Listening to Relaxing Music Improves Physiological Responses in Premature Infants

A Randomized Controlled Trial

Rafael A. Caparros-Gonzalez, MSc, RN; Alejandro de la Torre-Luque, MSc; Carolina Diaz-Piedra, PhD; Francisco J. Vico, PhD; Gualberto Buela-Casal, PhD

ABSTRACT
Background: Premature infants are exposed to high levels of noise in the neonatal intensive care unit (NICU).
Purpose: This study evaluated the effect of a relaxing music therapy intervention composed by artificial intelligence on respiratory rate, systolic and diastolic blood pressure, and heart rate.
Methods: A double-blind, randomized, controlled trial was conducted in the NICUs of 2 general public hospitals in Andalusia, Spain. Participants were 17 healthy premature infants, randomly allocated to the intervention group or the control group (silence) at a 1:1 ratio. To be included in the study, the subjects were to be 32 to 36 weeks of gestation at birth (M = 32.33; SD = 1.79) and passed a hearing screening test satisfactorily. The intervention lasted 20 minutes, 3 times a day for 3 consecutive days, while infants were in the incubator. Infants' heart rate, respiratory rate, and blood pressure were assessed before and after each intervention session.
Results: After each session, the respiratory rate decreased in the experimental group (main between-groups effect ($F_{1,13} = 6.73$, $P = .022$, $\eta^2_{\text{partial}} = 0.34$). Across the sessions, the heart rate increased in the control group (main between-groups effect, $F_{1,11} = 5.09$, $P = .045$, $\eta^2_{\text{partial}} = 0.32$).
Implications for Research: Future studies can use this music intervention to assess its potential effects in premature infants.
Implications for Practice: Nurses can apply the relaxing music intervention presented in this study to ameliorate the impact of the stressful environment on premature infants.
Key Words: heart rate, music therapy, premature infant, randomized controlled trial, respiratory rate

BACKGROUND AND SIGNIFICANCE

Advances in therapeutic interventions on premature infants have increased during the past decade.[1-3] Nevertheless, prematurity continues to be associated with short-term and accumulative negative outcomes resulting in respiratory disorders and cardiovascular instability.[4-6] The neonatal intensive care unit (NICU) environment has been described as stressful in itself, and it is related to adverse consequences on infants' health and safety.[7] For example, premature infants might be particularly vulnerable to unpredictable noise from the NICU (such as alarms or staff conversations), which might produce health disturbances.[8] Thus, noise would have an impact on the cardiac and respiratory systems, placing stress on premature infants.[9,10] Loud noise levels above 70 decibels in the NICU increases the respiratory and heart rates of premature infants.[8,9] High levels of noise in the NICU would have detrimental effects on the premature infant physiological state and future neurodevelopment.[8,10]

Intentional sounds such as music, through its unique acoustic properties, can reduce stress and hyperalertness in premature infants.[11,12] Relaxing music (characterized by slow tempo, regular rhythmic, and low pitches) was an effective nonpharmacological intervention to stabilize physiological measures,[13,14] as it reduces the release of certain neuroendocrine agents (eg, cortisol) and enhances the action of the

Author Affiliations: Mind, Brain, and Behavior Research Center (CIMCYC), University of Granada, Granada, Spain (Mr Caparros-Gonzalez, Dr Diaz-Piedra, and Dr Buela-Casal); Faculty of Psychology, University of Balearic Islands, Balearic Islands, Spain (Mr de la Torre-Luque); School of Computer Science, University of Malaga, Malaga, Spain (Dr Vico); and Gynecology and Obstetric Department, Hospital Poniente, El Ejido, Almeria, Spain (Mr Caparros-Gonzalez).

Institutions where the work occurred: Hospital Poniente, El Ejido, Almeria, Spain; and Hospital Costa del Sol, Marbella, Malaga, Spain.

This study was funded by a Spanish Ministry of Science and Innovation grant (INNPACTO IPT300000-2010-10). R.C.G. is supported by the I+D Project "PSI2015-348 63494-P" of the Spanish Ministry of Science and Innovation. A.T.-L. is supported by an FPI grant from the Spanish Ministry and Competitiveness (BES-2013-064257). C.D.-P. is supported by a UGR Postdoctoral Fellowship (2013 University of Granada Research Plan).

None of the authors has biomedical financial interests or potential conflicts of interest.

Correspondence: Rafael A. Caparros-Gonzalez, MSc, RN, Mind, Brain, and Behavior Research Center (CIMCYC), Campus de Cartuja s/n, 18011, Universidad de Granada, Granada, Spain (rcg477@correo.ugr.es; rafawolfy@gmail.com).

DOI: 10.1097/ANC.0000000000000448

parasympathetic nervous system, lowering heart rate, respiratory rate, and other stress-related responses.[15,16] Music can be perceived even in early fetal life.[17] Although the maturation of the cochlea occurs around 35 weeks of gestation,[18] hearing development starts earlier, with most fetuses reacting to sounds of 110 decibels or more at 20 weeks of gestation.[19] Thus, music therapy protocols for premature infants can be applied after 28 weeks of gestation.[20]

Although some evidence supports the use of music-based interventions in premature infants in the neonatal period,[21] there still remain some inconsistencies.[22,23] Music therapy in the NICU has soothing properties that may improve brain development (eg, larger brain volume and better microstructure) measured through 3-dimensional volumetric magnetic resonance, increase nonnutritive sucking, and positively influence physiological parameters.[12,24-26] For example, music therapy can stabilize physiological parameters including heart rate,[27-29] respiratory rate,[27,29] oxygen saturation,[28] and systolic blood pressure parameters.[28,30,31]

Music protocols recommended for infants in the NICU include a constant volume level below 70 decibels, a maximum time of 1.5 hours of music each day, and an avoidance of sounds generated by toys and mobile phones.[20] While most interventions using music in the NICU have been associated with an increased focus on developmental care and the potential for optimal maturation of premature infants, inconsistency in findings persist, with greatest benefits on premature infants born before 28 weeks of gestation.[24,28] A recent randomized controlled trial using lullaby music via headphones at a volume of 50 to 60 decibels reported no significant differences in mean values of the respiratory and heart rates, oxygen saturation, and behavioral states of premature infants.[32] This study did not find beneficial effects of music on premature infants with gestational age ranging from 28 to 37 weeks.[32] Previous studies showed a lack of commonly applied definitions for the outcome variables of interest.[28,32]

The possible mechanism implicated in the effects of a relaxing music intervention is its influence on the relative dominance of the autonomous nervous system on the heart rate. During stress-related states, the sympathetic–parasympathetic balance is altered as a consequence of a higher dominance of the sympathetic nervous system on the heart rate with a subsequent parasympathetic withdrawal.[33] Besides, the sympathetic–parasympathetic balance and the reflex that interrelates the respiratory and heart rates are altered in premature infants.[34]

In the present double-blind, randomized, controlled trial, we aimed to clarify the effects of a relaxing music therapy intervention, known to diminish stress responses in adults,[35] on the respiratory rate (breathings per minute), oxygen saturation (percentage of oxygen in the bloodstream), systolic (during the contraction of the heart) and diastolic (between contractions of the heart) blood pressure (compression blood makes against its walls), and heart rate (beats per minute) of premature infants hospitalized in an NICU. Terms and definitions are presented in Table 1. We studied both their immediate physiological responses in the particular sessions and the accumulative effect of the relaxing music therapy intervention during the 8 sessions while the premature infants were in the NICU. We hypothesized to find changes in the respiratory and heart rates but not oxygen saturation or blood pressure.

