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COMPREHENSIVE REVIEW

Heart rate variability in neonatal seizures: Investigation and implications for management

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Abstract Many factors acting during the neonatal period can affect neurological development of the infant. Neonatal seizures (NS) that frequently occur in the immature brain may influence autonomic maturation and lead to detectable cardiovascular signs. These autonomic manifestations can also have significant diagnostic and prognostic value. The analysis of Heart Rate Variability (HRV) represents the most used and feasible method to evaluate cardiac autonomic regulation. This narrative review summarizes studies investigating HRV dynamics in newborns with seizures, with the aim of highlighting the potential utility of HRV measures for seizure detection and management. While HRV analysis in critically ill newborns is influenced by many potential confounders, we suggest that it can enhance the ability to better diagnose seizures in the clinical setting. We present potential applications of the analysis of HRV, which could have a useful future role, beyond the research setting.

Introduction

The perinatal period is a critical time for the development of a healthy nervous system that can meet internal and environmental demands in adulthood. The central autonomic network (CAN) in particular, as well as the parasympathetic and sympathetic peripheral systems, goes through a prolonged maturation period before reaching an advanced level

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of control of vital functions. This process may be affected by various factors, potentially leading to delayed or dysfunctional autonomic maturation [49]. The occurrence of seizures may play an important role in this context. Significantly, several autonomic changes have been recognized as seizure manifestations in newborns, and the International League Against Epilepsy (ILAE) has recently presented a novel classification for neonatal seizures (NS), where "autonomic seizures" are defined as electro-clinical events that can involve cardiovascular, pupillary, gastrointestinal, sudomotor, vasomotor, thermoregulatory and respiratory changes [58]. However, autonomic changes observed in neonates with seizures may also be secondary to a more general condition of autonomic immaturity. For instance, autonomic cardiac signs (e.g., bradycardia) may be related to apnea and an immature control of breathing rather than directly due to seizures. Accordingly, when critically ill newborns are monitored for suspected seizures, a critical assessment of autonomic features is advised, as suggested by Falsaperla and his colleagues, commenting on the first draft of the new ILAE neonatal seizure classification (for the web reference, please see the end of the reference list). Indirect assessment of cardiac autonomic activity via analysis of heart rate variability (HRV) appears to be the most suitable way to achieve this goal. Specifically, HRV analysis provides relevant information about autonomic input to the heart [68, 77] and has multiple research and clinical applications due to its non-invasive nature and the availability of easy-to-use software tools. However, despite a large number of HRV studies that have been published over the last thirty years in clinical and non-clinical populations, there is still a paucity of HRV data from newborns with NS and it is now timely that the potential applications of HRV analysis are examined also in this clinical context. Starting from the relationship between the CAN and seizures, this narrative review discusses recent HRV findings from neonates with NS with the aim of highlighting the clinical value of HRV derived information and the potential contribution of HRV analysis in NS management. Finally, the difficulties of using HRV analysis in this patient group are discussed.

Central autonomic network and seizures

The CAN was first described as a large network that controls efferent information relayed to the heart and involves cortical, subcortical (forebrain) and brain stem regions [4]. Within this network, higher interconnected cortical regions, including the orbitofrontal, insular and cingulate cortex, process afferent signals from other brain areas and the periphery, and project to pivotal subcortical structures, like the amygdala and hypothalamus [78, 16]. The former modulates the effects of emotional stimuli on the heart and is connected with hypothalamic and brain stem nuclei [72]. The hypothalamus, in turn, integrates the forebrain control of autonomic function sending projections to key autonomic structures within the brainstem (periaqueductal gray matter, parabrachial region, rostral ventrolateral medulla, raphe pallidus, the nucleus tractus solitarius, among others) [16, 64]. Therefore, a complex of higher neural influences descends in a cascade fashion and ultimately reaches sympathetic and parasympathetic preganglionic neurons that modulate cardiac function via the peripheral arms of the autonomic nervous system [72].

