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Authors

Parga, Joanna J
Bhatt, Ravi R
Kesavan, Kalpashri
et al.

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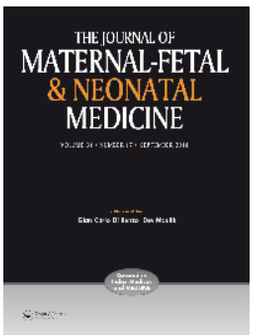

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ORIGINAL ARTICLE

A prospective observational cohort study of exposure to womb-like sounds to stabilize breathing and cardiovascular patterns in preterm neonates

Joanna J. Parga[a], Ravi R. Bhatt[a], Kalpashri Kesavan[a], Myung-Shin Sim[a], Harvey N. Karp[b], Ronald M. Harper[a] and Lonnie Zeltzer[a]

[a]Mattel Children's Hospital, University of California, Los Angeles, CA, USA; [b]University of Southern California, Los Angeles, CA, USA

ABSTRACT

Purpose: We exposed premature infants to womb-like sounds to evaluate such exposure on breathing and cardiovascular patterns. We hypothesized that these sounds would reduce apnea and intermittent hypoxemia, enhance parasympathetic outflow, and improve cardiovascular patterns.

Methods: A total of 20 cases and 5 control infants at ≤32–36 weeks corrected gestational age participated in a prospective observational cohort study. Twenty-four hours of continuous ECG, respiratory and oxygen saturation data were collected in all infants. Womb-like sounds were played intermittently in 6-hour blocks. Salivary samples were collected at study beginning and end for cortisol. Apnea, intermittent hypoxemia, and bradycardia were evaluated, and heart rate variability was assessed by time domain and spectral techniques.

Results: Intermittent hypoxemia and bradycardia significantly declined after sound exposure. No significant differences in apnea, cortisol levels, or heart rate variability were evident among the study infants.

Conclusions: Exposing premature infants to womb-like sounds has the potential to reduce hypoxemic and bradycardic events, and be used as an intervention to stabilize breathing and cardiac control in preterm infants.

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Bradycardia; intermittent hypoxemia; neonatal intensive care unit; parasympathetic tone; prematurity

Introduction

Breathing and control of the cardiovascular system are mediated by multiple brain stem structures, with immaturity of these structures contributing to breathing and cardiovascular instability in preterm infants [1]. Fewer synaptic connections, reduced dendritic arborization, and poorly developed myelination appear with symptomatic apnea, intermittent hypoxemia, and bradycardia in premature neonates [2]. Affected infants show declines in certain aspects of autonomic expression, with low parasympathetic activity (indexed via vagal tone) leading to concerns that cardiovascular control may be compromised [3]. This impaired neural development may affect subsequent breathing and oxygenation efforts in these premature infants.

Reduced cardiovascular and respiratory control in preterm neonates is not considered pathological, with increasing gestational age and maturation decreasing destabilizing events [4]. However, intermittent hypoxemia introduced by successive apneic periods has the potential to induce serious central neural injury [5,6] and substantially damage cardiovascular ganglia and regulation [7]. Until maturity is achieved, the current standard of care includes treatment strategies aimed at decreasing apnea, such as caffeine therapy, continuous positive pressure ventilation, and prone positioning [8], and do little to assist development of the immature mechanisms in central neural respiratory control.

Another approach to promote cardiac and respiratory stability in preterm infants is to employ stimuli mimicking the *in utero* environment. Vibratory stimulation (typically arising *in utero* from maternal blood flow and digestion) is a notable intervention, as it may impinge on neural oscillators and promote breathing stability [9]. The assumption is that such stimuli could alter membrane potentials and transform immature chaotic neural impulses into synchronized bursts of activity [9]. Noninvasive external periodic influences can alter spontaneous fluctuations in an individual and help random impulses become synchronous, changing nonspecific patterns of activity into oscillatory forms and ultimately influencing state control [10]. Given the

CONTACT Joanna J. Parga jo.parga@gmail.com Department of Pediatrics, Division of Neonatology, David Geffen School of Medicine at UCLA, Room B2, 375 MDCC, Los Angeles, CA, USA

close association between vestibular and auditory pathways, and the demonstrated role of vestibular processes to modulate sympathetic outflow [11], stimulation from womb-like sounds reintroduced to premature neonates may lessen cardiorespiratory instability and strengthen regulatory autonomic action.