What This Study Adds

- A relaxing music tune developed by artificial intelligence has potential to stabilize the respiratory and heart rates among NICU premature infants lying in incubators.
- This is the first double-blind, randomized, controlled trial conducted on premature infants using a relaxing music tune composed with no human intervention.

METHODS

Design

A double-blind, randomized, controlled trial was conducted to evaluate a relaxing music therapy intervention on premature infants hospitalized in the NICU. Participants were randomly allocated to the study groups. The independent variable or intervention, *exposure to the relaxing music therapy*, was used as the between-subjects factor, with 2 levels: (1) exposure to music, and (2) silence, considered as the control condition. Participants assigned to the

TABLE 1. Table of Terms[a]

Terms	Definition
Heart rate	The number of times a heart beats per minute
Respiratory rate	The number of breaths per minute
Oxygen saturation	The amount (percentage) of oxygen transported by red blood cells in the bloodstream
Blood pressure	The amount of pressure the blood makes against the arteries
Systolic blood pressure	The amount of pressure the blood makes against the arteries after a heart contraction
Diastolic blood pressure	The amount of pressure the blood makes against the arteries before a heart contraction

[a]*Definitions of terms were obtained from the Kingston Health Sciences Centre glossary of terms—Pediatric Care, and reprinted with permission.[36]*

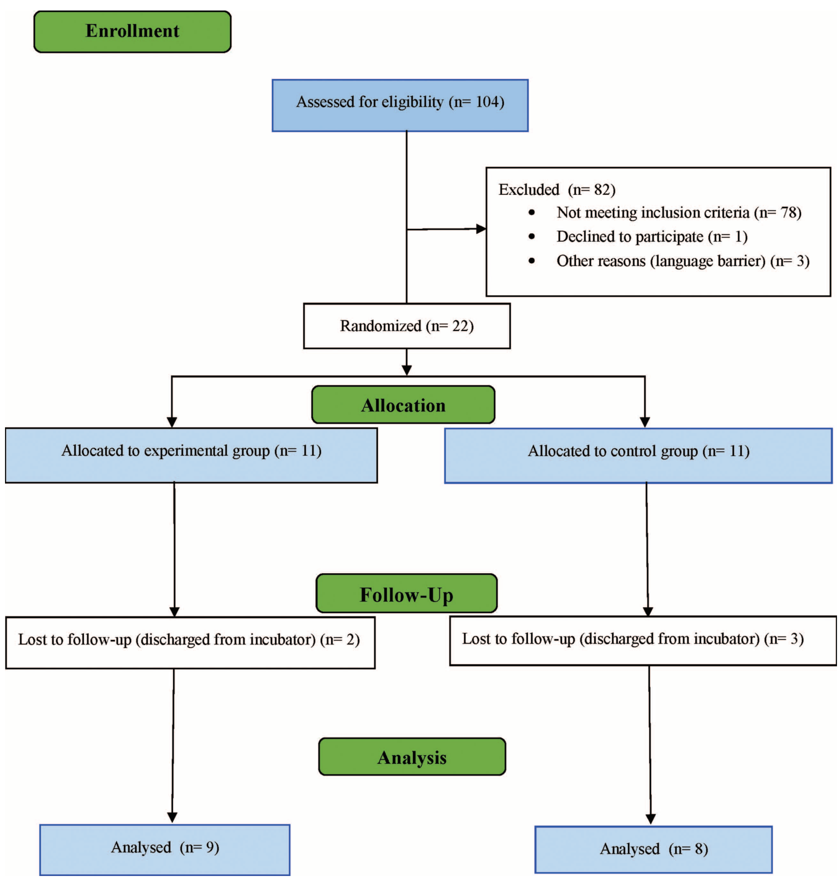
experimental condition (exposure to music) were exposed to 20 minutes of relaxing music, 3 times a day for 3 consecutive days. Participants assigned to the control condition (silence) were exposed to the same protocol but using a 20-minute track of silence. Silence was defined as the absence of any sound and noise within the played track. In addition, the current study included repeated measures to observe the effects of a relaxing music intervention on physiological parameters across the whole intervention, not just pre-/posttest values. This is important in the context of our theoretical underpinnings due to repeated-measures studies that reflect more efficiently the effects of music therapy interventions on physiological parameters.[12,14,20] The CONSORT flow diagram[37] is presented in the Figure 1.

Study Setting

Participants were recruited while in the NICU of 2 general public hospitals in Andalusia, Spain (Figure 1). The inclusion criteria were premature infants who had a satisfactory hearing screening test through a brain stem auditory evoked potentials test[38] and were in the incubator while in the NICU. Premature infants were excluded if they were being treated with sedative, analgesia medications, caffeine, or steroids; if they were supported by ventilation, continuous positive airway pressure, or nasal cannula; if they had any auditory impairment, malformation, or disease; if they were exposed to any potentially central nervous system depressor prenatally; or if they were diagnosed with a heart, lung, or congenital disease. Premature infants received standard medical care in the NICU.

The study protocol was approved by the institutional review board of the University of Granada. The Research Ethics Committees of the hospitals also approved the study protocol. We obtained written informed consent from all the participants' parents (mother or father, indistinctly) prior to the start

FIGURE 1



CONSORT flow diagram of participants. Infants were randomized into 2 groups. In the experimental group, infants were exposed to a relaxing music therapy intervention 3 times per day during consecutive days; in the control group, infants were exposed to the same protocol but using a silence track instead of music.

of the study. The experimental protocol was implemented between February 2014 and May 2015 in accordance with the guidelines for music therapy interventions, selection, and acoustic exposure for premature infants in the NICU.[39,40] All data were collected without interfering with the healthcare provider routine.

Sample Size and Randomization

Sample size calculations (carried out by G*Power 3.1.3)[41] were conducted to visualize interaction effects considering a between-groups variable with 2 levels and a within-subjects variable with 8 levels.

