Effects of CO_2 rebreathing on pulmonary mechanics in premature infants

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MILLER, MARTHA J., JULIANN M. DiFIORE, KINGMAN P. STROHL, WALDEMAR A. CARLO, AND RICHARD J. MARTIN. *Effects of CO_2 rebreathing on pulmonary mechanics in premature infants.* J. Appl. Physiol. 70(6): 2582–2586, 1991.—The effects of hypercapnia produced by CO_2 rebreathing on total pulmonary, supraglottic, and lower airway (larynx and lungs) resistance were determined in eight premature infants [gestational age at birth 32 ± 3 (SE) wk, weight at study 1,950 ± 150 g]. Nasal airflow was measured with a mask pneumotachograph, and pressures in the esophagus and oropharynx were measured with a fluid-filled or 5-Fr Millar pressure catheter. Trials of hyperoxic (40% inspired O_2 fraction) CO_2 rebreathing were performed during quiet sleep. Total pulmonary resistance decreased progressively as end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) increased from 63 ± 23 to 23 ± 15 $cmH_2O \cdot l^{-1} \cdot s$ in inspiration and from 115 ± 82 to 42 ± 27 $cmH_2O \cdot l^{-1} \cdot s$ in expiration between room air ($P_{ET_{CO_2}}$ 37 Torr) and $P_{ET_{CO_2}}$ of 55 Torr ($P < 0.05$). Lower airway resistance (larynx and lungs) also decreased from 52 ± 22 to 18 ± 14 $cmH_2O \cdot l^{-1} \cdot s$ in inspiration and from 88 ± 45 to 30 ± 22 $cmH_2O \cdot l^{-1} \cdot s$ in expiration between $P_{ET_{CO_2}}$ of 37 and 55 Torr, respectively ($P < 0.05$). Resistance of the supraglottic airway also decreased during inspiration from 7.2 ± 2.5 to 3.6 ± 2.5 $cmH_2O \cdot l^{-1} \cdot s$ and in expiration from 7.6 ± 3.3 to 5.3 ± 4.7 $cmH_2O \cdot l^{-1} \cdot s$ at $P_{ET_{CO_2}}$ of 37 and 55 Torr ($P < 0.05$). The decrease in resistance that occurs within the airway in response to inhaled CO_2 may permit greater airflow at any level of respiratory drive, thereby improving the infant's response to CO_2.

supraglottic airway; resistance; larynx; genioglossus

INHALATION OF CO_2 has been observed to stimulate ventilatory drive in premature infants, although to a lesser extent than in full-term babies (18, 25). This response predominantly may be due to activation of central medullary chemoreceptors in response to rising arterial P_{CO_2} (Pa_{CO_2}) (18). In adult humans, variable responses of the total pulmonary system to CO_2 inhalation have been reported. Three groups have found either an increase in specific conductance (1, 19) or a decrease in resistance (22) in adult humans. Two further studies, however, have noted no change in airway resistance (4, 16), and Sterling (28) has reported a decrease in specific conductance in response to CO_2 inhalation. The etiology of this variability in reported response in adults is unclear.

In the premature infant with lung disease such as respiratory distress syndrome or bronchopulmonary dysplasia, Pa_{CO_2} may increase as lung function deteriorates. However, no information is currently available on the changes in resistance or compliance that may occur in the infant's airway or its segments (lung, larynx, supraglottic airway) in response to increasing Pa_{CO_2}. This study was designed to determine in premature infants how total pulmonary resistance changes in response to hyperoxic CO_2 rebreathing, and furthermore, to separately evaluate the changes in resistance of the infant's supraglottic and lower airway (larynx and lungs), which occur in response to this stimulus.

METHODS

The study population consisted of eight premature infants, birth weight 1,570 ± 400 (SD) g, gestational age at birth 32 ± 3 wk, postnatal age at study 2.4 ± 1.3 wk, and weight at study 1,950 ± 150 g. Mean duration of mechanical ventilation was 0.5 days (range 0–3 days), and mean oxygen dependence was 1.3 days (range 0–5 days). None of the infants were on oxygen therapy; however, three infants were receiving theophylline therapy for apnea of prematurity, serum level 6.3 ± 1.9 μg/ml. The response of these infants to CO_2 inhalation did not differ from that of the remainder of the group, therefore the data from all infants were pooled. Studies were performed in the neonatal physiology laboratory with the infant maintained in a neutral thermal environment. The investigation was approved by the institutional human research committee, and informed consent was obtained from the parents before study.

