intermittent hypoxemia (oxygen saturations < 90%) was independently associated with unfavorable outcomes at 40 weeks postmenstrual age, defined as death or requirement for respiratory medications, oxygen, or respiratory support [27▪▪]. Importantly, short apneas and periodic breathing have also been shown to affect autonomic cardiorespiratory control and are associated with cerebral hypoxia [28▪,29▪,30]. Furthermore, frequent apneas are a major source of distress for patients, their parents, and caregivers, and are the most common reason for failure of noninvasive respiratory therapy and reintubation [31], which further increases respiratory morbidities [32]. Finally, with apneas often persisting beyond 35 weeks, and with most NICUs observing infants 5–10 days from the last event prior to discharge, apneas are a leading cause of prolonged hospitalization and increased costs [33,34,35▪].

THE CURRENT LIMITATIONS OF APNEA MONITORING IN THE NEONATAL ICU

In current practice, pulse oximetry, electrocardiography, and transthoracic impedance are continuously captured to provide measures of oxygen saturation, heart rate, and respiratory rate at the patient's bedside, respectively. Clinicians primarily rely on these vital signs to identify apneas and make informed decisions about their management. For instance, when a value falls outside a specified modifiable range, an alarm sounds to alert the nurse that intervention may be needed. Unfortunately, the alarm burden in the NICU is notoriously high. The majority of bedside monitor alarms are nonactionable, resulting in alarm fatigue and increased response time among nurses [36–38]. With nurses often relying on their clinical judgment to inform responses to bedside alarms, documentation and management of events tend to be highly variable, with apneas being the least reliably documented cardiorespiratory event [39–42]. Several factors contribute to this suboptimal monitoring and management of apneas in the NICU (Fig. 1).

Apneas cannot be differentiated using transthoracic impedance

Understanding whether an apnea is central, obstructive, or mixed requires, at minimum, continuous