We hypothesized that exposure of premature infants to womb-like sounds would enhance sensory processes that mediate breathing and cardiovascular control. Specifically, the goals were to evaluate the impact of womb-like sounds on rates of intermittent hypoxemia, bradycardia, and apnea episodes, measure biomarkers related to stress and sympathetic tone (assessed by salivary cortisol), and assess changes in respiratory related heart rate variability (HRV) in premature infants.

Materials and methods

Study design

We recruited infants from two level III open-bed Neonatal Intensive Care Units (NICUs). The NICUs were affiliated with the University of California, Los Angeles (UCLA), located in Santa Monica and Westwood, California, USA. Patients were recruited from July 2015 to January 2017. The UCLA Institutional Review Board approved this study, and written informed consent was obtained from parents or caregivers.

Study participants

Inclusion criteria required infants be at least 3 days old, with a corrected gestational age of $\geq$32–36 weeks. Participants included premature infants for whom organ system maturation was the only barrier to discharge. Infants were on room air; those on higher degrees of respiratory support (high-frequency oscillatory ventilation, synchronized intermittent mandatory ventilation, Vapotherm, high flow nasal cannula, continuous positive airway pressure) were excluded. Infants were also excluded if they had confirmed congenital infections, birth asphyxia, grade III or IV intraventricular hemorrhage, confirmed congenital anatomic anomalies (i.e. gastroschisis, omphalocele, congenital heart anomalies, agenesis of the corpus callosum), or confirmed genetic disorders.

Study definitions

The American Academy of Pediatrics defines apnea of prematurity in infants less than 37 weeks gestation as breathing cessations lasting at least 20 s, or any pause in breathing accompanied by bradycardia or oxygen desaturation with cyanosis [12]. Shorter apneas lasting less than 10 s are noted to be secondary to immaturity, but not considered clinically relevant [13]. However, to include any and all signs of immature respiratory and cardiovascular tone in this pilot study, we included any breathing pause lasting greater than 5 s. Breathing pauses were further categorized into three groups for analysis: 5–10 s, 11–19 s, and $\geq$20 s. Bradycardia was defined as a decline in heart rate below 100 beats per minute for greater than 5 s, and intermittent hypoxemia was defined as a decline in oxygen saturation below 90% for greater than 5 s. Womb-like sounds consisted of rhythmic, low-frequency (500–1000 Hz) sound stimulation meant to mimic sound levels generated by the pulsatile blood flow of umbilical and placental arteries.

Sound quality and delivery

The sound intervention was a specially engineered sound track derived from The Happiest Baby on the Block white noise collection entitled Track four: Mellow. The sound was designed to mimic intra-abdominal bruits through umbilical and maternal arteries heard by the fetus. This sound track was modified to reduce the high pitch frequencies over 1000 Hz and amplify frequencies below 1000 Hz, approximating the pitch profile experienced by an infant in the womb [14]. The sound volume was set at 65–70 dB to match the baseline sound level in a room and loosely approximated the decibel level an infant experiences *in utero* [15]. The pitch and decibel level were verified for each infant using a type I sound level meter (Reed SL-4022, Reed Instruments, USA). The sound intervention was delivered through a commercially available infant sound machine (Sweet Slumber Sound Machine, Graco, Minneapolis, MN, USA). The sound machine was equipped with an MP3 player plug in, and a commercially available MP3 player (iPod Nano, Apple, Cupertino, CA) was used to customize sound delivery. Sound output was presented 4–6 inches from the infant's ears in a consistent manner to all study infants.