Disorganized electrical discharges within the brain, and specifically within the CAN, can thus affect cardiac autonomic function [19]. In patients with epilepsy, autonomic dysfunction frequently occurs during seizures, which may elicit detectable cardiovascular changes [10, 57]. For example, transient changes in blood pressure (BP) and heart rate (HR) are some of the most common autonomic manifestations of seizures in the neonatal period [57, 94]. Moreover, cardiac manifestations of seizures that range from sinus tachycardia to atrial or ventricular fibrillation have been reported in both children and adults [50, 89, 72, 3]. A retrospective study identified tachycardia and oxygen desaturation (from 60 s before electrographic seizure onset to 60 s after seizure offset) as the most common autonomic peri-ictal signs observed in 49 children with temporal lobe seizures [95]. Post-ictal bradycardia is a less common cardiac sign of seizures, which, in children, could be related to syncope [37] and secondary to severe hypoxemia induced by central apnea. Severe bradycardia may progress to asystole and thus represent a potential underlying mechanism of sudden death associated with seizures [5, 48, 84]. Seizures within the insular cortex have been associated with cardiac repolarization abnormalities (e.g., long QT, larger QT dispersion) that may result from reduced inhibition of sympathetic activity and increased release of catecholamines, and trigger serious arrhythmias and sudden death [76]. Notably, both tachy- and brady-arrhythmias have been described during and/or after different types of seizures. Cortical stimulation studies of the anterior insula [51, 52, 53], have shown evidence that electrical discharges arising from the right hemisphere produce cardiac effects driven by the sympathetic nervous system, whilst seizures arising from the left result in parasympathetic effects. Furthermore, a recent study suggests that bi-temporal seizure activity may significantly increase heart rate [54]. Higher mortality risk has been associated with post-ictal rather than ictal arrhythmias, suggesting that seizures may trigger life-threatening cardiac events [89].

Curiously, seizures have been also reported following cardiac surgery in newborns, the mechanisms of which have not yet been fully elucidated [15]. No link to CAN dysregulation has been demonstrated, but cerebral anoxia may be involved. For example, as early as 1999, a case study described the onset of seizures following sudden cerebral anoxia in a newborn with congenital atrio-ventricular block and Wolff-Parkinson-White syndrome [38]. Nevertheless, seizures secondary to cerebral anoxia are very common in newborns and, thus, a link to the CAN remains elusive.

Taken together, these findings suggest that the CAN is a critical neural substrate involved in the generation of seizure-related cardiac complications that, in turn, may worsen post-hypoxic brain damage and contribute to seizure onset [12] (Fig. 1). Several alterations of cardio-respiratory autonomic function (e.g., severe bradycardia, central apnea, dysregulation of blood pressure control with impaired baroreflex sensitivity) can indeed compromise systemic or cerebral blood flow and oxygen supply. The resultant hypoxemia could thus induce the progression of brain injury underlying seizures.

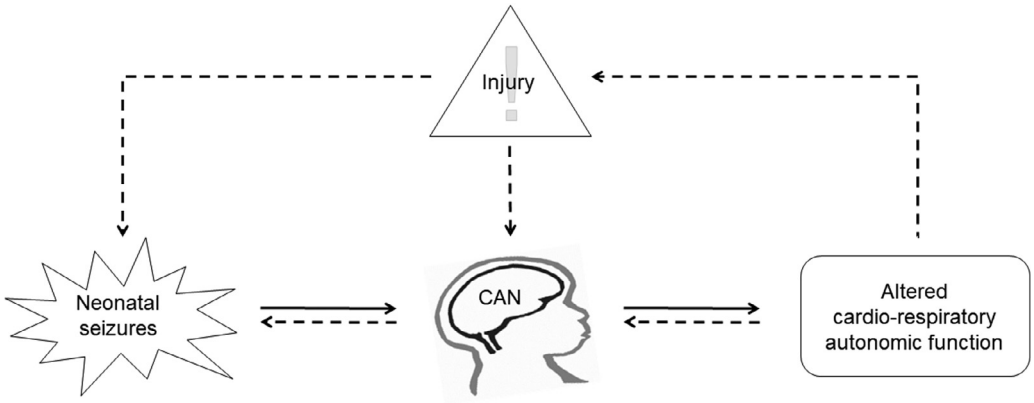

Fig. 1 Neonatal seizures and central autonomic network (CAN). Seizures can result in altered autonomic regulation of vital functions. In turn, these autonomic changes may actually play a role in seizure onset, especially when pre-existing damage (e.g., ischemic hypoxia) affects the immature brain.

