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REVIEW

Heart rate variability as possible marker of brain damage in neonates with hypoxic ischemic encephalopathy: a systematic review

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Abstract

Heart rate variability (HRV) is currently considered the most valuable non-invasive test to investigate the autonomic nervous system function, based on the fact that fast fluctuations might specifically reflect changes of sympathetic and vagal activity. An association between abnormal values of HRV and brain impairment has been reported in the perinatal period, although data are still fragmentary. Considering such association, HRV has been suggested as a possible marker of brain damage also in case of hypoxic-ischemic encephalopathy following perinatal asphyxia. The aim of the present manuscript was to review systematically the current knowledge about the use of HRV as marker of cerebral injury in neonates suffering from hypoxic-ischemic encephalopathy. Findings reported in this paper were based on qualitative analysis of the reviewed data.

Conclusion: A growing body of research supports the use of HRV as non-invasive, bedside tool for the monitoring of hypoxic-ischemic encephalopathy. The currently available data about the role of HRV as prognostic tool in case of hypoxic ischemic encephalopathy are promising but require further validation by future studies.

What is Known:
- *Heart rate variability (HRV) is a non-invasive monitoring technique to assess the autonomic nervous system activity.*
- *A correlation between abnormal HRV and cerebral injury has been reported in the perinatal period, and HRV has been suggested as possible marker of brain damage in case of hypoxic-ischemic encephalopathy.*

What is New:
- *HRV might provide precocious information about the entity of brain injury in asphyxiated neonates and be of help to design early, specific, and personalized treatments according to severity.*
- *Further investigations are required to confirm these preliminary data.*

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Keywords Heart rate · Heart rate variability · Neonate · Brain damage · Hypoxic ischemic encephalopathy · Asphyxia · Therapeutic hypothermia

Abbreviations

ANS	Autonomic nervous system
ECG	Electrocardiogram
HF	High-frequency band
HR	Heart rate
HRV	Heart rate variability
Hz	Hertz
LF	Low-frequency band
NN	Normal-to-normal R-R interval
pNN50	Percentage of normal R-R intervals that differ by 50 milliseconds
rMSSD	Root mean square of successive R-R interval differences
SDANN	Standard deviation of the average normal R-R interval differences
SDNN	Standard deviation of normal R-R intervals

Introduction

Perinatal asphyxia and hypoxic ischemic encephalopathy

Perinatal asphyxia (PA) is a major cause of morbidity and mortality in infants. A severe complication of PA is the hypoxic-ischemic encephalopathy (HIE), often associated with impaired neurodevelopment [1–3]. Hypothermia, begun within the first 6 h of life, provides neuroprotection and improves neurological outcome in mild/moderate forms of HIE, but has poor effect in case of severe HIE [4–7]. Recent progresses in the search for neuroprotective compounds suggested that the optimal therapeutic strategy for HIE might be the use of combined treatments, i.e., the use of hypothermia in association with neuroprotective drugs. Therefore, the early identification of neonates at the highest risk for abnormal neurodevelopment who would benefit from additional neuroprotective drugs would be crucial, especially considering that neonates might show only mild symptoms of cerebral injury in the first period after the hypoxic insult, due to the intrinsic pathophysiologic mechanisms leading to brain damage or to the therapies which may inhibit symptoms development [8–11].

Currently, standard monitoring techniques of brain damage in asphyxic neonates may sometimes be insufficient for a precocious overview about the entity of brain injury and a proper prognostication. The role of magnetic resonance imaging (MRI), the gold standard technique for the prediction of neonatal neurologic outcome in neonates with HIE, is unfortunately limited in the first hours after birth [12]. Continuous electroencephalogram recordings, amplitude-integrated electroencephalography (aEEG) has an important and well-established role for HIE diagnosis and monitoring [13] but is not always available for logistic issues, and its evaluation requires specific training being influenced by multiple factors (muscular activity, medications, electrocardiographic (ECG) signal) [14, 15]. Furthermore, false normal aEEG background patterns are possible in neonates with HIE treated with hypothermia [16]. Multiple biomarkers of brain activity have also been investigated in different biologic fluids, but none of them has still been included in the international guidelines for the assessment of HIE despite an increasing body of evidence concerning their reliability [17]. As a whole, this means that clinicians still lack a reliable and precocious marker of brain injury in daily clinical practice and that the measurement of quantitative parameters able to diagnose sub-clinical lesions at an early stage and to evaluate the effectiveness of the therapeutic strategies could be especially useful.