Infants were evaluated for 60–90 min during sleep. To ensure a steady ventilatory baseline, quiet sleep (as verified by behavioral criteria) (21) was chosen for evaluation of the response to CO_2 inhalation. Two to four trials of CO_2 rebreathing were performed per infant by the technique of Read as modified by Moriette et al. (18). This technique was chosen so that the response of the infant over a large range of end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) could be sampled in a relatively short period of time, within a uniform sleep state. Trials in which the infant aroused during CO_2 rebreathing were not analyzed. Two infants opened their mouths during CO_2 inhalation, resulting in combined oronasal breathing (3 trials in total), and these trials were not utilized for analysis. During each study, the infant breathed through a nasal pneumotachograph (dead space 2 ml, resistance 5.5 $cmH_2O \cdot l^{-1} \cdot s$, linear to a flow of 8 l/min) connected to a Validyne MP45 transducer (±5 cmH_2O, Validyne, Northridge, CA). Flow was integrated to give tidal volume (V_T). During the control period, the infant inhaled room air. During CO_2 re-

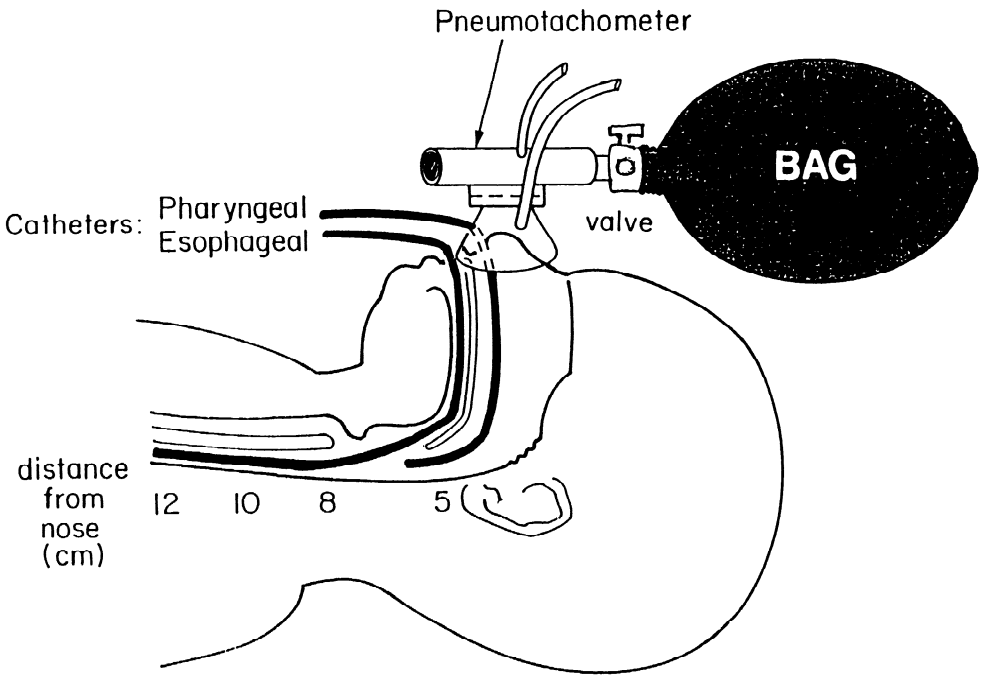

FIG. 1. Apparatus for measurement of nasal airflow as well as pharyngeal and esophageal pressure during CO_2 rebreathing in infants.

breathing, the pneumotachograph was connected to a 500-ml bag containing 75 ml/kg of 5% CO_2 (in 40% O_2, 55% N_2), and the infant was allowed to breathe this mixture for 2–3 min (114 ± 36 s) (Fig. 1). $P_{ET_{CO_2}}$ and transcutaneous oxygen saturation (Nellcor, Hayward, CA) were recorded continuously. Oxygen saturation did not significantly decrease during CO_2 rebreathing (mean saturation 100 and 98 ± 2% at the beginning and end of the studies, respectively). As described by Coates et al. (9), esophageal pressure was measured at 11–12 cm from the mouth (14–16 cm from the nares) with a per-oral 5-Fr pressure catheter (Argyle) connected to a Statham P23 ID transducer (Gould, Cleveland, OH). Pressure in the oropharynx was measured with a 5-Fr Millar pressure catheter, placed transnasally (Millar Instruments, Houston, TX), and nasal mask pressure was measured with an air-filled catheter attached to a Validyne MP45 pressure transducer (±25 cmH_2O). The frequency response of each catheter was evaluated with a square-wave pressure change and was satisfactory to 12 Hz. Pressure and flow monitoring systems were in phase. Validity of pressure determination at each site was checked by the occlusion test during the control period of the study; a 5% error was considered acceptable.

