Stochastic Resonance Effects on Apnea, Bradycardia, and Oxygenation: A Randomized Controlled Trial

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abstract

OBJECTIVE: To evaluate the effect of stochastic resonance (SR) stimulation on preterm infant oxygen desaturation, bradycardia, and apnea events. We hypothesized that SR stimulation will reduce these events.

METHODS: This was a randomized crossover study conducted from April 2012 to July 2014. Eligible preterm infants were not receiving ventilation support and had at least 1 clinically documented apnea, bradycardia, and/or oxygen desaturation event. The 3 outcome variables were as follows: oxygen desaturation, bradycardia, and apnea events. Infants received up to two 3- or 4-hour intervention periods of 30-minute alternating intervals of SR stimulation and no SR stimulation. The first intervention period was randomly assigned to begin with SR stimulation either on or off, whereas the next intervention period automatically began with the opposite on/off state. We compared the SR stimulation "on" periods with the SR stimulation "off" periods with each infant serving as his or her own control.

RESULTS: The sample consisted of 36 infants with a mean (±SD) gestational age of 30.5 ± 3 weeks and a birth weight of 1409 ± 450 g. SR stimulation decreased the number of apneic events by 50%. SR stimulation ameliorated every aspect of clinically significant oxygen desaturation events, with a 20% to 35% decrease in the number, duration, and intensity of oxygen desaturation events when SR stimulation was on. Also, SR stimulation produced a nearly 20% reduction in the intensity of bradycardia events.

CONCLUSIONS: SR stimulation may be a noninvasive and nonpharmacologic treatment option for apnea, oxygen desaturation, and some aspects of bradycardia in premature infants.

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WHAT'S KNOWN ON THIS SUBJECT: Apnea of prematurity occurs in >50% of preterm infants and is almost universal in infants with a birth weight of <1000 g. Currently, caregivers treat apnea events with drugs (ie, methylxanthines) or assisted ventilation support.

WHAT THIS STUDY ADDS: Stochastic resonance stimulation may be a safe, effective, noninvasive, and nonpharmacologic supplemental treatment of apnea of prematurity, oxygen desaturation, and some aspects of bradycardia.

Apnea of prematurity (AOP) is a primary concern in the NICU.[1] AOP is often defined as a cessation of breathing that lasts for at least 20 seconds or at least 10 seconds followed by bradycardia and hypoxemia.[2] AOP occurs in >50% of preterm infants (those born <37 weeks' completed gestation) and is almost universal in infants with a birth weight of <1000 g.[3] Although the pathophysiology of AOP is poorly understood, it is often attributed to immature respiratory control mechanisms.[4,5] To date, no consensus has been reached regarding the diagnosis or treatment of apnea. Although caregivers treat apnea events with drugs (ie, methylxanthines) or assisted ventilation, the benefit of treatment is unproven and long-term neurodevelopmental effects are unknown.[3]

Despite current treatment options, infants continue to have apnea. Stochastic resonance (SR), the introduction of noise to a system to alter the system's behavior, may offer a supplementary option. SR has been used to stabilize other biological systems[6] and has been examined in previous medical applications (eg, improving balance in elderly people) with significant success.[7] Previous research suggests that stochastic vibro-tactile stimulation can stabilize breathing patterns in premature infants.[8] Using a specialized SR mattress that provides mechanosensory stimulation via gentle subarousal vibrations, Bloch-Salisbury et al[8] found that stimulation resulted in significant reduction in the variance of interbreath intervals, the incidence of apneic pauses, and the duration of hypoxia in 10 preterm infants.

The current study provides a systematic evaluation of the effect of SR stimulation on preterm infant oxygen desaturation, bradycardia, and apnea. We hypothesized that SR stimulation will reduce the incidence of oxygen desaturation, bradycardia, and apneic events.

METHODS

Clinical Setting

Study infants were cared for in the NICU (level IIIB designation) at Beth Israel Deaconess Medical Center (BIDMC), a Harvard Medical School teaching hospital.

Study Design

This was a randomized crossover study in which the patient served as his or her own control to compare the effects of SR stimulation for each infant.

