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Olfactory Stimulation Prevents Apnea in Premature Newborns

Luc Marlier, PhD*; Christophe Gaugler, MD‡; and Jean Messer, MD‡

ABSTRACT. Objective. Methylxanthines and doxapram are currently used to treat apnea of prematurity but are not fully effective and often present undesirable side effects. The present study examines whether exposure to an odor known to modulate the infant's respiratory rate could reduce the frequency of apneic spells.

Method. Fourteen preterm newborns born at 24 to 28 gestational weeks presenting recurrent apnea despite caffeine and doxapram therapy were exposed to a pleasant odor diffused during 24 hours in the incubator. Efficiency of the olfactory treatment was judged by comparing frequency and severity of apneas occurring during the day of odorization with that observed the day before (baseline) and the day after (posttreatment control). Apnea was defined as any complete cessation of breathing movements for >20 seconds, or less if associated with hypoxia or bradycardia.

Results. Concerning all types of apneas, a diminution of 56% was observed and seen in 12 of 14 infants. Apneas without bradycardia were reduced (44%) during the day with odorization, and this diminution affected all the infants. The frequency of apnea with moderate bradycardia (heart rate between 70 and 90 beats per minute) was maintained while the frequency of apnea associated with severe bradycardia (heart rate <70 beats per minute) decreased strongly (45%) and affected all the infants. No side effects were observed.


Abbreviations. RR, respiratory rate; HR, heart rate; SpO₂, oxygen saturation; bpm, beats per minute.

Recent apnea is common in premature newborns, particularly at early gestational ages. It affects ~80% of infants born at <30 weeks of gestation.¹ Causal factors include immature neurologic and respiratory systems, reduced hypercapnic and hypoxic responses, and difficulties with central respiratory control.² These cessations of breathing can lead to hypoxemia and bradycardia,³,⁴ therefore increasing the risk of cerebral injury as attested by several studies showing noticeable decreases in cerebral blood flow velocity and cerebral oxygenation during apneic episodes.⁵⁻⁹

Since the 1970s, the first-line treatment for apnea of immaturity has been pharmacological treatment with methylxanthines (theophylline and caffeine), the efficiency of which in preventing apneas has been well documented.¹⁰⁻¹² Doxapram, an analeptic agent and powerful respiratory stimulant, has been used more recently for controlling apneas unresponsive to methylxanthines alone.¹³⁻¹⁵ However, none of these substances administered alone or in combination seem to be fully effective. Some treated newborns continue to have frequent spells of apnea and may need more vigorous ventilatory techniques such as nasal continuous positive airway pressure or mechanical ventilation.¹³ Additionally, several undesirable side effects such as hyperactivity, irritability, alteration of sleep organization, tachycardia, metabolic, gastrointestinal, and urinary disorders have been noticed in treated infants.¹³,¹⁵⁻¹⁷ Caffeine has also been suspected to reduce cerebral blood flow¹⁸ and doxapram to increase blood pressure, thus enhancing the risk of cerebral hemorrhage.¹⁴,¹⁹ Therefore, there is clearly a need for additional studies for a more effective treatment with fewer side effects.

During an investigation on the ability of premature infants to detect and discriminate odors, we observed that the infant's respiratory rate (RR) was modulated according to the hedonic value of the odorants. Pleasant odors elicited increasing responses, whereas unpleasant odors elicited decreasing responses.²⁰ Moreover, the power of odors to affect the RR seemed particularly effective during active sleep,²¹ a sleep state during which apneas are most likely to occur.²²,²³ We were thus interested in verifying whether the stimulating effect of a pleasant odor could counterbalance (at least partly) the respiratory fall observed during apneic spells. For ethical reasons, we were reluctant to replace the pharmacological treatment applied to premature infants suffering from apnea by an olfactory treatment, the efficiency of which had to be proved. So we decided, as a first step, to examine the effect of odor exposure on apneas unresponsive to the traditional pharmacological substances, thus sparing any intervention on the current treatment. More precisely, we tested whether the introduction of a slight pleasant odor into the incubator was beneficial for infants who continued to suffer from apneic spells while receiving caffeine-plus-doxapram therapy.
Methods

