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Efferent inhibition of otoacoustic emissions in preterm neonates☆

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Premature infant;
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Abstract
Introduction: Abnormalities in auditory function of newborns may occur not only because of preterm birth, but also from the use of medications and from diseases related to prematurity.
Objective: To analyze the inhibitory effect from stimulation of the olivocochlear efferent system on transient evoked otoacoustic emissions in preterm neonates, comparing these data with those from full-term neonates.
Methods: This was a prospective, cross-sectional, contemporary cohort study with 125 neonates, pooled into two groups: full-term (72 full-term neonates, 36 females and 36 males, born at 37–41 weeks of gestational age); and preterm (53 neonates, 28 males and 25 females, born at ≤36 weeks of gestational age, evaluated at the corrected gestational age of 37–41 weeks). Otoacoustic emissions were recorded using linear and nonlinear click-evoked stimuli, with and without contralateral stimulation.
Results: The inhibitory effect of the efferent pathway in otoacoustic emissions was different ($p = 0.012$) between groups, and a mean reduction of 1.48 dB SPL in full-term births and of 1.02 dB SPL in preterm births was observed for the non-linear click-evoked stimulus.

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Conclusion: The results suggest a reduced inhibitory effect of the olivocochlear efferent system on otoacoustic emissions in preterm neonates.

PALAVRAS-CHAVE
Prematuro;
Audição;
Recém-nascido;
Emissões otoacústicas espontâneas;
Vias auditivas

Inibição eferente das emissões otoacústicas em neonatos prematuros

Resumo
Introdução: Alterações na função auditiva de recém-nascidos prematuros podem ocorrer não só devido ao nascimento antecipado, mas também pelo uso de medicamentos e por doenças relacionadas à prematuridade.
Objetivo: Analisar o efeito inibitório da estimulação do sistema eferente olivo coclear sobre a amplitude das emissões otoacústicas evocadas transientes em recém-nascidos prematuros, comparando esses dados aos de recém-nascidos a termo.
Método: Estudo prospectivo, de coorte contemporânea com corte transversal, com 125 recém-nascidos, distribuídos em dois grupos: a termo (72 recém-nascidos a termo, 36 feminino e 36 masculino, nascidos entre 37-41 semanas de idade gestacional), e pretermo (53 recém-nascidos, 28 masculino e 25 feminino, nascidos com idade gestacional $\leq$ 36 semanas avaliados entre 37-41 semanas de idade gestacional corrigida). As emissões otoacústicas foram registradas a partir de estímulos clique lineares e não lineares, com e sem estimulação contralateral.
Resultados: O efeito inibitório da via eferente nas otoemissões foi diferente (p = 0,012) entre os grupos, sendo observada uma redução média de 1,48dB SPL nos nascimentos a termo e 1,02dB SPL no grupo pretermo para o estímulo clique não-linear.
Conclusão: Os resultados sugerem efeito inibitório do sistema eferente olivococlear reduzido sobre as emissões otoacústicas em recém-nascidos prematuros.

Introduction

Preterm newborns are at risk of changes in auditory function[1] that occur in a manner inversely proportional to gestational age; hearing loss is observed in approximately 7% of infants with gestational age <33 weeks.[2]

The impaired auditory function may result not only from preterm birth, which arrests the process of natural development, but also from the use of certain medications and diseases related to prematurity. Therefore, studies seeking to find increasingly far-reaching processes to minimize hearing complications arising from prematurity and aiming a better quality of life through appropriate interventions are needed.

Hearing screening of newborns has been carried out through the analysis of otoacoustic emissions (OAE), a non-invasive, quick procedure that evaluates the function of outer hair cells of the cochlea. The presence of normal responses in an OAE test is a strong predictor of a full hearing function. The procedure of OAE suppression allows for a functional investigation of the efferent olivocochlear system, which plays an important role in auditory information processing. The function of the efferent system can be assessed by analyzing OAE when these are analyzed in the presence of a simultaneous ipsilateral, contralateral, or bilateral noise.[3,4] The determination of the contralateral inhibition of OAE, also known as the OAE suppression, is a non-invasive and objective method to evaluate the efferent olivocochlear system; the active, nonlinear, micromechanical properties of outer hair cells of the cochlea; and more generally, the integrity of the brainstem.[4,5] There are few studies evaluating the inhibitory effect of the efferent pathway on OAE in newborns.[6–13] In a recent study involving school-aged children (8–10 years old), OAE suppression was found less robustly in preterm *vs.* full-term children.[14] Therefore, the aim of this study was to evaluate the inhibitory effect of noise on transient evoked otoacoustic emissions (TEOAE) by linear or nonlinear click-evoked stimulation in preterm newborns.