Participants meeting selection criteria were assigned a numerical code that linked them to a randomization sequence (Figure 1). These codes were matched to an experimental condition randomly at a 1:1 ratio by means of an Excel RAND function (Microsoft Excel, 2010). To ensure allocation concealment, a third researcher was responsible for this task. This researcher stored the experimental music tracks on a secure digital card, depending on this randomized matching. According to this, when the participant's code was matched to the experimental condition, the Melomics relaxing music track was recorded; otherwise, the track consisted of silence.

Twenty-two premature infants were recruited and randomized to either the experimental group (n = 11) or the control group (n = 11). Five participants were discharged from the incubator before finishing the intervention. These participants were excluded from the data analysis, as major protocol violations happened (they received only the adaptation session of the intervention). Therefore, results from 17 infants with gestational age at the time of delivery ranging from 32 to 36 weeks (M = 32.33; SD = 1.79) were analyzed. According to an updated meta-analysis,[28] we estimated that a sample size of 8 subjects was needed to obtain a good effect size of the relaxing music therapy intervention ($f = 0.41$; $\alpha = .05$, $1 - \beta = .80$), assuming a correlation between the levels of the within-subjects variable = 0.50.

Measures

Single values of an infant's heart rate, respiratory rate, oxygen saturation, and blood pressure were measured using the Nihon Kohde Vismo PVM-2703 patient monitor (Nihon Kahde Inc, Tokyo, Japan). Given these values are always changing, the interventionist (the person who applied the experimental protocol) recorded the value that appeared on the patient monitor at each measurement time point during the intervention. It was previously reported that change scores account for the effects of the intervention, independently of the basal state or pretest differences.[42] The respiratory and heart rates were obtained through 3 electrodes applied in a triangular pattern on the infant's chest according to the specifications of the manufacturer. Noninvasive blood pressure was obtained through a blood pressure cuff on the infant's legs. Blood pressure data were collected before each session and afterward at 0 and 20 minutes of the intervention/silence. Oxygen saturation data were obtained through a sensor attached to the infant's feet.

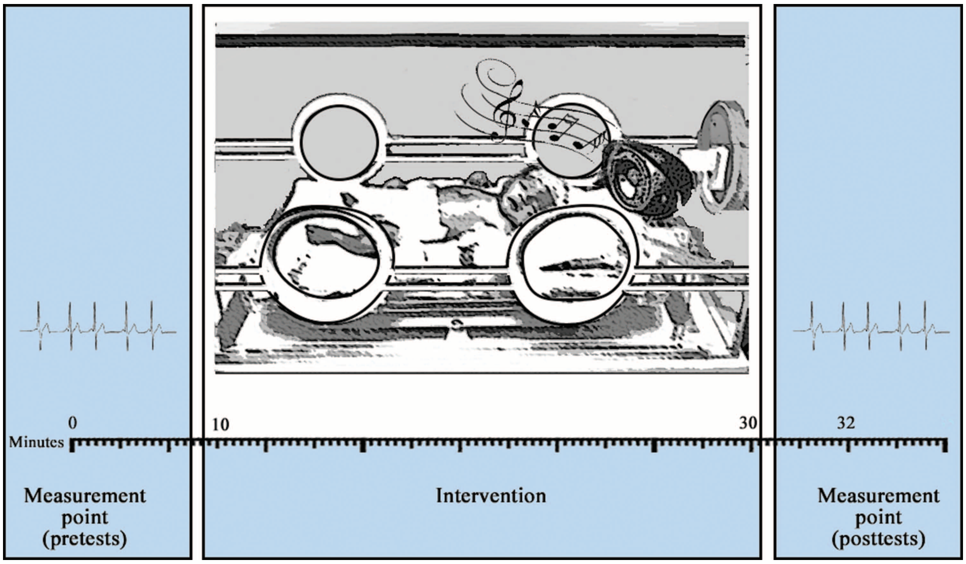
Procedure

The relaxing music therapy intervention consisted of a relaxing tune composed and synthesized by Melomics computer system with no human intervention and following the recommendations of 10 expert musicians.[43,44] It also followed the scientific recommendations for creating relaxing music[45-48]: slow tempo (up to 52-54 beats per minute), string and wind instruments, highly predictable melody, low tone, lack of dissonances, and at a volume below 50 decibels. Moreover, a group of expert musicians and a small segment of the general population endorsed this tune as relaxing.[49] The tune has been previously applied successfully in a randomized controlled trial with laboratory-induced stress protocol on healthy undergraduates.[13] The audio file can be found on http://j.mp/melomics-prematures. Its score is displayed on https://goo.gl/AhcWY9. Both music alone or music combined with human voice are beneficial for premature infants.[28] A music track was used in this protocol because of its previously reported beneficial effects on infants and adults.[13,43]

The study protocol consisted of 8 sessions across 3 consecutive days (in the morning between 9 AM and 10 AM, in the afternoon between 2 PM and 3 PM, and in the evening between 9 PM and 10 PM). These times were chosen to avoid interfering with typical healthcare routines in these NICUs. The first session was considered an adaptation session to music devices and was not included in the analyses. Intervention sessions were carried out separate from any caregiving interactions such as routine assessments or infant feeding time. Parents and relatives were not present at the bedside during the intervention but were not asked to be present or avoid visiting during the time of the intervention. To standardize the protocol among participants, the overall NICU sensory environment during the intervention was free of tactile, gustative, and multimodal stimulation. The number of stressful procedures the infant had been exposed to during those 3 days was not considered.

The experimental sessions took place in the incubators (Giraffe Incubator Carestation, GE Healthcare) and lasted 32 minutes each. This length of time was selected according to international guidelines for use of music with premature infants.[20] The session was divided up by an initial 10-minute baseline period (presession measurement), followed by a 20-minute music/silence period. Finally, there was a 2-minute postsession measurement (Figure 2).

FIGURE 2



Visual summary of each session of music intervention. Ten minutes before the experimental condition was implemented, the baseline measurement was taken and then the experimental condition was implemented for 20 minutes. Finally, the posttest measures were taken 2 minutes after the intervention delivery.

Before, during, and after the intervention, the general sound level in the overall environment was controlled using a multifunctional environmental controller PCE-222 (PCE Iberica SL, 2013) and was always below 70 decibels.[8,20]

The interventionist began with wiping the speaker surface with an antimicrobial skin cleanser (HibiScrub) containing 4% chlorhexidine gluconate to avoid a potential transmission of pathogenic microorganisms.[50] The interventionist played the tape and recorded the measures. The baseline physiological parameters were obtained 10 minutes before starting the music/silence session (presession measurement). After this time, according to previous recommendations for conducting a randomized controlled trial on the use of music therapy in premature infants, the interventionist placed the speaker in the incubator 20 cm from the infant's left ear and then turned it on.[26,28] The music was set to 30 decibels. Because of its low volume, it could not be heard outside the incubator. Therefore, the interventionist was unaware of whether a particular infant had been assigned to the experimental group or the control group. This procedure ensured the blinding of the researchers. A nurse with earphones verified that the track was either music or silence and gave confirmation to the interventionist that the equipment was operating correctly before placing the speaker in the incubator. The nurse verified that silence was the appropriate intervention and not just a music recording that was not playing by controlling the track counter of the speaker. Two minutes after the music/silence session had finished, the physiological measures were obtained again (postsession measurement). The 2-minute postsession measurement was timed to avoid overstimulation of premature infants.[12] Afterward, the interventionist opened the incubator, turned off the speaker, took it out, and closed the incubator.