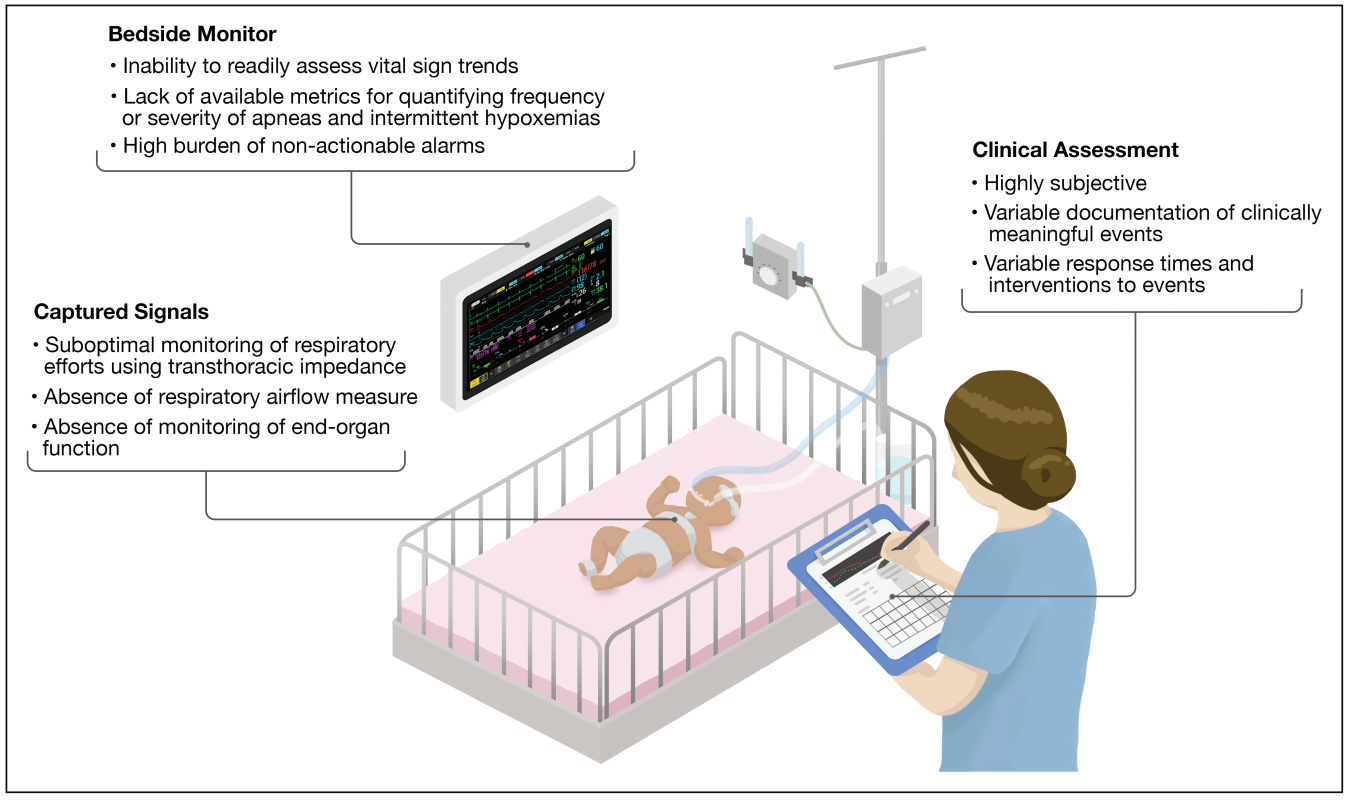

FIGURE 1. Current limitations of apnea monitoring in the NICU.

monitoring of both airflow and respiratory efforts. Transthoracic impedance, which measures fluctuations in electrical impedance caused by air and fluid movement with each breath, can monitor respiratory efforts but has several limitations when used in neonates, in part due to their unique respiratory physiology and highly variable breathing patterns. On one hand, transthoracic impedance is vulnerable to motion artefact, tends to miss breaths following large sighs, and sometimes misidentifies breaths during apneas [7,8]. For instance, a drop in heart rate secondary to a prolonged apnea can sometimes cause the electrocardiograph signal to encroach on the respiratory frequencies captured by impedance, resulting in cardiac artefact to be misidentified as breaths [43–45]. On the other hand, impedance-based monitoring cannot capture instances of airway obstruction, leading to underreporting of obstructive apneas in the NICU [45–47]. During a partial or complete airway obstruction, transthoracic impedance detects an infant's attempt to breathe against a collapsed airway regardless of whether ventilation successfully occurs. Without a measure of respiratory airflow, obstructive apneas are either missed or assumed to have occurred by nurses due to seemingly isolated bradycardias and desaturations. Consequently, obstructive apnea remains underreported and cannot be used to inform respiratory interventions. Existing methods for capturing respiratory airflow, such as oronasal thermistors, nasal pressure transducers, capnography, and pneumotachometers are not adequate for continuous use in the NICU, as they are impractical for clinicians, require the application of a facemask or nasal prongs, and may involve the addition of bulky and wired sensors, often leading to patient agitation. Such devices, though recommended reference methods in research studies, are typically only employed clinically in the context of polysomnography or specialized sleep studies [48]. Without understanding the mechanism underlying an apnea, interventions cannot be tailored to maximize efficacy.

Apnea burden cannot be assessed

Further limiting our understanding of apneas is the absence of monitoring tools to better quantify and assess the clinical implications of different apnea types on patient outcomes. In recent years, research studies have shown that cardiorespiratory signals from the bedside monitors contain a rich amount of information about the infant's cardiorespiratory

wellbeing and autonomic nervous system maturation when analyzed over time [16▪▪,29▪,49]. However, since bedside data are typically not stored in most NICUs, only a snapshot is observed at the bedside. Moreover, it is currently unclear how different apneas affect oxygenation of vital organs like the brain or gastrointestinal tract. Lower cerebral saturations have been associated with adverse neurological outcomes in preterm infants [50,51], while lower splanchnic saturations have been linked to increased intestinal ischemia [52]. Without such measures, it is difficult to decide how many and which apneas can be tolerated. In fact, as recently shown, there is a very poor agreement in clinical practice on the threshold of apneas at which to reintubate infants with frequent cardiorespiratory events [53▪].