Furthermore, it should be highlighted that the neonatal condition represents a period of extreme vulnerability. The complex interconnections between hindbrain, midbrain, and forebrain structures of the CAN begin to develop during the intrauterine phase and strengthen throughout life. Similarly, the peripheral autonomic nervous system develops during the fetal period and matures during the first years of life, when increased cortical development allows better control over the brainstem via direct (e.g., corticobulbar) and indirect (e.g., corticoreticular) neural pathways, and a simultaneous increase in myelinated vagal fibers number leads to a new balance promoting parasympathetic over sympathetic activity [49]. During the third trimester of pregnancy in particular, an acceleration in autonomic maturation occurs that is associated with an important increase in vagal tone [67]. However, the intense synaptogenesis and developmental mechanisms, including rapid microglia activation [40], in addition to the pronounced excitability of the immature brain [57], enhance seizure susceptibility in response to external insults. This might be exacerbated when preterm birth causes a premature transition from the intra- to extrauterine environment. Nevertheless, the higher risk of experiencing NS in preterm babies is strongly associated with illness (e.g., intraventricular hemorrhage) [73]. In addition, the well-known developmental gap in cardiac autonomic control between preterm and full-term infants at birth persists at the time of their expected delivery, and seems to resolve only at age two if no further complications occur [17]. Accordingly, preterm babies could be more likely to show seizure-related autonomic signs and future adverse outcomes [73, 35, 97].

Cardiac autonomic function and HRV

HRV analysis of the electrocardiogram (ECG) signals in neonates provides a useful method of evaluating cardiac autonomic regulation in a non-invasive and indirect manner, for the investigation of the cardiac autonomic correlates of NS. HRV describes the oscillation in the interval between consecutive normal heartbeats (RR intervals) and, thus, the continuous HR fluctuations around the mean value [79]. This phenomenon is mainly driven by the activity of higher autonomic control centers coupled with peripheral feedback mechanisms and intrinsic sinoatrial node dynamics, which modulate the rhythmicity of the cardiac pacemaker [88]. Importantly, HR shows periodic respiratory-related changes. This phenomenon, in which HR increases during inspiration and decreases during expiration, is known as respiratory sinus arrhythmia and it is closely related to vagal tone [39].

HRV is generally investigated through linear methods in the time- or frequency-domain (see table 1 for a summary of the main HRV parameters in newborns), although non-linear methods have also been used for this purpose. For time-domain analysis, geometrical patterns and many statistical indices can be derived from direct RR interval measurements or the differences between RR intervals [79, 41]. Among these indices, the most routinely used are: the standard deviation of RR intervals (SDNN) that reflects all the cyclic components responsible for variability; and the root mean square of successive RR interval differences (RMSSD), which describes short-term variation in heart rate and thus estimates the vagal input to the heart [79]. For frequency-domain, spectral analysis of interbeat interval time series indicates the distribution of absolute or relative power as a function of frequency [79]. Both parametric and non-parametric procedures can be used for estimating power spectral density, but the latter, based on the Fast Fourier Transform (FFT) algorithm, are often preferred. Indeed, although it requires a stationary data segment of a minimum length and needs artificial interpolation, FFT ensures faster and easier calculation of the power spectral density. On the contrary, autoregressive parametric methods, which provide high-resolution spectra, are computationally demanding and need a careful evaluation of the chosen model and its order [43]. The power spectrum of short-term time series contains three major components: i) the high frequency (HF) component, which is related to respiration and reflects cardiac vagal tone [82]; ii) the low frequency (LF) component, which includes both sympathetic and vagal influences and is associated with baroreceptor activity [98]; and iii) the very low frequency (VLF) component, which is less defined and seems to be related to the renin-angiotensin-aldosterone system, thermoregulation and the peripheral vasomotor tone [91].