Heart rate variability

Neonatal cardiovascular system is characterized by physiological modifications, allowing a proper adaptation to the extrauterine life. Hearth rate (HR) regulation is achieved through the sympathetic and parasympathetic components of the autonomic nervous system (ANS). Neonates typically show high HR compared with older infants, corresponding to a cardiac-linked predominance of the sympathetic activity and to a decreased vagal activity [18]. Heart rate variability (HRV) is a physiologic phenomenon describing the oscillations in the interval between consecutive heartbeats as well as the oscillations between consecutive instantaneous heart rates (HRs) [19, 20]. HRV is currently considered the most valuable non-invasive test to investigate ANS function, based on the evidence that fast fluctuations might specifically reflect changes of sympathetic and vagal activity [21]. Overall, low HRV values usually reflect a relative sympathetic dominance achieved by high sympathetic tone and/or low parasympathetic tone, while high HRV values mirror an increased vagal activity.

HRV measures are mainly classified into two categories: *standard linear time-domain* and *standard linear frequency-domain* [19].

- *Time-domain* measures in long-term ECG recordings (24-h Holter monitoring) allow the assessment of both the instant HR and the intervals between consecutive normal QRS complexes (normal-to-normal R-R interval,

NN). They also permit the registration of further variables derived from NN intervals, of which the most relevant are (1) SDNN (standard deviation of normal R-R intervals) and SDANN (standard deviation of the average normal R-R interval differences), which reflect either the sympathetic or the parasympathetic regulatory effect on the HR and (2) rMSSD (root mean square of successive R-R interval differences) and pNN50 (percentage of normal R-R intervals that differ by 50 milliseconds), which exclusively assess the parasympathetic modulatory effect [21, 22].

- The *frequency-domain* methods, with spectral analysis using Fast Fourier Transform, analyze HR variations by subdividing HR signal into its constituents and quantifying their relative intensity (power) [21]. However, the analysis of frequency-domain measures requires a more sophisticated technical assessment and is subject to greater risk of error compared with the time-domain measures. Such short-term recordings of HRV (usually 5–10 min) identify four main spectral components: (1) high frequency (HF, ranging between 0.15 and 1.5 Hz), a measure assessing the parasympathetic activity [23]; (2) low frequency (LF, ranging between 0.04 and 0.15 Hz), considered, although not univocally, as marker of sympathetic tone by some authors and of autonomic balance by others [18, 24]; (3) very low frequency (VLF, ranging between 0.0033 and 0.04 Hz), a less defined component with an unclear specific physiological process attributable to these heart period changes; (4) ultra-low frequency (ULF, band ≤ 0.003 Hz), which requires a recording period of at least 24 h and is highly correlated with the SDANN time-domain index. There is no consensus regarding the mechanisms that generate ULF power; very slow-acting biological processes in newborn are implicated, such as circadian rhythms. Measurement of HF, LF, VLF, and ULF is usually made in absolute values of power (ms^2), but LF and HF may also be measured in normalized units (n.u.), which represent the relative value of each power component in proportion to the total power minus the VLF component. The representation of LF and HF in n.u. emphasizes the controlled and balanced behavior of the two branches of the autonomic nervous system. Moreover, normalization tends to minimize the effect on the values of LF and HF components of the changes in total power. Nevertheless, n.u. should always be quoted with absolute values of LF and HF power in order to describe in total the distribution of power in spectral components. Lastly, LF/HF ratio is a better index of sympathetic-parasympathetic balance and an expression of sympathetic modulations on the HR. Decreased LF/HF ratio reflects sympathetic withdrawal and consequent vagal predominance [21, 22]. Basically, HF power correlates with rMSDD and pNN50 index whereas LF power correlates with SDNN index [25].

