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Review Article

A Systematic Review of Cardiac Autonomic Modulation in Mothers and Their Infants

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Abstract

Objective: The aim of this study was to perform a systematic review of the publications that have examined cardiac autonomic modulation and to verify how the relationship between mothers and preterm infants can influence cardiac autonomic parameters.

Method: The articles identified by the search strategy were assessed independently and blinded by two researchers, strictly adhering to the next inclusion criteria: (1) published between 01/01/2004 and 06/02/2014; (2) written in English; (3) had an available abstract; and (4) pertained to the mothers and/or their premature babies.

Results: Of 83 publications originally found, 5 eligible studies were ultimately identified. Of these five articles pertaining to Heart Rate Variability, two articles studied preterm infants, two articles studied a sample of mothers and one article evaluated the association between Heart Rate Variability and mothers of preterm infants.

Conclusion: Mothers and their relationships with their preterm infants are essential for increased cardiac autonomic modulation.

Keywords: Heart Rate Variability; Mothers; Preterms; Autonomic Modulation

Abbreviation

ANS: Autonomic Nervous System;

ECG: Electrocardiogram;

HR: Heart Rate;

HRV: assess Heart Rate Variability;

iRR: R-R interval;

KC: Kangaroo Care;

rMSSD: Square Root of the Mean Squared Differences of successive RRi divided by the number of RRi minus one;

SD1: Standard Deviation of Points Perpendicular to the Axis of Line-of-Identity;

SD2: Standard Deviation of Points along the Axis of Line-Of-Identity;

SDNN: Root Mean Square of Differences from Mean Rri, Divided by the Number of Rri

Introduction

This study was motivated by a clinical concern about infant growth, seeking to contribute to the comfort and wellbeing of preterm neonates. Neurobehavioral development can be improved through kangaroo care (KC), particularly when this care begins early. It is known that heart activity is largely modulated by the autonomic nervous system (ANS), which promotes rapid adjustments to the cardiovascular system in reaction to different stimuli such as stress, physical exercise and postural changes in normal and pathological conditions [1,2].

Another aspect of the situation of preterm neonates is their contact with their mothers, who are totally influenced by their children's health status and equally able to affect their own behavior, thus influencing the maturation of the ANS [3]. This modulation is mediated by neurotransmitters that act directly on the heart through adrenergic receptors (alpha and beta), as well as sympathetic and parasympathetic muscarinic cholinergic receptors [4].

Given the importance of the ANS to cardiovascular health, several analytical measures, grouped into linear and non-linear methods have been developed to assess Heart Rate Variability (HRV). The assessment of HRV is a non-invasive task used to analyze the influence of the ANS on the heart and to provide information about both sympathetic and parasympathetic contributions to consecutive HR oscillations. These rhythmic fluctuations of R-R intervals (RRi) in electrocardiograms (ECG) have been quantified using power spectral analysis as a noninvasive assessment of the influence of ANS on the heart. It has been proposed that a decrease in HRV may be a powerful predictor of morbidity and mortality [5-7].

Previous research has demonstrated that HRV decreases with age[8-10] as a consequence of parasympathetic reduction and increased predominance of sympathetic modulation [11]. Furthermore, HRV indices have been linked to factors such as fatigue and stress,[12,13] quality of life, depression and anxiety [14]. These factors all contribute to imbalance within the ANS and impairments to cardiac neural integrity [5]. Research studies published in the literature report that HRV indices tend to be lower in preterm infants than in young adults, most likely due to the fact that the ANS is not yet fully developed [15-19]. The literature describe that preterm neonates (newborns less than 37 weeks gestational age) exhibited less complex HRV behavior than term neonates (newborns between 37 weeks and 41 weeks gestational age), as observed from the temporal index, power spectral analysis and non-linearly by chaotic behavior. In addition to age, other factors such as power and alertness also exerted an influence on HR [17].

Analyses of heart rate variability demonstrate the effects that development has on vagal modulation of heart rate in healthy children. One of these effects is the decrease in heart rate maturation, which is connected with the increase in parasympathetic influence (vagal tone) on heart rate and greater sympathovagal balance and stability. Maturation provides a neural platform to support the infant's increasing ability to engage with objects and people in a dynamic environment. The high-frequency component, an index of cardiac autonomic tone, increases significantly between the ages of 3 to 6 years and then decreases between the ages of 6 to 15 years, and the magnitude of high-frequency is significantly correlated with the R-R intervals.[20] Studies have also shown that preterm infants are often fed less efficiently than full-term babies, and this nutritional deficit influences the HR [21,22].