Infants

Measurements were conducted on 14 premature newborns (7 females) in the neonatal intensive care unit at the University Hospital at Strasbourg (Alsace, France). All the infants had recurrent central apneas unresponsive to caffeine-plus-doxapram therapy. Caffeine was administered by enteral route (5 mg/kg per day; n = 14) and doxapram either by enteral route (30 mg/kg per day; n = 10) or continuous intravenous infusion (12–30 mg/kg per day; n = 4). This pharmacological treatment was maintained for each subject throughout the study. Central apnea was diagnosed only when causes other than immaturity (ie, infections, anemia, hypocalcemia, hypoglycemia, hyperthermia, or hypothermia) were eliminated. Radiography was used to confirm lack of respiratory disorders; echocardiography was used to exclude patent ductus arteriosus; and cranial ultrasounds were used to exclude intraventricular hemorrhage larger than grade 1 and periventricular leukomalacia. Infants were also free of major complications (ie, chromosomal abnormalities, congenital malformations, or cardiovascular or brain disorders). They were not on nasal continuous positive airway pressure, and their clinical status was stable (during at least 48 hours before enrollment). Their gestational ages ranged from 24 to 28 weeks (mean: 26.5 weeks), birth weight ranged from 815 to 1680 g (mean: 1169 g), and postnatal ages ranged from 11 to 33 days (mean: 22.4 days). In accordance with ethical standards, parents were informed and had to give written consent.

Procedure

Because of great variability of incidence and severity of apneic spells between patients, we used a protocol in which each infant was considered as his or her own control. The study was conducted over 3 consecutive 24-hour periods. Day 1 served to obtain baseline values. Odorization of the incubator was applied during day 2. Finally, to ensure that eventual changes of responses were not caused by rapid maturational processes, a third day of observation without any experimental intervention was considered. During the study, infants were kept supine in the incubator (8000 SC, Dräger Technology, Lübeck, Germany) under continuous monitoring. Heart rate (HR) and RR were recorded by using a Viridia monitor (V24C, Agilent Technologies, Bäblingen, Germany). Oxygen saturation (Spo2) was measured by using a pulse oximeter. No specific guidelines concerning the treatment of apnea were given to the caregivers. Following the usual rule, caregivers had to stimulate the infant by gentle tactile stimulation if the resolution of apnea was not spontaneous. If the number of such interventions exceeded 3 per hour, then mechanical ventilatory assistance (continuous positive airway pressure) was provided. Nursing habits and the method and rhythm of feeding were held constant during the complete duration of the study. Temperature (mean ± SD: 36.4 ± 0.4°C), ventilation (7.3 ± 0.7 L/minute), and heart rate (63.7 ± 6.3 bpm) of the incubator and environment of the incubator could change slightly from 1 infant to the other, but care was taken to keep them constant for each subject throughout the study. Six infants benefited from skin-to-skin contact with the mother (duration: 1–1.5 hours per day). In these cases, the mothers were asked to establish this daily contact at the same time window in the course of the day and for approximately the same duration.

After a 1-day observation without any experimental intervention (baseline period), the olfactory stimulus was introduced in the time window in the course of the day and for approximately the 24-hour period in the course of the day and for approximately the 24-hour period. Finally, we found that 15 drops at the beginning of the session and a second 15-drop dose 12 hours after the onset of odorization offered the best result. A persistent slight vanillin odor was thus perceptible by adults’ nose during the stimulation period. Because it was probable that the nursing staff detected the presence of the stimulus, information concerning the introduction of an odor in the incubator was given, but extreme care was taken not to inform the staff about the aim of the study and specifically the focus on apnea. After the end of the olfactory treatment, the odorized pillow was removed, the complete incubator was washed and aired, and a clean pillow was installed. The third day of observation was free of any experimental intervention. The present protocol was approved by the local ethical committee (Alsace no. 1, Agreement no. 02/120).

Classification of Apnea and Data Analysis

According to common acceptance,2,9 central apnea was defined as any complete cessation in breathing movements >20 seconds, or less if associated with hypoxia (blood oxygen saturation <88%) or bradycardia (HR <90 beats per minute [bpm]). Apneic episodes associated with bradycardia were classified into 2 different groups. Apnea with moderate bradycardia was defined as a cessation of breathing followed by a diminution of the HR between 90 and 70 bpm. Apnea was considered as associated with severe bradycardia if the HR fell to <70 bpm. HR, RR, and Spo2 were recorded throughout the study. A paper graph of these 3 signals was obtained (and alarm activated) when HR <90 bpm, RR <20 bpm, or Spo2 <88%. The frequency, duration, and degree of severity of the apneic spells were extracted from the printed graphs. A minimal interval of 2 minutes was used to consider 2 apneic spells as independent and to code them as 2 separate events. Two raters (C.G. and J.M.), expert in respiratory data reading and blind during coding, coded separately all the recordings. Inter-rater reliability of the measurements was computed by calculating the percentage of agreement between the 2 raters for each category of apnea. The correlations in all cases were >.92. If a disagreement was noted, each case was reexamined, and a decision was taken together.