PROPOSED SOLUTIONS TO IMPROVE NEONATAL APNEA MONITORING

In an ideal setting, management of apneas in the NICU should be tailored to the specific cause of each event and should rely on objective assessment of each event's severity and clinical significance (Fig. 2). Fortunately, achieving this management framework is increasingly possible thanks to recent advancements in sensor technologies and data integration platforms that have the potential to improve apnea monitoring in the NICU.

Optimizing current respiratory monitoring standards

Much research has been conducted with the aims of optimizing the use of existing monitoring infrastructure in the NICU. For instance, a number of quality improvement studies to reduce nonactionable ('false') alarms have demonstrated how various interventions, from simple revisions of alarm limits and alarm delays to more complex machine-learning algorithms, could significantly reduce the alarm burden in the NICU [54▪,55–57]. Furthermore, with advances in signal processing and machine-learning methodology, algorithms have been developed to enhance the accuracy of central apnea detection by the bedside monitor. Notably, several algorithms have been devised to diminish the presence of cardiac and motion artefact in the respiratory impedance signal, thereby improving the detection of apnea-bradycardia-desaturation events using standard bedside monitor signals (as was done in the PreVent study) [58–61]. As it stands, such systems are not designed for real-time use, but rather to use retroactively on collected data for research purposes. Meanwhile, efforts have similarly been made to enhance patient and caregiver comfort by way of wearable and wireless technology. For instance, chest belts integrating diaphragm electromyography have shown promise for computing respiratory rates or detecting central apneas [62▪▪,63▪]. With the