Study Population

Enrollment occurred from April 2012 to July 2014. Eligible infants were born at a gestational age of <36 weeks, with a postmenstrual age (PMA) of <45 weeks at the time of study (calculated by adding gestational age at birth in weeks to the number of weeks since birth). Infants had at least 1 clinically documented apnea, bradycardia, and/or oxygen desaturation event before enrollment. We excluded infants who were receiving mechanical ventilation or continuous positive airway pressure at the time of the study. There were no birth weight restrictions. All decisions pertaining to diagnosis and treatment of the enrolled infant, including treatment with caffeine and/or supplemental oxygen, were at the discretion of the local clinician providing care in the NICU. The BIDMC Institutional Review Board approved the study, and Harvard Medical School Institutional Review Board ceded review.

Study Protocol

All families provided written informed consent to participate in the study. No remuneration was offered or provided to any family for participating. The protocol consisted of a baseline period of at least 1 hour with no SR stimulation followed by up to two 3- or 4-hour intervention periods (Fig 1). During an intervention period, each infant received 30-minute alternating intervals of SR stimulation and no SR stimulation. The first intervention period was randomly assigned to begin with stimulation either on or off (Fig 1), whereas the second intervention period automatically began with the opposite on/off state as the previous intervention. The session ended with a baseline period of at least 1 hour with no stimulation. The infant's vital signs were simultaneously and continuously recorded during the entire session. All other aspects of the infant's care, including feeding, clinical procedures, and assessments, were unaffected by participation in this study.

SR Stimulation

We replaced the standard mattress in the infant's crib or isolette with a custom-built SR mattress. SR stimulation was delivered in the form of gentle, low-amplitude displacements at the surface of the mattress with a frequency bandwidth of 30 to 60 Hz and displacements of 10 to 20 microns. In 13 infants we used a signal generator (Balance Engineering, Lexington, MA) and mattress (TheraSound), which provided vibration of the entire bedding surface, described previously by Bloch-Salisbury et al.[8] In the remaining 23 infants, we used the Wyss Institute–developed signal generator and mattress, which contains an isolation unit that significantly dampens vibration to the rostral third of the mattress.[9] Otherwise, the 2 mattresses provided identical stimulation. The equipment underwent rigorous validation procedures at the Wyss Institute, including frequent maintenance checks throughout the study period.

Data Acquisition

Study data were recorded by using the VueLogger Patient Monitoring System, a novel data-acquisition system, developed by the Wyss Institute. The VueLogger is a portable, computer-based system that connects

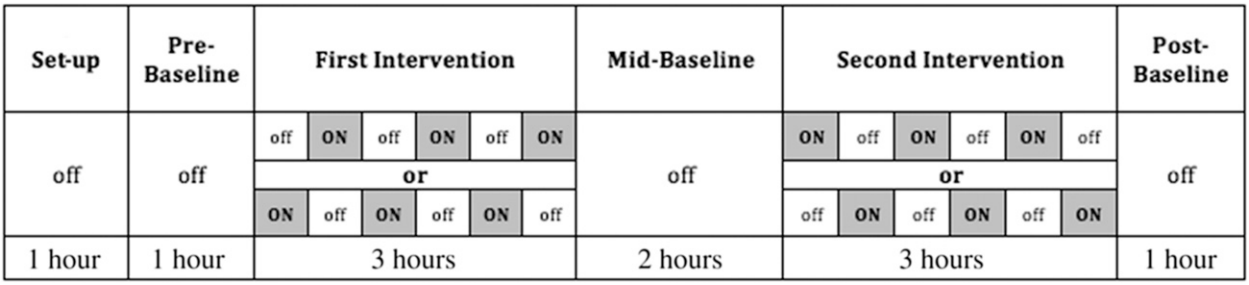

FIGURE 1
Schematic of a common protocol sequence.

to the existing Philips "Intellivue" patient bedside monitor used in the NICU, allowing it to retrieve and record the same physiologic signals that are gathered for clinical purposes without placing additional sensors on the patient. The VueLogger records the signals captured by the patient monitor without alteration or filtering.