A neonatal nurse evaluated infant's potential distress symptoms during the intervention. The participation of the premature infants in this study would have been discontinued if they had shown distress symptoms such as startles, tremor, irregular respiration, flushing of skin, flayed fingers or hand in stop position, gagging, spitting up, grunting, or hiccupping.[28] No distress symptoms were noted among any of the infants. All premature infants were awake during the intervention.

Data Analysis

To ensure the homogeneity between study groups, anthropometric variables related to newborns and birth delivery were explored. Thus, the presence of significant differences between groups was studied using t tests for independent samples when scalar variables were considered and χ^2-based independency tests for categorical variables.

The fixed-effects variable (or independent variable by itself) was the relaxing music intervention, with 2 levels: exposure to Melomics music or exposure to silence. The random-effects variables (the covariates) were the posttest outcomes from the first (adaptation) session for each dependent variable.

Short-term effects of the music intervention were evaluated within each intervention session using an independent analysis of covariance (ANCOVA) separately for each dependent variable (mean heart rate, respiratory rate, oxygen saturation, and systolic and diastolic blood pressure). Thus, a model with a between-groups variable (exposure to the relaxing music therapy intervention) and a within-subjects variable (intervention session) with 8 levels (from second to ninth sessions) was tested. The dependent variable was conceptualized as the change score in each session. We opted for using change scores to control for potential accumulative effects of the intervention. Measurements of the changes were taken from subtracting the posttest values observed in that dependent variable minus the pretest ones. The postsession physiological values from the adaptation session were added as covariates to deal with the reactivity due to the experimental protocol.

We conducted another series of ANCOVAs for each dependent variable to evaluate the long-term effects of the intervention; that is, the accumulative effects of the intervention. Each model included a between-groups factor (exposure to the relaxing music therapy intervention) and an 8-level within-subjects factor (intervention pretest values). In the case of the within-subjects factor, we used the pretest values of each session to evaluate the influence of the intervention on physiological variables before each subsequent session was delivered. Likewise, we used pretest values from the adaptation session as covariates. Ambient noise levels captured by the multifunctional environmental controller PCE-222 decibel levels during the intervention were controlled for in analysis.

Post hoc tests based on the Bonferroni adjustment were used. The Greenhouse-Geisser correction was applied when the violation of sphericity was detected. Effect size estimates were reported by means of $\eta^2_{partial}$.[26,51]

RESULTS

Table 2 shows demographic characteristics of the participants by study group. There were no significant differences between groups. Participants' primary medical diagnoses were prematurity at birth. All infants were enrolled in the intervention at less than a week of life and were generally healthy, given the exclusion criteria.

Although the ambient noise experienced by the experimental group using the multifunctional environmental controller PCE-222 during the intervention was higher (M = 37.28 decibels; SD = 1.09) than the control group (M = 36.25 decibels; SD = 1.34), no significant differences were found between groups (t = 1.75, P = .78).

We found that change measures were significantly reduced for respiratory rate ($F_{1,13}$= 6.73, P = .022, $\eta^2_{partial}$= 0.34) for infants who experienced the relaxing music therapy intervention. Moreover, those reductions became lower in session 7 of the intervention (P = .041) (Figure 3). No other main, or interaction, effects were observed (all P values >.05). The direct values obtained at every assessment point for every dependent variable are displayed in Table 3.

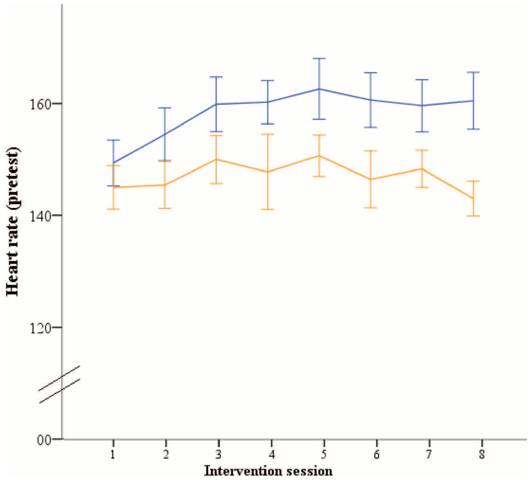
TABLE 2. Infant Demographics by the Intervention Group[a]

	Control Group	Experimental Group	Contrast Test	*P*
No. participants	8	9		
Sex, % males (n)	69.23 (5)	56.25 (5)	χ^2 = 0.51	.47
Weeks of gestation[b]	33.04 (1.74)	32.96 (1.84)	t = 0.11	.91
Corrected age, wk	34.75 (1.98)	33.77 (1.56)	t = 1.13	.27
Days of life	5.87 (1.64)	3.55 (1.81)	t = −0.62	.54
Birth weight, g	1719.92 (434.39)	1615 (329.28)	t = 0.74	.47
Apgar test score (5 min)	7.85 (1.95)	7.10 (2.22)	t = 0.98	.34
Birth delivery, % (n)			χ^2= 3.78	.15
Vaginal (without instrument assistance)	30.77 (3)	6.25 (1)	χ^2 = 3.22	.08
Vaginal (with instrument assistance)	30.77 (3)	25 (2)	χ^2 = 0.12	.73
Cesarean	38.46 (2)	68.75 (6)	χ^2 = 2.66	.10

[a]*The values for scalar variables are displayed as means (standard deviations), with t tests as contrast tests; the percentage of cases are displayed for dichotomic or categorical variables, with χ^2 tests as contrast tests.*

[b]*Weeks of gestation at the time of delivery.*

FIGURE 3



Heart rate taken in the pretest assessment across the intervention sessions. Values for the heart rate are displayed as the mean. The orange line depicts the trajectory of the heart rate for the experimental group. The blue line depicts the trajectory of the heart rate for the control group. Error bars depict the standard error of the mean.