Methods

Subjects

Newborns were evaluated at the Teaching Hospital of Universidade de São Paulo (USP). The sample size was determined by statistical analysis for a statistical power of 96% with a 0.05 significance level. The study was approved by the Institutional Ethics Committee (Protocol 122/00). Parents invited to participate in the study expressed their agreement after reading and signing the informed consent.

Study participants complied with the following inclusion criteria: presence of TEOAE in both ears, in a noise-free condition and in the ''QuickScreen'' mode with general reproducibility above 50% and, from necessity, with specific reproducibility in frequency bands $\geq$70% for 2, 3, and 4 kHz. For inclusion in this study, in addition to the reproducibility criterion, during the TEOAE evaluation the newborn needed to present a signal to noise ratio $\geq$6 dB at the frequency bands of 1.5, 2, 3, and 4 kHz, and a signal to noise ratio $\geq$3 dB at 1 kHz. Only TEOAE tests with probe stability $\geq$70% were considered. The noise adjustment control was positioned at its minimum value. The rejection level was adjusted up to 6 MPa or 49.5 dB SPL.

In order to maintain sample homogeneity, a balance in the proportion of female and male infants was provided. A total of 125 infants, all born in the maternity ward of the Teaching Hospital of USP were evaluated, after their allocation into two groups:

1. Full-term group: Comprised 72 full-term newborns (36 boys and 36 girls) without hearing risk indicators. The mean weight at birth was 3240 $\pm$ 320 g, the mean Apgar score was 9 $\pm$ 1, and the mean gestational age was 38.6 $\pm$ 1 weeks. For participants of this group, TEOAE collection occurred between 48 and 72 h of life.
2. Preterm group: Comprised 53 preterm infants (28 males and 25 females). The average weight at birth was 1491 $\pm$ 471 g, the mean Apgar score was 6 $\pm$ 2, and the mean gestational age was 32.6 $\pm$ 2.6 weeks. For participants of this group, the evaluation was performed with the corrected gestational age between 37 and 41 weeks of life, to prevent the combined effect of maturation.

Procedure

All newborns were evaluated in their natural sleep, during the postpartum hospital stay, in a quiet but acoustically-untreated environment.

Otoacoustic emission capture

This study used the ILO 292/ECHOPORT PLUS Otodynamics Analyser linked to a notebook, allowing OAE capture and Fast Fourier Transform (FFT) analysis. Both the stimulation to evoke otoacoustic emissions and the contralateral acoustic stimulation were elicited by the device, through TE SNS-8 insertion probes.

Otoacoustic emissions were collected in ''Quickscreen'' mode and the results of these were used with the sole aim to ascertain the inclusion criteria. As to the inhibitory effect research, an analysis window collection of 4–20 ms (*i.e.*, the standard analysis protocol) was used.

Thus, the following order/form responses were obtained: nonlinear click-evoked TEOAE without contralateral noise, 100 stimulus/response scans; nonlinear click-evoked TEOAE with contralateral noise, another 100 stimulus/response scans. To obtain the inhibitory effect of linear click-evoked TEOAE, a different protocol was used. Captures with and without contralateral noise were alternately and automatically obtained: each set of ten stimulus-response scanning captures without contralateral noise was collected in alternation with ten scanning captures in the presence of contralateral noise in an automated procedure, until reaching 200 scans (100 in each mode, with or without the presence of contralateral stimulation). At the end of this automatic collection, the equipment displayed the total response of 100 scans obtained without contralateral noise in a separate screen from those scans collected in the presence of contralateral noise. The procedure was repeated in the same order for the second ear to be tested.