The following clinical signals were recorded: heart rate (HR), respiratory rate (RR), electrocardiogram, peripheral capillary oxygen saturation, and pulse plethysmography (Nellcor oximeters). The VueLogger also recorded the mattress vibration signal, as well as the light and sound levels in the crib/isolette. A sound meter (Extech 407764) to record sound intensity and a light meter (Hioki 3423 Lux HiTester) to measure brightness and changes in light levels were both placed next to the infant. Sound and light were continuous measures. Data were recorded at sampling rates that varied from 1 Hz (oxygen saturation) up to 500 Hz (electrocardiogram) and streamed to the VueLogger's hard-disk at the bedside, and then exported for analysis. Clinical monitoring information (eg, HR, RR) was collected directly from the patient bedside monitor without alteration and was used to retrospectively determine the incidence of relevant events. Our review and analysis indicated no systematic issues with the collection, management, or quality of the data acquired with the use of the VueLogger system.

Variables

We had 3 outcome variables, oxygen desaturation, bradycardia, and apnea events, for which we studied the number and duration of events. For oxygen desaturation and bradycardia events, we also studied the intensity of the events. We defined our outcomes on the basis of BIDMC NICU clinical definitions. An oxygen desaturation event was defined as oxygen saturation $<87\%$ for infants <35 weeks' PMA and 90% for infants with a PMA of ≥ 35 weeks. A bradycardia event was defined as an HR of <100 beats per minute for infants <34 weeks' PMA and <80 beats per minute for infants with a PMA of ≥ 34 weeks. For oxygen desaturation and bradycardia, there was no specified length of the event (ie, it had to last for at least 1 second to meet the definition). If there were successive values that fell below the threshold, they were counted as part of 1 event (ie, if the oxygen level dropped below the threshold for 10 seconds in a row without rising above the threshold, that would be counted as 1 not 10 events). Apnea was defined as a pause in respiration (ie, RR of zero) of ≥ 10 seconds.

The duration of an event was defined as how many seconds the event lasted before the parameter returned to normal. For both oxygen desaturation and bradycardia events, we also studied intensity as a composite outcome that took into account how far below the threshold the parameter dropped and how long the event lasted. Intensity was calculated as the area under the curve for the event. All outcome parameters were ascertained automatically (ie, no manual coding of outcomes) by computer code during analysis.

Other neonatal variables were obtained from the medical record, including information about the infant at birth (ie, weight and gestational age) and at the time of study (ie, current weight, PMA, and whether the infant was being treated with supplemental oxygen and/or caffeine). Race and ethnicity were per maternal self-report on the birth certificate.

Statistical Analysis

We compared each infant's SR stimulation "on" periods with the SR stimulation "off" periods, such that each infant served as his or her own control. We used Poisson regression with random effects for both bivariate and multivariable analyses. For each individual infant we analyzed the number, duration, and intensity of oxygen and bradycardia desaturation events. To demonstrate an effect of SR stimulation, analysis of the measured data would have to show that the number, duration (in seconds), and intensity (in cumulative percentage below the locally defined limit) of the clinically defined outcome were lesser, shorter, and weaker, respectively, for those events when SR stimulation was on. Independent clinical variables (eg, current weight, PMA, $\pm$ oxygen, $\pm$ caffeine) that were statistically significant in bivariate analyses were