Regarding the cumulative effects, infants in the control group had significantly higher heart rates ($F_{1,11}= 5.09$, $P = .045$, $\eta^2_{partial}= 0.32$) than infants exposed to the relaxing music therapy intervention (Figure 4). We also found a significant main within-subjects effect for the respiratory rate ($F_{7,91}= 3.34$, $P < .001$, $\eta^2_{partial}= 0.20$) and an interaction effect between respiratory rate and the pretest values from the adaptation session (used as a covariate) ($F_{7,91}= 3.58$, $P < .001$, $\eta^2_{partial}= 0.22$). Figure 5 shows the association between the adaptation session respiratory levels and session 1 pretest levels. The pattern of association is depicted by the regression line. These results suggest that the respiratory rate tended to slow down over sessions but showed a peak rise during the eighth session. No main, or interaction, effects were observed on oxygen saturation or blood pressure (all P values $>.05$).

DISCUSSION

A double-blinded, randomized, controlled trial was conducted to evaluate the effects of a relaxing music therapy intervention on heart rate, respiratory rate, oxygen saturation, and blood pressure of a group of healthy hospitalized premature infants. The change of slowing down in heart rate and lowering in the respiratory rate during music interventions among premature infants in the NICU falls within published literature.[31,52,53] This change is hypothesized to be due to a potential protective effect of music against NICU noise, as well as a summative effect on heart rate variability. Similarly to other research with premature infants, no significant differences were found in blood pressure.[14,28] Unlike previous research,[54,55] we found no changes in oxygen saturation. Other studies did show stabilization in oxygen saturation as a consequence of implementing music-based interventions. However, they did not use relaxing music alone or used lullabies as music stimuli in low birth-weight infants of 24 to 30 weeks of gestation age.[54,55] Our study offers support for the beneficial effects of a music therapy intervention on premature infants using a relaxing tune developed with no human intervention,[13,44] without any harmful effects.

A variety of studies have pointed out several good outcomes of music interventions in premature infants,[28] including lowering heart rate,[56] lowering respiratory rate,[30] lowering blood pressure,[31] and stabilizing oxygen saturation.[57] The potential mechanism involved in their effects could be that relaxing music may act on the relative dominance of the autonomous nervous system on the heart rate. Overall, the basal state of the heart involves a higher dominance of the parasympathetic branch of autonomous system on heart beating. Several physiological states characterized by an altered sympathetic–parasympathetic balance (for instance, stress-related states) are derived from a higher dominance of the sympathetic nervous system on the heart rate with a subsequent parasympathetic withdrawal, reflected, for instance, by higher levels of heart rate and lower sinus arrhythmia respiratory reflex indexes.[58] This unbalance is also shown when the respiratory rate is altered, such as in hyperventilation.[33] It has been reported that the sympathetic–parasympathetic balance is altered in premature infants, as well as the reflex that interrelates cardiac rate and breathing.[59]

We propose that relaxing music by means of emotion contagion mechanisms[60] leads to a more balanced sympathetic–parasympathetic regulation of the heart rate probably due to a reduction of parasympathetic withdrawal, a physiological shift toward becoming relaxed—which promotes a slower respiratory rate. In turn, the stabilization of the respiratory rate influences the cardiac regulation, resulting in a lower heart rate. On the contrary, no effects were shown to be of significance on the other dependent variables analyzed (oxygen saturation, systolic and diastolic blood pressure). These results may support the idea that relaxing music could promote a slower withdrawal of the parasympathetic nervous system on the heart rate, taking into account the sympathetic control of blood pressure.[61] Thus, relaxing music can improve physiological cardiac and respiratory variables in premature infants through the promotion of a healthier regulation of the autonomous nervous system on the heart.

TABLE 3. Physiological Parameters Across the Intervention Sessions Displayed by Study Groups[a]

	No. Participants	Intervention Session 1 Pretest	1 Posttest	2 Pretest	2 Posttest	3 Pretest	3 Posttest	4 Pretest	4 Posttest
HR									
CG	8	150.42 (12.11)	147.25 (13.85)	156.57 (14.83)	151.17 (16.78)	159.57 (17.19)	155.45 (17.12)	160.29 (11.88)	156.90 (9.96)
EG	9	142 (11.16)	139.67 (15.01)	141 (9.81)	138.54 (17.48)	145 (7.37)	141.27 (19.57)	144.14 (8.93)	139.50 (14.80)
SBP									
CG	8	64.83 (7.65)	67.75 (7.82)	68.17 (8.59)	64.17 (6.71)	67.25 (9.63)	68.82 (10.41)	70.90 (8.61)	64.20 (3.97)
EG	9	68.13 (11.72)	63.60 (12.22)	62.92 (13.86)	59.25 (10.65)	64.33 (12.51)	65.33 (10.22)	62.79 (10.41)	61.07 (8.78)
DBP									
CG	8	37.00 (8.80)	43.58 (10.40)	38.17 (5.73)	38.92 (5.16)	40.25 (7.45)	40.36 (8.39)	39.00 (8.99)	35.90 (6.35)
EG	9	38.33 (8.58)	35.20 (4.07)	37.31 (12.03)	34.75 (8.32)	39.20 (7.78)	35.07 (5.62)	36.43 (6.79)	36.00 (4.67)
RR									
CG	8	50.17 (10.62)	60.33 (21.58)	50.17 (17.80)	48.92 (18.63)	52.58 (9.67)	56.45 (15.76)	47.90 (14.51)	46.10 (11.95)
EG	9	45.73 (12.39)	42.87 (17.22)	50.23 (15.24)	46.15 (13.86)	46.40 (11.29)	46.43 (10.59)	48.36 (9.32)	43.36 (11.08)
OS									
CG	8	97.40 (2.07)	96.70 (2.50)	96.40 (3.78)	96.50 (2.99)	98.10 (1.91)	97.89 (1.54)	96.80 (1.99)	96.20 (2.04)
EG	9	92.71 (1.75)	96.71 (1.90)	93.46 (13.19)	95.85 (2.44)	91.93 (17.36)	96.86 (2.14)	96.14 (2.54)	96.86 (1.61)
		5 Pretest	**5 Posttest**	**6 Pretest**	**6 Posttest**	**7 Pretest**	**7 Posttest**	**8 Pretest**	**8 Posttest**
HR									
CG	8	165.71 (13.72)	154.70 (15.51)	163.14 (12.72)	153.18 (11.98)	163.43 (8.32)	150.30 (18.27)	163.43 (12.61)	159.50 (12.64)
EG	9	148 (11.15)	140.29 (12.12)	145.43 (15.82)	145.73 (16.90)	146.86 (10.85)	141.00 (15.70)	140.57 (6.48)	140.07 (13.99)
SBP									
CG	8	65.00 (9.40)	63.60 (11.72)	66.82 (8.20)	61.73 (5.71)	69.40 (11.83)	65.50 (6.96)	61.38 (10.70)	62.25 (5.06)
EG	9	64.21 (9.44)	68.79 (11.44)	64.18 (9.35)	63.45 (8.82)	66.55 (14.97)	61.45 (7.38)	65.50 (8.85)	63.29 (11.44)
DBP									
CG	8	35.55 (6.74)	35.56 (8.26)	33.73 (3.85)	34.91 (6.11)	37.90 (8.62)	34.40 (7.82)	33.13 (7.70)	36.13 (6.96)
EG	9	35.14 (6.33)	37.86 (10.84)	33.27 (4.22)	34.82 (8.75)	38.18 (7.45)	36.27 (10.93)	34.93 (6.93)	33.50 (5.68)