Data collection procedures

The sound intervention was designed to act as an adjunct to patient care; thus, nursing staff was advised to continue routine care in the presence of sound machines. The study was conducted over a 24-h period and broken into four 6-h time blocks: baseline from hours 1 to 6 (no sound presentation), womb-like

sounds played during the daytime from hours 7 to 12, postsound from hours 13 to 18 (no sound presentation), and womb-like sounds presented at night from hours 19 to 24. Continuous vital signs were monitored in control infants, but no sound stimulation was presented, and events of intermittent hypoxemia, bradycardia, and apnea were analyzed in four 6-h time blocks to mirror analyses of the study subject's data. Monitoring began at a time between 7AM and 9AM and was completed between 7AM and 9AM the next day. No extra leads or devices other than standard NICU monitoring equipment were placed on the infants. Continuous vital sign information (heart rate, respiratory rate assessed through an impedance probe monitoring thoracic wall movement, oxygen saturation assessed through a foot oxygen saturation sensor) was obtained from the NICU monitors (General Electric Healthcare Systems, Boston, MA, USA). An analog-to-digital converter (NI-USD-62188, National Instruments, Austin, TX, USA) acquired information from the monitors onto a study computer.

A salivary sample was obtained from each infant receiving sound stimulation to evaluate salivary cortisol at the beginning and end of the study period. These samples were obtained when the infant was calm and settled in the crib with a cotton infant buccal swab, and were frozen immediately after collection at −80 °C. The 40 samples, comprised of two samples per infant, were delivered on ice to Salimetrics, LLC in Carlsbad, CA, USA for analysis.

Data analysis

A sample size of 20 infants was chosen, based on use of similar numbers in prior studies involving sound stimulation showing an effect size could be achieved with such a sample [16]. An additional five infants served as controls. Demographic variables examined included gestational age at birth, corrected gestational age on study, ethnicity, caffeine usage, and isolette usage. Descriptive statistics, including means and standard deviations, were computed in each of the four time epochs (baseline, womb-like sounds played during the day, postsound, nighttime repeated womb-like sounds) to summarize the outcomes for all variables, including intermittent hypoxemia, bradycardia, and apnea. To determine how events of intermittent hypoxemia, bradycardia, and apnea were affected by group (cases versus controls) and throughout time epochs (the 6-h time blocks), two-way analyses of variance (ANOVAs) were processed for each measure along with Fisher's least significant difference (LSD) tests for multiple comparisons. Cortisol levels were evaluated in duplicate at the Salimetrics, LLC laboratory. Matched pair *t*-tests were used to compare the changes in cortisol at the beginning and end of the study period for all infants with resulting pre- and poststudy samples.

For analysis of heart rate variability, 24-h R–R intervals for each infant were extracted from AD Instruments LabChart 7 (AD Instruments, Sydney, Australia) and analyzed in Kubios (Heart Rate Variability Analysis Software, Kubios, Kuopio, Finland) to remove any artifacts. The root mean square of successive differences (RMSSD) of R–R intervals was used as a time domain measure reflecting vagally mediated HRV [17]. Spectral estimates of heart rate variation were calculated, and high-frequency/low-frequency values assessed to determine high-frequency (respiratory) variation to indicate parasympathetic influences of vagal activity [18]. To correct for non-normally distributed data, both measures of RMSSD and spectral estimates were natural log (ln) transformed to meet the assumptions of linear analysis (lnRMSSD and lnHF, respectively), thus allowing use of parametric tests [19]. Mixed *t*-tests were used for comparison of the means to account for intrasubject variability. Changes in HRV were analyzed over time using a repeated-measures ANOVA design.

A probability level of 0.05 was adopted for significance for all tests. Analyses were carried out using SPSS 22 (IBM Corp Released 2013. IBM SPSS Statistics for Macintosh, Version 22.0, Armonk, NY), GraphPad Prism 7 (GraphPad Software, La Jolla, CA), and SAS 9.4 (Cary, NC).

Results

A total of 25 preterm infants were recruited: 20 infants received the sound intervention, and 5 infants acted as controls. The study sound intervention was never discontinued on any infant, and all were perceived to tolerate it well. Demographic and neonatal characteristics for cases and controls are listed in Table 1.

Table 1. Demographic and neonatal characteristics ($N = 25$).