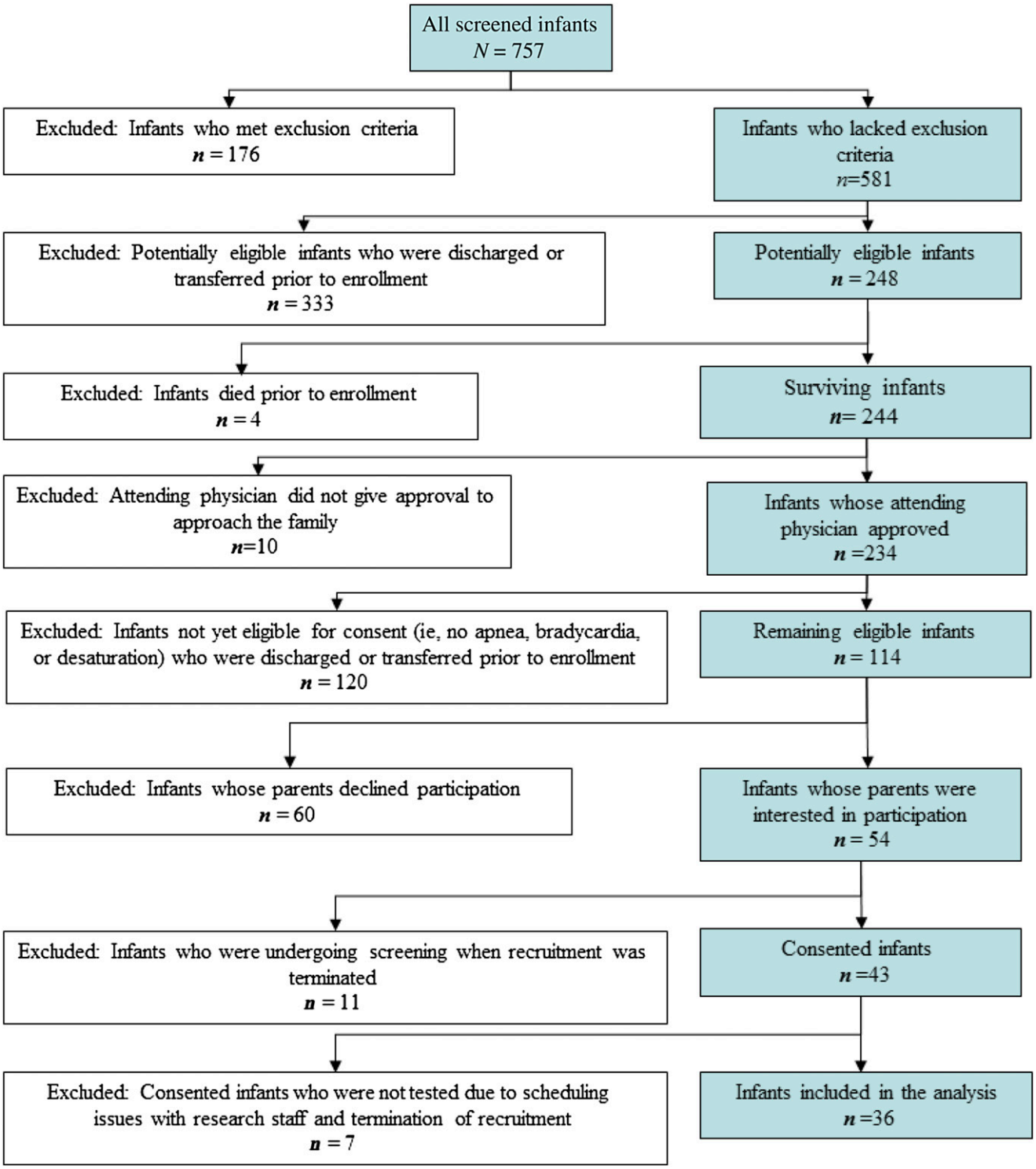

FIGURE 2
Flow diagram of patient enrollment.

individually added to the significant SR stimulation Poisson models to assess the effect of SR stimulation, controlling for the selected clinical variable.

Mixed Poisson modeling is an appropriate statistical modeling because the "mixed" aspect allows fitting random-effects terms for each infant within each session to absorb individual differences in risk of events. Counts are all positive integers, and for rare events, the Poisson distribution (rather than the normal) is more appropriate because