Table 1 Summary of the main time- and frequency-domain parameters of heart rate variability in neonates.

	Index	Description	Physiological origin
Time-domain	SDNN	Standard deviation of all R-R intervals	Cyclic components responsible for heart rate variability
	RMSSD	Root mean square of successive R-R interval differences	Vagal tone
	PNN25	Percentage of successive normal R-R intervals that differ by more than 25 ms	Vagal tone
Frequency-domain	LF	Low frequency spectral power (0.05—0.25 Hz), Schneebaum Sender et al., 2014 [66] (0.04—0.2 Hz), Goulding et al., 2017 [30] (0.04—0.5 Hz), Vesoulis et al., 2017 [93] (0.04—0.3 Hz), Statello et al., 2018 [74]	Combination of sympathetic and vagal activity, baroreflex activity
	HF	High frequency spectral power (0.3—1 Hz) Schneebaum Sender et al., 2014 [66] (0.2—2 Hz), Goulding et al., 2017 [30] (0.5—1.3 Hz), Vesoulis et al., 2017 [93] (0.3—1.3 Hz), Statello et al., 2018 [74]	Vagal tone
	LF/HF	Low frequencies/high frequencies ratio	Combination of sympathetic and vagal activity

The HF and LF components (usually reported as absolute values, ms^2) can also be expressed in normalized units (n.u.), which represent the relative proportion of each component of the total power (TP) minus the VLF component [11]. Lastly, the ratio between LF and HF (LF/HF) was long used as a marker of sympathovagal balance, although this concept has been extensively challenged [8]. In fact, given that the LF band does not reflect sympathetic activity [28, 59, 36], there is now a consensus to say that the precise physiological underpinnings of the LF/HF ratio are still unclear [42]. Finally, although complex techniques based on nonlinear dynamics and chaos theory have been developed to evaluate in greater detail the intrinsic complexity of HRV, these tools require more powerful computing and are still under development and evaluation.

HRV findings in newborns with NS

Despite the use of HRV as a proxy for cardiac autonomic function in several clinical and investigational domains, there is a paucity of data about HRV features in newborns with seizures. The majority of these findings comes from studies conducted on newborns with hypoxic-ischemic encephalopathy (HIE), the most frequent etiology of NS. For example, a retrospective study of ECG recordings from term HIE newborns related the location of cerebral injury to a decrease or increase in the LF/HF ratio, depending upon the hemispheric lateralization of focal brain injuries revealed by brain magnetic resonance imaging (MRI). A multiple linear regression model was used to relate location of injury to spectral features of HRV extracted from 20-min seizure-free ECG recordings. The authors found that lesions of the right cerebral cortex and right cerebellum were associated with decreased LF/HF ratio, whereas damage to corresponding regions of the left hemisphere were associated with increased LF/HF ratio. However, these findings, which may indicate autonomic lateralization in term newborns, were not confirmed when HF (0.3—1 Hz) and LF (0.05—0.25 Hz) spectral powers were considered separately. Also, because the brain was divided into 13 areas to score injury sites, possible interregional influences and the involvement of more restricted areas may not have been detected [66]. Goulding et al. [30] compared HRV in normothermic and hypothermic newborns with different EEG grades of HIE severity (i.e., mild, moderate and severe). For each patient, 1 h epochs were selected at 6, 12, 24, 36, 48, and 72 h after birth and those with poor ECG quality, as well as with seizure activity, were excluded. Time-domain parameters were calculated and modified frequency bands (HF, 0.2—2 Hz; and LF, 0.04—0.2 Hz) were applied for HRV spectral analysis. The authors found that HRV inversely correlated with HIE severity in full-term newborns and that therapeutic hypothermia enhanced HF-HRV with a putative neuroprotective effect in babies with moderate HIE [30]. Similarly, Vesoulis et al. [93] evaluated the effect of therapeutic hypothermia on HRV in two groups of full-term neonates with favorable and unfavorable outcomes based on the occurrence of seizures, abnormal MRI findings and neurodevelopmental impairment. Sixty minute segments were selected during hypothermia (at 24 and 48 h) and normothermia (at 96 h). Adapted frequency bands (HF, 0.5—1.3 Hz; and LF, 0.04—0.5 Hz) and time-domain measures were considered. An increase over time was observed for HR and its variability in babies with favorable outcomes, suggesting a gradual improvement in cardiac autonomic control that, according to the authors, could be independent of hypothermia. Indeed, temperature conditions affected HR in both groups, whereas an effect on breathing rate and HF spectral power was detected only in patients with favorable outcomes. Therefore, the authors concluded that the underlying brain injury produced persistent changes in HRV, whereas hypothermia induced mild bradycardia in infants with moderate HIE. However, the potential influence of anticonvulsant drug administration in critically ill infants on HRV was not considered [93].