For HRV analysis in newborns, also nonlinear dynamics-based methods, including Poincarè plot geometry, sequence plot, Approximate Entropy, SampEn Entropy, symbolic dynamics methods, and time irreversibility analysis were applied [26]. In addition to the traditional linear methods, such nonlinear methods can provide some additional information, i.e., the Poincaré plot geometry provides a graphical representation of the correlation of successive R-R intervals, the balance between short and long-term variability, and is related to rMSSD, while Approximate Entromy and SampEn entropy depend on autonomic nervous system activity with different mechanisms.

HRV is controlled by complex regulatory mechanisms involving the cardiovascular system and the central nervous system, and peculiarities in its regulatory mechanisms are detectable during fetal/neonatal life phases [20, 27]. HRV is influenced by genetic factors [20, 28, 29], gestational age [20, 22, 30], postnatal age [18, 30, 31], postconceptional age [32], birth weight [20, 31, 33–37], delivery mode [18, 38], and gender (the latter with discordant results) [20, 27, 37, 39–44]. Moreover, a combination of multiple factors such as respiratory sinus arrhythmia, postnatal maturation, withdrawal of perinatal stress, and exercise/sleep stage may affect HRV in the early postnatal period as well [20, 45–48]. If the state of the patient varies during recording, the dominant results of spectral methods correspond to the changes in patient behavior rather than to the changes in sympathovagal tone. For this reason, a precise validation of spectral results requires that recordings are made during a "steady state." Also, pathologic conditions such as respiratory distress syndrome [41, 49], clinically significant patent ductus arteriosus [50], congenital heart defects [51, 52], neonatal sepsis [53, 54], necrotizing enterocolitis [55], and brain damage (traumatic injury/seizures/edema/periventricular hemorrhage/hydrocephalus/PA) [45, 56–63] may influence HRV values in the neonatal period [20]. Furthermore, decreased HRV was reported in very low-birth-weight neonates with abnormal neurodevelopment [64, 65] As a whole, since reduced HRV values are detected in case of perinatal brain injury and tend to improve consensually with disease improvement, HRV might (1) be useful for an early diagnosis of disease, (2) represent a possible prognostic physiomarker in the neonatal period, and (3) reflect the efficacy of therapeutic interventions throughout time.

Heart rate variability and hypoxic ischemic encephalopathy

Considering the reported association between HRV and neurologic impairment, HRV has been suggested as possible marker of brain damage also in case of PA. Data from animal models support this hypothesis [66].

The mechanisms leading to depressed HRV in neonates as a consequence of a hypoxic-ischemic injury are multiple:

