Effect of Feeding on the Chemical Control of Breathing in the Newborn Infant

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Summary

To examine the influence of feeding on the chemical control of breathing in neonates, we studied the ventilatory response to 3% CO₂ in air in nine bottle fed (BOT) and eight breast fed (BR) term infants during feeding while the infants were alert. Control responses were obtained either before or after feeding. $\dot{V}_E$, respiratory frequency, tidal volume, inspiratory time, expiratory time, and sum of inspiratory and expiratory time, V_T/T_i , T_i/T_{tot} , $PACO_2$ and slope (S) of CO₂ response (liter/min/kg/mmHg) were determined. During 3% CO₂ while resting BR had a lower $\dot{V}_E$, V_T , V_T/T_i than BOT and S in BR was 40% of BOT ($P < 0.05$). During feeding and CO₂ when compared to resting and CO₂ there was no difference in either BR or BOT in V_T/T_i but T_i/T_{tot} decreased in both groups. During feeding, S in BOT was reduced from 0.049 ± 0.012 (mean $\pm$ S.E.) to 0.013 ± 0.002 (74% reduction) and in BR from 0.020 ± 0.002 to 0.009 ± 0.002 (55%). Thus, behavioral activity (either BR or BOT) markedly depresses the ventilatory response to chemical stimuli (CO₂). This modification is primarily related to changes in "effective" respiratory timing (T_i/T_{tot}) rather than mean inspiratory flow (V_T/T_i).

Speculation

This is the first demonstration in the newborn infant that behavioral activity (feeding) can override the usual ventilatory control mechanisms. The precise mechanism is unknown and requires further study.

Breathing is controlled by two functionally integrated elements: the behavioral (voluntary) control system, which originates in the forebrain, is involved in activities such as phonation; and the metabolic (automatic) respiratory control system, centered in the brain stem (2, 12). Studies in healthy adult subjects have shown that during normal speech there is a marked disruption of the ventilatory response to CO₂ (3, 15), suggesting that during phonation there is a relaxation or overriding of metabolic respiratory control. The influence of behavioral activity on the chemical control of breathing in neonates has not been studied. We designed this study, therefore, to examine the interaction of the metabolic and behavioral respiratory control systems, by comparing the ventilatory response to CO₂ in bottle fed and breast fed infants while resting and during feeding.

MATERIALS AND METHODS

We studied nine bottle fed healthy term infants (BOT): birth weight (mean $\pm$ S.E.) 3.15 ± 0.15 kg; gestational age 39.2 ± 1.0 wk; postnatal age 6.4 ± 2.4 days; and 8 breast fed healthy term infants (BR): birth weight 3.35 ± 0.14 kg; gestational age 39.8 ± 0.3 wk; postnatal age 4.2 ± 0.7 days. There were five males and four females in the BOT group, and five males and three females in the BR group. The study was explained to the parents of each subject and informed consent obtained.

A nosepiece with a constant background flow and a screen

flowmeter was used to record flow, tidal volume, end-tidal CO₂ and O₂ concentrations, according to methods described in detail previously (18, 19), and recording was done with a Gould Brush 480 Recorder. The ventilatory response to 3% CO₂ in air was assessed before or after feeding (resting) and during feeding in the BOT group, while the infants were alert. Alertness was defined by open eyes for more than 2 min and presence of purposeful movements. For BR it was only possible to obtain control responses after feeding in all but one infant. $\dot{V}_E$, respiratory frequency (f), tidal volume (V_T), inspiratory time (T_i), expiratory time (T_e), sum of inspiratory and expiratory time (T_{tot}), V_T/T_i , T_i/T_{tot} , $PACO_2$ and slope of CO₂ response (liter/min/kg/mmHg) were determined (1, 6, 11). The ventilatory response to CO₂ was analyzed by measuring and summing each tidal volume during 1 min periods, before and during the fifth min following CO₂ administration. End-tidal PCO₂ was estimated during the same time interval and assumed to be equivalent to alveolar PCO₂. T_i and T_e were measured for each breath from the flow tracing during the same time interval that minute ventilation ($\dot{V}_E$) was measured. The fifth min was chosen for analysis because previous work from this laboratory has shown that a steady state has been achieved by neonates during this time interval (4, 9, 20).

Infants were clothed and bundled as is usual for term infants. Bottle fed neonates were fed by a nurse and breast fed infants by their own mothers, in the usual feeding position. All tolerated the procedure well and did not seem to be disturbed during the study. Statistical significance of the differences was assessed using the paired *t* test for feeding *versus* not feeding values and the unpaired *t* test for bottle *versus* breastfeeding values.