Statistical Analysis

To verify whether there was a significant change in the frequency of apnea over the 3 days of the study, repeated-measures analysis of variance was computed, where the day of observation constituted the intrasubject factor. If a change was noticed, we tested specifically the hypothesis of a reduction of the number of apnea only during an olfactory treatment (day 2 compared with days 1 and 3) by using the statistical method of contrasts.26 If our hypothesis was confirmed, we tested its strength by examining the percentage of the total variance that could be explained by the predicted effect. A high percentage was considered as indicative of a strong impact of the olfactory treatment on the frequency of apnea. Finally, to examine individual responses to odor exposure, the number of infants presenting a reduction of the number of apneas was compared (using the y2 test) with the number of infants who maintained or increased the number of apneas (day 2 compared with day 1). A P value of <.05 was considered significant. All statistical treatments were conducted by using SAS/STAT 8.2 software (SAS Institute, Cary, NC).

Results

All 14 infants enrolled completed the study, and no one needed mechanical ventilatory assistance. Efficiency of olfactory treatment was judged by the frequency and severity of the occurring apneas.

Frequency of Apnea Without Distinction of the Type

When the totality of apneas was considered, a decrease in frequency could be observed during odor exposure. The mean number of events (see Table 1 for SDs) fell from 34.7 (day before odor application) to 22.2 (day with odor application), representing a diminution of 36% (Fig 1). After cessation of odor application, the mean frequency of apnea returned to the baseline value (33.2). The difference between the 3 days of study appeared highly significant (F2,26 = 10.06; P < .001). It is more interesting that the predicted effect of a reduction of apneic episodes only during the day of odor application was
confirmed by the statistical method of contrasts 
\( \text{F(1,26)} = 19.87; P < .001 \). Furthermore, 98.8% of the 
variance could be explained by the predicted effect. 

![Fig 1. Mean percent difference in the number of apneic spells 
occurring during (day 2) and after (day 3) olfactory treatment, 
compared with baseline (day 1), according to the type of apnea in
the 14 premature newborns. *P < .05, which indicates a 
significant difference with baseline.

When individual data were considered, it seemed 
that 12 of 14 infants presented a reduction of the

![Table 1. Number of Apneic Spells Occurring During the Day Before, the Day of, and the Day After Olfactory Treatment According to the Type of Apnea in the 14 Premature Newborns]

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Total No. of Events</th>
<th>Apnea Without Bradycardia</th>
<th>Apnea With Moderate Bradycardia</th>
<th>Apnea With Severe Bradycardia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>After</td>
<td>Before</td>
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<tr>
<td>1</td>
<td>24</td>
<td>17</td>
<td>23</td>
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<tr>
<td>14</td>
<td>62</td>
<td>22</td>
<td>39</td>
<td>54</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>34.7 ± 24.1</td>
<td>22.2 ± 18.5</td>
<td>33.2 ± 24.4</td>
<td>17.9 ± 18.8</td>
</tr>
</tbody>
</table>
number of apneaic events (Table 1), a proportion that was significantly different from a proportion predicted by chance ($\chi^2 = 7.14; P < .01$). Taken together, these results indicate that the presence of vanillin in the incubator reduces significantly the frequency of apneic spells.

**Frequency of Apneas Without Bradycardia**

The number of apneas for $>20$ seconds, or less if associated with hypoxia but without bradycardia, was particularly affected by odor exposure. A decrease of $44\%$ could be observed (Fig 1). From a mean of $17.9$ apneic events recorded the day before odor application, this number fell sharply to $10$ during the day with odor application before regaining the initial value ($17.8$) after the stimulation was removed. This variation was significant ($F[2,26] = 7.26; P < .01$) and followed the predicted curve characterized by a significant diminution only during odor exposure ($F[1,26] = 14.51; P < .001$). The predicted effect explained $99.9\%$ of the variance. All infants without exception benefited from a reduction of the number of apneic spells during odor exposure (Table 1).

