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COMMENT

Towards precision medicine for extubation of extremely preterm infants: is variability the spice of life?

Wissam Shalish[1]✉ and Guilherme M. Sant'Anna[1]

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In 1785, English poet William Cowper first penned the proverbial phrase "Variety's the very spice of life, that gives it all its flavour". While commonly understood to signify that new and diverse experiences make life more enjoyable, the quote equally holds true when examining the many biological systems around us[1]. In humans, the presence of complex, nonlinear, and interdependent patterns of variations in heart beats, breathing patterns, temperature, and blood pressure are prerequisites to maintaining physiological homeostasis and sustaining life. Any disruption in this so-called "orderly disorder" can be an imminent sign of underlying illness or can contribute, in itself, to disease progression. Fortunately, the field of medicine has long recognized the value of physiological variability as a means to derive vital clues about a patient's well-being and response to illness. The most studied metric, heart rate variability (HRV), measures variations in beat-to-beat intervals over time and is a robust marker of autonomic nervous system maturity and integrity. In fact, even the subtlest imbalances in sympathetic and/or parasympathetic activities of the autonomic nervous system can be uncovered through HRV analyses. As a result of this powerful analytical tool, an extensive body of research spanning all age groups have demonstrated an association between decreased (or altered) HRV and several pathological conditions, including sudden cardiac death, cardiovascular disease, renal failure, sepsis, psychiatric illnesses, sleep apnea, and extubation failure.[2] Interestingly, the latter application has been of particular interest to the neonatal community, since rates of extubation failure exceed 50% amongst the most extremely preterm infants and are associated with serious short and long-term morbidities.[3]

In this issue of the journal, Hoffman et al. conducted a single-center retrospective study looking at the clinical value of autonomic imbalance, as measured using HRV metrics, in predicting extubation success in a cohort of 89 preterm infants with gestational age less than 28 weeks.[4] Decisions surrounding extubation were left to the discretion of the clinical team, and extubation failure was defined as reintubation within 72 h from extubation. Continuous electrocardiogram signals from the 24 h preceding extubation were extracted from the archived data warehouse and diligently processed to compute HRV metrics using frequency domain and detrended fluctuation analyses. Frequency domain analysis provides a quantitative account of the power contained within the various frequency components of the signal, with high frequency bands characterizing parasympathetic tone and low frequency bands characterizing both sympathetic and parasympathetic tones[2]. In contrast, detrended fluctuation analysis provides a scale-invariant, long-range assessment of the intrinsic variability of the signal after removing nonstationary short-range trends, and its metrics α_1, RMS_1, and RMS_2 typically characterize the integrity of the sympathetic tone.[2] Out of 89 included infants, 24 infants (27%) failed extubation. These infants had significantly lower α_1, RMS_1, RMS_2, and normalized low-frequency power, and significantly higher normalized high-frequency power compared to infants with successful extubation, suggesting an autonomic imbalance through lower sympathetic and higher parasympathetic tones. In the univariate analyses, the HRV metric with highest accuracy was α_1, with an area under the receiver-operating characteristic curve (AUC) of 0.73. When α_1 was combined with known clinical covariates (including gestational age at birth and postmenstrual age, tidal volume, and fraction of inspired oxygen at extubation), the accuracy of the prediction model improved to an AUC of 0.81, with sensitivity 81% and specificity 78% at predicting extubation success.