	Cases (20)	Controls (5)	*p*-Value
Gestation age at birth, weeks, mean ± SD	30 ± 1.98	30 ± 2.28	.96
Corrected gestational age at start of study, weeks, mean ± SD	34 ± 1.29	33 ± 1.79	.67
Males sex, *n* (%)	8 (40)	3 (60)	.62
Race/ethnicity, *n* (%)			
African American	2 (10)	0 (0)	1
Asian	3 (15)	2 (40)	.25
Latino	5 (25)	1 (20)	1
White	10 (50)	2 (40)	1
In isolette, *n* (%)	4 (20)	1 (20)	1
On caffeine, *n* (%)	12 (60)	5 (100)	.14

The primary outcome measure was the change in the number of hypoxemic, bradycardic and apneic events. The secondary outcomes were markers of the autonomic nervous system (HRV) and salivary cortisol levels.

Effect of womb-like sounds on intermittent hypoxemia, bradycardia, and apnea

For intermittent hypoxemic events, there were no significant differences between cases and controls ($F_{(1,92)} = 0.29$, $p = .59$), when examining events over time ($F_{(3,92)} = 0.48$, $p = .70$) or when the interaction of group and time block was accounted for ($F_{(3,92)} = 0.83$, $p = .48$) However, Fisher's LSD tests revealed episodes of intermittent hypoxemia dropped significantly between baseline and daytime womb-like sound exposure ($t = 1.20$, $p = .048$).

During hours 1–6, a significant decrease in bradycardic events was seen in the cases ($t = 2.18$, $p = .03$) and not the controls. There was no interaction effect regarding group and time epoch ($F_{(3,92)} = 1.52$, $p = 0.21$). Despite this outcome, Fisher's LSD tests revealed bradycardic episodes significantly declined from baseline compared to hours 12–24 [postsound] ($t = 2.80$, $p = .01$) and hours 13–18 [nighttime sound] ($t = 2.28$, $p = .025$).

Notable for both intermittent hypoxemia and bradycardia a pattern of lowered events for cases seen