(1) Effects of asphyxia on the cardiovascular system, since PA is often associated with hemodynamic instability characterized by myocardial dysfunction, right and left ventricular failure, hypotension, and eventual arrest [67–70]. Multiple factors such as low HR, acidosis, and cardiac hypoperfusion with ischemic injury are responsible for this condition [70, 71]. Furthermore, hypothermia induces peripheral vasoconstriction which may mask hypotension by increasing diastolic pressure [72]. To date, inconclusive data assessing HRV modifications during neonatal heart failure exist. However, extrapolating information from studies performed in adults with heart failure (although affected by chronic heart disease, mostly related to coronary disorders), it seems possible to speculate that acute myocardial dysfunction may be associated with a significant reduction of HRV values also in neonates, especially of the SDNN/SDANN parameters among the time-domain components and of the LF among the frequency-domain components.
(2) Direct subcortical or brainstem injury leading to autonomic dysfunction is one possible physiopathologic mechanism [73]. This condition is supported by studies in animal models, showing that acute asphyxia stimulates the ANS leading to fetal distress [66]. As already mentioned above, depressed HRV in the perinatal period is associated with different forms of brain damage including traumatic injury, seizures, edema, periventricular hemorrhage, hydrocephalus, and PA [20, 45, 56–63]. Overall, HRV values following brain damage suggest modifications of the ANS with a shift in the balance between cardiac autonomic activity toward increased vagus nerve signaling [74, 75].
(3) Pro-inflammatory status with increased release of inflammatory cytokines able to influence HRV values. Interestingly, such physiopathologic mechanisms seem to be the same leading to neonatal sepsis, which, as for asphyxia, is associated with low HRV values [20, 39, 54, 76, 77].
(4) The presence of seizures, since autonomic alterations often occur during such events [58–61, 78], although only very poor data are currently available in neonates with HIE. Malarvilii et al. assessed HRV changes in eight neonates with EEG-documented seizures, finding that HRV was sensitive to changes in the cardioregulatory system induced by seizure occurrence and suggesting a possible role for HRV as physiomarker for an automatic seizure detection [60]. Statello et al. investigated the reliability of HRV indexes of cardiac autonomic regulation for the detection of neonatal seizures by contemporary assessments of ECG tracings and video-EEG monitoring. The authors found that infants with seizures had lower resting-state HRV compared with controls and that seizure episodes were characterized by a short-lasting increase in vagal indexes of HRV. They also found GA-depending modifications of HRV, since premature neonates had lower HRV values at rest compared with term neonates. Furthermore, compared with the respective baseline HRV values, preterm infants showed no changes in HRV values before and during seizures whereas term neonates showed a significantly increased HRV [61].
(5) Presumably, a combination of all these mechanisms could be responsible for a depressed HRV in neonates with HIE.

The number of studies focusing on the role of HRV as marker of brain damage in humans is limited. Continuous monitoring of the fetal HR has been widely used by obstetricians to achieve detailed information about fetal status. Also, abnormal HRV during fetal life correlates with a higher risk of subsequent neonatal HIE [79–81]. Such abnormal HRV detected in fetal monitoring may reflect placental hypoperfusion leading to chronic hypoxemia [79]. In agreement with such observations, some authors addressed HRV in the early postnatal period to investigate whether this parameter may be of help for the early diagnosis, stratification, and monitoring of neonates affected by HIE. On this basis, we performed a systematic review of the current literature focusing on available studies performed in asphyxic neonates with HIE to address the reliability of HRV as biomarker of brain damage [82].

Methods

Search strategy and selection criteria

This systematic review was conducted in agreement with the PRISMA guidelines [82]. For reliability, two review authors (I.B. and F.P.) independently analyzed the available literature through database searching (PubMed, Cochrane Library, Scopus, Web of Science) from January 1976 to June 2020. Search terms included "heart rate variability" AND "neonatal brain injury" OR "neonatal asphyxia" OR "perinatal asphyxia" OR "hypoxic ischemic encephalopathy" OR "hypoxic ischaemic encephalopathy" OR "neonatal encephalopathy" OR neonatal hypoxia." English-language, peer-reviewed studies were included. Case reports, animal studies, and conference absracts were excluded. We considered the studies eligible if including term/late preterm (≥ 35 weeks gestational age) infants affected by HIE with a postnatal age ≤ 7 days at the beginning of HRV assessment. Possible biases that were considered were the different holter-ECG techniques that were used and the heterogenicity of the studies, as some babies underwent therapeutic hypothermia and some did not. Any disagreement about study eligibility was resolved by discussion with a third review author (C.D.M) until consensus.

Data extraction

Data from eligible studies were indipendently extracted by two review authors (I.B. and F.P.). We included all prospective cohort studies, retrospective cohort studies, and case-control studies assessing the HRV of asphyxic neonates in comparison with abnormal neonatal neurologic outcome or abnormal brain imaging on MRI. Any disagreement about data extraction was resolved by discussion with a third review author (C.D.M) until consensus. Pertinent findings from the included studies were tabulated under the following headings: study design; number, GA, BW of the HIE neonates included; treatment with hypothermia; main outcomes (Table 1). Disagreements about data extraction were resolved by discussion with a third review author (C.D.M.) until consensus. Disagreements about data extraction were resolved by discussion with a third review author (YH) until consensus.