The study by Hoffman et al. corroborates findings from a number of studies that have equally established a link between different cardiorespiratory variability metrics and extubation success. For instance, our research group has demonstrated that infants who fail extubation have reduced HRV metrics (using frequency domain analysis),[5] decreased tidal volume and inspiratory time variability during a spontaneous breathing trial,[6] and decreased respiratory rate variability compared to infants with successful extubation.[7] In our more recent multicenter study, where machine learning methodology was applied to develop an automated predictor of extubation readiness using both clinical and cardiorespiratory variables, metrics of heart rate and respiratory variability played a major contributory role to the predictor.[8] In addition, the use of the commercially available heart rate characteristics index, which was originally developed and validated for the prediction of sepsis, was also recently shown to predict extubation outcomes with good accuracy in preterm infants.[9]

The study by Hoffman et al. expands on existing literature by reaffirming the role of autonomic imbalance, particularly the presence of low sympathetic tone, as a marker of cardiorespiratory immaturity and as a potential indicator of maladaptive response to physiological stress following extubation. Contrary to many previously evaluated predictors of extubation readiness, the predictor in this study had a high balanced accuracy of 80%, which indicates its potential to identify infants with failed extubation without compromising on misclassifying infants with

[1]Department of Pediatrics, Neonatology, McGill University Health Center, Montreal, Quebec, Canada. ✉email: wissam.shalish@mcgill.ca

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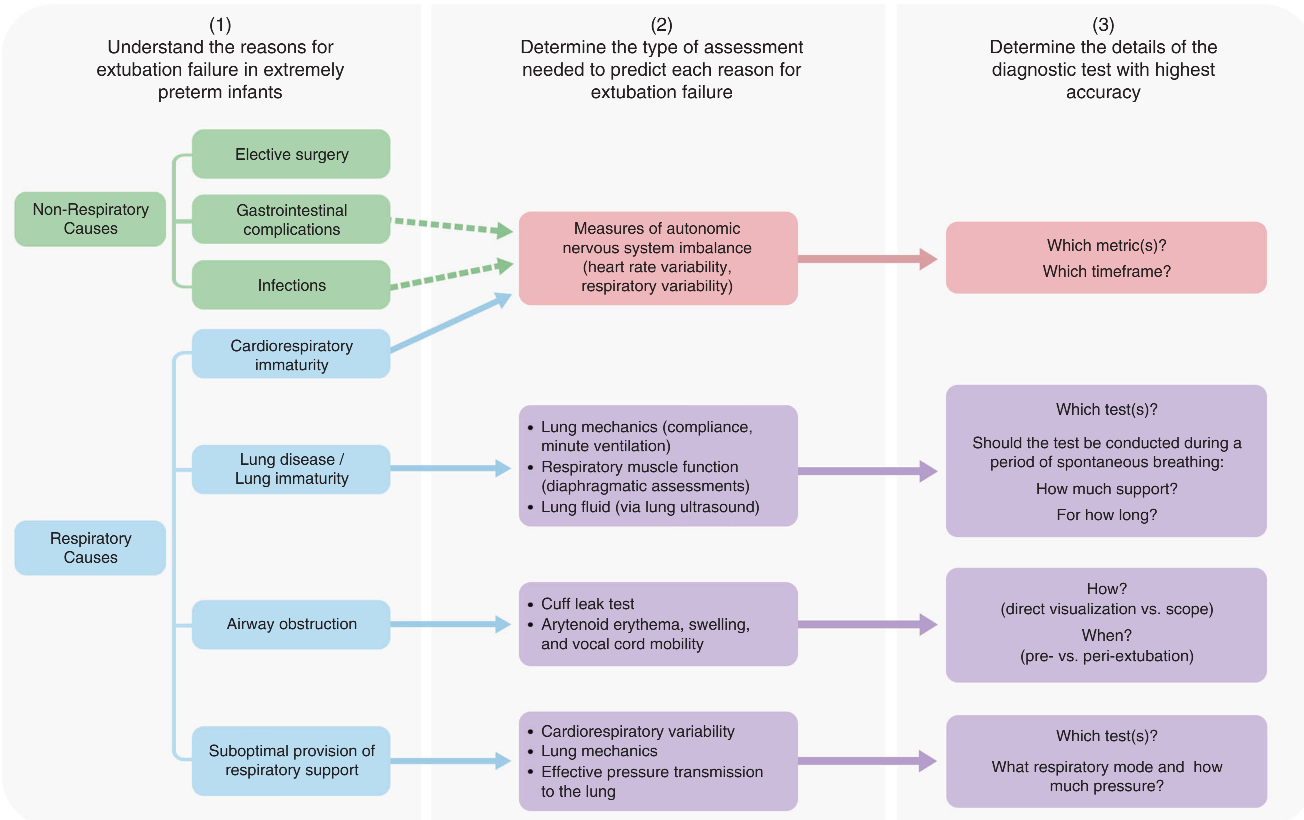