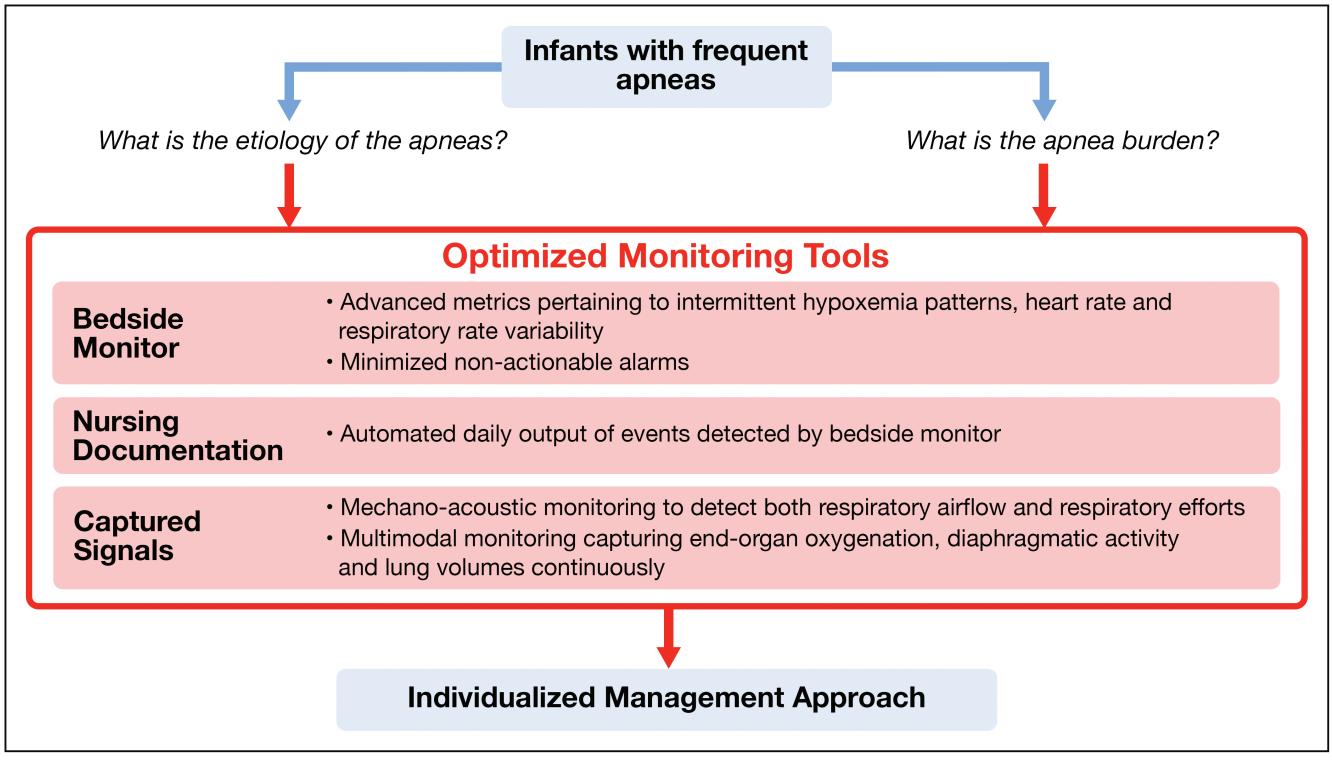

FIGURE 2. A framework for optimized assessment and management of apneas in the NICU.

development of miniaturized Bluetooth- and Wi-Fi-enabled technology, the shift to wireless monitoring devices holds the potential of facilitating nursing care, reducing the risk of nosocomial infection and promoting parent-infant bonding in the NICU [64–66]. Noncontact methods have been developed using camera-based motion detection or thermography to capture respiration [67–69]. Although they hold valuable potential to enhance accessibility of cardiorespiratory monitoring in low-resource settings, these methods are still impractical for use in critical settings such as the NICU.

Capturing respiratory airflow

The literature exploring novel methods for achieving practical, continuous airflow monitoring in preterm neonates is scarcer. One promising solution lies in acoustic respiratory monitoring. Respiratory sounds, as heard through a stethoscope, are routinely used in the NICU to assess airflow, but can also be converted to electronic signals for further analysis. Studies in adults and infants have used respiratory acoustics to detect apneas, showing that they were as accurate in the detection of airflow as reference standards [70–75]. Moreover, studies have harnessed the value of motion sensors to capture a wide-range of mechano-acoustic signals, including swallowing sounds, speech, body orientation, and respiration [76–80]. In neonates, the application of respiratory acoustics had been limited by the bulky nature of existing electronic stethoscopes or custom-made microphones and accelerometers [81,82]. Recently, Yoo *et al*. [83▪] developed a novel, wireless acoustic sensor equipped with dual contact microphones and an inertial measurement unit specifically tailored for neonatal applications. The dual microphones allow for the selective removal of ambient noise from obtained body sounds, while the inertial measurement unit uses accelerometry to capture movements of the chest associated with breathing efforts. Preliminary studies in spontaneously breathing preterm infants have shown high reliability of the acoustic sensor microphone for quantifying the intensity of air flow, and of both the microphone and inertial measurement unit for computing respiratory rates relative to reference standard measurements [83▪]. The application of a single wireless sensor for the simultaneous detection of respiratory airflow and breathing efforts holds strong potential for the continuous characterization and quantification of central, obstructive, and mixed apneas in the NICU. Acoustic respiratory monitoring may additionally allow for spatiotemporal mapping of the lung. Moreover, programs may be developed to identify and characterize abnormal lung sounds in real time, including crackling, wheezing, and stridor, informing clinicians to a potential issue early in the disease course [72,84].