This study is justified by the fact that few studies have evaluated autonomic modulation of HR in a physician-assisted hospital setting involving preterm infants and/or their mothers, in addition to any type of intervention or assessment that could influence physiological parameters, based on temporal analysis, [8,23,24] spectral analysis, [25,26] and analysis in the field of chaos (nonlinear) [27,28].

This systematic review discusses the analysis of HRV and the results of autonomic control data for mothers and the relationship modifications of preterm infants' heart conditions. The aim of this study was to perform a systematic review of the publications that have examined cardiac autonomic modulation and to verify how the relationship between mothers and preterm infants can influence cardiac autonomic modulation.

Methods

Study identification and selection

This systematic review was conducted and is reported according to the recommendations of the Preferred Reporting

Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Figure 1) [29]. The first stage of the review was conducted on February 6, 2014, at which time the electronic searches were executed in PubMed (MEDLINE; EMBASE), SciELO and Scopus using the following search terms and phrases: *"Cardiac Autonomic Modulation and Mothers"; "Cardiac Autonomic Modulation and Neonatal"; "Cardiac Autonomic Modulation and Premature"; "Cardiac Autonomic Modulation and Preterm"; "Heart Rate Verification and Mothers"; "Heart Rate Verification and Neonatal"; "Heart Rate Verification and Premature"; "Heart Rate Verification and Preterm"; and "Heart Rate Variability in Mothers and Preterms."* By the end of this step, we had identified a total of 83 articles. Of these, 47 were indexed in the PubMed database and 36 were indexed in the Scopus database. Searches within the SciELO database yielded no hits from any of the nine search strategies mentioned above.

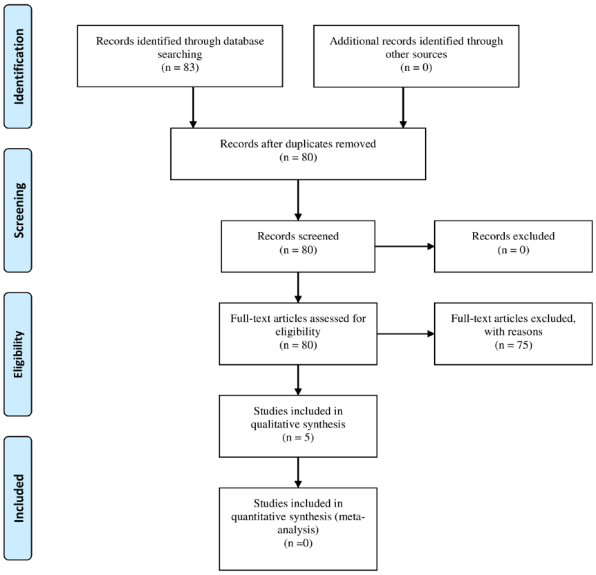

Figure 1. Flow diagram.

Eligibility criteria

In the second stage of the review, the bibliographies within all of the potentially relevant articles were manually searched to identify any additional articles of potential relevance. The selection of articles in the first stage was based on the following inclusion criteria: (1) published between 01/01/2004 and 06/02/2014; (2) written in English; (3) the title and/or summary contained "Heart rate variability" and / or "autonomic modulation of heart rate, Premature or preterm"; (4) had an available abstract; and (5) pertained to the mothers and/or their premature babies. Articles that did not meet these criteria were automatically excluded. At the end of the second stage, after the removal of duplicate studies and of those whose theme was inconsistent with the study's purpose, five articles remained. These articles were types of clinical trials, which were retained for the next stage of the review. In the third stage of the review, study investigators fully read each article that had been identified and retained up to this point (Figure 2).

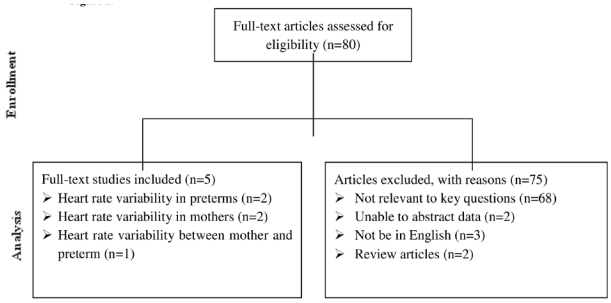

Figure 2. The total number of articles in the exclusion categories exceeded the number of articles excluded, because most of the articles fit into multiple exclusion categories.