Fig. 1 A backwards approach to developing the optimal predictor of extubation readiness in extremely preterm infants.

successful extubation, and vice versa. Furthermore, the proposed HRV metrics were obtained without the need for extra instrumentation and without submitting the infants to an imposed workload during a period of spontaneous breathing via the endotracheal tube, which could lead to clinical instability. Lastly, the study's rigorous HRV analyses were the first to account for non-stationarity by normalizing the total power when computing frequency domain metrics, and also accounted for multiple sleep-wake cycles by averaging 10-min epochs over a 24-h period. In fact, the unique derivation of long-range HRV metrics that are invariant to short-term physiological fluctuations make them attractive tools for monitoring longitudinal trends of autonomic maturity across time in extremely preterm infants. Such tools would have the potential to identify infants who might have the autonomic maturity to tolerate an extubation attempt sooner than anticipated by the clinical team, thereby expediting weaning and reducing exposure to mechanical ventilation.

As highlighted by Hoffman et al. the study was limited by its retrospective design, the relatively small sample size, the lack of standardized extubation and reintubation practices, and the use of a short observation window of 72 h to define extubation failure, which likely underestimated the true number of failed extubations attributable to respiratory-related causes.[3] Moreover, the included cohort may have been exposed to center-specific weaning and extubation practices that may not necessarily apply to other centers' experiences. For instance, infants had a mean gestational age of 25–26 weeks but were only extubated at a mean corrected age of 30–31 weeks (5–6 weeks of life), which indicates that very few infants were extubated in the first week of life, a critical window where extubation is often advocated. As such, the accuracy of HRV metrics may be different when applied during the first week of life, since physiological conditions are unique to this period and distinct from conditions encountered after prolonged exposure to mechanical ventilation. Finally, it is important to note that not all infants fail extubation due to autonomic cardiorespiratory immaturity. Indeed, several infants will fail extubation due to upper airway obstruction, underlying lung immaturity, inflammation or edema, low functional residual capacity, poor compliance, surfactant dysfunction, and/or diaphragmatic weakness. These important etiological contributors may require more precise assessments aside from measures of autonomic dysfunction, such as lung mechanics, lung fluid (via lung ultrasound), and/or respiratory muscle function during a period of spontaneous breathing without mechanical inflations. Such assessments would likely add value to the accuracy of any future predictor of extubation readiness in this vulnerable population (Fig. 1).

All in all, with extubation undeniably being a complex problem in extremely preterm infants, the study by Hoffman et al. highlights that complex measures of variability should be considered as a part of the solution. With technology becoming increasingly more accessible and user-friendly, measures of HRV can provide valuable longitudinal feedback pertaining to the infant's autonomic maturity and potential to tolerate an extubation attempt. Future studies should prospectively validate the clinical usefulness of these HRV metrics, alone or in combination with other clinical or physiological parameters, in predicting extubation success and ultimately reducing respiratory morbidities in extremely preterm infants. At the same time, with HRV's usefulness continuing to expand, it is imperative for the neonatal community to come together and standardize the methodologies used for HRV analyses in neonates.[10]

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WS and GMS were involved in reading and interpreting the results of the article for which a commentary has been written. WS wrote the first draft of the commentary. WS and GMS reviewed and revised the draft of the commentary and approved the final version of the commentary.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Wissam Shalish.

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