In all collections, an analysis window of 4–20 ms was used. The level of intensity of broadband click was maintained between 60–65 dB SPL peq with 100 recordings collected, both for linear and non-linear click-evoked stimulation under conditions with and without contralateral noise. The contralateral suppressor stimulus applied was a white noise, presented at 60–65 dB SPL.

For each stimulation mode (linear and nonlinear), the inhibitory effect was calculated by subtracting the response obtained in the ''with noise'' condition from the response obtained in the ''without noise'' condition.

As for the statistical analysis of our data, exploratory statistical techniques were used through measures of central tendency and an analysis of variance with repeated measures (ANOVA).

The 0.05 significance level (5%) was adopted.

Results

The test results of TEOAE are shown in Fig. 1. There was no statistical difference between the following variables: right and left ears ($p > 0.05$) regardless of the stimulus used (linear or nonlinear click-evoked stimulus), gender, presence or absence of contralateral stimulation, or group (full-term or preterm neonates).

In the preterm group, the responses obtained with nonlinear click-evoked stimuli in female infants were stronger, although without statistical difference (Fig. 1). However, there was a significant difference between genders for responses obtained with linear click-evoked stimuli, and females again showed stronger responses ($p < 0.05$).

As for the inhibitory effect of the efferent pathway on otoacoustic emissions (Tables 1 and 2), there was no significant difference between genders and ears, both for linear as for nonlinear stimuli.

As shown in Fig. 2, a significant difference between full-term and preterm groups was noted only for nonlinear click-evoked stimulation ($p = 0.012$).

Discussion

The inhibitory effect of the efferent pathway in TEOAE was lower in the preterm group compared to the full-term group, when nonlinear click-evoked stimuli were used ($p = 0.012$); no significant difference was observed between full-term *vs.* preterm groups for linear click-evoked stimuli ($p = 0.28$).

This difference observed between full-term *vs.* preterm groups, *i.e.*, the occurrence of a weaker inhibitory effect observed in preterm group, could be interpreted as a maturational feature. Studies on preterm-born children assessed when in their school age showed worse performance in auditory processing[15] and also a reduced suppression effect.[14]