Assessing apnea burden

The storage and longitudinal analysis of existing physiological data may allow for more clinically meaningful interpretations of bedside monitoring data. A number of studies have identified several signatures of oxygen saturation, heart rate variability, and breathing patterns that may be used as early warning systems to predict impending respiratory deterioration, sepsis, or other inflammatory states [85–87,88▪,89▪▪,90▪]. In the largest neonatal randomized controlled trial of its kind, implementing and displaying a measure of heart rate variability at the bedside was associated with reduced mortality in a cohort of more than 3000 very low birth weight infants [49]. Furthermore, capturing trends in breathing throughout hospitalization, whether by the computation of respiratory rate variability or the characterization of breathing patterns, may prove efficacious in assessing a patient's clinical status and predicting the likelihood of apneas or respiratory decompensation in preterm infants admitted to the NICU [91,92]. An SpO_2 histogram, which shows the percentage of time a patient has spent at different oxygen saturation levels over some chosen preceding period, is similarly useful for assessing trends in oxygenation status and oxygenation instability at the bedside. In addition to being more objective and accurate than hand-transcribed SpO_2 values, pulse oximetry histograms integrating data over periods ranging from 30 min to 24 h may capture intermittent hypoxemia with increased accuracy and be more informative in guiding respiratory management decisions [93–95]. Along with extracting vital information from the bedside monitor, the integration of biomedical signals from different modalities may be crucial for better understanding and managing the morbidities associated with apneas. In fact, multimodal monitoring has already been proven beneficial, and even become standard of care, in neonates requiring neurocritical care [96,97]. As an example, near-infrared spectroscopy (NIRS), which uses infrared light to measure regional tissue oxygenation in organs like the brain and gut, could be used to inform clinicians about the repercussions of recurrent apneas on cerebral and splanchnic oxygenation, thereby allowing targeted treatment of apneas with the greatest end-organ burden. As another example, the increasing adoption of electrical impedance tomography (EIT) in research and in clinical practice may prove valuable in enhancing our understanding of apneas. To illustrate, EIT has already been

Table 2. Reimagining apnea monitoring in the NICU: future research directions

Themes	Research areas to explore
Documenting apneas of clinical interest	•Determine the relationship between different apnea types (with variable frequencies and severities) and intermittent hypoxemia. •Study the impact of apneas and intermittent hypoxemias on long-term neurodevelopmental impairment, growth, autonomic cardiovascular control, lung development, and sleep. •Describe the perceived impact and burden of apneas from the viewpoint of healthcare providers and caregivers. •Develop standardized apnea definitions and documentation practices for both research and clinical purposes.
Differentiating apneas	•Establish the longitudinal occurrence of different apnea types (central, obstructive, mixed) and other respiratory events during neonatal hospitalization in a contemporary cohort of term and preterm infants. •Establish a repository of manually scored apneas which can be used to train different machine learning models for the automated detection and classification of apneas.
Improving respiratory monitoring	•Determine the reliability of respiratory acoustics as a novel avenue for continuous airflow monitoring. •Develop and evaluate alternatives or adjuncts to transthoracic impedance for respiratory effort monitoring (e.g. accelerometers and diaphragm electromyography). •Develop algorithms for minimizing false alarms without losing information about valuable cardiorespiratory events. Explore the feasibility, safety, and accuracy of wireless wearable sensors for cardiorespiratory monitoring in neonates.
Assessing apnea burden	•Develop and/or evaluate different cardiorespiratory metrics (e.g. heart rate and respiratory variability) derived from the bedside monitor data to enhance the assessment of respiratory instability. •Determine optimal thresholds when using oxygen saturation histograms and evaluate their clinical usefulness (e.g. when weaning continuous positive airway pressure, weaning caffeine, or discontinuing cardiorespiratory monitoring predischarge). •Evaluate the impact of different apnea and intermittent hypoxemia patterns on cerebral and splanchnic oxygenation. •Evaluate the impact of different apnea and intermittent hypoxemia patterns on lung volumes using electrical impedance tomography.

employed to assess the effects of apneas on regional lung ventilation of preterm infants receiving various respiratory support modalities [98▪].

CONCLUSION

Apneas and intermittent hypoxemic events are important morbidities that occur frequently in the NICU yet are associated with important adverse outcomes. Despite this, apnea monitoring remains suboptimal, as the assessment of these events' etiologies and burden on end-organ function remains inadequate. As outlined in Table 2, understanding the mechanisms by which apneas occur and developing more objective assessments of the burden of apneas may help clinicians establish more individualized management approaches and lead to better outcomes.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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- ▪ of special interest
- ▪▪ of outstanding interest

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