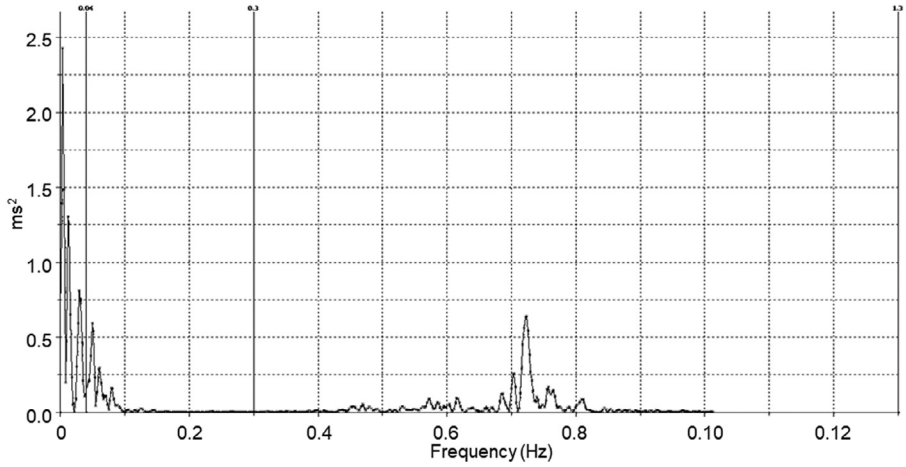

Fig. 2 A representative power spectrum of Heart Rate Variability (HRV) in a newborn. An HRV spectral estimate has been obtained through the application of the Fast Fourier Transform method on a 3-min ECG recording. The respiratory sinus arrhythmia peak occurs at 0.73 Hz (∼44 breaths per minute).

Recently, a meta-analysis was attempted on 1187 studies involving 248 neonates. As stated by the authors, very high heterogeneity among these studies allowed only a narrative description of four observational studies (including the work by Goulding et al. [30] described above) showing that HRV indices were reduced in newborns with moderate or severe HIE compared to neonates with mild or no HIE [1]. However, a critical aspect to consider is that these studies did not fully address HRV changes during NS, but predominantly focused on the association between HRV and HIE during seizure-free periods.

As a first attempt to fill this knowledge gap, a retrospective study conducted by our group reported that newborns with NS showed lower resting state HRV compared to matched controls. Moreover, a short-lasting increase in parasympathetic indices of HRV was observed during seizures only in full-term newborns. We hypothesized that this effect could be due to the relatively advanced degree of maturation of the autonomic nervous system in full-term neonates, and we have interpreted it as a potential protective mechanism aimed at limiting sympathetic hyperactivity [74].