Results

The searches identified 1556 potentially relevant papers, 687 after duplicates were removed. After title and abstract screening, 84 full-text studies were consided potentially eligible for inclusion and (77 studies were excluded for the following reasons: (1) animal poopulation (n = 12); (2) fetal population (n = 33); (3) not relevant comparators (n =25); (4) study design (n = 5); (5) preterm population (n = 1); (6) non-English language (n = 1) (Fig. 1). Of the 7 included studies, 5 were retrospective [78, 84–87] and two prospective [39, 83].

A total number of 297 HIE neonates was included in the present review. Of these, 253 received hypothermia, while 44 did not since hypothermia was not a standard of care at the study time. The characteristics and most relevant findings of the included studies are reported in Table 1.

Table 1 Studies assessing HRV as marker of brain damage in asphyxic neonates with HIE

Study design	HIE neonates (n)	GA (weeks)	Mean BW (g)	Therapeutic hypothermia	Main outcomes	Reference
Prospective, observational	16	Mean 37.8 ± 2	> 1800 g	Yes	Lower low-frequency power associated with more severe brain injury pattern on MRI	Barbeau et al. [39]
Prospective, observational	49	38.6 ± 1.5	3.2 ± 0.8	Yes	Correlation between the absolute spectral powers in three frequency bands (very LF (0.016–0.04 Hz)/LF (0.05–0.25 Hz)/HF (0.3–1 Hz)) and SDNN with brain injury patterns on MRI	Govindan et al. [83]
Retrospective, observational	44	HIE group: median 39 (36–42)	HIE group: 3384 (1830, 5040) Controls: 3601 (2980, 4060)	No	HRV negatively associated with EEG grade at 12–48 h after birth, with significant differences in HRV between mild/moderate and mild/severe EEG grades Correlation between HRV and neurodevelopmental outcome at 2 years of age	Goulding et al. [84]
Retrospective, observational	67	Mean 38.4 ± 1.4	3236 ± 511	Yes	Day 1 HRV and HRC Index associated with moderate/severe EEG, moderate/severe MRI, death Low HRV and high HRC index remained significantly associated with moderate/severe encephalopathy on EEG after rewarming	Vergales et al. [78]
Retrospective, observational	74	≥ 35	≥ 1800	Yes	Correlation between brain injury pattern on MRI and degree of HRV suppression Negative associations between pattern of brain injury and RMSS, RMSL, and LF power	Metzler et al. [85]
Retrospective, observational	27	38.3 ± 2.1	3240 ± 894	Yes	Correlation between brain injury patterns on MRI and heart rate characteristic (HRC) index score	Kayton et al. [86]
Retrospective, case-control	20	Adverse outcome: mean 38.9 ± 0.4 Favorable outcome: mean 38.5 ± 0.6	Adverse outcome: 3630 ± 150 Favorable outcome: 3330 ± 290	Yes	Correlation between HRV and death/neurologic outcome at 15 months	Massaro et al. [87]

HIE Hypoxic ischemic encefalopathy, *GA* gestational age, BW birth weight, *HRV* heart rate variability, *EEG* electroencephalography, *MRI* magnetic resonance imaging, *rMSSD* Root mean square of successive R-R interval differences, *HF* High-frequancy band, LF low-frequency band