Nasal airflow and pressures in the nasal mask, oropharynx, and esophagus were recorded on a Gould 8-channel recorder and stored on magnetic tape. For data analysis over 15 breath epochs, nasal airflow and the corresponding pressure across the segment of the airway to be analyzed were sampled at 100 Hz with an IBM AT computer. Flow was integrated digitally to give V_T, and flow-zero crossing was utilized to mark the beginning and end of each breath. Breaths associated with startles, sighs, or body movement were not analyzed.

Total pulmonary resistance (R_T) in inspiration and expiration was calculated from the flow-resistive pressure change during respiration between the nasal mask and esophageal catheter, at a flow of 1.0 l/min (linear portion of pressure-flow curve) in inspiration and expiration. This strategy was chosen so that resistance could be compared between breaths of increasing amplitude without the confounding variable of change in resistance with change in flow. The difference in volume of the breath at which resistance was measured when flow was 1 l/min in the control period and the highest level of $P_{ET_{CO_2}}$ ranged from 0.7 to 1.44 ml. To utilize the subtraction technique described by Mead and Whittenberger (17) for measurement of dynamic compliance and inspiratory and expiratory resistance, the compliance of the lung is determined from the slope of the line connecting the points of zero flow on the pressure-volume curve. All breaths in all epochs were displayed, and if the pressure-volume loop could not be bisected by a line connecting the points of zero flow, the breath was rejected. If 15 breaths were not analyzable over each epoch, the study was rejected. In one infant, R_T in inspiration and expiration could not be separately determined (13). Supraglottic airway resistance (Rs) (from the level of the epiglottis to anterior nares) was determined in all eight infants from the nasal airflow and pressure change with respiration between the oropharyngeal catheter and the nasal mask at a flow of 1 l/min in inspiration and expiration. Lower airway resistance (Rla, lung and larynx) in inspiration and expiration was also measured from the flow and flow-resistive pressure change with respiration between the esophagus and oropharynx at a flow of 1 l/min. R_T, Rla, and Rs were calculated during the control period on room air and at 50 ± 1.0 and 55 ± 1.2 Torr $P_{ET_{CO_2}}$.

Data are expressed as means ± SD in the text. Statistical analysis was performed by analysis of variance (ANOVA) and the Newman-Keuls procedure.

RESULTS

During CO_2 rebreathing, respiratory rate increased from 52 ± 12 to 63 ± 15 and 65 ± 9 breaths/min accompa-

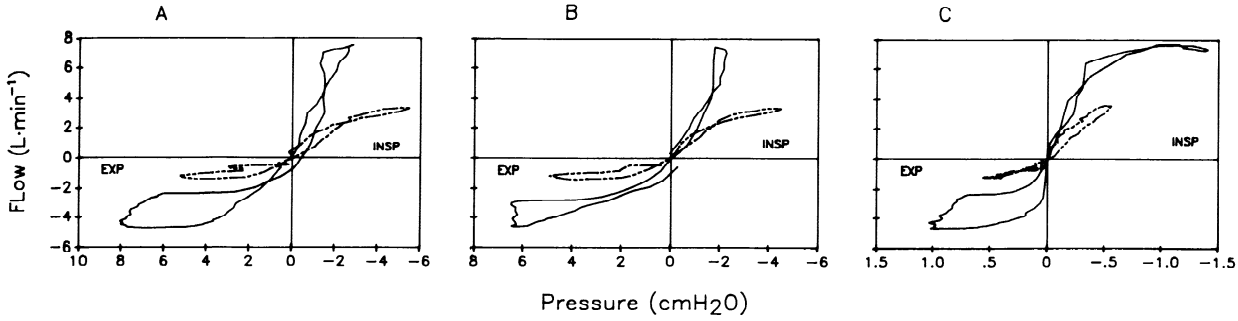

FIG. 2. Representative pressure-flow curves for total pulmonary system (*A*), lower airway (larynx and lungs) (*B*), and supraglottic airway (*C*). - - -, Room air (37 Torr $P_{ET_{CO_2}}$); ——, 55 Torr $P_{ET_{CO_2}}$.

nied by an increase in VT from 10 ± 3 to 18 ± 6 and 24 ± 7 ml at 37, 50, and 55 Torr $P_{ET_{CO_2}}$, respectively. As illustrated in Fig. 2*A*, at any given flow, transpulmonary pressures were lower during CO_2 rebreathing in both inspiration and expiration, reflecting decreased RT. Specifically, RT during inspiration decreased from 63 ± 23 to 35 ± 20 and 23 ± 15 $cmH_2O \cdot l^{-1} \cdot s$ and during expiration decreased from 115 ± 82 to 54 ± 27 and 42 ± 27 $cmH_2O \cdot l^{-1} \cdot s$ with increasing inhaled CO_2 (Table 1, Fig. 3) ($P < 0.05$, ANOVA).