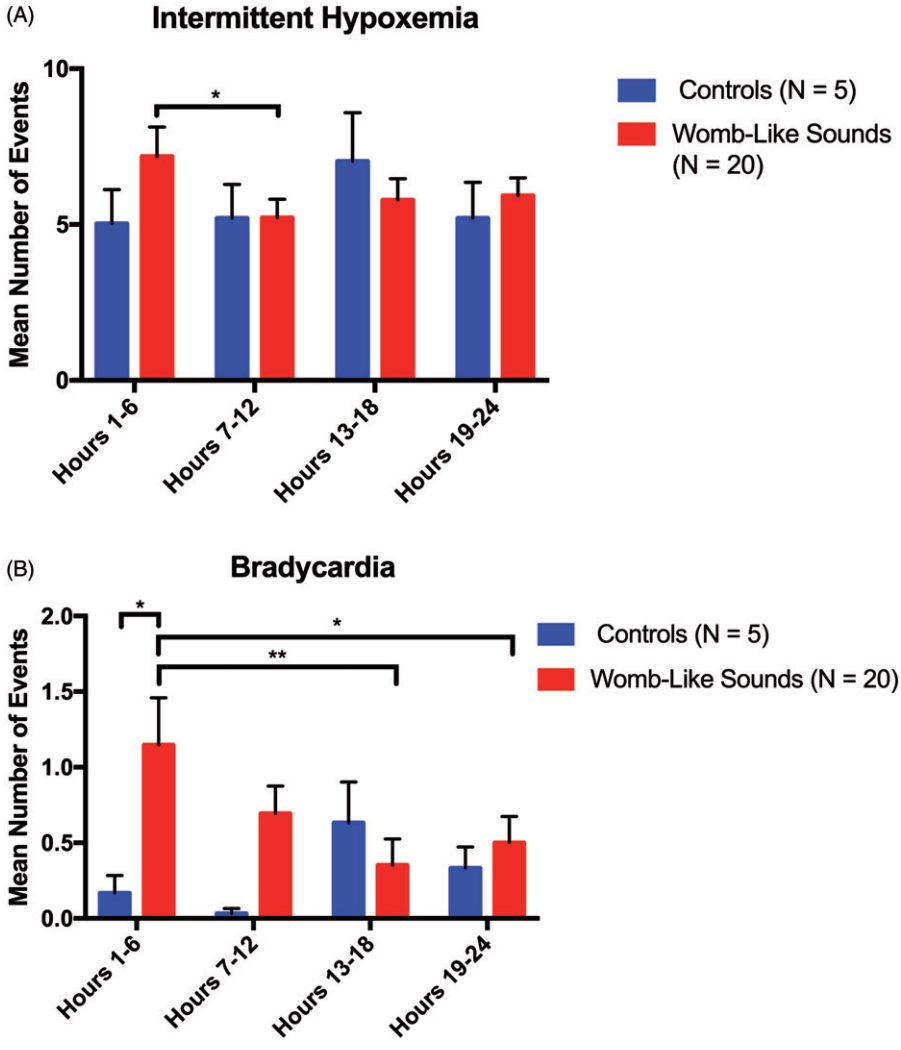

Figure 1. (a) Intermittent hypoxemia: there were no significant difference between cases and controls receiving womb-like sounds ($F_{(1,92)} = 0.29$, $p = .59$) or in events over time for the study period ($F_{(3,92)} = 0.48$, $p = .70$). However, intermittent hypoxemia episodes declined significantly between baseline and daytime womb-like sound exposure ($t = 1.997$, $p = .048$). (b) Bradycardia: during hours 1–6, a significant difference in bradycardic events is seen between cases and controls ($t = 2.18$, $p = .03$). Despite this, a notable trending time epoch effect was revealed ($F_{(3,92)} = 2.887$, $p = .093$) in episodes of bradycardia throughout the study period. For infants exposed to womb-like sounds, these episodes significantly declined from baseline compared to hours 12–24 [postsound] ($t = 2.80$, $p = .01$) and hours 13–18 [nighttime sound] ($t = 2.28$, $p = .025$). For both intermittent hypoxemia and bradycardia, a visual pattern of lowered events was seen in the presence of womb-like sound stimulation.

graphically (Figure 1). These findings show promise for the sound stimulation effect being sustained, at least for the duration of the study.

For apneic events, there was no effect of group ($F_{(1,92)} = 1.68$, $p = .20$) or time epoch ($F_{(1,92)} = 1.26$, $p = .29$). There was no interaction effect of group in time epoch regarding apneic events ($F_{(3,92)} = 0.45$, $p = .72$). Additionally, there were no significant differences testing across time epochs within groups using *post hoc* Fisher's LSD tests. No significant differences in apneic events appeared even when apnea durations were divided into three groups: 5–10 s, 11–19 s, and $\geq$20 s.

No significant differences were found in the cases between infants receiving caffeine versus those off-caffeine, or infants in an open crib versus an isolette when these variables were added in the statistical modeling.

Effect of womb-like sounds on salivary cortisol and HRV

The goal of the salivary studies was to determine whether a biomarker level related to stress changed for those infants receiving sound stimulation; however, 11 of the 20 infants had one or both samples that were of insufficient quantity for analysis. Of the nine remaining infants, seven showed a decrease in cortisol levels of 0.02 μg/dl, but the decline was not significant ($p = .17$).

Additionally, there were no significant trends among the 20 infants receiving sound stimulation in HRV markers for parasympathetic tone, RMSSD, and HF variation (where higher values reflect high parasympathetic input), even when these markers were adjusted for age.

Discussion

We showed that exposing premature infants to womb-like sound stimulation significantly reduced episodes of intermittent hypoxemia and bradycardia. These physiologic benefits appear to outlast auditory stimulation for several hours, supported by the finding of larger *F*-values in statistical analysis. We suggest the findings in this pilot study may be secondary to auditory stimulation exerting sustained effects on fast acting autonomic inputs to the cardiovascular and respiratory systems.

The potential for sound to influence neural development has been shown in ultrasound studies where significant enlargement of the auditory cortex followed womb-like sound stimulation from maternal heartbeat and voice [20]. The processes underlying the interactions between sound and the brain likely follow shared processes with the vestibular system, which exerts profound effects on transient changes to autonomic outflow [11], as illustrated by simple tests such as the tilt table challenge. The auditory system has close anatomical relationships with the vestibular system, and auditory–parasympathetic interactions have the potential to influence cerebellar cortical circuitry. The anatomic plausibility for this scenario is illustrated in Figure 2. Thus, mechanisms underlying the findings here may depend on sound processes influencing pre-existing neural circuitry in aiding the maturation of parasympathetic tone. However, we did not find significant differences in parasympathetic activity (RMSSD and HF) during the sound intervention.