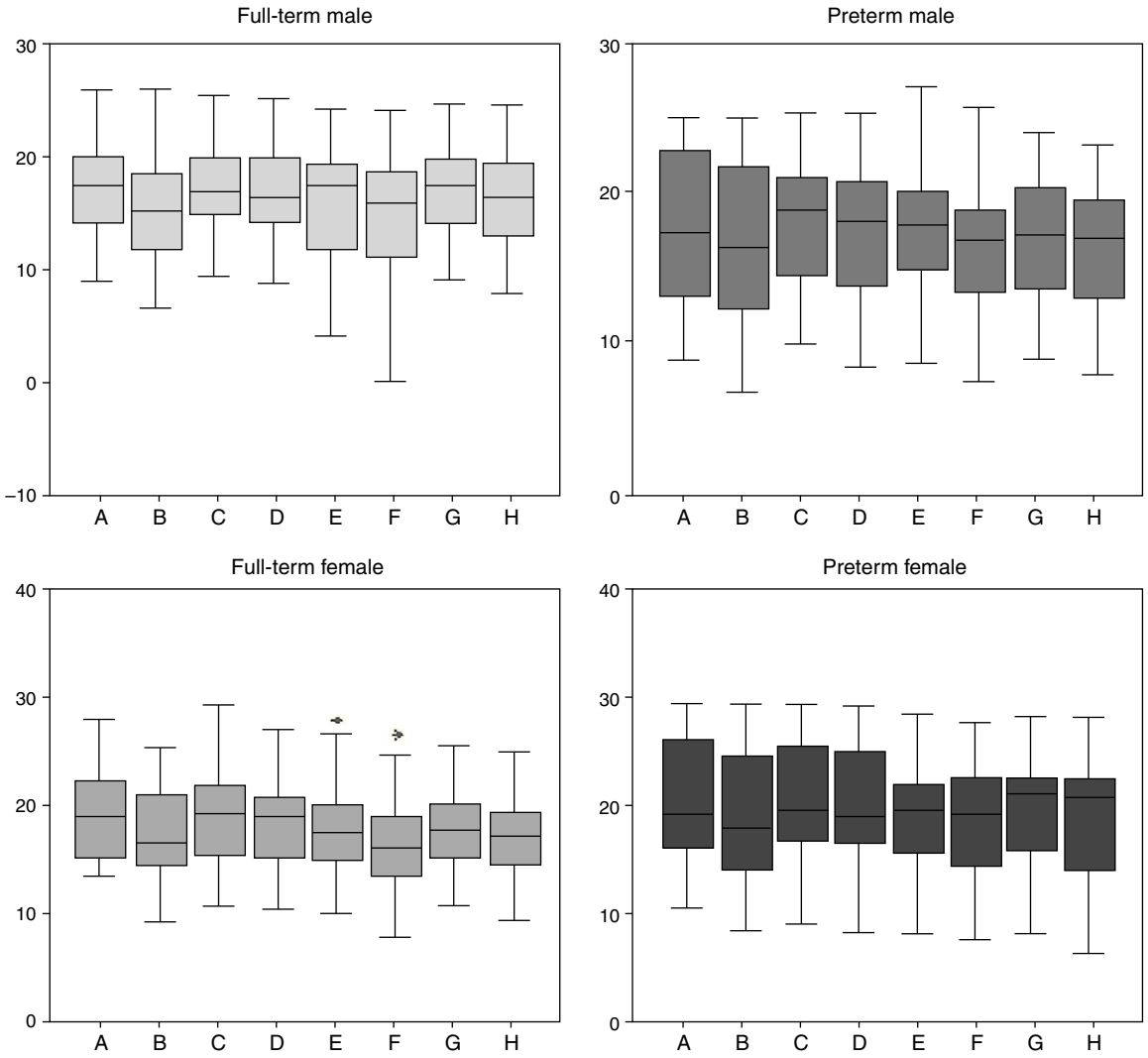

Figure 1 Response levels of transient evoked otoacoustic emissions (TEOAE; dB SPL) for linear and non-linear click-evoked stimulus presented at 60 dB SPL, by gender, ear, and presence of contralateral noise, for full-term and preterm groups. (A) Right ear nonlinear click-evoked stimulus with contralateral noise; (B) right ear nonlinear click-evoked stimulus without contralateral noise; (C) right ear linear click-evoked stimulus with contralateral noise; (D) right ear linear click-evoked stimulus without contralateral noise; (E) left ear nonlinear click-evoked stimulus with contralateral noise; (F) left ear nonlinear click-evoked stimulus without contralateral noise; (G) left ear linear click-evoked stimulus with contralateral noise; (H) left ear linear click-evoked stimulus without contralateral noise. Comparison between right and left ear with no difference ($p > 0.05$); Comparison between genres: amplitude for linear click-evoked stimulus stronger for female gender ($p < 0.05$).

Thus, it is suggested that, over time, the weakest suppression effect observed in preterm-born children's group could be associated with a difficulty in the hearing ability for sound source localization and performance in auditory discrimination tasks, as well as with auditory processing disorders,[16–18] learning problems,[19,20] and speech.[21] Therefore, the identification of a minimal or non-inhibitory effect on newborns would act as a marker for risk of hearing disorder and its consequences, suggesting a closer monitoring of this population.

Considering prematurity as a risk factor for auditory neuropathy, a post-mortem histological study on preterm infants (26–36 weeks) revealed a higher occurrence of changes in histopathological pattern of inner hair cells, compared to a control group.[22] Theoretically, the authors attributed the probable cause of neuropathy in preterm infants to a selective loss of inner hair cells. The authors also argue that a probable occurrence of otoacoustic emissions in these cases may be related to the preservation of the cochlear amplifier system, including the vascular stria, thus allowing the functioning of the outer hair cell mechanism.[22] The existence of this condition is just one more factor in favor of evaluation of the efferent system in preterm infants.

In the present study, which assessed a group of preterm infants at the corrected gestational age of 37–41 weeks, a difference in the suppression effect was evident compared to the full-term group. When performing the evaluation with the corrected age, it was considered that both groups had the same maturational conditions to generate the same level of suppression effect. Studies

Table 1 Inhibitory effect of efferent TEOAE with linear and nonlinear clicks (dB SPL) for full-term neonates.