RESULTS

Effect of feeding on the ventilatory response to CO₂. During feeding, the slope of CO₂ response (mean $\pm$ S.E.) in BOT infants was reduced by 74% from 0.049 ± 0.012 to 0.013 ± 0.002 liter/min/kg/mmHg ($P < 0.01$) when compared to the resting CO₂ response. In BR infants the slope was also reduced during feeding, from 0.020 ± 0.002 to 0.009 ± 0.002 ($P < 0.01$), representing a 55% reduction. Thus, while feeding, there was a pronounced decrease in the ventilatory response to CO₂ in both groups of infants (Fig. 1 and 2). The slope of the CO₂ response during feeding was not significantly different for the BOT and BR groups. The significant decrease in $\dot{V}_E$ with CO₂ during feeding when compared to the resting state plus CO₂ was accounted for by a significant decrease in V_T in both groups (Fig. 3). There was no significant effect of feeding on respiratory frequency (f) (Fig. 4). Because of this decrease in $\dot{V}_E$, $PACO_2$ was greater with CO₂ during feeding than during rest by 2.8 mmHg in the BF group and 3.6 mmHg in the BOT group ($P < 0.05$).

Effect of feeding on mean inspiratory flow (V_T/T_i). While resting, the addition of CO₂ increased V_T/T_i (mean inspiratory flow) from 38.2 ± 3.3 ml/sec to 63.2 ± 4.3 in BOT and from 31.8 ± 3.1 to 43.4 ± 4.2 in BR ($P < 0.05$) (Fig. 5). During feeding, the addition of CO₂ also increased V_T/T_i from 48.6 ± 3.0 ml/sec to 63.8 ± 4.1 in BOT and from 34.4 ± 5.2 to 44.8 ± 5.0 in BR ($P < 0.05$). There

Fig. 1. $\dot{V}_E$ in bottle and breast fed infants plotted against $PACO_2$ during resting and feeding, and after the addition of 3% inspired CO_2 .

Fig. 2. Slope (S) of CO_2 response in bottle fed and breast fed infants during resting and during feeding.

Fig. 3. V_T versus $PACO_2$. During CO_2 administration, V_T significantly decreased during feeding when compared to rest.

Fig. 4. f versus $PACO_2$. There is no significant effect of feeding on respiratory frequency in either group of infants.

was no difference in V_T/T_i during feeding plus CO_2 when compared to resting plus CO_2 for either the BOT or BR groups.

Effect of feeding on "effective" respiratory timing (T_i/T_{tot}). During feeding and CO_2 when compared with resting and CO_2 , the T_i/T_{tot} decreased significantly from 0.384 ± 0.018 to 0.311 ± 0.019 ($P < 0.05$) in the BOT group and from 0.399 ± 0.018 to 0.303 ± 0.017 ($P < 0.05$) in the BF group (Fig. 6). The decrease in T_i/T_{tot} was entirely accounted for by a decrease in T_i since T_{tot} did not change significantly. Thus, the major effect of feeding on the ventilatory response to CO_2 was an early termination of inspiration.

Effect of the type of feeding (BOT and BR) on ventilation. Interestingly, the BOT group had a significantly greater control response (in the absence of feeding) to CO_2 than did the BF group ($P < 0.05$) (Fig. 1). The slope of BF infants was 40% of the BOT group and was accounted for by a significantly lower $\dot{V}_E$, V_T and V_T/T_i in response to CO_2 ($P < 0.05$), despite comparable values before CO_2 was added (Figs. 2, 3, 5). The control response curves

for the BF group in seven of eight instances were obtained after feeding. In the six BOT infants studied before feeding, S was 0.058 ± 0.016 liter/min/kg/mmHg and in the three infants studied after feeding S was 0.031 ± 0.011 ($P > 0.1$). Despite the fact that these slopes are not significantly different, the differences seen between BR and BOT slopes in the absence of feeding may not be valid because only one infant in BR was studied before feeding.

Fig. 5. Changes in V_T/T_i with CO₂ administration during rest and feeding in bottle and breast fed infants.

Fig. 6. Changes in T_i/T_{tot} with CO₂ administration during rest and feeding in bottle and breast fed infants.

During feeding, in the absence of CO₂, BOT had a greater reduction in T_i than BR (0.37 ± 0.02 sec versus 0.45 ± 0.05 ; $P < 0.05$). Thus, V_T/T_i increased significantly in BOT in the absence of CO₂ from 38.2 ± 3.3 to 48.6 ± 3.0 ml/sec ($P < 0.05$) but no significant change occurred in the BF group (Fig. 5).