Data collection

The articles that our search strategy identified were assessed independently and blinded by two study investigators (authors), each of whom strictly applied the inclusion criteria. Such strategies maximized our search results, which was important given the scarcity of the related studies in the literature. Any disagreements were resolved by discussion between these two reviewers, who then referred the studies to a third party when necessary. Review authors were not blinded to any features of the studies because blinding has a minimal impact on selection bias. The method is classified based on evidence risk of bias, consistency, directness, precision, plausible confounders that would decrease the observed effect, strength of association, and publication bias. Possible ratings are as follows: High = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. Insufficient = Evidence either is unavailable or does not permit a conclusion.

Results

From each study, then, the following data were extracted: (1) study population, (2) type of study, (3) processing and analysis of HRV, (4) methods and details of any interventions, and (5) main characteristics of the study. The five selected studies were conducted in different countries, specifically, two in the United States, and one each in Holland, Canada and Israel. The publication years of these studies ranged from 2005 to 2013. In these five articles pertaining to HRV, two studies investigated preterm infants (Table 1), two articles studied a sample of mothers (Table 2), and one article assessed the association between the HRV of mothers and preterm infants (Table 3).

Regarding the primary findings from the surveyed articles on preterm infants was observed that the effect of phototherapy on neonatal HRV and complexity by Poincaré analy-

sis [30]. The Quantitative Poincaré plot of RRi is one of the techniques used in HRV analysis. In addition to being a quantitative technique, it is a useful visual tool capable of summarizing an entire RRi time series derived from an ECG in one picture, providing information on the long- and short-term HRV.

HRV behavior than term neonates based on facts of time and frequency [17]. They also observed that the variables RRi average, root mean square of differences from the mean RRi, divided by the number of RRi (SDNN) and the square root of the mean squared differences of successive RRi divided by the number of RRi minus one (rMSSD) were significantly higher in term infants than in preterm infants.

Table 1. Main characteristics of studies with preterm and cardiac autonomic modulation.

Reference	Database	Descriptors	Study design	Sample	Processing and analysis of HRV	Main characteristics of the study	Main findings
(41)	Pubmed	Cardiac Autonomic Modulation and Neonatal	Prospective and longitudinal study	30 full-term jaundiced infants were studied before and during phototherapy.	Time domain, Power Spectral Analyzis (High Frequency and Low Frequency) and Poincaré plots.	Investigated the effects of phototherapy on the autonomic nervous system modulation of HRV in healthy, full-term jaundiced neonates. There was a significant decrease of the time domain. There were no statistically significant changes between the three phases of the study in any of the frequency bands. There were significant changes in the quantitative measurements of the Poincaré plots. The SD1 and SD2 were significantly lower during phototherapy than at baseline.	A significant diminution in heart rate variability was documented during phototherapy.
(30)	Pubmed	Cardiac Autonomic Modulation and Premature	Longitudinal study	Preterm (n=25) and age matched term infants (n=31) were studied 6 months after term-corrected age.	Spectral Analyzis (High Frequency and Low Frequency and Ratio.	Low Frequency no changed with age. High Frequency increased with advancing postnatal age and ratio LF/HF decreased from 2 to 4 weeks 5 to 6 months.	In preterm infants, parasympathetic modulation of the heart increases while sympathetic modulation of blood pressure decreases. Compared to term infants, preterm infants exhibit lesser parasympathetic modulation of the heart.

In this study, the short-term variability of HR was significantly lower during phototherapy, as reflected by the Poincaré plot standard deviation of points perpendicular (SD1) and along (SD2) the axis of the line-of-identity. A significant diminution in HRV was documented during phototherapy, a phenomenon assumed to be centrally mediated. The other study evaluated the development of autonomic cardiovascular control by preterm birth. In preterm infants, an increase in parasympathetic modulation was observed but sympathetic modulation of blood pressure decreased. Compared to term infants, preterm infants exhibited lesser parasympathetic modulation of the heart. These studies provides evidence for a moderate association of HRV in mothers and preterm infants.

This study corroborates data from the literature, which demonstrated that preterm infants exhibit less complex

Regarding the primary findings from the surveyed articles on mothers, was used spectral analysis to examine maternal HRV and fetal behavior in hypertensive and normotensive pregnancies [31]. They found an increase in sympathetic nervous system modulation in the hypertensive group during gestation, but no such relationship was observed in the normotensive group. The other study examined the effects of breast-feeding on ANS. Breast-feeding shifts maternal ANS balance toward relatively greater parasympathetic and lesser sympathetic activity; the opposite occurs with bottle-feeding [32]. When compared to the reference data, was observed that the decrease in HRV was related to low fetal viability because studies have shown that the formation of the cardiovascular system has an extensive relationship with HRV [5]. These studies presented "insufficient" evidence of an association of HRV in mothers and preterm infants.