**Frequency of Apneas With Moderate Bradycardia**

For the frequency of apneas followed by an HR situated between 70 and 90 bpm, no significant difference was noted between the days before, during, or after odor application (8.6, 7.9, and 8.8 during days $1, 2, \text{and } 3$, respectively; Fig 1). When individual data were considered, mitigated results were also apparent. Only $8$ of the $14$ infants seemed to derive benefit from olfactory stimulation (Table 1), a proportion that was not significantly different from a proportion given by chance.

**Frequency of Apneas With Severe Bradycardia**

For the whole group, the baseline mean number of apneas associated with severe bradycardias (HR $< 70$ bpm) was $8.2$. During the day on which the incubator was odorized, the frequency of apneas decreased to $4.5$, which represents a strong reduction of $45\%$ (Fig 1). The mean recorded was $6.6$ during the day after odor application. This variation of the number of apneic events during the $3$ days was significant ($F[2,26] = 5.39; P = .01$). The hypothesis of a significant diminution of the number of apneas only during the odorized day (compared with days $1$ and $3$) was confirmed further ($F[1,26] = 8.87; P < .01$), and the percentage of variance ($82.2\%$) could be explained in great part by the predicted effect. This effect concerned all the infants except $1$, who did not express any severe bradycardia during the $3$-day survey (Table 1; $\chi^2 = 10.29; P = .001$). Thus, odorization of the incubator reduces significantly the number of apneaic events associated with severe bradycardia.

**Side Effects**

No side effects in any of the patients were noticed. Daily weight gain was maintained throughout the study. Daily RRs and cardiac rates appeared stable regardless of whether the incubator was odorized (mean $\pm$ SD for daily RR: $44.4 \pm 4.4$, $43.3 \pm 3.3$, and $43.3 \pm 4$ cp; for daily cardiac rate: $148.2 \pm 11.9$, $146.9 \pm 12$, and $147.3 \pm 12.1$ bpm; for days $1, 2, \text{and } 3$, respectively). Gastrointestinal tolerance seemed unaffected by odor exposure, because neither gastric residuals nor regurgitations were observed. Finally, no behavioral changes such as excitability or increased activity were noted by the nursing staff among the infants during the study.

**DISCUSSION**

The present study addressed the question of whether the frequency of apneas unresponsive to caffeine and doxapram can be reduced in premature newborns exposed to a pleasant odor in the incubator. Our results indicate that odor exposure leads to a clear diminution of the incidence of apneas. This reduction reached $44\%$ for apneas without bradycardia and $45\%$ for apneas with severe bradycardia. Inspection of individual data revealed that this decrease was strongly consistent across subjects. Apparently, apneas associated with moderate bradycardia seemed unaffected by odor exposure. However, it can be noticed that a substantial proportion of subjects ($8$ of $14$ [$57\%$]) exhibited a reduction in the number of apneas with moderate bradycardia (in this subgroup, the reduction reached $37\%$), suggesting that odor exposure could affect this category of apnea as well. Additionally, it is not excluded that the olfactory treatment affects also the severity of bradycardia, so that less severe bradycardia would in consequence increase the amount of moderate bradycardia, or in our case, kept the frequency stable because of probable simultaneous reduction of the number of moderate bradycardia events. This possibility is supported by the fact that the $6$ infants who did not lower the frequency of moderate bradycardia expressed concomitantly a strong reduction ($51\%$) of the number of severe bradycardia events. Thus, despite the case of apneas with moderate bradycardia, the results of our study show that the introduction of a pleasant odor in the incubator is of therapeutic value in the treatment of apneas unresponsive to caffeine and doxapram.

In recent years, a growing number of studies have emphasized noticeable effects of ambient odors on psychologic$^{27–29}$ and physiologic$^{30–32}$ states in adults. Several studies have also reported physiologic variations during the inhalation of odors in both term$^{24,33,34}$ and, more recently, premature infants.$^{20,24,35,36}$ However, the specific relevance of olfaction in positively altering health has been poorly documented.$^{37}$ In $1$ case of temporal lobe epilepsy, an inhibition of seizures by unpleasant odor exposure was reported.$^{38}$ Similarly, it was observed that epileptic attacks could sometimes be stopped by a strong olfactory stimulus or by the application of ammonia.$^{39}$ Nevertheless, in these studies, the observed effects are most probably the result of trigeminal and not exclusively olfactory stimulation, and it is likely that patients are more responsive to the irritability than to the smell of the odor. Thus, it remains uncertain whether an exclusive olfactory stimulus can have some role in curing or preventing diseases. The reduction of the number of apnea
events during exposure to vanillin, a stimulus known to have no trigeminal component especially at low concentration such as that used in our study, may thus constitute the first evidence of the power of an olfactory stimulus to exert a significant beneficial effect on health.