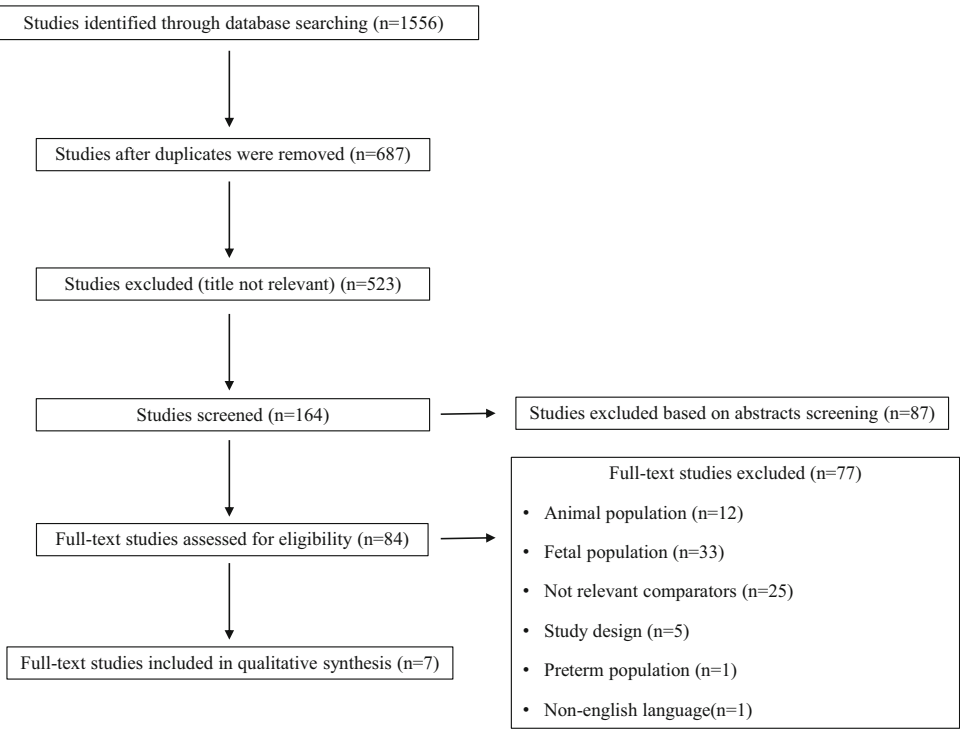

Fig. 1 Flow-chart of study selection process

Discussion

The number of studies dealing with the role of HRV as marker of brain injury in HIE infants has increased during the last decade. Despite promising results, however, inconclusive data exist about the accuracy of HRV as marker of HIE in asphyxic neonates. This is mainly due to the fact that the available studies on this topic are mostly retrospective, are affected by the heterogeneity of the index and the reference test, used no standardized methodology for HRV measurement, included small sample sizes, and did not investigate properly multiple confounding factors such as sedation/seizures/temperature [88, 89].

Aliefendoglu et al., who assessed for the first time HRV values by Holter ECG monitoring recordings in neonates with HIE based on the criteria described by Sarnat and Sarnat [73], found that HIE infants had significantly lower LF and LF/HF values and higher HF values compared with controls. Furthermore, cases with severe HIE showed decreased LF and LF/HF values and increased HF values compared with those with moderate HIE reflecting increased parasympathetic and decreased sympathetic drive [90].

Barbeau et al. prospectively assessed HRV as predictor for neurological impairment in infants with HIE treated with hypothermia. HRV measurement was achieved from a 300-s period of the ECG signal and measured first during cooling (6–72 h of life) and then after rewarming. Of the 16 included neonates, 11 had none/mild findings, and 5 had moderate/severe findings on MRI. According to the study results, during hypothermia: (1) neonates with no/mild injury showed higher levels of LF power than neonates with moderate/severe injury, with similar LF power between male and female infants; (2) comparable HF power and ratio of LF/HF power was detected between the two groups and between males/females; (3) mechanical ventilation did not significantly affect HRV, although LF power seemed to be weakly influenced; (4) the need for pressor drugs was comparable between the two groups. During normothermia, (1) there were no statystically significant differences in LF, HF, or LF/HF by severity powers; (2) HRV differed by gender, being higher in males, who also had a lower LF/HF ratio compared with females. Although limited by its small sample size, this study provides further evidence supporting the role of HRV as monitoring and prognostic tool in HIE neonates [39].