	Mean	Median	Standard deviation	Minimum	Maximum	*n*	95% CI
Full-term – Male							
Right							
Non-linear	1.58	1.50	1.69	−0.9	6.5	36	1.0–2.1
Linear	0.56	0.50	0.68	−1.4	2.2	36	0.3–0.7
Left							
Non-linear	1.19	1.10	1.19	−1.3	4.2	36	0.8–1.6
Linear	0.81	0.60	1.03	−2.0	4.0	36	0.5–1.2
Full-term – Female							
Right							
Non-linear	1.76	0.90	2.19	−1.3	11.0	36.0	1.0–2.5
Linear	0.77	0.50	0.92	−0.3	4.2	36.0	0.5–1.1
Left							
Non-linear	1.38	1.50	0.92	−1.0	3.0	36.0	1.1–1.7
Linear	0.66	0.50	0.85	−0.4	4.3	36.0	0.4–0.9

TEOAE, transient evoked otoacoustic emissions.
Inhibitory effect with no statistical difference between genders for linear ($p = 0.85$) and non-linear ($p = 0.48$) click-evoked stimulus.
Inhibitory effect with no statistical difference between ears for linear ($p = 0.64$) and nonlinear ($p = 0.15$) click-evoked stimulus.

Table 2 Efferent inhibitory effect of TEOAE with linear and nonlinear clicks (dB SPL) for preterm neonates.

	Mean	Median	Standard deviation	Minimum	Maximum	*n*	95% CI
Full-term – Male							
Right							
Non-linear	1.02	0.75	1.15	−1.4	3.7	24.0	0.6–1.5
Linear	0.51	0.40	0.49	−0.2	1.9	24.0	0.3–0.7
Left							
Non-linear	0.96	0.90	1.29	−2.2	4.3	24.0	0.4–1.5
Linear	0.81	0.60	0.70	0.0	2.5	22.0	0.5–1.1
Full-term – Female							
Right							
Non-linear	1.34	0.90	1.30	−0.4	4.0	28.0	0.9–1.8
Linear	0.53	0.30	0.68	−0.3	2.8	27.0	0.3–0.8
Left							
Non-linear	0.75	0.80	0.93	−1.2	3.9	28.0	0.4–1.1
Linear	0.51	0.30	1.06	−0.4	5.1	27.0	0.1–0.9

TEOAE, transient evoked otoacoustic emissions.
Inhibitory effect with no statistical difference between genders for linear ($p = 0.81$) and non-linear ($p = 0.39$) click-evoked stimulus.
Inhibitory effect with no statistical difference between ears for linear ($p = 0.44$) and nonlinear ($p = 0.13$) click-evoked stimulus.

in full-term and preterm infants attest to the occurrence of this effect,[11,12] observed in preterm infants from 32 weeks of gestational age on, reaching inhibitory effect values similar to those of adults from 37 weeks of gestational age.[12] However, in this study the difference between preterm *vs.* control groups persisted, even after the precautionary measure of performing the evaluation of preterm infants at their corrected gestational age.

Other studies[7,9,23,24] described the presence of an inhibitory effect with 1–2 dB SPL of mean suppression, which agrees with the findings of this study for non-linear stimuli. The balance in absence of inhibitory effect proportion between full-term *vs.* preterm groups (Fig. 1) agrees with the finding of another study,[10] in which an inhibitory effect was not present in all individuals studied. In neonates, it is more likely that the absences of an inhibitory effect are related to maturational processes.[6,8,9,11,12]

The comparison between linear and non-linear stimuli was adopted in order to get a functional profile of the efferent hearing pathway of full-term and preterm infants, when these neonates were submitted to linear and non-linear click-evoked stimuli. Many studies have adopted linear click-evoked stimuli to verify the inhibitory effect of the efferent pathway in otoacoustic emissions.[16,17,19,24] The justification for this choice is explained by the fact that the nonlinear click, by its presentation form, reduces the interference of the stimulus, also eliminating parts of the response. Conversely, the linear click favors the verification of the inhibitory effect in TEOAE, enabling an evaluation of the response as a whole.[4] This study observed a stronger suppression for nonlinear stimulation, compared to linear