The concept of appropriate auditory stimulation for infants in the NICU is controversial. In today's NICU environment, the sound profile vastly differs from the womb. The fetus begins to respond to sounds as early as 20-week gestation, when the bones in the middle ear have sufficiently developed [21]. *In utero*, exogenous sounds (e.g. mother's heartbeat, arterial blood flow, respiratory, and digestive sounds) range from 70 to 90 dB [22,23]. The presence of maternal tissues and amniotic fluid significantly dampen exogenous high-pitched noises above 500–1000 Hz [22], and attenuate sound pressures by 10–25 dB [23,24]. The maternal voice is an exception, with amplification of the mother's speech by ~5 dB, reaching levels of 60–75 dB [25,26]. Despite the substantial sound volumes routinely experienced by fetuses before birth, current recommendations attempt to prevent sound exposure in the NICU over 45–50 dB at baseline and 65 dB in transient spikes. There are no current recommendations on appropriate frequency or type of sound exposure [22]. These standards have been promulgated by the belief that quiet prevents hearing loss and promotes healthy physiologic and neurodevelopment [27,28]. Thus, hospitals have focused on minimizing loud noises through various tactics [29], and not on what sounds are developmentally appropriate. The most effective means to reduce sound levels is to move from open-bed NICUs to single-bed NICUs. With this now fast occurring shift, concerns are developing about the relative auditory deprivation experienced by premature infants in the single-bed NICU environments. Evidence is emerging that such deprivation could negatively affect long-term neurodevelopmental outcomes with respect to sound processing and language development [30]. Given that the womb provides rhythmic sound stimulation to growing fetuses at levels often in excess of 50 dB (especially for sounds