Potential application of HRV in seizure detection

The studies reviewed so far have limited their investigation to the description of the HRV changes that occur in neonatal patients during both seizures and seizure-free periods. However, another intriguing area of research would be the investigation of the extent to which HRV measures may inform about the onset and/or severity of seizure activity. A study reporting a decrease in RR intervals during NS suggested that significant changes in HR might alert the clinicians to the occurrence of subclinical events [32]. However, another work reporting a low occurrence of ictal HR variations indicated that these changes seemed to be insensitive for detecting seizures in neonates with severe birth asphyxia [13]. Recently, artificial intelligence has been widely employed in the context of cardiac bioelectrical signal analysis [14, 7]. A number of authors have proposed methods for the early detection or prediction of seizures based on time and frequency features of HRV [33, 34, 20, 22, 44, 45, 46]. For instance, machine learning based approaches focused on quantification analysis via Supporting Vector Machine (SVM) have been proposed to predict neonatal seizures [80]. However, a thorough delineation of these algorithms that, in some cases, reached promising specificity and sensibility values but remain outside the routine clinical practice, is beyond the scope of this review. (For a review of automatic seizure detection methods see [60]).

As far as NS detection is concerned, electroencephalography (EEG) represents the fundamental examination. However, EEG alone may miss seizures which do not involve cortical regions. In these cases (e.g., in a preterm newborn with autonomic seizures originating from limbic structures) evaluating autonomic signs could be very helpful. Therefore, rather than the easier and time-saving amplitude integrated EEG (aEEG) [29] or conventional EEG, continuous long-term video-EEG (multiple channel v-EEG) must be used whenever possible [63, 69, 70]. Specifically, multiple channel v-EEG allows for evaluation of electrooculogram (EOG), electromyogram (EMG), ECG, breathing rate and other respiratory measures in addition to both electroencephalographic patterns and behavioral manifestations. Consequently, autonomic features of NS can be investigated in depth, leading to better seizure detection and characterization.

The main difficulties of HRV assessment in newborns with seizures

Currently, the investigation of HRV dynamics in newborns with seizures is not without limitations. For instance, the relatively small number of patients included in each study (e.g., n = 16, [93]; n = 28, [74], 2018; n = 40, [66]; n = 118 [30]) could affect results and conclusions. Since this is primarily due to difficulties in recruiting good quality ECG recordings, using animal models or computer simulations of NS could be a viable strategy to overcome this problem

depending on the aims of the study. Moreover, when considering the methodological heterogeneity of these studies (e.g., inclusion criteria, modality of analysis and indices calculated, experimental design, etc.) that may also derive from their retrospective nature, comparison of results between studies is challenging. It is known that sampling frequency, recording period length, RR detection and artifact removal methods are just some of the factors that can influence HRV assessment [68, 79]. In addition, several characteristics of newborns with NS should be taken into account. Besides sex and health status (e.g., the occurrence of primary brain conditions; Apgar score; cerebral ultrasound evaluation; etc.), heart and respiration rates may affect proper computation of HRV. As a rule, variability decreases when RR intervals get shorter [47], and a reduction in respiratory rate increases the amplitude of HR oscillations [8]. Accordingly, healthy newborns whose normal HR is higher than 90 beats per minute (bpm) show lower HRV than children and adults [61]. Moreover, their respiration rate is about 50 breaths/min and therefore respiratory sinus arrhythmia peak is around 0.8 Hz (Fig. 2). For these reasons, frequency bands recommended for adult population (VLF $<$ 0.04 Hz $<$ LF $<$ 0.15 Hz $<$ HF $<$ 0.4 Hz) are not suitable for HRV spectral analysis in infants [26]. Consequently, in order to use more appropriate spectral bands, many authors have employed different frequency ranges adapted from the Task Force guidelines (e.g., 0.05 Hz $<$ LF $<$ 0.25 Hz and 0.3 $<$ HF $<$ 1 Hz, [66]), leading to results that are not comparable between studies. The gestational and post natal age of newborns must also be taken into account. Maturation of autonomic control starts in the fetus, and continues for many years. Accordingly, preterm infants have lower HRV than full-term babies [97]. Several authors have also suggested that postnatal autonomic maturation may differ between pre- and full-term infants at least for the first two years of life [17]. Another issue to consider is that HRV investigations use different time lengths of selected ECG recordings in newborns. It is well established that HRV is affected by the length of analyzed epochs and its parameters give different information when they are calculated from ultra-short-, short-term or 24-hour period [42, 79]. Govindan et al. have recently proposed that a 2-min period could represent the optimal epoch length to analyze RR interval variability in ill infants. Indeed, HRV dynamics of newborns can be more accurately characterized using a short epoch length of data because of their higher HR compared to children and adults, for which analyzing a 5-min period is recommended [31]. Furthermore, based on their relation to a given seizure event, several periods within the acquired recordings can be defined as follows: pre-ictal (immediately before seizure); ictal (during a seizure); post-ictal (immediately after seizure); or inter-ictal (between and far from seizure events) [24, 74]. Therefore, one or more periods can be selected and analyzed, according to the specific purpose of the study. However, mainly (but not exclusively) due to the type and duration of seizure, accurately defining the boundaries of each period remains challenging and could require a thorough EEG evaluation [56]. Lastly, many other potential confounding factors (e.g., drug administration, behavioral state, etc.) can result from study design and/or clinical setting. Therefore, their influence on HRV assessment should be taken into account.