Pressure-flow curves across the lower airway (larynx and lung) are illustrated in Fig. 2*B*. Rla also exhibited a significant decrease from 52 ± 22 to 29 ± 16 and 18 ± 14 $cmH_2O \cdot l^{-1} \cdot s$ in inspiration and from 88 ± 45 to 40 ± 20 and 30 ± 22 $cmH_2O \cdot l^{-1} \cdot s$ in expiration at 37, 50, and 55 Torr $P_{ET_{CO_2}}$ ($P < 0.05$, ANOVA) (Table 1, Fig. 3).

Resistance across the supraglottic airway also diminished during CO_2 rebreathing (Fig. 2*C*). During inspiration Rs decreased from 7.18 ± 2.5 to 5.1 ± 2.5 and 3.6 ± 2.6 $cmH_2O \cdot l^{-1} \cdot s$ and in expiration from 7.6 ± 3.3 to 5.9 ± 3.4 and 5.3 ± 4.7 $cmH_2O \cdot l^{-1} \cdot s$ at 37, 50, and 55 Torr $P_{ET_{CO_2}}$, respectively ($P < 0.05$, ANOVA) (Fig. 3).

DISCUSSION

This study has demonstrated that the healthy premature infant is able to decrease RT in response to continuously increasing inhaled CO_2. Furthermore, this response may occur at two levels, the supraglottic airway and the lower airway (lung and larynx). The supraglottic airway comprises the oro- and nasopharynx plus the parallel nasal passages. In this study, we have not partitioned resistance across these sections and can only speculate on how the infant is able to decrease resistance in each of these areas. The alae nasae are mechanically positioned to effect a decrease in nasal resistance as respiratory drive increases, as has been previously shown in infants (6) and in adults (29). At the level of the pharynx, the genioglossus muscle may be activated in infants in response to increasing level of CO_2 (7) and may widen the pharyngeal passage through anterior displacement of the tongue (3, 14, 24). Recently, a decrease in nasal and pharyngeal resistance has been demonstrated in human adults in response to increasing inhaled CO_2 (26), a finding that supports the active role of upper airway dilating muscles in the response to increasing respiratory drive.

Changes in both respiratory frequency and lung volume could theoretically contribute to the decrease in resistance of the pulmonary system detected in this study (20, 27). However, frequency dependence of resistance has not been observed in infants in the range of breathing frequency in this study. Resistance could also decrease if lung volume increases during CO_2 inhalation. From the data of Polgar (23), we have estimated that a 25-ml change in lung volume (equivalent to the highest change in VT observed in this study) in an infant would be accompanied by only a small decrease in RT of ~1.7 $cmH_2O \cdot l^{-1} \cdot s$, an effect an order of magnitude smaller than the changes we observed. We conclude, therefore, that neither frequency nor volume dependence of resistance would have contributed substantially to the change in RT with CO_2 inhalation in these infants.

This study was designed to determine the response of

TABLE 1. *Change in total pulmonary resistance and lower airway resistance in response to inhaled CO_2*

	RT, $cmH_2O \cdot l^{-1} \cdot s$						Rla, $cmH_2O \cdot l^{-1} \cdot s$					
	Room Air		$P_{ET_{CO_2}}$, 50 Torr		$P_{ET_{CO_2}}$, 55 Torr		Room Air		$P_{ET_{CO_2}}$, 50 Torr		$P_{ET_{CO_2}}$, 55 Torr	
Subj No.	R_{insp}	R_{exp}	R_{insp}	R_{exp}	R_{insp}	R_{exp}	R_{insp}	R_{exp}	R_{insp}	R_{exp}	R_{insp}	R_{exp}
1	67	283	41	47	24	35	56	157	34	41	22	30.6
2	63	67	8.3	34	10	30	38	54	7	21	4.8	11.8
3	70	95	46	85	38	94	66	88	34	54	36	61.2
4	87	106	58	77	26	46	76	99	34	51	22	39.6
5	64	93	53	80	47	58	59	79	41	67	32	51.0
6	76	134	24	35	9.4	23	55	121	6.6	33	4.8	7.8
7	13	23	13	18	6.0	10	9.1	19	4.2	8.8	3.7	7.2
Mean ± SD	63±24	115±82	35±20	54±27	23±15	42±27	51±22	88±45	23±16	40±20	18±14	30±22

RT, total pulmonary resistance; Rla, lower airway resistance; $P_{ET_{CO_2}}$, end-tidal P_{CO_2}; R_{insp} and R_{exp}, resistance, inspiration and expiration, respectively.