To date, we cannot fully explain the efficacy of vanillin exposure in these cases of relative caffeine and doxapram failure. Here we propose 2 hypotheses, which are not mutually exclusive. First, it is possible that vanillin possesses pharmacological properties and therefore has direct or indirect effects on the respiratory centers. The absorptive capacity of the nasal mucosa has been known for decades. Chemical compounds have the possibility to cross the nasal mucosa, enter the bloodstream through microcapillary channels, and finally reach cerebral structures. More recently, it was demonstrated that particles or viruses can also be caught by olfactory neuroreceptor cells and carried along the axons to the olfactory bulbs, and from there to more central structures. Until now, the possible mechanisms of action of vanillin have not been identified but could be 1 or both of these routes. Interestingly, it has been found that a lower dosage of pharmacological substances is often sufficient when administered via the olfactory pathway as compared with the intravenous or enteral routes, which suggests that the olfactory pathway may constitute a more direct route to the brain centers than other more traditional routes used by physicians, and this should be a route explored further in the future.

A second explanation is that the mere presence of a pleasant odor in the environment may help the subject to regulate his psychologic and physiologic states. This possibility is supported by several observations. For example, a reduction in the duration of crying could be obtained swiftly after exposure to maternal or familiar odors in term newborns. Inversely, term infants in a low level of activation before a feed increased their body, head, and mouthing movements with the presentation of milky odors. In the same way, it was suggested that preterm infants who received oral tactile stimulation with a lemon-flavored swab stick tended to restore an appropriate RR after a breathing fall. Taken together, these data indicate that the presentation of pleasant or familiar odors (alone or in association with other stimulations) can be of clinical usefulness in subjects presenting adaptive difficulties by helping them to reestablish an appropriate state of activation. In this context, the odorization of the incubator may represent a particular interest for premature infants. First, because studies have attested that premature newborns perform poorly on measures of self-regulation as well as autonomic regulation and even more poorly than term infants. Second, premature infants spend the first few weeks or months of their lives in an environment that is, by its nature, more stressful (because of overstimulations, frequent handling, painful procedures, separation from the mother) than the intrauterine milieu. Pleasant and familiar ambient odors thus may represent an interesting means to facilitate the psychophysiologic adaption of the premature newborn to its initial environment.

Because apneas of prematurity occur mainly during active sleep, it cannot be excluded that ambient odor would be of particular effectiveness on the infants’ sleep quality. However, because of the absence of clear indicators of sleep/wake states during this first step of study, it was not possible to provide more details on this potential effect. Additional explorations are therefore needed to examine the impact of an odorized environment on sleep organization, and particularly to verify that the benefit observed is not caused by a relative deprivation of active sleep.

This study presents several limitations. First, because our patients were chosen selectively because of relative caffeine-plus-doxapram failure, we cannot comment on the overall effectiveness of vanillin in apnea of prematurity. A study is currently being undertaken to verify whether vanillin treatment could be beneficial to a larger sample of subjects. Second, because vanillin was the only stimulus used in our study, the relative contribution of what is specific to vanillin and what is imputable solely to the presence of a pleasant odor in the incubator could not be established. The effect of qualitatively different odorants on incidence of apnea still remains to be analyzed at this point. Finally, the effect of ambient odor on the incidence of apneic spells was investigated only during a 24-hour period. The impact of shorter or longer durations has yet to be examined.

The apparent absence of undesirable side effects suggests that olfactory treatment remains within a good margin of safety. All potential side effects, nevertheless, have to be reexamined, particularly if longer periods of odor exposure are considered.

CONCLUSIONS

We think that the practice of odorizing incubators with pleasant (for infants) odors should not be discarded a priori. Moreover, it may constitute a valuable help for premature infants who continue to suffer from apneic spells despite caffeine and doxapram therapy. Based on our results, we believe that such a new approach should be explored further.

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