HRV dynamics and sleep in newborns

Undoubtedly, besides the above reported confounding factors, the evaluation of sleep and waking states deserves a separate discussion, since physiological functions are dramatically affected by different behavioral states.

Cardiac autonomic changes occur during sleep. Specifically, in healthy adults, different sleep stages are characterized by different sympathovagal regulatory patterns. A predominant sympathetic activity can be observed during REM sleep, whereas vagal modulation characterizes the NREM phase and prevails especially during deep sleep [85, 86]. A more complex picture results from several studies describing HRV dynamics during sleep in newborns. Doyle et al. provided normative time- and frequency-domain data for healthy full-term neonates during quiet and active sleep in the first 12 h of life. Specifically, 30 babies with mature sleep-wake cycles were studied and significant between-states differences in HRV measures were found. Vagal tone was dominant in quiet sleep as suggested by HF power. However, time-domain indices of parasympathetic tone (i.e., RMSSD and PNN25 (percentage of successive NN intervals that differ by more than 25 ms)) did not significantly differ between the two sleep phases, probably because these parameters could not be appropriate to quantify HF activity during quiet sleep. Moreover, the HF respiratory peak was missing in 6 newborns during quiet sleep. The authors suggested that immature cardiorespiratory control could lead to the lack of respiratory sinus arrhythmia peak, but an artificial loss of this peak could also be due to "cardiac aliasing" [21, 62]. These findings confirmed that neonatal HRV is strongly influenced by sleep state and the degree of maturation of the autonomic nervous system, as previously described elsewhere. In 1993, a study by Eiselt et al. [23] showed that full-term newborns had lower HR and higher HRV than pre-term neonates of the same postconceptional age (i.e., 37−41 weeks) during both quiet and active sleep. Furthermore, lower HR and higher amplitude of HF characterized quiet sleep as compared to active sleep but only in full-term newborns. Presumably, the pronounced immaturity of the parasympathetic branch of the autonomic nervous system concealed this difference between sleep states in preterm babies [23]. Vandeput et al. reported significantly lower HR and SDNN in non-REM than in REM sleep of preterm neonates at 34 weeks' postconceptional age. The authors suggested the use of nonlinear methods that revealed a less chaotic RR interval series during NREM sleep periods to discriminate between neonates with and without abnormal polysomnography findings [90]. Moreover, some factors could influence HRV independent of the sleep stages. For instance, Stephan-Blanchard et al. showed that non-neutral ambient temperature affects autonomic regulation in sleeping preterm babies and warm thermal conditions are associated with lower vagally mediated HRV, independently of the sleep stage [75]. Some studies demonstrated that even sleeping position affects newborns' HRV that is reduced by prone sleeping, independent of gestational age [71, 25].