(*continues*)

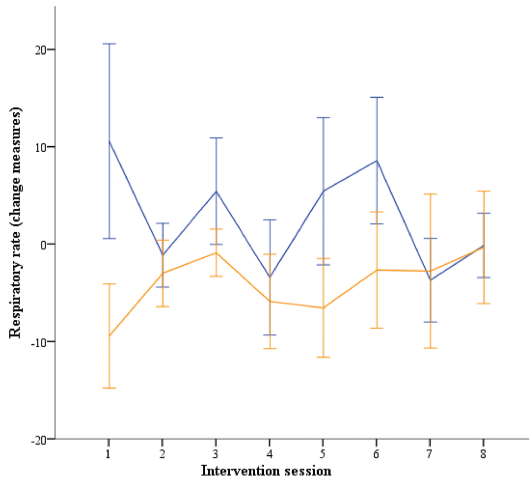
TABLE 3. Physiological Parameters Across the Intervention Sessions Displayed by Study Groups[a], Continued

	No. Participants	Intervention Session							
		5		6		7		8	
		Pretest	Posttest	Pretest	Posttest	Pretest	Posttest	Pretest	Posttest
RR									
CG	8	47.36 (15.95)	54.30 (13.28)	44.09 (10.78)	56.00 (20.01)	52.60 (14.25)	49.50 (16.03)	52.50 (13.30)	49.00 (19.00)
EG	9	46.43 (10.14)	40.43 (10.94)	46.45 (13.36)	42.82 (9.46)	46.70 (6.33)	48.36 (15.23)	44.57 (8.11)	44.64 (12.80)
OS									
CG	8	95.80 (2.97)	96.67 (3.16)	96.20 (1.62)	95.80 (3.08)	96.90 (1.97)	96.80 (2.49)	94.63 (4.72)	95.25 (3.65)
EG	9	96.29 (3.34)	96.71 (2.23)	96.64 (2.69)	96.00 (2.65)	95.80 (2.25)	95.50 (2.01)	96.31 (1.93)	95.54 (3.02)

Abbreviations: CG, control group, exposed to silence; DBP, diastolic blood pressure (in mm Hg), pressure in artery walls between beats; EG, experimental group, exposed to the relaxing music therapy intervention; HR, heart rate (in bpm), the number of heartbeats per minute; OS, oxygen saturation, fraction of oxygen-saturated hemoglobin in the blood (in percentage); RR, respiratory rate (in breaths per minute), the number of inspirations and expirations per unit time; SBP, systolic blood pressure (in mm Hg), pressure in artery walls when the heart beats.

[a]*The values are displayed as means (standard deviations).*

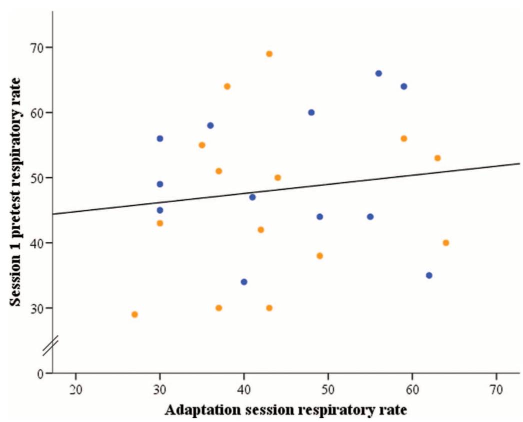
FIGURE 4



Respiratory rate change measures across the intervention sessions. Values for respiratory rate are displayed as the average of change measures. Change measures were conceptualized as the subtraction between posttest scores minus the pretest ones. The orange line depicts the trajectory of change measures for experimental group. The blue line depicts the trajectory of change measures for control group. Error bars depict the standard error of the mean.

Due to the fact that premature infants from both groups had the same standard care, and infants in the relaxing music exposure group received the music-based intervention, we have confidence that changes in the pretest levels from the second session of exposure are due to the effect of the intervention.

FIGURE 5



Association between the adaptation session respiratory rate and session 1 pretest respiratory rate. Each dot represents the respiratory rate of each baby. The regression line depicts the association between measures ($r = 0.36$, $P = .086$). The orange dots depict the intervention group respiratory rates. The blue dots depict the control group respiratory rates.

These effects often result in physiological, maturational, and overall improvements in premature infants' well-being while in an NICU.[62,63]

Our results come from a rigorous randomized control trial designed with robust supervision in two NICU settings. Moreover, the incubators where the intervention was carried out re-created a context as highly controlled as the one in a laboratory setting. The data captured with the multifunctional environmental controller PCE-222 during the experimental session substantiate that the noise environment was controlled for.

A limitation of this study was its small sample size to account for possible confounding influences; however, the assumptions required for conducting the appropriate data analyses were satisfied.[41] To control the potential influence of blood pressure measurements on stress levels and therefore the physiological parameters, heart rate, respiratory rate, and oxygen saturation were measured before inflating the blood pressure cuff. Moreover, our study did not conduct analysis of electrocardiographic frequency bands or nonlinear measures that allowed for distinguishing the relative influences of the autonomous nervous system on the heart rate. We did not collect information on the severity of illness scores. Assessing the severity of illness scores would have provided the specific benefits of music on concrete subgroups of premature infants. Future studies would benefit by using validated assessment tools such as the Score for Neonatal Acute Physiology with Perinatal Extension-II (SNAPPE-II).[64] Some premature infants may have a delayed or recycled response to noises. Controlling whether the premature infants have a delayed or recycled response to auditory stimulation would improve prospective studies by evaluating the impact of a music therapy protocol on a range of premature infants. Future studies would benefit from controlling the presence of a delayed response to auditory stimulation on statistical analysis. Although noise levels were always below 70 decibels before, during, and after the intervention, the exact light and sound/noise levels during each intervention/control session were not recorded. Participants discharged from the incubator before finishing the intervention were excluded from data analysis, and intention-to-treat analyses were impossible to perform. Finally, because of the stressful events premature infants are exposed to while in the NICU, future studies should explore the effects of interventions based on relaxing music on other physiological systems such as the endocrine system and integrating measures such as salivary cortisol.