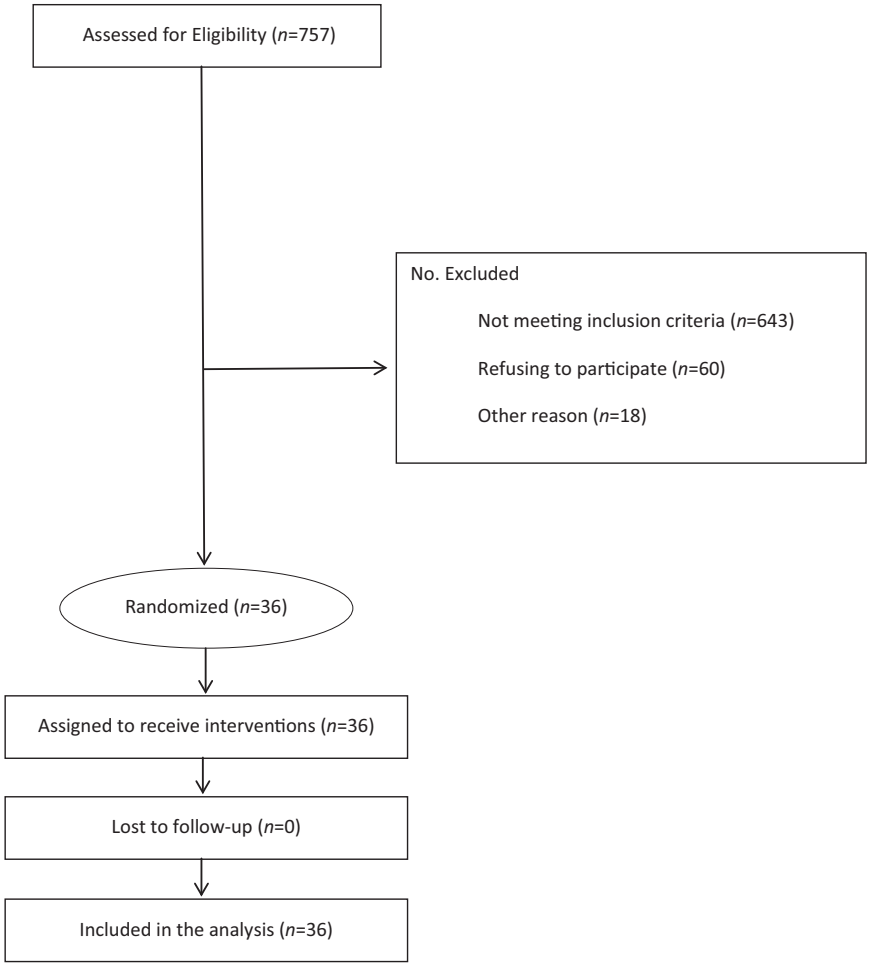

FIGURE 3
CONSORT (Consolidated Standards of Reporting Trials) flow diagram of patient enrollment.

the Poisson mean is >0. The typical Poisson regression model expresses the log outcome rate as a linear function of a set of predictors. Poisson modeling is classically a method used to test for differences in outcome measures that are explicitly count variables (ie, whole numbers) that may be applied to dependent variables that are continuous as well.[10] A Poisson regression is a test of whether the change in regression parameters will influence the probability of a unit increase. In this sense, Poisson regression is a close cousin of the logistic regression that is not limited to modeling the occurrence or nonoccurrence of a single outcome. We used Poisson regression to model the effect of SR stimulation on the occurrence of each outcome, confirming that residuals were uncorrelated across model-predicted values according to assumptions of Poisson modeling. Poisson regression was conducted with SAS version 9.4 (2000; SAS Institute, Cary, NC) by using the proc glimmix procedures.

RESULTS

Figure 2 shows the screening and enrollment for the study. We had a sample of 36 infants (Fig 3). Table 1 presents some descriptive characteristics of the study population. Subjects' race was white (n = 27), black or African American (n = 5), and other/unknown/unreported (n = 4). Two infants were of Hispanic or Latino ethnicity. Thirteen (36%) were receiving caffeine, and 5 infants (14%) were receiving supplemental oxygen at the time of testing. No adverse events, adverse device effects, or unanticipated problems were encountered.

Table 2 describes the outcome events. There was a reduction in the number and duration of oxygen desaturation events when SR stimulation was on. There was no meaningful change in the number of bradycardias when SR stimulation was on, but there was a decrease in the duration and intensity. There was a reduction in the number and duration of apneic events when SR stimulation was on.

Although not specifically studied, the study staff did not notice an obvious change in the infants' arousal state related to the use of the SR mattress. In fact, anecdotally, nursing staff and parents reported that the infants seemed to sleep more comfortably on the SR mattress than on their standard mattress.

Oxygen Desaturation

The median interquartile range (IQR) number of oxygen desaturation events per infant during the study period was 3.0 (0–18) when the SR stimulation was on and 3.5 (1–18) when it was off. Poisson modeling showed significant effects of the SR stimulation: an 18% (95% confidence interval [CI]: 5%–29%) reduction in the number of the oxygen desaturation events (P = .01), a 35% (95% CI: 33%–37%) reduction in the duration of each oxygen desaturation event ($P < .0001$), and a 21% (95% CI: 20%–22%) reduction in the intensity of each oxygen desaturation event ($P < .0001$).