The sleep cycle in newborns differs quite dramatically compared with adults. Currently, polysomnographic and behavioral evaluations allow the identification of five main neonatal sleep-wake states: "active sleep"; "quiet

sleep"; "active wakefulness"; "quiet wakefulness"; and "indeterminate sleep". Except for the indeterminate sleep, these states are marked by several physiological and behavioral features (e.g., active sleep are characterized by rapid eye movements, irregular cardiorespiratory patterns, continuous EEG background activity and facial movements, whereas regular cardiorespiratory patterns, dis- or semi-continuous EEG background activity and lack of movements are typical of quiet sleep) that differs according to gestational age [18]. Indeed, immature sleep states appear after 24 weeks of gestational age [65, 92]. As vigilance states mature (with active sleep that appears first, followed by quiet sleep, active wakefulness and, lastly, quiet wakefulness), the time spent in the indeterminate state decreases. However, mature and recognizable states occur only near term, when the sleep cycle amounts to ~ 60 min and a clear ultradian rhythm can be observed [9]. Importantly, the maturation of the wake-sleep cycle is thought to indicate brain integrity and cortical organization, but also to take an active part in the development, as well as in the consolidation, of cerebral functions [9, 87]. Preterm birth as well as various postnatal factors and comorbidities can have an unfavorable impact on sleep maturation (e.g., in HIE and other conditions, sometimes it is impossible to assess the occurrence of different sleep phases) and may lead to impaired neurological functions [27]. It is particularly important for newborns with seizures that can be premature, have serious underlying conditions and undergo various therapeutic treatments. There is currently little agreement on preterm EEG scoring due to the lack of definitive guidelines. Nevertheless, it is acknowledged that appropriate identification and evaluation of behavioral state are fundamental for carrying out any neurophysiological investigation, including HRV assessment, in the neonatal period and particularly in at-risk neonates.

Perspectives and limitations

Despite a paucity of data about HRV measures as a proxy of cardiac autonomic function in newborns with NS, several potential applications of HRV emerge from the available literature. Firstly, HRV analysis give information about seizure burden. Furthermore, since cardiac autonomic changes during seizure may depend on which brain areas are involved, HR and HRV dynamics could provide relevant information about the ictal onset area, propagation and severity of seizures [83]. HRV measures have also been proposed as possible prognostic markers of neurological underlying injury (e.g., hypoxic-ischemic encephalopathy) in newborns, as suggested in a recent review [6]. Moreover, in order to make precision medicine even more feasible in critically ill newborns and since genetic testing currently plays an important role in the management of NS with genetic etiology [2], correlating HRV-derived autonomic features with specific pathological mutations represents an intriguing clinical challenge. Similarly, the development of novel HRV-based algorithms and tools for automatic seizures detection remains an ambitious and promising research topic. However, although HRV analysis can provide supplemental information for EEG-based diagnosis, NS cannot be diagnosed with HRV analysis alone. Despite the progress made to date, it is still not feasible to use HRV parameters as predictive/diagnostic markers of NS, since many differences exist between different newborns with NS and this could require previous individualized characterizations. Fetal HRV that may be informative of fetal maturation level and the possible occurrence of injuries could also be useful in this respect [55, 81, 96]. Certainly, HRV measures can provide important information about the impact of different therapies for NS on cardiac autonomic activity and maturation.

Conclusion

Newborns may show impaired autonomic cardiovascular function during an episode of seizures and seizure-free periods, which might be indicative of a compromised neurovegetative maturation or possible multiorgan failure. However, for the suggested HRV applications and future purposes, it is pivotal to define standard guidelines for HRV analysis in newborns, with appropriate corrections for pre-term babies. Indeed, the wide availability of easily accessible HRV-dedicated software represents a valuable opportunity but also a dangerous shortcut that could lead to result misinterpretation and hasty conclusions especially when non-specific indexes (e.g., LF/HF) are reported and/or their interpretation is oversimplified. In conclusion, HRV analysis represents a powerful research tool that supplies valuable insights into the cardiac autonomic regulation of newborns. Further studies are needed to fully elucidate HRV dynamics in neonates with seizures and, although the clinical applications of HRV for NS detection and management may appear attractive, it is advisable to remain cautious about their practical feasibility at present in neonatal intensive care unit (NICU) clinical settings.

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