In conclusion, using relaxing music therapeutically appears to improve physiological parameters in premature infants during their hospitalization[20,21,29] with no observed negative effects. Our findings are encouraging, and neonatal nurses should feel relatively secure in the use of music therapy interventions with generally healthy premature infants between 32 and 36 weeks of gestational age in an NICU.[20,52,65] Although more research is needed, music therapy can be a helpful intervention for premature infants.[52]

Implications for Research

Our results suggest that the physiological mechanism of relaxing music underpins regulatory changes on heartbeat. However, some gaps arise in terms of concrete aspects of this mechanism. In this regard, future research should study the timing by which music influences on heartbeat regulation (eg, the time frame when the sympathetic–parasympathetic balance on heartbeat changes within a music exposition session or whether changes in physiological parameters remain over time). Future studies should explore the benefits reported in this randomized

Summary of Recommendations	
What we know	• Prematurity has been associated with negative outcomes resulting in respiratory disorders and cardiovascular instability. • Premature infants, while staying for long periods in an NICU after birth, are exposed to chronic and often noxious sounds. • Therapeutic interventions for premature infants, including music, have increased during the last decade.
What needs to be studied	• Effective and low-cost interventions that will promote health development in premature infants. • Additional studies applying a wide range of research designs including randomized controlled trials on the use of music in premature infants. • Comparison of a range of relaxing music tunes on the benefits in premature infants.
What we can do today	• Reduce environmental noise in the NICU. • Nurses can apply relaxing music to premature infants according to protocols. • Premature infants' physiological parameters can be improved through listening to relaxing music while in the NICU.

controlled trial using a relaxing music tune composed by artificial intelligence in a larger, more diverse population of high-risk infants across different nursery settings. Although a previous study reported the benefits of listening to this relaxing music tune to recover after stress exposure,[13] assessing its advantages on various health environments could promote major benefits. Future research should investigate long-term effects after exposure to this relaxing music tune using biological and behavioral measures.

Implications for Practice

This study provides additional evidence that premature infants may benefit from relaxing music tune without negative impacts while in an NICU. According to this study, it is safe for nurses to use this relaxing tune with premature infants between 32 and 36 weeks of gestational age in the NICU. Intubated infants were not included in our study. Therefore, our study does not support the use of this relaxing music tune with this population.

References

1. Zegers-Hochschild F, Adamson GD, de Mouzon J, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. *Fertil Steril*. 2009;92(5):1520-1524.
2. Delnord M, Blondel B, Zeitlin J. What contributes to disparities in the preterm birth rate in European countries? *Curr Opin Obstet Gynecol*. 2015;27(2):133-142.
3. Katz M. Preventing preterm birth. *J Perinat Med*. 2016;44(5):483-484.
4. Axelrod DM, Chock VY, Reddy VM. Management of the preterm infant with congenital heart disease. *Clin Perinatol*. 2016;43(1):157-171.
5. Moss TJM. Respiratory consequences of preterm birth. *Clin Exp Pharmacol Physiol*. 2006;33(3):280-284.
6. Gilbert W. The cost of prematurity: quantification by gestational age and birth weight. *Obstet Gynecol*. 2003;102(3):488-492.
7. Smith GC, Gutovich J, Smyser C, et al. Neonatal intensive care unit stress is associated with brain development in preterm infants. *Ann Neurol*. 2011;70(4):541-549.
8. Wachman EM, Lahav A. The effects of noise on preterm infants in the NICU. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(4):305-309.
9. Williams AL, Sanderson M, Lai D, Selwyn BJ, Lasky RE. Intensive care noise and mean arterial blood pressure in extremely low-birth-weight neonates. *Am J Perinatol*. 2009;26(5):323-329.
10. Zahr LK, Balian S. Responses of premature infants to routine nursing interventions and noise in the NICU. *Nurs Res*. 1995;44(3):179-185.
11. Keith DR, Russell K, Weaver BS. The effects of music listening on inconsolable crying in premature infants. *J Music Ther*. 2009;46(3):191-203.
12. Standley JM. Music therapy for premature infants in the neonatal intensive care unit: health and development benefits. In: Robb S, ed. *Music Therapy in Pediatric Healthcare: Research and Evidence-Based Practice*. Silver Spring, MD: American Music Therapy Association; 2003:19-30.
13. De la Torre-Luque A, Caparros-Gonzalez RA, Bastard T, Vico FJ, Buela-Casal G. Acute stress recovery through listening to Melomics relaxing music: a randomized controlled trial. *Nord J Music Ther*. 2017;26(2):124-141.
14. Haslbeck F. Music therapy for premature infants and their parents: an integrative review. *Nord J Music Ther*. 2012;21(3):203-226.
15. Iwanawa M, Tsukamoto M. Effects of excitative and sedative music on subjective and physiological relaxation. *Percept Motor Skills*. 1997;85(1):287-296.
16. Lai HL, Good M. An overview of music therapy. *J Nurs*. 2002;49(2):80-84.
17. Kisilevsky BS, Hains SM, Jacquet AY, Granier-Deferre C, Lecanuet JP. Maturation of fetal responses to music. *Dev Sci*. 2004;7(5):550-559.
18. Lasky RE, Williams AL. The development of the auditory system from conception to term. *NeoReviews*. 2005;6(3):141-152.
19. Standley JM. Pre and perinatal growth and development: implications of music benefits for premature infants. *Int J Music Educ*. 1998;31(1):1-13.
20. Standley JM. A meta-analysis of the efficacy of music therapy for premature infants. *J Pediatr Nurs*. 2002;17(2):107-113.
21. Palazzi A, Nunes CC, Piccinini CA. Music therapy and music stimulation in prematurity: a literature review from 2010 to 2014. *Nord J Music Ther*. 2016;25(1):144.
22. Dearn T, Shoemark H. The effect of maternal presence on premature infant response to recorded music. *J Obstet Gynecol Neonatal Nurs*. 2014;43(3):341-350.
23. van der Heijden MJE, Oliai Araghi S, Jeekel J, Reiss IKM, Hunink MGM, van Dijk M. Do hospitalized premature infants benefit from music interventions? A systematic review of randomized controlled trials. *PLoS One*. 2016;11(9):e0161848.
24. Gooding LF. Using music therapy protocols in the treatment of premature infants: an introduction to current practices. *Arts Psychother*. 2010;37(3):211-214.
25. Haslbeck F. Creative music therapy with premature infants: testing a possible influence on brain structure, function and development. *Nord J Music Ther*. 2016;25(1):32-32.
26. Wirth L, Dorn F, Wege M, et al. Effects of standardized acoustic stimulation in premature infants: a randomized controlled trial. *J Perinatol*. 2016;36:486-492.
27. Loewy J, Stewart K, Dassler AM, Telsey A, Homel P. The effects of music therapy on vital signs, feeding, and sleep in premature infants. *Pediatrics*. 2013;131(5):902-918.
28. Standley JM. Music therapy research in the NICU: an updated meta-analysis. *Neonatal Netw*. 2012;31(5):311-316.
29. Tramo MJ, Lense M, Van Ness C, Kagan J, Settle MD, Cronin JH. Effects of music on physiological and behavioral indices of acute pain and stress in premature infants: clinical trial and literature review. *Music Med*. 2011;3(2):72-83.
30. Arnon S, Shapsa A, Forman L, et al. Live music is beneficial to preterm infants in the neonatal intensive care unit environment. *Birth*. 2006;33(2):131-136.
31. Lorch CA, Lorch V, Diefendorf AO, Earl PW. Effect of stimulative and sedative music on systolic blood pressure, heart rate, and respiratory rate in premature infants. *J Music Ther*. 1994;31(2):105-118.
32. Alipour Z, Eskandari N, Ahmari Tehran H, Eshagh Hossaini SK, Sangi S. Effects of music on physiological and behavioral responses of premature infants: a randomized controlled trial. *Complement Ther Clin Pract*. 2013;19(3):128-132.
33. Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. *Front Psychol*. 2014;5:1040.
34. Guyenet PG. The sympathetic control of blood pressure. *Nat Rev Neurosci*. 2006;7(5):335-346.
35. De la Torre-Luque A, Diaz-Piedra C, Buela-Casal G. Effects of preferred music after acute stress exposure: a randomized controlled trial. *Psychol Music*. 2017. doi:10.1177/0305735617689953.
36. Kingston General Hospital. Kingston General Hospital glossary of terms—Pediatric Care http://www.kgh.on.ca/pediatric-care/glossary-terms-pediatric-care. Published January 2017. Accessed August 10, 2017.
37. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010;63(8):834-840.
38. Nuwer MR, Aminoff M, Goodin D, et al. IFCN recommended standards for brain-stem auditory evoked potentials. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol*. 1994;91(1):12-17.
39. American Academy of Pediatrics. Committee on Environmental Health. Noise: a hazard for the fetus and newborn. *Pediatrics*. 1997;100(4):724-727.
40. Standley JM. Music therapy for the neonate. *Newborn Infant Nurs Rev*. 2001;1(4):211-216.
41. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39(2):175-191.
42. Oakes JM, Feldman HA. Statistical power for nonequivalent pretest-posttest designs ñ The impact of change-score versus ANCOVA models. *Eval Rev*. 2001;25(1):3-28.
43. Requena G, Sánchez C, Corzo-Higueras JL, et al. Melomics music medicine (M3) to lessen pain perception during pediatric prick test procedure. *Pediatr Allergy Immunol*. 2014;25(7):721-724.
44. Sanchez-Quintana C, Moreno-Arcas F, Albarracin-Molina D, Fernandez-Rodriguez JD, Vico FJ. Melomics: a case-study of AI in Spain. *AI Magazine*. 2013;34(3):99-103.
45. Bradt J, Dileo C. Music for stress and anxiety reduction in coronary heart disease patients. *Cochrane Database Syst Rev*. 2013;12:CD006577.
46. Elliott D, Polman R, McGregor R. Relaxing music for anxiety control. *J Music Ther*. 2011;48(3):264-288.