Table 2. Main characteristics of studies with mothers and cardiac autonomic modulation.

Reference	*Database*	*Descriptors*	*Study design*	*Sample*	*Processing and analysis of HRV*	*Main characteristics of the study*	*Main findings*
(31)	Scopus	Cardiac Autonomic Modulation and Mothers	Trasversal study	mothers- 40 fetal pairs (n=20 normotensive mothers; n=20 hypertensive (33-41weeks' gestacional age) and HRV .fetal	Spectral analysis and number of HR accelerations and decelerations observed during the 20-min procedure as well as the magnitude of the greatest HR acceleration and deceleration and the degree .of HRV	There was an increase in iRR, low-frequency, and total power for the hypertensive group over gestation, while no such relations were observed in the normotensive group. Also, within the hypertensive group, there was an increase in both low-frequency and high-frequency .power	The maternal autonomic system influences fetal cardiac function in pregnancies complicated by .hypertension
(32)	Scopus	Cardiac Autonomic Modulation and Mothers	Trasversal study	Women who were either exclusively breast feeding n=14) or) nonexclusively breast feeding (n =14), and in nonpostpartum controls (n .(=15	Beat-to-beat averages for HR were calculated for the last minute of the baseline period preceding each task, during each 1-min task, and during the 1 min of recovery following each task. The HRV was ana- .lized in time domain	There was strong evidence of lower HR in exclusively breast-feeding mothers than in nonexclusively breast-feeding mothers and non-postpartum controls. The lower HR is due to higher vagal cardiac modulation in the exclusively breast-feeding group compared with the other two groups, as evidenced by .time domain	The frequency of feeding was influenced on maternal autonomic nervous system function. Breast feeding shifts maternal autonomic nervous system balance toward relatively greater parasympathetic and lesser sympathetic activity and the opposite occurs with bottle feeding. Mothers who breast-fed exclusively showed greater levels of parasympathetic cardiac modulation and slower HR throughout .the session

Reference	*Database*	*Descriptors*	*Study design*	*Sample*	*Processing and analysis of HRV*	*Main characteristics of the study*	*Main findings*
(33)	Scopus	Cardiac Autonomic Modulation and Mothers	Prospective and longitudinal study	14 mothers in 528 infants	100 to 180 seconds of the ECG; Fourier Transformation and Power Spectral Analysis (High Frequency and Low Frequency.	Evaluated the relationship of maternal psychopathology with heart rate and heart rate variability.	The maternal lifetime psychiatric diagnosis were associated with lower vagal modulation.

Table 3. Main characteristics of studies relative the relationship between Mother and Preterm on the Cardiac Autonomic Modulation.

Only a single study has identified parameters affecting ANS autonomic control of both preterm infants and their mothers. In this study, the autonomic nervous system as measured by HR and HRV is considered a biological marker of psychopathology in children. Moreover, postnatal maternal anxiety and depression symptoms were associated with infant higher mean HR and lower vagal modulation. Further analyses of depressive symptoms versus mean HR level yielded no between-group differences. Additionally, maternal psychopathology influenced infant HRV. Specifically, a maternal history of a psychiatric diagnosis of anxiety and depression was associated with lower vagal modulation [33].

Discussion

To our knowledge, this is the first systematic review to specifically evaluate the relationship between the HRV of mothers and preterm infants, in other words, to examine parameters that could modify the autonomic heart conditions in both individuals. The results from the present systematic review support the hypotheses that changes to physiological parameters such as hypertension, the use of phototherapy, the presence and frequency of breastfeeding,[32] psychiatric disorders,[33] and stress[34,35] contribute to the increase in the cardiac autonomic modulation and in the quality of life of mother and/or baby [33,36,37].

This study corroborates data from the literature, which demonstrated that preterm infants exhibit less complex HRV behavior than term neonates based on facts of time and frequency [17]. They also observed that the variables RRi average, root mean square of differences from the mean RRi, divided by the number of RRi (SDNN) and the square root of the mean squared differences of successive RRi divided by the number of RRi minus one (rMSSD) were significantly higher in term infants than in preterm infants.