Bradycardia

The median (IQR) number of bradycardia events per infant during the study period was 0 (0–2) when the SR stimulation was on and 0 (0–1) when it was off. With the use of Poisson modeling, there was no change in the number of bradycardia events or duration of each bradycardia event when the SR

TABLE 1 Characteristics of the Study Population

	Value
Gestational age, wk	30.5 ± 2.9
PMA at time of testing, wk	35.0 ± 1.5
Birth weight, g	1409 ± 450
Weight at time of testing, g	2013 ± 453
Caffeine at time of testing, *n* (%)	13 (36)
Supplemental oxygen at time of testing, *n* (%)	5 (14)
Female gender, *n* (%)	19 (44)

Data are presented as means ± SDs unless otherwise indicated.

stimulation was on. However, there was an 18% (95% CI: 15%–22%) reduction in the intensity of each bradycardia event ($P < .0001$).

Apnea

The median (IQR) number of apnea events per infant during the study period was 0 (0–1) when the SR stimulation was on and 0 (0–1) when it was not. For the entire sample, SR stimulation decreased the number of apneic events by 50%. There were not enough apnea events per infant to analyze at the infant level with the use of Poisson modeling.

Other Clinical Features

Supplemental Oxygen

Infants receiving supplemental oxygen at baseline were sicker than infants not receiving supplemental oxygen (ie, they had more oxygen desaturation events, which lasted longer and were greater in intensity than infants not receiving supplement oxygen). For infants receiving supplemental oxygen, the effects of SR stimulation remained significant in multivariable analyses and practically unchanged from the bivariate analysis by adding supplemental oxygen into the 3 Poisson models for oxygen desaturation events. The magnitude of improvement in the number, duration, and intensity of oxygen desaturation events was the same for infants with and without supplemental oxygen. In bivariate analysis, supplemental oxygen was not significantly associated with the intensity of bradycardia.

Caffeine

The effects of SR stimulation on the number, duration, and intensity of oxygen desaturation events and the intensity of bradycardia events were the same as in infants being treated with caffeine.

PMA

We conducted bivariate analyses of PMA with the 3 Poisson models for oxygen desaturation events and found that none of them were significant. Bivariate analyses of PMA with the Poisson model for intensity of bradycardia events were significant, but the effects of SR stimulation were unchanged when adding PMA to a multivariable model with SR stimulation.

Current Weight

We conducted bivariate analyses of weight on the day of testing with the 3 Poisson models for oxygen desaturation as well as the model for intensity of bradycardia events and found that none of them were significant.

Light and Sound

We collected data on the infant's exposure to light and sound during the study. In bivariate analysis using the Poisson models, light was not significantly associated with the number of oxygen desaturation events. However, it was significantly associated with the duration and intensity of oxygen desaturation events. In bivariate analysis that used the Poisson models, sound was not significantly associated with the number or intensity of oxygen desaturation events. However, it was significantly associated with the duration of oxygen desaturation events. Although they were significant, the relative sizes of the light and sound effects were very small compared with effects of SR stimulation. We attempted multivariable models with SR stimulation that included either light or sound, but these models did not converge. The multivariable model for intensity of bradycardia with SR stimulation and sound revealed a slight change associated with SR stimulation, a 17% (95% CI: 14%–21%) reduction in the intensity of each bradycardia event controlling for sound ($P < .0001$).

DISCUSSION

In our study in 36 preterm infants, SR stimulation decreased the number of apnea events by half. SR stimulation ameliorated every aspect of clinically significant oxygen desaturation events, with a 20% to 35% decrease in the number, duration, and intensity of

TABLE 2 Description of Events When SR Stimulation Was On or Off During the Intervention Periods for the Entire Sample

		SR Stimulation	
	All Events	On	Off
Oxygen desaturation events, number of events	709	315	394
Oxygen desaturation duration (median [IQR]), seconds per event	17.9 (8.7–28.3)	17.6 (8.4–25.4)	18.5 (8.9–31.5)
Oxygen desaturation intensity (median [IQR]), cumulative percentage[a] desaturation per event	34.6 (10.1–87.3)	31.6 (8.3–79.1)	39.2 (11.5–91.7)
Bradycardia events, number of events	73	38	35
Bradycardia duration (median [IQR]), seconds per event	7.5 (3.1–11.3)	7.5 (3.1–10.2)	7.9 (3.1–13.3)
Bradycardia intensity (median [IQR]), cumulative percentage bradycardia per event	63 (24.0–127.7)	61 (28.0–97.0)	80.9 (22.5–182.0)
Apnea events, number of events	39	13	26
Apnea duration (median [IQR]), seconds per event	22.5 (20.5–88.1)	20.7 (14.9–60.4)	28.7 (22.5–105.3)

[a] Cumulative percentage is a measure of area under the curve that takes into account how far below the threshold the event went and how long the event lasted.

oxygen desaturation events when the SR stimulation was on. Although SR stimulation did not change the number or duration of bradycardia events, we found a nearly 20% reduction in the intensity. All of these findings were noted without any adverse effects, providing proof-of-concept that SR stimulation may be a viable supplementary treatment option.