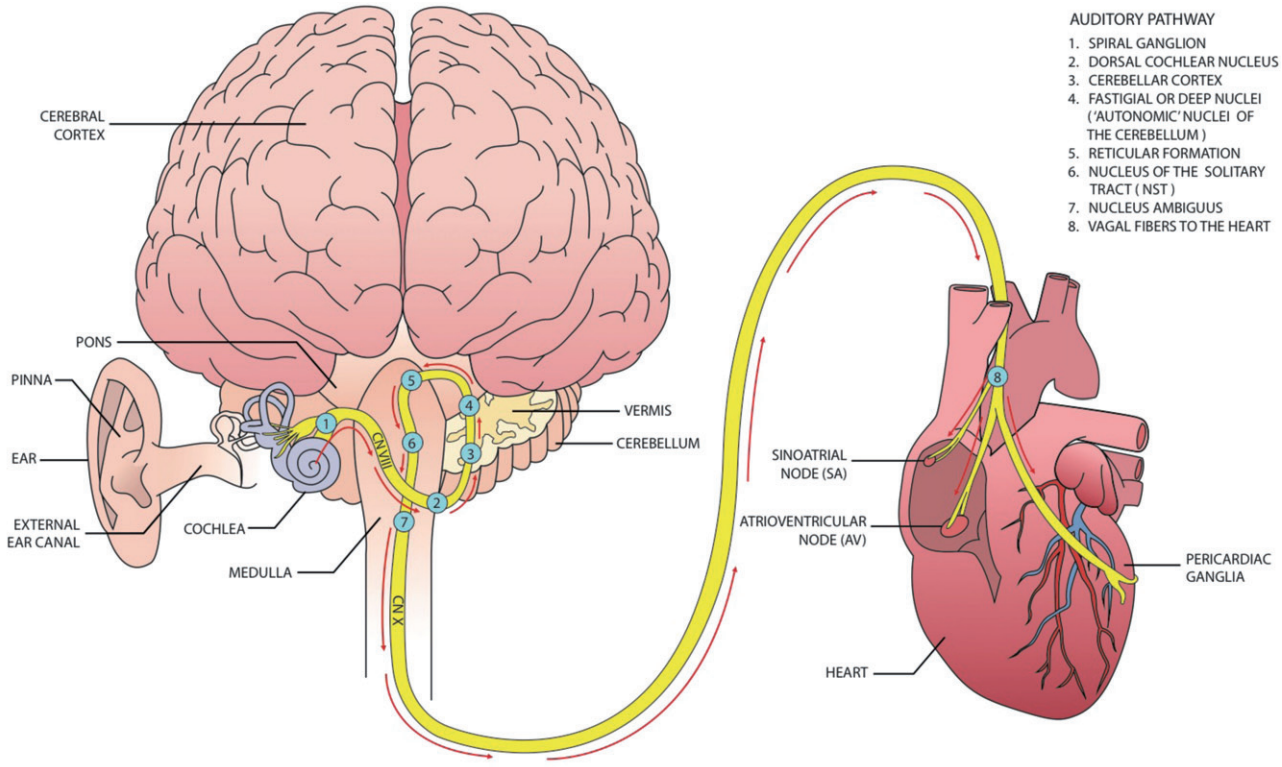

Figure 2. Like vestibular pathways, auditory neural pathways have close anatomical connections to the autonomic nervous system. A proposed auditory–parasympathetic pathway is outlined here, demonstrating that the significant reductions in bradycardia and intermittent hypoxemia found in this study may result from the influence of sounds on preexisting neuronal circuitry. The structures numerically labeled in the pathway are as follows: (1) spiral ganglion, (2) dorsal cochlear nucleus, (3) cerebellar cortex, (4) fastigial or deep nuclei ("autonomic" nuclei of the cerebellum), (5) reticular formation, (6) nucleus of the solitary tract (NST), (7) nucleus ambiguus, and (8) vagal fibers to the heart. [This image solely for inclusion in this manuscript by artist Andrew Collora.].

<1000 Hz), providing a sound profile more accurately mirroring the normal, *in utero* sensory milieu may help promote neurodevelopment and act as an intervention to stabilize immature autonomic functioning. Efforts should begin to diversify from simply emphasizing quiet toward discovering what sounds support appropriate physiologic development.

Despite the well-known effects of certain forms of sound (e.g. classical music) to influence cardiovascular activity and well-being in adults, it is unusual that sound has not been used as a noninvasive intervention to stabilize cardiorespiratory tone in the neonatal period. The outcomes of this pilot study suggest that the sound/autonomic interaction can exert significant effects on vital physiology. Sound studies are complicated by an inability to blind the staff when the sound stimulation occurs, but randomization is possible and should be performed with controls being sampled at the same time as those receiving the study stimulus. Altering this study's methodology (i.e. time that sound is played) may strengthen the associations with sound and cardiorespiratory stability found here. Our results are unlikely to be secondary to maturation of the preterm infant over the course of 24 h, given that the control infants had no decrease in their events. Future investigations should be mindful of extending the sound stimulus over greater than several days because of concerns of preterm infant maturation. When compared to those receiving womb-like sound stimulation, controls had lower amounts of bradycardia and this is likely due to low power and small sample size. It should also be noted that 100% of controls and only 60% of study subjects received caffeine. In our statistical analysis, no significant effects from caffeine use were found on the physiologic measures; however, such use needs to be examined in future studies as a potential confounder.

This study was a pilot and revealed definitive outcomes on two measures, bradycardia and hypoxemic episodes to womb sounds. Suggestions of other physiologic changes appeared, and with greater subject numbers, they may be shown to be real. Given the biological plausibility, we would propose that the intervention has potential to reduce those two biomarkers, and further studies may solidify these findings.

Conclusion

This study showed that exposing premature infants to womb-like sounds has the potential to reduce hypoxemia and bradycardic episodes. The mechanisms underlying the diminished hypoxemia and changes in cardiac slowing remain unclear, but the close association of the auditory and vestibular systems and the well-described vestibular/auditory–autonomic pathway could mediate these novel findings. We suggest the focus of the NICU sound environment should move from promoting quiet toward discovering what sounds have the potential to foster physiologic stability and neurodevelopment.

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Disclosure statement

None of the authors have potential conflicts of interest to disclose except Harvey Karp, owner of THB Media, LLC, who provided the CD from which the womb-like sounds were taken.

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