Govindan et al. prospectively investigated HRV as monitoring tool in HIE neonates receiving hypothermia. The authors found that the absolute spectral powers in three different frequency bands, i.e., very low frequency (0.016–0.04 Hz), low frequency (0.05–0.25 Hz), and high frequency (0.3–1 Hz), correlated with brain injury/death [83].

In a retrospective, observational study including neonates born prior to the introduction of hypothermia, HRV was negatively associated with EEG grade at 12–48 h after birth, with significant differences in HRV between mild/moderate and mild/severe EEG grades [84]. Such findings could be of special help for clinicians, since although the clinical distinction between mild and severe forms of HIE is usually easy, a proper identification between the mild and moderate forms of HIE

may sometimes be challenging [91]. The authors found a correlation between HRV and neurodevelopmental outcome at 2 years of age. Considering that only a minority of neonatal intensive care units have a 24-h/day access to EEG monitoring, such results are promising [84]. However, as the authors themselves state in the text, this study had multiple limitations: (1) the intrinsic nature of a retrospective study; (2) being the primary outcome the assessment of EEG activity in HIE neonates, ECG quality was sometimes suboptimal; (3) these data did not assess the EEG within the first 6 h of life which, to date, represent a crucial cut-off for the beginning of hypothermia.

Vergales et al. analyzed records of neonates with moderate-severe HIE receiving hypothermia. HRV was significantly lower within the first 24 h from birth in neonates with moderate-severe abnormalities on EEG recordings compared with those with mildly abnormal/normal EEG. Neonates with moderate-severe anomalies on MRI also had depressed HRV on day 1 of life compared with those with normal or mildly abnormal MRI. Furthermore, HRV on the first day of life was lower in neonates who died compared with survivors. Considering that hypothermia itself may affect HRV, the authors also assessed HRV before, during, and after rewarming and found no statistical differences. This may reflect a progressive improvement in ANS function in the days after an acute ischemia-reperfusion insult. They also found that HRV was not influenced by plasma phenobarbital levels. HRV values progressively improved in the first week of life, but a statistical association between lower values of HRV and moderate-severe anomalies on EEG after the rewarming phase persisted. As a whole, these data suggested that HRV may represent a precocious and noninvasive prognostic marker for HIE. However, no data about the long-term neurologic outcome were provided [78].

Metzler et al. investigated the presence of any correlation between HRV values and brain injury patterns on MRI in neonates with HIE treated with hypothermia, describing a correlation between HRV low values at 24–27 h of life and brain injury severity on MRI [85]. These results may be relevant considering that although MRI provides accurate anatomical information, its accessibility within the first 24 h of life is limited due to clinical/logistic issues. Some limitations of the study include the small sample size and the fact that covariates which could have an impact on HR and HRV, such as intrinsic myocardial dysfunction, dose/cumulative amount of vasopressors required, and respiratory oscillations related to the ventilator, were not exactly considered [85]. Kayton et al. assessed the correlation between the so-called HRC index score, based on a regression model including measures of HRV and patterns of brain injury on MRI in neonates with HIE. The authors found statistically significant correlations between HRC index scores and brain injury patterns on MRI at baseline, 24, and 96 h [86].