DISCUSSION

While the metabolic respiratory control system is involved primarily in acid-base and oxygen homeostasis, the behavioral control system is involved in activities such as phonation (10, 12). Feeding also uses the ventilatory apparatus for nonrespiratory functions and is a necessary behavioral activity of normal newborn infants. In an earlier study on adults, Bunn and Mead (3) showed that during phonation minute ventilation ($\dot{V}_E$) increases slightly,

and the ventilatory response to hypercapnia was diminished. Phillipson *et al.* (15) demonstrated in adult subjects that even for degrees of hypercapnia considerably higher than might be encountered during speech, the behavioral respiratory control system can effectively override the metabolic system without there being a conscious effort to underbreathe or hold the breath. The present study extends these earlier observations to human neonates and demonstrates that during feeding there is a marked reduction in the ventilatory response to CO₂. Interestingly, this reduction in the slope of CO₂ response was greater in BOT neonates (74%) when compared with BF infants (55% reduction). However, this difference is accounted for by the higher control slope in the BOT group because the slopes during sucking were not different. The BF group had a lower $\dot{V}_E$ but the same PACO₂ as the BOT fed group suggesting that there was a greater metabolic rate in the BOT group. Alternatively, feeding artificial formula which has a greater protein content than breast milk might decrease total buffer base and thus alter CO₂ response. Unfortunately, arterial pH measurements were not done.

It is possible that the large reduction in slope may be in part related to changes in lung mechanics, due to feeding (14, 17, 21). The control responses to CO₂ were obtained in a random manner either before or after feeding in BOT infants and there was no difference in S done before or after feeding. Indeed seven out of eight control studies were done after feeding in the BF group and yet S during feeding was significantly reduced. Thus, mechanical factors cannot account for the reduction of S during feeding. The reduction in CO₂ response during feeding is comparable to decreases reported in adults during phonation (3, 15).

The major effect of feeding was an early termination of inspiration (T_i was markedly reduced), whereas T_{tot} remained unchanged. The precise mechanism for this effect is unknown. V_T was also reduced during feeding plus CO₂ and V_T/T_i did not change, indicating that mean inspiratory flow is maintained during functional interaction between the behavioral and metabolic control systems.

It is possible that during feeding, shortening of T_i is the primary event leading to a decrease in V_T , decrease in $\dot{V}_E$ and eventual reduction in CO₂ response. Despite this, there is some response to CO₂ since V_T/T_i increases with the addition of CO₂ during feeding to the same value as that found in the absence of feeding. This response is somewhat different than that found in the adult during phonation since Phillipson *et al.* (15) reported that V_T/T_i did not change during phonation with the addition of CO₂.

Whether or not the above changes are mediated through reflexes in the airways or esophagus during feeding remains to be determined. For instance, sucking might potentiate the inspiratory inhibitory pulmonary reflex (8, 13). Alternatively, intrinsic changes in the rhythmicity of the respiratory center during feeding could account for the reduced response to CO₂ because the changes in ventilation during sucking appear to be related to the motor activity involved in feeding. In support of this notion is the demonstration in adult subjects that the CO₂ response was unaffected by quiet reading without vocalization and decreased by reading aloud (15). In addition, gustatory activity is modulated by the hypothalamus and hypothalamic impulses are known to modify neuronal firing in the nucleus of the tractus solitarius. More specifically, studies in rats have demonstrated the presence of descending input from the lateral hypothalamic area-medial forebrain bundle to brain stem neurons possibly involved in oropharyngeal sensation and gustatory evoked phenomena (2). We are not aware of studies in the neonatal animal of the effect of hypothalamic stimulation on ventilatory responses.

The effect of feeding on the chemical control of breathing in neonates in different sleep states has not been studied, although several recent reports (4, 7, 9, 16) suggest that CO₂ response is not different when comparing REM versus non-REM sleep. Our subjects were studied while alert, both before and after feeds and it seems unlikely that different states of consciousness can explain the results.

Interestingly, there was a difference in respiratory pattern during feeding in the absence of CO₂ between BR and BOT. V_T/T_i

increased significantly during feeding before CO₂ ($P < 0.05$) in the BOT group whereas in the BR group feeding alone did not change V_T/T_i . The increase in V_T/T_i in BOT was entirely accounted for by a reduction in T_i since V_T did not change. Thus, bottle feeding alone significantly alters T_i and hence mean inspiratory flow compared to breast feeding and this could be related to the very different motor activity associated with feeding between the two groups (5, 22).

In summary, our findings indicate that feeding (either BR or BOT) markedly depresses the ventilatory response to chemical stimuli (CO₂). This modification is primarily related to changes in "effective" respiratory timing (T_i/T_{tot}) rather than mean inspiratory flow (V_T/T_i). The specific mechanism for this interaction between the behavioral and automatic ventilatory control systems is unknown.

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