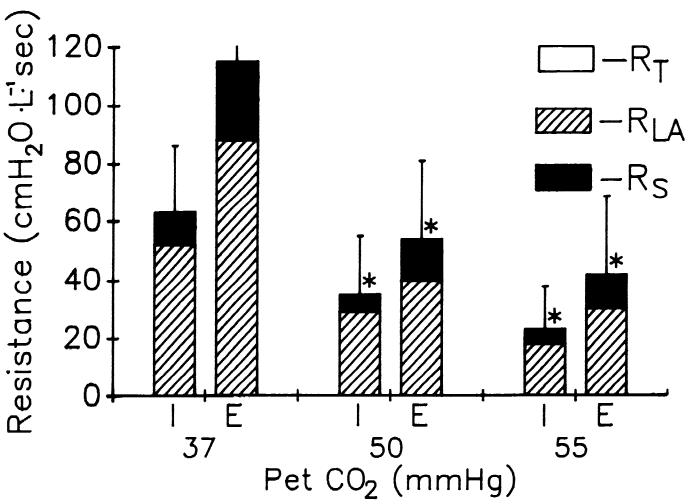

FIG. 3. Total pulmonary resistance (RT), lower airway resistance (Rla), and supraglottic airway resistance (Rs) measured at a flow of 1 l/min decreased significantly between 37, 50, and 55 Torr $P_{ET_{CO_2}}$. Values are means ± SE. I, inspiratory; E, expiratory. *$P < 0.05$ (analysis of variance).

the premature infant to a continuous increase in inhaled CO_2. As such, the study is limited in that it cannot address the adaptation that might occur if the infant were exposed to stepwise changes in inhaled CO_2 over a period required to reach a steady-state ventilatory response.

The alteration in pressure-flow characteristics of the supraglottic airway observed in this study may be directly attributable to an increase in size of this segment of the airway. As the radius of the airway increases flow resistance would decrease, and laminar flow conditions would also be expected to occur at a higher rate of flow. This would have the net effect of allowing increasing flow at higher ventilatory drive without an associated increase in resistance due to the contribution of transitional or turbulent flow.

The lower airway, as evaluated in this study, comprised the larynx and lung. Increasing Pa_{CO_2} theoretically may have opposite effects on these two areas with their balance determining the net result. At the level of the larynx inhaled CO_2 has been shown to cause widening of the glottic aperture through activation of the posterior cricoarytenoid (PCA) muscle in both animals (2, 12) and preterm infants (5). England et al. (12) found that phasic inspiratory activity of the PCA in unanesthetized dogs increased during hypercapnia and was accompanied by a tonic and/or phasic increase in expiratory activity as P_{CO_2} rises during rebreathing. In addition Carlo et al. (5) observed in infants that CO_2 inhalation produced an increase in laryngeal muscle electromyographic activity attributed predominantly to activation of the PCA. Thus active dilatation at the larynx would be expected to occur during CO_2 rebreathing.

Hypercapnia may produce an opposite effect within the tracheobronchial tree. CO_2 inhalation has been shown to produce reflex bronchoconstriction in dogs (10, 15, 19, 30). Chemoreceptors in the ventral medulla and the carotid body are believed to respond to an increase in arterial CO_2, producing an elevation in vagal tone to airway smooth muscle that results in vagally mediated reflex bronchoconstriction (11). In the dog, reflex bronchoconstriction in response to hypercapnia is present in the newborn period (30). In the human infant the response of the isolated tracheobronchial tree to an increase in inhaled CO_2 has not been characterized to date. We infer from our results that any reflex bronchoconstriction that may occur in the lower airways of the infant could be obscured by dilatation at the level of the larynx. It is possible that the individual variation in reported responses of the total pulmonary system to CO_2 inhalation in adults may be due in part to the opposing contributions of the larynx, supraglottic airway, and bronchial system.

We conclude that the premature infant can respond to CO_2 inhalation with an overall decrease in RT in both inspiration and expiration. This response has a number of beneficial consequences; it allows the infant to achieve greater airflow at any level of respiratory drive and, in addition, may decrease the energy expenditure for work of breathing in response to rising Pa_{CO_2}. Furthermore, we speculate that "unloading" the respiratory system via reflex dilatation within the airway could potentially improve the infant's ventilatory response to CO_2, as has been reported in human adults (8).

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