In a significant pilot study including 20 term neonates with HIE treated with hypothermia, Massaro et al. investigated whether a longitudinal assessment of HRV over the course of hypothermia and rewarming phases was able to predict death or impaired neurodevelopment at 15 months of life. The authors found lower HRV values in neonates with adverse outcome. HRV was mostly affected at two main time points: (1) at 24 h of life and (2) after 80 h of life, after rewarming was completed [87]. These results are of particular interest since such time-points reflect the pathophysiologic events which are known to be crucial for HIE evolution. In fact, it is known that a hypoxic-ischemic insult triggers a cascade of excitotoxic, proinflammatory, oxidative stress, and proapoptotic pathways, which peak at 24 h after the insult [92]. Although hypothermia might improve the impact of such dangerous cascade of events in most neonates, it might be unable to annihilate such process in those who will develop adverse outcomes despite cooling. Furthermore, the significant HRV reduction assessed after 80 h of life may imply a progression of brain injury after hypothermia cessation. As a whole, these data could lay foundations for a cautious reconsideration of the optimal duration of hypothermia based on HRV monitoring [87]. However, as stated by the authors themselves, the study had limitations which need to be taken into account: (1) small sample size; (2) the authors were unable to differentiate whether decreased HRV was related to a direct effect of asphyxia on the myocardium or rather to an indirect effect of medications/critical care interventions, seizures, or ANS dysfunction following brainstem damage; (3) neurologic outcome was assessed at 15 months of life, a relatively early age for conclusive considerations; (4) missing data in EEG/ECG recordings, due to clinical/logistic issues.

In particular, the effect of hypothermia itself on cardiac function should be considered properly before definitely assigning HRV the role of brain physiomarker [93]. This is of particular importance considering that hypothermia has an influence on the cardiovascular equilibrium and is associated with increased risk of bradycardia, arrhythmias, transitory prolonged QTc interval, hypotension, and pulmonary hypertension [7, 94–100]. The direct effect of hypothermia on HRV was assessed in a prospective case-control study including 44 neonates with moderate/severe HIE treated with hypothermia. The authors analyzed the data achieved by continuous ECG monitoring begun 2 h prior to rewarming through 2 h after completion of rewarming, to assess the effect of decreased esophageal/axillary temperature on HRV. HRV decreased as temperature increased toward normothermia. Such results underline the importance of assessing for core temperature in future analyses aimed at verifying the reliability of HRV as marker for HIE monitoring, i.e., to verify whether HRV modifications in asphyxic neonates receiving hypothermia reflect disease severity/evolution rather than the changes in

body temperature throughout the hypothermia/rewarming phases [101]. However, as stated by the authors, this study had limitations including that in some cases, ECG monitoring was stopped prematurely due to clinical reasons, some data were incomplete/altered by artifacts, temperature assessment was not continuous, and the sample size limited the ability to clearly elucidate the relationship of HRV/temperature in neonates with severe HIE [101]. As a whole, despite the small number of studies and the heterogeneous study designs, all the above mentioned studies provided evidence of a good reliability of HRV as precocious prognostic marker of brain injury in HIE neonates which deserves further investigations.

Future perspectives

A growing body of research supports the use of HRV as non-invasive, bedside tool for HIE monitoring. The available data about the role of HRV as prognostic marker in case of HIE are promising but still fragmentary, and no conclusive considerations are allowed yet. In particular, future investigations should assess the ability of HRV to differentiate between mild and moderate/severe forms of HIE and the ability of HRV to identify within a narrow therapeutic window (i.e., within the first 6 h of life) neonates who would profit from adjuvant neuroprotective interventions. Such data are eagerly awaited in order to design precocious, specific, and personalized treatments according to HIE severity.

Authors' contributions Iliana Bersani contributed to the conceptualization, systematic review, investigation, supervision, writing—first draft, review, and editing. Fiammetta Piersigilli contributed to the conceptualization, systematic review, investigation, supervision, writing—first draft, review, and editing. Corrado Di Mambro contributed to the conceptualization, systematic review, investigation, supervision, writing—first draft, review, and editing. Diego Gazzolo contributed to the conceptualization, investigation, writing—review and editing. Immacolata Savarese contributed to the conceptualization, investigation, writing—review and editing. Francesca Campi contributed to the conceptualization, investigation, writing—review and editing. Andrea Dotta contributed to the conceptualization, investigation, writing—review and editing. Pietro Paolo Tamborrino contributed to the conceptualization, investigation, writing—review and editing. Cinzia Auriti contributed to the conceptualization, investigation, writing—review and editing. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors

Consent to partecipate N/A

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