These results are similar to previous work that used the SR mattress. Like Bloch-Salisbury et al,[8] we observed a 50% reduction in apneic events, but their definition of an apneic event was a pause in breathing of >5 seconds and ours was defined as a pause of ≥10 seconds. Similarly, Bloch-Salisbury et al showed a 65% reduction in the duration of oxygen desaturation, although we observed a more modest 35% reduction in the duration and a 21% reduction in the intensity of each oxygen desaturation event. We did not notice any obvious change in infant state, which is consistent with the findings of Bloch-Salisbury et al that the SR stimulation was below the arousal threshold based on polysomnographically and behaviorally defined criteria using video-EEG recordings.

Our study has substantial strengths. The use of each infant as his or her own control provides the highest strength of evidence for individual infants by removing the interpatient variability from the comparison between the intervention periods, and provides unbiased estimates for the differences associated with SR stimulation.[11] Because we did not otherwise alter the clinical care of the infants in the NICU, the effects of the SR stimulation were in addition to those of supplemental oxygen and caffeine, because several infants were already receiving these treatment modalities. Infants who were clinically receiving supplemental oxygen and/or caffeine received an additional benefit from the SR stimulation, which was similar in magnitude of improvement in the number, duration, and intensity of oxygen desaturation events and intensity of bradycardia events.

Our small sample size is a study limitation. Specifically, subgroup analyses were insufficiently powered to address which group of infants would benefit most from this intervention. Despite the statistical and clinical significance of our results, the effect estimates were unstable. Some infants saw up to 40% to 50% reductions in oxygen desaturation events, whereas others had more modest results. The small sample size, coupled with the limited information we collected about each patient, limits our ability to speculate which subgroups would benefit most from this intervention. It is highly likely that a subset of infants would benefit more from SR stimulation than other infants. With our current study, we are unable to further elucidate the characteristics of these infants. Identifying the ideal candidate patients for SR stimulation would be an appropriate focus for a larger study.

It is important to note that this study was not a head-to-head comparison with current standard treatments for AOP; thus, we are not in a position to address whether SR stimulation might have a potential advantage over standard treatments. Further study, specifically a randomized controlled trial of caffeine and/or supplemental oxygen versus SR stimulation, is called for to address this issue.

The mechanism of action by which SR exerts its effect is unknown. It is postulated that SR promotes stability and robustness of eupneic respiratory rhythm, modifying unstable respiratory pacemaker rhythms into a more stable rhythm,[12–14] possibly via visceral or somatic mechanoreceptors.[8] Another explanation for the efficacy of SR on the respiratory system is a direct pulmonary enhancement of gas exchange through mechanical perturbations of the network architecture of lung tissue.[15] With an unclear mechanism of action, there could be unanticipated short- and long-term benefits or risks. Although there were no adverse device effects, adverse events, or unanticipated problems associated with the SR stimulation in the current study, further study is required to establish the safety and efficacy of this intervention.

CONCLUSIONS

Methylxanthines like caffeine are and have been the primary treatment choice for AOP for decades.[1,5] The results of our study provide proof-of-concept that SR stimulation may be a safe, effective, noninvasive, and nonpharmacologic supplemental treatment option for AOP, oxygen desaturation, and some aspects of bradycardia. It could be included in the armamentarium of resources available to NICU providers caring for preterm infants. Future studies, with a larger patient population, are needed to further evaluate the effects of SR and its potential to influence clinical treatment and outcomes.

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ABBREVIATIONS

AOP: apnea of prematurity
BIDMC: Beth Israel Deaconess Medical Center
CI: confidence interval
HR: heart rate
IQR: interquartile range
PMA: postmenstrual age
RR: respiratory rate
SR: stochastic resonance

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