In the present review, we observed two clinical lines: the presence or absence of the mother. Both contributed to ANS changes in babies. It may be noted that premature neonates exhibited worse HRV compared to term neonates, and we can infer that this may have been due to the absence of contact between the mother and her baby [17]. In this sense, there are physiological parameters that change based on mother-infant interactions. Among the main parameters identified in this review were the presence and frequency of breastfeeding. Studies have indicated that the contact between the mother and her baby through breastfeeding promotes an increase in parasympathetic indices; for instance, one article found parasympathetic predominance in the breast-feeding group from their temporal analysis [32]. Oxytocin has been shown to play a key role in the initiation of maternal behavior and the formation of bonds between mothers and babies, influencing neuroadaptations that improve the framework of anxiety and irritability[38,39]. The authors of this study suggested that these adaptations may provide a parasympathetic predominance with improvement in the sympathovagal balance of mothers who are emotionally connected to their babies. Studies have speculated that music improved the preterm clinical status, reducing maternal anxiety and leading to autonomic stability and stress regulation in preterm infants [1,40].

There are different factors that can promote stress in preterm infants, including the feeding, cocooning and transport of ill neonates. The feeding from the mother promotes an increase in the baby's parasympathetic indices because the baby does not require nasogastric feeding, which is an invasive procedure that limits mother-infant interaction, causing greater stress in preterm infants. Feeding from the mother promotes a friendly increment. The nasogastric feeding in the context of neurodevelopmental delays, and hence, the neurocardiac innervation [34]. The feeding and breastfeeding during heel-lancing were the most effective method for relieving pain and stress [41]. Another factor influencing stress is the cocooning associated with the human voice. This behavior has been shown to enhance HRV in the preterm newborn infant; this enhancement indicates an increase in parasympathetic activity following cocooning associated with the human voice, alleviating stress and discomfort in the premature newborn infant [42]. Furthermore, while the transport of ill neonates imposes a measurable degree of stress, no differences were found, except that the nighttime ambulance group had a statistically higher HRV than the daytime ambulance group [43].

The existence of postnatal maternal psychiatric symptoms could be an early stressor for the infant, perhaps altering the mother-child interaction [33,44,45]. The detachment between mother and baby promotes higher levels of stress. This causes sympathetic predominance and affects the baby's sympathetic-vagal modulation [44,46]. Such stress-mediated sympathetic overstimulation might increase protein kinase C activity in central structures, such as the prefrontal lobe, leading to a dysregulation of thought, affect or behavior [47]. Moreover, the fetal physiological systems adapt to the characteristics of the intrauterine environment. This adaptation may permanently alter the set points of these physiological systems [48]. Research has shown that women's acute emotional reactivity during pregnancy can influence fetal HR patterns [49,50].

Moreover, [51] demonstrated the role of early skin to skin contact in the maturation of the autonomic and circadian systems in preterm infants. This study examined the effects of Kangaroo Care (KC) over 24.31 days on vagal tone in 70 preterm infants. The skin to skin contact accelerated the neuromaturation rate and that infants receiving KC would show higher vagal tone and more organized state, in terms of longer periods of quiet sleep and wakefulness and less active sleep states at 37 weeks.

With regard to the analytical methods for assessing HRV observed in the eligible articles examined here, we found multiple applications of HRV and different linear, frequency domain, wavelet domain, and nonlinear techniques were used for analyses. The electrocardiogram (ECG), for example, is recorded with the subject in a steady state (when rhythms are stationary) for a sufficiently long period to determine events occurring within the frequencies of interest.

RRi spectral power is calculated from this series of intervals using an autoregressive algorithm, which yields center frequencies and absolute power of component fluctuations [5].

The scope of our review was limited by the restriction of searches to conventional English-language databases [52,53]. The strengths of this review, however, include the diverse and complementary methods of analyses beyond the first systematic review to evaluate specifically the relationship of HRV in preterm infants and mothers. Thus, the need for more scientific research is evident, studies that primarily assess the influence of interventions on mothers admitted to the neonatal intensive care unit, evaluate the autonomic control of heart rate, and correlate data between mother and infant are particularly needed.

Future studies should incorporate all types of interventions, for example, physical and music therapy, nutrition, and breastfeeding in mothers and/or their babies that promote changes in the HRV correlation of mothers and their infants. Additional studies should continue to assess the relationship of HRV in preterm infants and their mothers.

Conclusion

The current systematic review showed that, despite the scarcity of relevant studies in the literature, the relationship between mothers and their pre-term infants is essential for the increase of cardiac autonomic modulation. More scientific research with clinical evidence demonstrating the impact of any type of intervention with preterm infants or mothers on the ANS or assessment of biological parameters is needed. The intervention with the mother will produce a stronger bond with her baby, promoting adequate neurocardiac and sympathovagal balance development.

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