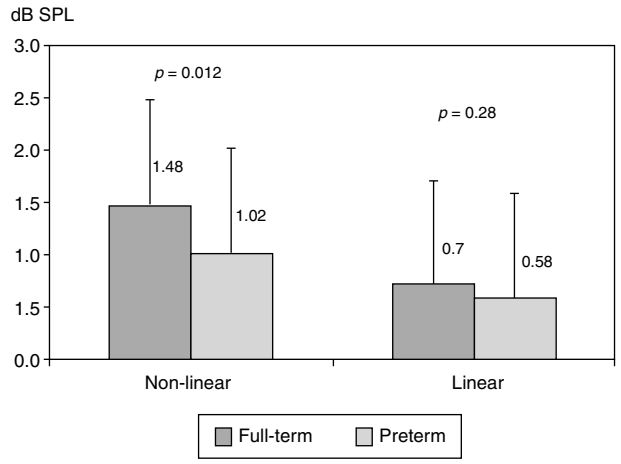

Figure 2 Efferent inhibitory effect: comparison between full-term *vs.* preterm newborns for linear and non-linear click-evoked stimuli (mean ± SD).

stimulation; these data differ from those found in literature. The difference in mode of collection, or even in terms of analysis, may justify this occurrence.

The present study has certain limitations, including the fact that the results with linear click-evoked stimulation were not analyzed in the 8–18 ms window, which, according to the literature, could also show an increased suppression effect. However, in both types of stimulation used (linear and nonlinear clicks) the analysis was carried out in the same response window (4–20 ms). Furthermore, the measure for suppression of the linear click was performed with an alternating presentation of white noise at every set of ten stimulus-response scans. Inhibitory effect measurements obtained through alternate collections generally tend to present lower amplitude of the inhibitory effect.[25] However, with respect to the non-linear click, a collection without the contralateral noise in 100 full scans was performed, followed by a collection of 100 scans with the contralateral noise. This form of response acquisition may have influenced the final result, suggesting that perhaps even alternate collection (with and without noise) at 10-scan intervals is not actually suitable for this investigation. Studies employing the same stimulus in different forms of presentation could better address this question.

Response amplitude of TEOAE without contralateral stimulation

The fact that preterm neonates had risk factors for hearing impairment did not affect the integrity of cochlear responses, since all infants showed OAE at appropriate levels for their age. The distribution of the results of otoacoustic emission response levels analyzed in the overall response revealed, in the study sample, certain homogeneity in response for both groups, with a standard deviation of the same magnitude in the different measures. On average, response levels were evaluated between 15.09 and 17.21 dB SPL for male neonates and between 16.25 and 19.24 dB SPL for female neonates, even though these variables were measured with a stimulus at a lower intensity level than usually utilized, indicating a normal cochlear function in preterm infants. The click intensity at 60 dB peak-equivalent was chosen based on previous studies in humans,[3,10,26] in order to eliminate the possibility of involvement of middle ear mechanisms when determining the inhibitory effect.

The fact that there was no statistical difference between full-term *vs.* preterm groups, with respect to the response level of TEOAE, agrees with the literature.[13] A gender difference in the responses of TEOAE was observed; this difference was higher in full-term female neonates, compared to male neonates of the same group, when using a nonlinear stimulation. For the preterm group, more robust responses for female neonates were noted, compared to male responses, though this latter difference was not significant. Most of the literature also shows a tendency to higher amplitudes of OAE in female neonate populations.[6–8,10] However, some studies with different sampling procedures did not show this tendency.[13,27,28]

Conclusion

The results of this study reveal a reduced inhibitory effect of olivocochlear system in preterm infants, when assessed by TEOAE with nonlinear click-evoked stimulation. Thus, in view of the involvement of efferent pathways in the auditory stimulus processing tasks, the authors emphasize the need for monitoring the auditory skills of preterm infants early in their life. Future longitudinal studies would allow a better analysis of the impact of this reduced inhibitory effect on communication development.

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Conflicts of interest

The authors declare no conflicts of interest.

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