47. Västfjäll D, Juslin PN, Hartig T. Music, subjective wellbeing, and health: the role of everyday emotions. In: MacDonald R, Kreutz G, Mitchell L, eds. *Music, Health and Wellbeing.* New York, NY: Oxford University Press; 2013:405-423.
48. Yamamoto M, Naga S, Shimizu J. Positive musical effects on two types of negative stressful conditions. *Psychol Music*. 2007;35(2): 249-275.
49. Benitez I, Hita-Yáñez E, De la Torre-Luque A, Del Rio-Bermúdez C, Díaz-Piedra C, Buela-Casal G. A methodological proposal to create music within a therapeutic context. Paper presented at: the 12th European Conference on Psychological Assessment; July 17-20, 2013; San Sebastian, Spain.
50. Hartz LE, Bradshaw W, Brandon DH. Potential NICU environmental influences on the neonate's microbiome: a systematic review. *Adv Neonatal Care*. 2015;15(5):324-335.
51. Fritz CO, Morris PE, Richler JJ. Effect size estimates: current use, calculations, and interpretation. *J Exp Psychol Gen*. 2012;141(1):2-18.
52. Allen KA. Music therapy in the NICU: is there evidence to support integration for procedural support? *Adv Neonatal Care*. 2013; 13(5):349-352.
53. Amini E, Rafiei P, Zarei K, Gohari M, Hamidi M. Effect of lullaby and classical music on physiologic stability of hospitalized preterm infants: a randomized trial. *J Neonatal Perinatal Med*. 2013;6(4):295-301.
54. Cassidy JW, Standley JM. The effect of music listening on physiological responses of premature infants in the NICU. *J Music Ther*. 1995;32(4):208-227.
55. Standley JM, Moore RS. Therapeutic effects of music and mother's voice on premature infants. *Pediatr Nurs*. 1995;21(6):509-512.
56. Coleman JM, Pratt RR, Stoddard RA, Gertsmann DR, Abel HH. The effects of the male and female singing and speaking voices on selected physiological and behavioral measures of premature infants in the intensive care unit. *Int J Arts Med*. 1997;5(2):4-11.
57. Chou L, Wang H, Chen S, Pai L. Effects of music therapy on oxygen saturation in premature infants receiving endotracheal suctioning. *J Nurs Res*. 2003;11(3):209-215.
58. Thayer JL, Lane RD. Claude Bernard and the heart–brain connection: further elaboration of a model of neurovisceral integration. *Neurosci Biobehav Rev*. 2009;33(2):81-88.
59. Yiallourou SR, Witcombe NB, Sands SA, Walker AM, Horne RS. The development of autonomic cardiovascular control is altered by preterm birth. *Early Hum Dev*. 2013;89(3):145-152.
60. Juslin PN, Västfjäll D. Emotional responses to music: the need to consider underlying mechanisms. *Behav Brain Sci*. 2008;31: 559-575.
61. Yehuda N. Music and stress. *J Adult Dev*. 2011;18(2):211-216.
62. Diego MA, Field T, Hernandez-Reif M. Vagal activity, gastric motility, and weight gain in massaged preterm neonates. *J Pediatr*. 2005; 147(1):50-55.
63. Knox SM, Lombaert IM, Haddox CL, et al. Parasympathetic stimulation improves epithelial organ regeneration. *Nat Commun*. 2013; 4:1494.
64. Chow V, Shellhaas R. Acoustic environment profile of neonatal intensive care unit: high ambient noise and limited language exposure. *J Neonatal Nurs*. 2016;22(4):159-162.
65. Macho P. Individualized developmental care in the NICU: a concept analysis. *Adv Neonatal Care*. 2017;17(3):162-174.